NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Contents:

The Final Scope and Final Matrix are available on the NICE website.

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

BMJ TAG

Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis

MTA Report

December 2021

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135138.

Title:	Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR. Charlotta Karner, Clinical Evidence Manager, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR. Tracey Jhita, Health Economics Manager, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR. Samantha Barton, Principal Clinical Evidence Analyst, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR. Gemma Marceniuk, Senior Health Economist, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR. Zenas Yiu, NIHR Clinical Lecturer in Dermatology, University of Manchester, Manchester, M15 6GZ. Miriam Wittmann, Associate Professor in Inflammatory Skin Diseases, University of Leeds, LS2 9JT.
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	03/12/2021
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135138.
Declared competing interests of the authors	No competing interests were declared by SE, CK, TJ, SB, GM or ZY which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG. In the past 36 months, MW has received research grants from AbbVie, the British Skin Foundation, Janssen, Lupus UK, Novartis, Pfizer Global, and UCB. MW has received a consultancy fee from UCB for acting on an advisory board, and remuneration from various companies for carrying out educational lectures.
Acknowledgments:	The ERG would like to thank Victoria Wakefield (Principal Clinical Evidence Analyst, BMJ-TAG), Ben Mayer (Senior Clinical Evidence Analyst, BMJ-TAG) and Conor Hickey (Associate Health Economist, BMJ-TAG) for their assistance with title and abstract appraisal and data extraction and quality assurance of the model.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards, S. J., Karner, C., Jhita, T., Barton, S., Marceniuk, G. Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis: A Multiple Technology Assessment. BMJ Technology Assessment Group, 2021.

Contribution of authors:

Steve Edwards	Project lead: supervised the production of the final report; critical appraisal of the clinical evidence; and critical appraisal of the economic evidence.
Charlotta Karner	Study selection, data extraction, critical appraisal of the clinical evidence; carried out network meta-analyses; and contributed to writing the clinical sections of the report.
Samantha Barton	Devised and carried out the literature searches on clinical effectiveness; contributed to study selection, data extraction, critical appraisal of the clinical evidence; and contributed to writing the clinical sections of the report.
Tracey Jhita	Study selection; data extraction; critical appraisal of the economic evidence. Development of the conceptual model, quality assurance of the economic model and writing the economic sections of the report.
Gemma Marceniuk	Devised and carried out the economic literature searches; study selection; data extraction; critical appraisal of the economic evidence. Development of the economic model and carried out the economic analysis and contributed to writing the economic sections of the report.
Zenas Yiu	Supplied expert clinical advice throughout the project - including reading and commenting on the final report
Miriam Wittmann	Supplied expert clinical advice throughout the project - including reading and commenting on the final report

All authors read and commented on draft versions of the EAG report.

Abstract

Background

Atopic dermatitis (AD), often referred to as atopic eczema, is a chronic relapsing inflammatory skin condition. One of the most common skin disorders in children, AD typically manifests before the age of 5 years, but can develop at any age. AD is characterized by dry, inflamed skin accompanied by intense itchiness (pruritus).

Objectives

To appraise the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib within their marketing authorisations as alternative therapies for treating moderate-to-severe AD compared to systemic immunosuppressants (first-line ciclosporin A or second-line dupilumab and baricitinib).

Data sources

Studies were identified from an existing systematic review (search date 2019) and update searches of electronic databases (MEDLINE, EMBASE, CENTRAL) to November 2021, from bibliographies of retrieved studies, clinical trial registers, and evidence provided by the sponsoring companies of the treatments under review.

Methods

A systematic review of the clinical effectiveness literature was carried out and network meta-analysis (NMA) undertaken for adults and adolescents at different steps of the treatment pathway. The primary outcome of interest was a combined response of EASI 50 + DLQI ≥4, where this was consistently unavailable for a step in the pathway an analysis of EASI 75 was conducted. A *de novo* economic model was developed to assess cost-effectiveness from the perspective of the NHS in England. The model structure was informed through systematic review of the economic literature and by consulting clinical experts. Effectiveness data were obtained from the NMA. Costs and utilities were obtained from the evidence provided by sponsoring companies and standard UK sources.

Results

NMAs indicate that abrocitinib 200 mg and upadacitinib 30 mg may be more effective, and tralokinumab may be less effective than dupilumab and baricitinib as second-line systemic therapies. Abrocitinib 100 mg and upadacitinib 15 mg have a more similar effectiveness to dupilumab. Upadacitinib 30 mg and 15 mg are likely to be more effective than ciclosporin A as a first-line therapy. Upadacitinib 15 mg and abrocitinib (200 mg and 100 mg) may be more effective than dupilumab in adolescents. The cost-effectiveness of upadacitinib for both doses is dependent on the subgroup of interest. Both doses of abrocitinib and tralokinumab could be considered cost-effective use of NHS resources.

Conclusions

The primary strength of the analysis of the three new drugs compared with current practice for each of the subpopulations is the consistent approach to the assessment of clinical and cost-effectiveness. However, the conclusions are limited by the high uncertainty around the clinical effectiveness and lack of data for the primary outcome for comparisons with baricitinib and for the adolescent and adult first-line populations.

Study registration

The protocol for the systematic review is registered on PROSPERO (registration number CRD42021266219).

Funding

The National Institute for Health Research Health Technology Assessment programme.

Suggested key words: atopic dermatitis; abrocitinib; tralokinumab; upadacitinib; cost effectiveness

Scientific summary

Background

Atopic dermatitis (AD), often referred to as atopic eczema, is a chronic relapsing inflammatory skin condition. One of the most common skin disorders in children, AD typically manifests before the age of 5 years, but can develop at any age. AD is characterized by dry, inflamed skin accompanied by intense itchiness (pruritus). As many as one in five children and one in ten adults in the UK are estimated to have AD, with about 18% of cases of childhood AD categorised as moderate and 2% as severe. Of adults with AD, it has been reported that 5% of cases are severe. Of the people who need treatment for AD, 7% are estimated to have moderate-to-severe disease.

AD is currently uncurable, and the goal of treatment is to improve symptoms and achieve long-term disease control. Those with moderate-to-severe AD that only partially responds to treatment, and those presenting with severe disease, are referred to secondary care for more specialised therapy, where phototherapy (predominantly UVB) is frequently the first treatment option. If phototherapy is unsuccessful, subsequent treatment typically constitute systemic treatments.

Systemic treatment options available within the NHS for the management of AD in line with their marketing authorisations are ciclosporin (CsA) in the first-line setting, and baricitinib and dupilumab as subsequent therapies. The three interventions for which an evaluation of the clinical and cost effectiveness in the treatment of moderate-to-severe AD form the basis of this report are abrocitinib, tralokinumab and upadacitinib. The clinical and cost effectiveness of these treatments at their recommended dose or doses versus treatment options available in the NHS for moderate-to-severe AD, was evaluated in the positions in the treatment pathway proposed by the sponsoring company.

The proposed positions are:

- Abrocitinib:
  - Second-line systemic therapy for adolescents;
  - Second-line systemic therapy for adults.
- Tralokinumab:
  - Second-line systemic therapy for adults.
- Upadacitinib:
  - Adolescents;

- First-line systemic therapy for adults;
- Second-line systemic therapy for adults.

Objectives

The research objectives of the MTA are to appraise the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib within their marketing authorisations as alternative therapies for treating moderate-to-severe AD in the UK clinical setting compared to systemic immunosuppressants (first-line ciclosporin A or second-line dupilumab and baricitinib).

Methods

Studies were identified from an existing systematic review (search date 2019) and update searches of electronic databases (MEDLINE, EMBASE, CENTRAL) up to November 2021, from bibliographies of retrieved studies, clinical trial registers, and evidence submissions provided by companies. Clinical studies and economic evaluations were included based on pre-specified inclusion criteria. Screening of title and abstracts to identify potentially relevant studies and evaluation of full-text publications were done independently by two reviewers. Data from included studies were extracted into a standardised data extraction form by one reviewer and validated by a second. Quality of included studies was assessed independently by two reviewers using standard checklists. Extracted data and quality assessment for each study were presented in structured tables. Where sufficient comparable data were available for an outcome measure, network meta-analysis (NMA) were performed using a Bayesian Markov Chain Monte Carlo simulation. The primary outcome of the review of clinical effectiveness was EASI 50 + DLQI ≥4 and EASI 75 was explored as a scenario. Treatment effects were analysed as odds ratios (ORs).

A *de novo* hybrid economic model was developed to assess the cost-effectiveness of the three new drugs, comprising a short-term (1 year) decision tree component, to capture the treatment induction phase and treatment response assessments, followed by a long-term (lifetime), three-state Markov model. In consultation with clinical experts, the EAG selected baseline characteristics for the model from the upadacitinib trials, which were considered representative of the eligible patient population in England. Estimates of treatment response, based on the composite outcome of EASI 50 + DLQI ≥4 from the NMA of clinical effectiveness data were used in the short-term model.

Conditional discontinuation data (defined as people whose condition responded to treatment at Week 16 but withdrew from treatment for any reason at Week 52) were used to estimate Week 52 outcomes as well as long-term treatment discontinuation. Conditional discontinuation data were

provided by the companies. Where there was a paucity of data, the EAG adopted a drug class approach to fill the gaps, where upadacitinib was used to inform Janus Kinase inhibitors and tralokinumab was used to inform monoclonal antibodies. Additionally, in the long-term model treatment waning assumptions were applied to all treatments as patients may lose response to treatment over time and these were informed by assumptions accepted in TA534.

Rates of adverse events and flare (based on use of rescue medication) associated with each treatment were obtained from the companies and where data gaps existed, a similar drug class approach was adopted for the missing data. Utilities based on drug class were obtained from key trials of upadacitinib and tralokinumab. Costs were obtained from standard UK sources. Probabilistic, one-way, and scenario analyses were carried out to assess parameter uncertainty.

Results

The EAG identified 23 studies of relevance to the MTA. Most of the studies included in the assessment of clinical effectiveness were considered to be well-conducted and well-designed Phase III RCTs, and, as such, are at an overall low risk of bias. However, the identified studies predominantly included mixed populations of people with moderate-to-severe AD, with some studies comprising both adolescents and adults, as well as a combination of people receiving systemic therapy as a first-line or second-line regimen. Thus, data informing the NMAs for the populations and outcomes of interest to the MTA are predominantly derived from *post hoc* subgroups.

There were considerable amounts of uncertainty and the vast majority of results were not statistically significant. However, there were consistent trends across the outcomes (EASI 50 + ΔDLQI ≥4 and EASI 75), interventions (combination therapy or monotherapy), and populations (adults in the first- or second-line setting, and adolescents).

Treatment with abrocitinib 200 mg leads to a better response, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than dupilumab, whereas there was less of a difference in effectiveness between dupilumab and abrocitinib 100 mg with some comparisons showing a benefit in favour of dupilumab and others favouring abrocitinib 100 mg. Both doses of abrocitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second-line setting) and in the adolescent population both doses of abrocitinib were more effective than dupilumab (EASI 75). Although significantly better than placebo, tralokinumab treatment was numerically, but not statistically significantly, less effective than treatment with either dupilumab or baricitinib 4 mg (response assessed as either EASI

50 + ΔDLQI ≥4 or EASI 75). Similar to abrocitinib, treatment with upadacitinib 30 mg led to a better response (assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75) than dupilumab, whereas there was less of a difference in effectiveness between dupilumab and upadacitinib 15 mg with some comparisons showing a benefit in favour of dupilumab and others favouring upadacitinib 15 mg. Both doses of upadacitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second-line setting). In the adolescent population upadacitinib 15 mg was more effective than dupilumab (EASI 75).

The National Institute of Health and Care Excellence (NICE) typically considers interventions a cost-effective use of the National Health Service (NHS) resources if the incremental cost-effectiveness ratio (ICER) sits within a £20,000 – £30,000 threshold. The decision rule is reversed if an intervention is less costly and less effective (south-west quadrant), such that if the ICER is greater than the £20,000 – £30,000 threshold, it can be considered a cost-effective use of NHS resources.

For the adolescent population analyses, both doses of abrocitinib and upadacitinib 15 mg were less costly and more effective than dupilumab, resulting in dominant probabilistic ICERs. For the adult second-line monotherapy population, both doses of abrocitinib and upadacitinib 15 mg are less costly and more effective than dupilumab (dominant) and tralokinumab was less costly and less effective than dupilumab (south-west quadrant ICER of £388,870).

For the adult second-line combination therapy population, compared with dupilumab abrocitinib 200 mg was dominant and abrocitinib 100 mg, upadacitinib 15 mg and tralokinumab were associated with south-west quadrant probabilistic ICERs of £156,267, £185,453, and £232,282, respectively.

Compared with dupilumab, the following were not considered a cost-effective use of NHS resources with ICERs above £30,000 threshold commonly used by NICE: upadacitinib 15 mg/30 mg (adult first-line combination therapy), abrocitinib 100 mg/200 mg and upadacitinib 30 mg for both adult second-line monotherapy and combination therapy analyses.

The key drivers of cost-effectiveness were Week 16 response probabilities and conditional discontinuation probabilities (used to inform the week 52 response and annual discontinuation), which are as expected as these are the key effectiveness estimates in the model. In particular, the NMA for Week 16 response was associated with substantial uncertainty, especially for abrocitinib, due to small numbers informing the network.

Key scenarios that had a substantial impact on the cost-effectiveness results involved using data from TA534.

The EAG cautions the interpretation of the cost-effectiveness results presented in the MTA report as they are based on list prices for abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib but all have confidential patient access scheme (PAS) in place.

Conclusions

The population which is most likely to be important for decision making is the adult second-line systemic treatment subgroup, in particular the combination treatment analyses, as all three new drugs have a proposed position in this part of the treatment pathway. Furthermore, clinical experts advising the EAG considered combination therapy is more widely using in clinical practice in England. For this population, composite outcome data were available for each new treatment under consideration, as well as for one of the relevant comparators, dupilumab (which is approved for use by NICE at this step in the treatment pathway). Baricitinib in combination with TCS is also a relevant comparator in the adult second-line systemic treatment population. However, composite outcome data for baricitinib were not made available to the EAG for inclusion in the clinical effectiveness analysis. Instead, the EAG obtained EASI 75 data for baricitinib and included this in the adult second-line systemic combination treatment NMA. As such, a scenario looking at the cost-effectiveness of each of the three new drugs compared with baricitinib was explored to support decision making.

As the adult first-line systemic treatment and adolescent populations are also relevant for decision making, the EAG was able to produce base case cost-effectiveness results for the new drugs using the EASI 75 outcome, as the composite outcome was unavailable. However, RCT data for CsA were not available for the comparison with upadacitinib in the first-line setting, but observational data were identified that could be used in the NMA. Though the EAG notes that even though observational data for CsA is the best available evidence, it is associated with the bias inherent in observational studies and the results should be interpreted with caution. Additionally, for the adult first-line systemic treatment population, outcome data were only available for combination therapy, but the EAG's clinical experts considered it to be more relevant for clinical practice. Thus, the EAG considered missing monotherapy data is unlikely to be critical for decision-making for the adult first-line systemic treatment subgroup.

Analyses of the adolescent population were limited to assessing monotherapy, as combination data for dupilumab were unavailable to inform the NMA. Thus, the adolescent monotherapy analyses may potentially underestimate the relative effectiveness of the treatments when used in combination with TCS in clinical practice, as combination treatment results typically demonstrate higher treatment effectiveness.

The Summary of Product Characteristics for both abrocitinib and upadacitinib takes into consideration circumstances, where moving to the lower or higher dose of each drug may be beneficial and this is likely to happen in clinical practice. However, analyses exploring increasing or decreasing dose for abrocitinib and upadacitinib were not possible as efficacy data based on titrating dose are unavailable. Nonetheless, the EAG considers that clinical and cost-effectiveness results for abrocitinib and upadacitinib by low and high dose is useful to facilitate consideration of the impact of dose titration for each drug.

The robustness of the clinical and cost-effectiveness analyses is limited by the use of *post hoc* subgroups; while the use of subgroups increases the comparability and applicability of the analyses, it introduces bias and uncertainty to the results generated by the NMAs. In particular, the sample size of the second-line systemic therapy subgroup in the abrocitinib trials was very small as the majority of patients in the abrocitinib trials were eligible for first-line rather than second-line systemic therapy.

This research assesses the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib as alternative therapies for treating moderate-to-severe AD compared to standard practice with systemic immunosuppressants. At the different steps in the treatment pathway assessed, new options were identified that represent a cost-effective use of scarce NHS resources.

*Plain English summary

Atopic dermatitis (AD), which is also known as eczema or atopic eczema, is a condition that affects the skin. AD is one of the most common skin disorders in children, with symptoms usually showing before the age of 5 years. However, AD can also develop in adulthood. People with AD have dry, red (inflamed) skin that is also extremely itchy (pruritus). Oozing, weeping sores can occur in more severe forms of AD. There is no cure for AD, and the aim of treatment at first is to provide symptom relief and then to control symptoms in the longer term. Mild cases of AD, which most people have, are treated by General Practitioners (GPs). Therapy starts with topical treatments that are applied to the skin, such as emollients (a cream, lotion or ointment that soothes the skin). Those with more severe AD are likely to need stronger therapies, which are usually given by doctors who specialise in treating skin disorders. Severe forms of AD might be treated with phototherapy (exposure to ultraviolet light) or, more often, with systemic treatments, which are drugs that are provided as tablets or an injection to target the processes within the body that are causing the inflammation of

the skin. Ciclosporin A (CsA) is often the first systemic therapy given. If AD does not get better with CsA, options available in the National Health Service (NHS) after CsA are dupilumab and baricitinib. New therapies that have been evaluated in clinical trials for AD but have not been assessed for use in the NHS are abrocitinib, tralokinumab and upadacitinib.

The aim of this project is to review abrocitinib, tralokinumab and upadacitinib for the treatment of moderate-to-severe AD in a multiple technology appraisal (MTA). The medical benefits and risks associated with the three treatments will be assessed and compared against the available standard treatments for AD. In addition, this project will assess whether abrocitinib, tralokinumab and upadacitinib are likely to be considered good value for money for the NHS.

Our review found that,

- For children aged between 12 and 18 years who have moderate to severe AD, abrocitinib, which is available in two different doses, and a low dose of upadacitinib (15mg), work well at reducing the symptoms of AD and are good value for money for the NHS, even if they were not the most effective of all the treatments looked at.
- For adults with moderate-to-severe AD who need a first systemic treatment, upadacitinib, although probably better at reducing the symptoms AD than the alternative treatment, is unlikely to be good value for money for the NHS.
- For adults with moderate-to-severe AD who are still suffering from their AD after having a systemic treatment and need a different drug, abrocitinib, upadacitinib 15 mg and tralokinumab could be good value for money for the NHS if they are used on their own (not with additional steroid cream), even if other treatments were better at reducing the symptoms of AD.
- For adults with moderate to severe AD who are still suffering from their AD after having a systemic treatment and need a different drug but need to take it with steroid cream, abrocitinib, upadacitinib 15 mg and tralokinumab could all be good value for money for the NHS, even if other treatments were better at reducing the symptoms of AD.

Table of Contents

List of Tables

List of Figures

Definition of terms

Dominant	Treatment is less expensive and more effective than the comparator
Dominated	Treatment is more expensive and less effective than the comparator
North-east quadrant	The incremental cost effectiveness ratio lies in the north-east quadrant of the cost-effectiveness plane, which means it is more expensive and more effective than the comparator.
South-west quadrant	The incremental cost effectiveness ratio lies in the south-west quadrant of the cost-effectiveness plane, which means it is less expensive and less effective than the comparator.

List of Abbreviations

AD	Atopic dermatitis
A&E	Accident and emergency
AE	Adverse effect
BGR	Brooks-Gelman-Rubin
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CrI	Credible interval
CsA	Ciclosporin A
CSR	Clinical Study Report
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EASI	Eczema Area and Severity Index
eMIT	Electronic drug marketing tool
EQ-5D	EuroQol-5 dimensions
FAD	Final Appraisal Document
FBC	Full blood count
FE	Fixed effects
GP	General Practitioner
HOME	Harmonising Outcomes for Eczema
HRQoL	Health-related quality-of-life
HSUV	Heath state utility value
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IL	Interleukin
JAK	Janus kinase
LYG	Life years gained
MCMC	Markov Chain Monte Carlo
MTA	Multiple Technology Appraisal
NA	Not applicable
N/A	Not available

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NRS	Numerical rating scale
OD	Once daily
OR	Odds ratio
ONS	Office of National Statistics
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
POEM	Patient-Oriented Eczema Measure
PPSRU	Personal Social Services Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effects
SAE	Serious adverse effect
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard deviation
SF-6D	Short-form 6-dimension
SF-12	12-item short-form health survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TSD	Technical Support Document
TTO	Time trade-off
UK	United Kingdom
URTI	Urinary tract infection
USA	United States of America
UVB	Ultraviolet B

VAS	Visual analogue scale
WTP	Willingness to pay

1 Background

1.1 Description of health problem

1.1.1 Brief statement describing the health problem

Atopic dermatitis (AD), often referred to as atopic eczema, is a chronic relapsing inflammatory skin condition.[1] One of the most common skin disorders in children, AD typically manifests before the age of 5 years, but can develop at any age. AD is characterized by dry, inflamed skin accompanied by intense itchiness (pruritus). Oozing, weeping lesions can occur in more severe forms of the condition. Scratching constantly due to pruritus disturbs sleep patterns and is considered an important factor in the transition from acute to chronic AD. Bleeding and splitting of the skin, and increased prevalence of skin "superinfection" (infection in addition to AD) are also hallmark features of AD in most people with xerosis (dry skin).[1] Due to repeated episodes of skin infections, extensive antibiotic prescriptions are common among AD patients.

1.1.2 Aetiology, pathology and prognosis

Although a commonly occurring skin disorder in children, around 75% of those with onset of AD in childhood will experience spontaneous remission of symptoms before reaching adolescence. Some whose symptoms do not resolve in childhood continue to suffer from AD symptoms at varying degrees of severity, into adulthood. Some will experience constant symptoms of AD, whereas others will follow a chronic relapsing course of disease.[2]

AD is a multifaceted condition, the underlying cause of which has yet to be firmly established. Genetics, environmental factors, abnormal inflammatory responses to allergens, and disrupted function of the natural skin barrier all have roles in the development and extent of AD.[2, 3] The risk of developing AD is higher for those with a family member who also has this condition or another atopic disease, particularly for children whose parent or parents have AD: where both parents have AD, about 80% of children will develop AD compared with 60% of children with one parent affected.[4] In addition to other hereditary risks of developing AD, presence of mutations in genes encoding structural components of the skin barrier and cells involved in the innate immune response is known to predispose an individual to the development of AD.[5]

The stratum corneum, which is the outermost layer of the skin, is formed of skin cells (corneocyte) held together by lipids and acts as barrier to maximise retention of moisture by the body and to

prevent entry of external toxins through the skin.[6] The protein filaggrin, which connects structural proteins in the outermost skin cells, is essential for maintaining the integrity of the skin barrier.[6] In AD, loss-of-function mutations in the gene encoding filaggrin are considered to be the key genetic indicator for predisposition for development of AD, being linked with early-onset, severe disease.[7, 8] Specific proteases, protease inhibitors, and cytokines are also involved in maintaining the structural integrity of the skin, and mutations in the genes encoding some of these components also leads to structural abnormalities of and dysfunction of the skin barrier.[5]

Defects in the skin barrier enable allergens to penetrate the skin. On passing through the skin, allergens interact with local immune cells, which trigger the release of AD-related pro-inflammatory cytokines.[9] There are two modes of immune response, the innate and the adaptive response. Innate immunity is the immunity that is present from birth. By contrast, adaptive immunity is acquired after exposure to an allergen, more specifically a person develops “antigen-specific memory” to an allergen, which is a key feature of adaptive immunity. Keratinocytes are the most abundant cells of the skin outer layer and contribute to the innate immune defence by producing antimicrobial peptides, as well as mediators (chemokines), in response to presence of allergens or pathogens (e.g., virus, fungi, bacteria). The antimicrobial peptides and chemokines then direct effector white blood cells (T lymphocytes or T cells) into the skin. Dendritic cells (in the skin called Langerhans Cells or dermal dendritic cells) link components of the innate and adaptive immune response. On encountering allergens or pathogens, dendritic cells trigger activation of effector immune cells. The type of allergen or pathogen encountered elicits production of specific signalling molecules, with the resulting signalling cascade subsequently activating cellular mechanisms to eliminate the allergen or pathogen. Abnormal innate and adaptive responses to the presence of allergens/pathogens are thought to have a role in the complex immune network that exacerbates defects in skin barrier dysfunction and also facilitates the inflammatory responses characteristic of AD.[9] Consensus has not been reached on whether epidermal dysfunction precedes immune dysregulation, or vice versa.[9]

Children with AD are at risk of having concomitant asthma, food allergy and hay fever (rhinitis allergica), all of which are triggered by allergens and are also associated with an abnormal immune response.[9] A child with moderate-to-severe AD may be at a 50% risk of developing asthma and 75% risk of developing hay fever.[3] Allergens that are associated with triggering a flare of AD include house dust mites, pollen, pet hair/dander, moulds and some foods. Allergen and non-allergen triggers, such as cigarette smoke, exposure to cold or hot temperatures, and sweating, can exacerbate the symptoms of AD and trigger flares.

1.1.3 Epidemiology

1.1.3.1 Incidence and/or prevalence

As many as one in five children and one in ten adults in the UK are estimated to have AD,[3, 10] with about 18% of cases of childhood AD categorised as moderate and 2% as severe.[3] Of adults with AD, it has been reported that 5% of cases are severe.[11] Of the people who need treatment for AD, 7% are estimated to have moderate-to-severe disease, and, 27% of those receiving treatment will require systemic therapy to elicit sufficient symptom relief.[12, 13]

1.1.4 Impact of health problem

1.1.4.1 Significance for patients in terms of ill-health (burden of disease)

Although the impact of AD varies with age and disease severity, common across ages is that AD affects various aspects of day-to-day living, including emotional and mental well-being, and family and social interactions.[14] As a disease predominantly affecting children, AD can consequently have a substantial impact on parents and other family members due to potential changes in life-style management, such as diet and family routine, to help manage symptoms. The treatment regimen required to sooth symptoms can be time intensive, and children are likely to require assistance from older siblings or adults to apply the topical treatments at the intervals needed for optimal effectiveness. In addition to the physical symptoms of AD, many children and adults experience sleeplessness, anxiety, depression and other mental health problems related to their AD.[10, 14] Adults with AD frequently report decreased work productivity.[14]

People with AD may also face a financial burden arising from extra costs associated with purchasing cleaning and laundry detergents, and bathing products tailored to sensitive skin.[3] Other costs could be incurred from travelling to appointments for assessment or treatment, and for emollients and moisturisers potentially not provided by the National Health Service (NHS). A study focussing on adults with AD that encompassed nine European countries, including the UK, reported that AD was associated with an annual cost to the patient of about £800 (UK£).[15]

1.1.4.2 Significance for the NHS

In 2006, around 24% of people in England and Wales visited their General Practitioner (GP) with a skin disorder, which is equivalent to 12.9 million people.[16] Of those presenting to primary care with a skin disorder, 0.8 million (6.1%) are referred for specialist advice, with most (92%) attending

appointments with dermatologists within the NHS.[16] After diagnosis and establishing a treatment plan, the majority of care occurs at home, with topical treatments forming the mainstay of care, and many of which are purchased by the patient. Thus, it has been reported that, despite skin disorders being common, the cost of skin disease to the NHS is modest. In 2005/2006, the direct cost to the NHS in England and Wales for managing skin disease was reported to be around £1,820 million.[16] With the introduction of biological therapies for AD, which is one of the more common skin disorders, it is likely that the cost to the NHS for managing skin disease will rise in coming years.

1.1.5 Measurement of disease

Diagnosis of AD is based on the clinician's assessment together with patient history.[17] No laboratory test is available to diagnose AD. NICE guidance indicates that AD is likely if the following criteria are fulfilled, but alternative diagnoses may need to be excluded for different age groups:[17]

- An itchy skin condition (or parental report of scratching) plus three or more of the following:
  - Visible flexural eczema involving the skin creases, such as the bends of the elbows or behind the knees (or visible eczema on the cheeks and/or extensor areas in children aged 18 months or younger);
  - Personal history of flexural eczema (or eczema on the cheeks and/or extensor areas in children aged 18 months or younger);
  - Personal history of dry skin in the last 12 months;
  - Personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of a child aged under 4 years);
  - Onset of signs and symptoms before the age of 2 years (this criterion should not be used in children younger than 4 years of age).

In clinical practice, assessment of the degree of severity of AD is based on clinical judgement of the appearance, location and extent of lesions, patient-reported symptoms and quality of life (QoL) outcomes.[18] Various clinical scales and patient reported outcomes are available to assess whether a prescribed treatment is improving symptoms (Table 1). The scales vary considerably in the characteristics of AD evaluated to categorise severity of disease, which makes cross-comparison of the resulting categorisations applied in studies challenging. The Harmonising Outcomes for Eczema (HOME) initiative recommends the Eczema Area and Severity Index (EASI) to assess severity of clinical signs of AD.[19] A visual analogue scale (VAS) of itch and sleep loss due to AD are two

parameters that are important components of some composite scores, and are often used on their own to assess therapy efficacy. To account for patient preference and experience, the patient-reported Dermatology Life Quality Index (DLQI) is also captured in clinical practice, with an improvement in score of at least 4 points recommended to be clinically meaningful:[20] the DLQI is not specific to AD, but is tailored to evaluate QoL in skin diseases. In a clinical trial setting, additional tools used to assess severity of AD are the Investigator Global Assessment (IGA) and Scoring Atopic Dermatitis (SCORAD) index. Classification of disease as moderate or severe according to the various scales are:

- EASI: moderate AD, score of 6.0–22.9, severe AD score of 23.0–72;[21]
- IGA: moderate AD, score of 3, severe AD score of 4;[18]
- SCORAD: moderate AD, score of 25–50, severe AD, score of >50.[18]

Table 1. Overview of the key tools applied in the classification of severity of atopic dermatitis and the impact of the disease on patient quality of life[18]

Scale	Description
Disease severity	
EASI	The body is divided into four regions: • head and neck; • trunk; • upper limbs; • lower limbs. The extent of atopic dermatitis in each region is assessed and a score assigned based on the percentage of the region affected, scoring from 0 (no active eczema) to 6 (90%–100% of the region is involved). Severity of disease is assessed on a four-point scale, from none (0) to severe (3), where each region is evaluated for intensity of: • erythema; • oedema/papulation; • excoriation; • lichenification. The severity score is multiplied by the area score and a designated "multiplier" for the individual regions. The final EASI score is the total of the separate scores for the four regions, with a maximum EASI score of 72. Severity strata for EASI reported by Chopra *et al*:[21] • clear: 0; • mild:·1–5.9; • moderate: 6.0–22.9; • severe: 23.0–72. Response to treatment is the percentage reduction from baseline score.

SCORAD	Determines extent and severity of atopic dermatitis and includes a patient-reported assessment of itch and sleeplessness. The SCORAD score for an individual is calculated using the equation: A/5 + 7B/2 + C. A measures the extent of atopic dermatitis. The affected sites are shaded on a drawing of the body, with each part of the body assigned a different proportion: • head and neck 9%; • upper limbs 9% each; • lower limbs 18% each; • anterior trunk 18%; • back 18%; • genitals 1%. The score for A is the sum of the individual parts of the body, with a maximum score of 100%. B assess the intensity of disease. A representative area of atopic dermatitis is selected and, in that area, the intensity of the specific signs is assessed on a four-point scale (0=none through to 3= severe). Signs evaluated: • redness; • swelling; • oozing/crusting; • scratch marks; • skin thickening; • dryness. The score for B is the total of all intensity scores, with a maximum score of 18. C captures the symptoms of itch and sleep loss. The patient scores each symptom on a visual analogue scale from 0 (no symptom) to 10 (worst imaginable). The scores for each symptom are added together. The maximum SCORAD score is 103. Severity is defined as: • mild, score of <25 • moderate, score of 25–50 • severe, score of >50.
IGA	Assessment based on the overall appearance of lesions at a given point in time. Five-point score categorised as clear (0), almost clear (1), mild (2), moderate (3) and severe (4). Moderate is categorised as, “Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present”. Severe is defined as, ”Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present”.
Quality of life	
DLQI	Most commonly used QoL tool in dermatology. A self-administered, dermatology-specific questionnaire comprising 10 items that focus on six dimensions: symptoms; daily activities; leisure; work; personal relationships; and treatment. Designed to gauge the patients’ perception of the impact of their skin disease on QoL over the previous week.

	Each question is scored on a four-point scale from not at all (0) to very much (3). Maximum score of 30. The CDLQI is the children's version of the DLQI, and is completed by the child with the help of a parent or guardian. The CDLQI has the same format as the DLQI but the bands for categorisation of the level of impact of AD on quality-of-life differ between the two tools.
POEM	A self-administered disease-specific questionnaire, focusing on the illness as experienced by the patient. Involves seven questions about the frequency of eczema symptoms over the last week from no days (0), 1-2 days (1), 3-4 days (2), 5-6 days (3), to every day (4). Symptoms evaluated are: itch; sleep loss; bleeding; oozing/weeping; cracking of skin; flaking of skin; and skin feels dry/rough to the touch. POEM score is the total of scores reported for each question, with a maximum score of 28. Scores of 8–16, 17–24 and 25–28 represent moderate, severe and very severe atopic dermatitis, respectively.
Worst Pruritus NRS	WP-NRS is a single-item patient-reported outcome questionnaire designed to determine itch severity in the past 24 hours. Peak pruritis (worst itch) is evaluated using a rating scale from no itch (0) to worst imaginable itch (10). A change of 2–4-points in WP-NRS has been suggested as a clinically relevant, within-person response to treatment.[22]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; SCORAD, SCORing Atopic Dermatitis.

1.2 Current service provision

1.2.1 Management of disease

AD is currently uncurable, and the goal of treatment is to improve symptoms and achieve long-term disease control. Those with mild AD, who form the majority of cases, are predominantly managed in primary care.[23] Guidance for general practitioners (GPs) outlines a step-by-step approach to disease management for a person presenting with AD, starting with preparation of an individualised management plan.[23] Initial treatment focuses on topical therapy with emollients and moisturisers, which, as noted earlier, are the mainstay of therapy but their effectiveness is reliant on the patient applying the emollient as per the recommendations, which can be challenging. For those with mild AD, to achieve relief of dry skin, regular use of emollients is usually effective in controlling symptoms. Additionally, advice is given on identifying and controlling specific triggers of flare (a worsening of symptoms), for example, overuse of irritants including shampoo and detergents. Children (<12 years) and adolescents (aged 12–18 years) typically receive the same treatments as adults.

For someone presenting to primary care with a flare, initial treatment is typically a topical corticosteroid (TCS) to suppress inflammation, if this is an acceptable treatment option to the

patient. TCSs can be prescribed in different strengths, depending on the severity of disease and the areas of skin affected:[24]

- very mild (hydrocortisone);
- moderate (e.g., betamethasone valerate and clobetasone butyrate);
- strong (e.g., higher dose of betamethasone valerate and betamethasone dipropionate);
- very strong (e.g., clobetasol propionate and diflucortolone valerate).

The topical immunomodulators tacrolimus and pimecrolimus, both of which are calcineurin inhibitors, are additional treatment options in primary care for those patients whose preference is not to use a TCS (Figure 1).[23] Topical immunomodulators are also an option for AD affecting areas for which TCSs are not recommended, for example, the eyelids and peri-orbital skin, and for when there are signs of skin atrophy.

Those with moderate-to-severe AD that only partially responds to treatment, and those presenting with severe disease, are referred to secondary care for more specialised therapy, where phototherapy (predominantly UVB) is frequently the first treatment option (Figure 1). If phototherapy is unsuccessful, subsequent treatment typically on systemic therapies such as ciclosporin A (CsA), methotrexate, dupilumab and, more recently, baricitinib.

Systemic immunosuppressants with marketing authorisation for use in atopic dermatitis are:

- oral corticosteroids;
- CsA;
- dupilumab;
- baricitinib.

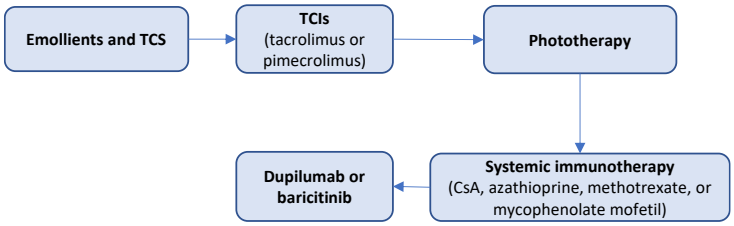
Additional systemic therapies used to manage atopic dermatitis and that are used outside of their marketing authorisations are:

- azathioprine;
- mycophenolate mofetil;
- methotrexate.

The order of systemic treatment is determined on a case-by-case basis, with treatment choice influenced by clinician and patient preference, and patient co-morbidities. Non-response to systemic

therapy could potentially indicate a more severe form of atopic dermatitis, which could influence prognosis and response to subsequent treatment. The immunosuppressant CsA has been among the first choice of systemic treatment, but some clinicians now favour methotrexate in the first-line setting. When CsA is given, it is administered for a relatively short term, with an advised maximum duration of treatment of 4 months.[25] However, if a patient is responding and does not show signs of adverse effects, treatment with CsA could be continued for up to a year. CsA and azathioprine both increase the risk of developing non-melanoma skin cancer and some other neoplasias, and there has been a decline in their use in clinical practice for the management of AD. Should a patient have inadequate response to first-line systemic immunosuppressant, the biological therapy dupilumab and the Janus kinase (JAK) inhibitor baricitinib are recommended by NICE as second-line treatment options.[12, 13] Subsequent treatment of therapy resistant cases is also influenced by location of treating centre, with some sites able to offer an inpatient service during which a patient would receive intense topical treatment. Where such services are not available, the patient may be treated with another systemic therapy, including CsA, or with best supportive care (BSC), the definition of which varies from practice to practice.

Figure 1. Overview of the treatment steps in atopic dermatitis



Abbreviations: CsA, cyclosporine A; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

1.2.2 Current service cost

Typically, TCSs and emollients are low-cost treatments, varying between £2.58 and £12.42, with TCIs costing £45.56 (please refer to Section 5.2.1.11.3 for further details). Systemic treatments incur higher costs, with the list price of CsA up to £41.59 depending on capsule size, baricitinib priced at £805.56 per pack and dupilumab costing £1,264.89 per two pre-filled pens or syringes. It should be noted that patient access scheme (PAS) discounts are in place for baricitinib and dupilumab.

1.2.3 Variation in services and/or uncertainty about best practice

The diversity in the symptoms experienced and the course of AD can make the condition challenging to diagnose and to treat. A diagnosis of atopic, rather than non-atopic (sometimes also referred to as intrinsic AD), dermatitis is often based on the clinical history of the patient. However, to differentiate AD from intrinsic AD, some centres may test for sensitisation to allergens, specifically immunoglobulin E (IgE). Intrinsic AD is characterised by failure to detect IgE in serum. Other non-atopic types of AD, which do not run in families, can be caused by direct contact with an irritant or contact allergen, which is a delayed type hypersensitivity and is not mediated by IgE antibodies. Consideration of AD versus other types of AD (contact AD, irritant AD) and potentially intrinsic AD is important because some systemic therapies (e.g., dupilumab and tralokinumab) act through inhibition of signalling molecules and other targets involved in the atopic pathway, and, therefore, might be less clinically effective in other forms of dermatitis.

Although guidelines are available on the management of aspects of AD, with a focus on primary care, [23, 26] the EAG's clinical experts highlighted that clarity is lacking on clinical practice in some areas, for example, the frequency of use of and withdrawal schedule for TCS, and use of TCS in combination with emollients and systemic therapies. Recommended use of TCSs is typically as an interval treatment and as a once daily application, but advice to patients on how to use TCS varies considerably, depending on the treating dermatologist. Additionally, guidance on the use of TCIs is lacking, and, thus, there is disparity across centres in administration of TCIs.

Uncertainty around the relative clinical effectiveness of systemic therapies considered to be traditional systemic treatments (i.e., CsA, azathioprine, methotrexate, and mycophenolate mofetil) in adolescents and adults has led to variation in clinical practice in their use in the management of AD. CsA is often effective in controlling AD symptoms but, because of the known adverse effects, recommendations on maximum duration of treatment vary, with some centres limiting use to 6 months compared with a maximum of one year in others. Clinical practice in the use of systemic corticosteroids and biological systemic therapies (i.e., baricitinib and dupilumab) also varies across centres, with areas of uncertainty including length of treatment with systemic corticosteroids, when to switch to a biological systemic therapy, choice of biological therapy (due to a lack of head-to-head data), the level of monitoring required for dupilumab, and identifying which patients are benefitting from treatment (responder versus non-responder).

Access to phototherapy varies across England. Use of the device that administers phototherapy requires specialised training and treatment is typically supervised by a consultant dermatologist. Shortage of trained staff in some centres limits the number of patients to whom phototherapy can be offered. Severe cases of AD may require intensive topical therapy, and centres with a dedicated dermatology ward can offer this service as a routine admission, but this is rare. Most centres do not have a dermatology ward and are only able to admit patients with severe AD on an emergency basis.

1.2.4 Relevant national guidelines, including National Service Frameworks

Although there is guidance for the treatment of AD in primary care, few guidelines address the management of AD in secondary care settings.[23, 26] The NICE pathway for management of AD outlines that, on inadequate response to first-line systemic immunosuppressant therapy, baricitinib and dupilumab are available treatment options.[17] However, recommendations on course of treatment on lack of response to second-line systemic therapy are not, at the time of writing, available.

1.3 Description of technology under assessment

1.3.1 Summary of Intervention

Systemic treatment options available within the NHS for the management of AD in line with their marketing authorisations are CsA in the first-line setting, and baricitinib and dupilumab as subsequent therapies, both of which are predominantly given in combination with TCS. The three interventions for which an evaluation of the clinical and cost effectiveness in the treatment of AD form the basis of this report are abrocitinib, tralokinumab and upadacitinib, all of which have been evaluated in clinical trials as a monotherapy and in combination with TCS. An overview of the characteristics of the interventions is provided below.

1.3.1.1 Available treatment options

Ciclosporin A

CsA is a calcineurin antagonist that prevents the nuclear translocation of NF-AT, which inhibits the production of cytokines involved in the regulation of T-cell activation: activation of T cells is thought to have a key role in the mechanism underlying development of AD. In dermatology, CsA only has marketing authorisation for the treatment of psoriasis and AD in those ≥16 years old.[25] CsA is taken orally, typically twice daily, and various formulations and doses are available to clinicians in England.

There is no recommended starting dose or maintenance dosing schedule for CsA, which are at the discretion of the treating clinician. An induction dose of 2.5–3 mg/kg daily of CsA is typical, increasing to 5 mg/kg daily if necessary. Alternatively, people may start on a higher dose of 5 mg/kg of CsA, decreasing to 3 mg/kg. Due to known adverse effects on kidney function and blood pressure, CsA is usually prescribed for a period of 2-4 months. Monitoring kidney function and blood pressure at fortnightly intervals in the initial stages of treatment is recommended, with a reduction in frequency of testing to every 2–3 months reported to be adequate on stabilisation of the dose of CsA.

Baricitinib

Baricitinib (Olumiant®, Eli Lilly and Company, Indianapolis, IN, USA) is a once-daily, oral treatment for moderate-to-severe AD that acts selectively and reversibly to inhibit JAK family of protein tyrosine kinases, specifically JAK1 and JAK2. JAKs are enzymes that mediate the transduction of intracellular signals also involved in the process of inflammatory responses. Baricitinib is recommended by NICE as an option for treating moderate-to-severe AD in adults if the disease has not responded to at least one systemic immunosuppressant, such as CsA, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable.[13] The recommended dose of baricitinib for AD is 4 mg once daily. Down-titration to 2 mg is appropriate for some patients, such as those aged 75 years or older, and may be appropriate for patients with a history of chronic or recurrent infections. In clinical practice in England, baricitinib is most likely to be given in combination with TCS. NICE recommends assessing response from 8 weeks and stopping treatment with baricitinib if there has not been an adequate response at 16 weeks, defined as a reduction of at least:[13]

- 50% in the EASI from when treatment started; and
- Four points in the DLQI from when treatment started.

Dupilumab

Dupilumab (Dupixent®, Sanofi [Paris, France] and Regeneron Pharmaceuticals, Inc. [Tarrytown, NY, USA]) is a fully human monoclonal antibody. Dupilumab binds to the shared α chain subunit of the receptors for the cytokines interleukin (IL)-4 and IL-13, thereby inhibiting signalling of the two cytokines, both of which are thought to be important drivers of atopic diseases, such as AD. Dupilumab is recommended by NICE as an option for treating moderate-to-severe AD in adults if the disease has not responded to at least one other systemic therapy, such as CsA, methotrexate,

azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated.[12] Dupilumab is given by subcutaneous injection into the thigh or abdomen. Treatment with dupilumab should be initiated by healthcare professionals experienced in the diagnosis and treatment of AD but can be self-administered in the longer-term. An initial loading dose of dupilumab is given of 600 mg (two 300 mg injections), followed by 300 mg once every 2 weeks (Q2W). As with other systemic treatments, in England, dupilumab is most likely to be given in combination with TCS. NICE recommends stopping treatment with dupilumab if there has not been an adequate response at 16 weeks, defined as a reduction of at least:

- 50% in the EASI from when treatment started; and
- Four points in the DLQI from when treatment started.

1.3.1.2 Interventions to be assessed

Abrocitinib

Abrocitinib (CIBINQO®, Pfizer, New York, NY) is a once-daily, oral treatment for moderate-to-severe AD for those aged 12 years and older, with a recommended daily dose of 100 mg or 200 mg. The company advises a starting dose of 200 mg once daily for most patients, with a dose of 100 mg once daily recommended for those aged ≥ 65 years. Abrocitinib is a selective JAK1 inhibitor. Abrocitinib has been studied in clinical trials as a monotherapy or in combination with TCS and compared with placebo or dupilumab in people with moderate-to-severe AD that is not adequately controlled with topical therapies or for whom topical treatments are not appropriate, or who are candidates for systemic therapy.[27-32] Based on the report submitted by the company as part of the MTA process, the populations of interest to the project are adolescents and adults who are aged over 12 years with moderate-to-severe AD and who have received one prior systemic therapy.

Contraindications included in the draft Summary of Product Characteristics (SmPC) for abrocitinib are:

- Hypersensitivity to the active substance or to any of the excipients;
- Active serious systemic infections, including tuberculosis;
- Severe hepatic impairment;
- Pregnancy and lactation.

Tralokinumab

Tralokinumab (Adtralza®, Leo Pharma UK, Hurley, UK) is a fully human IgG4 monoclonal antibody that binds to circulating IL-13, which is thought to be one of the key cytokines involved in triggering the signs and symptoms of AD.[33] Administered subcutaneously, tralokinumab has been evaluated in studies:

- as a monotherapy compared with placebo in adolescents[34] and adults[35,36] with moderate-to-severe AD;
- in combination with topical therapies compared with placebo in adults with moderate-to-severe AD;[37,38]
- in combination with topical therapies compared with placebo in adults with severe AD that is not adequately controlled with CsA or for whom CsA is contraindicated.[39]

In the studies evaluating tralokinumab, tralokinumab was given initially at a loading dose of 600 mg followed by tralokinumab 300 mg Q2W for a period of 16 weeks, the induction phase. After the induction phase, in some studies, those achieving a response, as defined in the study, could either remain on the Q2W regimen or move to tralokinumab 300 mg every 4 weeks (Q4W). The population and setting relevant to the MTA presented here is adults who have had an inadequate response, cannot tolerate, or are contraindicated to their first systemic treatment.

Upadacitinib

Upadacitinib (Rinvoq®, AbbVie, Lake Bluff, IL, USA) is a once-daily oral treatment for AD in those aged 12 years and older. The recommended daily dose of upadacitinib is 15 mg for adolescents and 15 mg or 30 mg for adults. Targeting JAKs, upadacitinib is a selective and reversible, second generation JAK inhibitor. Upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Upadacitinib has been assessed in clinical trials:

- as a monotherapy compared with placebo in people aged 12 years and over with moderate-to-severe chronic AD;[40]
- as a monotherapy compared with dupilumab in adults with moderate-to-severe AD;[41]
- in combination with TCS compared with placebo in people aged 12 years and over with moderate-to-severe chronic AD.[42]

Upadacitinib is proposed as an option for adolescents and adults with moderate-to-severe AD:

- as first-line systemic therapy for those having inadequate response to topical treatments;

or

- as a subsequent systemic therapy on failure to respond to first-line systemic treatment, or for those who cannot tolerate or are contraindicated to other systemic therapies.

1.3.2 Identification of important sub-groups

The final scope issued by the National Institute for Health and Care Excellence (NICE) for the project specifies the population to be those with moderate-to-severe AD, with no specification of previous treatment.[43] However, a subgroup of interest is specified as people for whom systemic therapies have been inadequately effective, not tolerated or contraindicated. Thus, for the purposes of this MTA, the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib are evaluated in the relevant setting and populations proposed by the companies, as outlined in Section 1.3.1.2. Clinical effectiveness of abrocitinib, tralokinumab and upadacitinib when given as a monotherapy and when administered with concomitant TCS is evaluated.

As AD is a common disease of childhood, the subgroup of adolescents (aged 12 to 18 years) is of particularly relevance and evidence is presented separately for this group. Skin colour is also of interest as research suggests that certain ethnic groups are at greater risk of developing AD.[44] However, evidence of clinical effectiveness based on ethnicity was reported in only one identified study evaluating dupilumab[45] and so will not be covered by this project.

1.3.3 Current usage in the NHS

Recent resource impact reports for baricitinib[46] and dupilumab[47] estimated that there are between 7,500 to 7,650 people in England with moderate-to-severe AD with a history of systemic therapy failure that are eligible for treatment. Of those eligible for second-line systemic treatment, annual uptake of baricitinib and dupilumab is expected to be around 25%[46] and 60%,[47] respectively.

As AD is incurable, patients are likely to be on some type of treatment for life. Furthermore, systemic treatments may be sequenced according to clinician and patient preference to maximise likely response to treatment to remaining options available to a patient. Thus, the EAG's clinical experts agree that there is no typical patient treatment journey and high variation in prescribing practices exist.

1.3.4 *Anticipated costs associated with intervention*

The interventions under assessment as part of this MTA are abrocitinib, tralokinumab and upadacitinib. Each of the interventions has a proposed PAS discount in place. The list prices for each of the interventions are presented in Table 2. Please refer to the MTA report confidential appendix for the interventions' PAS discounts. Each of the interventions can be given as a monotherapy or in combination with TCS (mometasone 0.1% ointment), with a cost of TCS per 100 g of £2.58.

Table 2. Intervention costs and patient access scheme discounts

Intervention	Pack size	Pack cost
Upadacitinib, Rinvoq 15 mg modified-release tablets (AbbVie Ltd)	28	£805.56
Upadacitinib, Rinvoq 30 mg modified-release tablets (AbbVie Ltd)	28	[redacted]
Abrocitinib, CIBINQO 100 mg and 200 mg tablets (Pfizer)	28	[redacted]
Tralokinumab, Adtralza 150 mg pre-filled syringes (Leo Pharma UK)	4	£1,070.00

Abbreviation: mg, milligram.

2 Definition of the decision problem

2.1 Decision problem

The final scope issued by the National Institute for Health and Care Excellence (NICE) outlined the parameters of interest for the Multiple Technology Appraisal (MTA) that is presented in this report.[43] As detailed in the final scope issued by NICE, the three treatments that are the focus of the project — abrocitinib, tralokinumab and upadacitinib — are systemic therapies that are potential additions to the treatments for atopic dermatitis (AD) currently available to the NHS. Scoping searches were carried out to gain an insight into the evidence base available based on the EAG's inclusion criteria (Table 3). The initial searches identified a systematic literature review (search date August 2019) that evaluated systemic treatments for moderate-to-severe AD and presented results from a network meta-analysis (NMA), which the EAG used as a source of randomised controlled trials (RCTs) published up to and including August 2019.[48] The systematic review included all interventions listed in the final scope issued by NICE.[43] Additionally, the companies seeking approval for abrocitinib, tralokinumab and upadacitinib submitted evidence as requested by the EAG from RCTs yet to be published in a peer reviewed journal.

Abrocitinib and upadacitinib both have marketing authorisations for the treatment of moderate-to-severe AD in adults and adolescents aged 12 years and over and who are candidates for systemic therapy, whereas the marketing authorisation for tralokinumab restricts its use to adults with moderate-to-severe AD and eligible for systemic therapy. The EAG considers the populations of relevance to be adolescents aged 12 to 18 years and adults aged 18 years and older, and, where possible, data are presented separately for the two groups. In the MTA, as requested by NICE, the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib have been evaluated for the position in the treatment pathway for moderate-to-severe AD proposed by the companies in their submissions to the Single Technology Appraisal (STA) process, which are restricted populations compared with the individual marketing authorisations. The proposed populations are:

- Abrocitinib:
  - Second-line systemic therapy for adolescents;
  - Second-line systemic therapy for adults.
- Tralokinumab:
  - Second-line systemic therapy for adults.

- Upadacitinib:
    - Adolescents;
    - First-line systemic therapy for adults;
    - Second-line systemic therapy for adults.

Candidates for systemic therapy can be those who are not responding to topical interventions and those who have already received systemic treatment. For the purposes of the MTA, first-line systemic therapy denotes those who are eligible for systemic treatment on inadequate response to topical treatments and who have not received prior systemic therapy, and second-line systemic therapy captures those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (often CsA, azathioprine or methotrexate), which, for the MTA, is limited to CsA (based on studies identified during scoping and expert clinical opinion). After discussion with clinical experts advising the EAG, to reflect clinical practice in England, the EAG deviated from the final scope issued by NICE in terms of the comparators evaluated. Given the positioning of abrocitinib, tralokinumab and upadacitinib as either first-line or second-line systemic therapies in adolescents or adults, depending on their proposed positioning, the EAG's advisors considered phototherapy and oral corticosteroids not to be relevant comparators, which is reflected in the EAG's eligibility criteria for the systematic review of the literature (Table 3).[49] In adults, the EAG considers the comparators of interest for abrocitinib, tralokinumab and upadacitinib to be:

- First-line systemic treatment:
    - Ciclosporin A (CsA);
- Second-line after prior systemic therapy/immunosuppressant:
    - dupilumab with or without concomitant topical corticosteroid (TCS);
    - baricitinib with or without concomitant TCS.

Clinical effectiveness of abrocitinib, tralokinumab and upadacitinib is evaluated when given as a monotherapy and when administered with concomitant TCS. The EAG's experts advised that, in clinical practice, systemic therapies are likely to be predominantly given concomitantly with TCS. Estimates of clinical effectiveness are reported for abrocitinib, tralokinumab and upadacitinib (as monotherapy or in combination with TCS) compared with treatments currently available in clinical practice in England. Where interventions are evaluated as a monotherapy, the intervention is compared with relevant monotherapies and not in combination with TCS, and vice versa.

For the purposes of the MTA, the EAG has focused on outcomes of clinical effectiveness that inform the economic evaluation, rather than address all the outcomes specified in the final scope issued by NICE.[43] In line with preferences expressed by the NICE Committee when evaluating the Single Technology Appraisals for dupilumab and baracitinib,[12, 13] a composite outcome of reduction in Eczema Area and Severity Index (EASI) score of 50% and improvement in Dermatology Life Quality Index (DLQI) of at least four points (EASI 50 + ΔDLQI ≥4) is the primary clinical outcome for the MTA. Clinical experts fed back that the patient-reported DLQI component of EASI 50 + ΔDLQI ≥4 renders the composite outcome open to recall bias. Consequently, although EASI 50 + ΔDLQI ≥4 informs assessment of treatment response, improvement in EASI by 75% is also considered, and is therefore captured as a secondary outcome. Additionally, the DLQI is not specific to AD but is tailored to evaluate QoL in skin diseases. An extensively validated generic QoL instrument is the EQ-5D, which, as a generic tool, facilitates comparisons of QoL across patient groups and health conditions. EQ-5D is the tool preferred by NICE to inform the reference case in economic evaluations,[50] and, thus, change from baseline in EQ-5D is evaluated.

Clinical experts informed the EAG that the outcomes listed in the final scope issued by NICE of disease-free period, maintenance of remission, time to relapse and prevention of relapse are not terms that are commonly used in clinical practice in AD and are not defined for AD.[43] Endpoints that could inform the duration of treatment response include:

- number of days free from TCS during treatment;
- proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved.

During the scoping stage, the EAG noted that many studies were designed such that people responding to their initial allocated treatment entered a long-term follow-up phase that may or may not have included a control group, and frequently involved re-randomisation. Thus, comparative results for treatment versus comparator are not consistently available for the pre-specified outcome of the proportion of people maintaining, for a set period of time, the level of response (as defined in the study) initially achieved. As data are not available for most of the included studies, and comparative effectiveness across interventions of interest cannot be assessed, the EAG decided not to report the limited details available for the outcome of maintenance of response. Data were captured at the end-of-treatment timepoint as reported in individual studies or as provided by the

companies, together with longer term or maintenance of treatment effect. Where data are available, the clinical outcomes evaluated are:

- proportion of people achieving EASI 50 + ΔDLQI ≥4;
- proportion of people achieving EASI 75;
- change in EQ-5D score from baseline;
- proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study);
- proportion of people requiring use of rescue therapy during treatment;
- number of days free from TCS during treatment;
- serious adverse effects of treatment.

Table 3. Eligibility criteria for search on clinical effectiveness

Factor	Inclusion criteria
Study design[a]	Randomised controlled trials
Population	People with moderate-to-severe AD
Interventions	The interventions below are considered as monotherapy or in combination with TCS: • Abrocitinib; • Baricitinib; • CsA; • Dupilumab; • Tralokinumab; • Upadacitinib.
Comparators	Specified interventions versus each other or BSC
Outcomes	• Proportion of people achieving EASI 50 + ΔDLQI ≥4; • Proportion of people achieving EASI 75; • Change in EQ-5D score from baseline; • Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study); • Proportion of people requiring use of rescue therapy during treatment; • Number of days free from TCS during treatment; • Serious adverse effects of treatment; ○ Adverse effects of special interest.

[a] For the observational search carried out to identify studies assessing CsA, inclusion criteria for study design were expanded to include non-randomised comparative studies and single-arm studies of CsA.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CsA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.

2.2 Overall aims and objectives of the assessment

The research objectives of the MTA are to appraise the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib within their marketing authorisations as alternative therapies for treating moderate-to-severe AD.

3 Review of company submissions

Before the introduction of the Multiple Technology Assessment (MTA) to assess abrocitinib, tralokinumab and upadacitinib for the treatment of moderate-to-severe atopic dermatitis (AD), each of the drugs was in the process of being assessed separately within a NICE Single Technology Appraisal (STA). In the MTA process, companies are invited to submit any relevant clinical- and cost-effectiveness evidence to NICE in order to assist the EAG with the development of their independent analyses. Thus, the companies for abrocitinib (Pfizer), tralokinumab (Leo Pharma) and upadacitinib (AbbVie) all gave permission for their company submission for their respective STA to be used for the purposes of this MTA. The EAG reviewed the submissions from each of the companies and compared the approaches with TA534 and TA681. A detailed summary is presented in Table 118 in Appendix 10.5, alongside the EAG's proposed approach for the MTA.

All of the companies followed a broadly similar approach to the clinical- and cost-effectiveness analyses, which are largely based on TA534[12] and TA681.[13] However, the abrocitinib model more closely followed the recommendations and preferred assumptions from TA534 and TA681, and the EAG considers that this is likely to be due to the company submission being produced after the publication of TA681.

Dupilumab and baricitinib are recommended for treating moderate-to-severe AD in adults if the disease has not responded to at least one other systemic therapy, such as CsA, methotrexate, azathioprine and mycophenolate, or these are contraindicated or not tolerated. The proposed positions of the drugs in the treatment pathway varied across the company submissions with the adult second-line systemic treatment population (those who achieve inadequate response to, cannot tolerate, or are contraindicated to CsA) being the only common position. The proposed position for upadacitinib is the broadest: upadacitinib is also positioned as a treatment for people who are eligible for systemic treatment on inadequate response to topical treatments, irrespective of prior systemic therapies. As such, upadacitinib was the only company model that explored every subgroup within the remit of this MTA.

Each of the companies followed the same model structure, a short-term decision tree followed by a long-term Markov Model, with health states based on response status, BSC and death. Treatment effectiveness estimates were based on outputs from network meta-analyses (NMAs). Where the data allowed, the outcome of EASI 50 + DLQI ≥4 was used in all of the companies' base case analyses

as this was the committee preference in TA534 and TA681. EASI 75 was used when the composite outcome was unavailable.

The clinical data informing TA534 and TA681 were limited to patients who had failed on, could not tolerated or were contraindicated to CsA, as CsA is the only first-line systemic treatment approved for use in the NHS. The clinical data informing the company's base case for tralokinumab were aligned with TA534 and TA681 and included patients who had inadequate control with, or intolerance or contraindications to CsA. However, the clinical data informing the base case for abrocitinib were for patients who were previously treated with at least one systemic treatment for AD (not restricted to CsA). Contraindication to prior AD treatment was not captured within the clinical trial programme for abrocitinib. For upadacitinib, the data informing the base case for the second-line population included people who had previously received CsA, irrespective of response to it and not including those for whom CsA was contraindicated. The clinical data for people who were candidates for conventional systemic treatment, the clinical data included patients who had been treated with conventional systemic therapies and thus overlaps with the second line population.

All companies explored the impact of differences in baseline risk (placebo response) on the results of the network meta-analyses (NMAs). However, the results of the baseline-risk adjustment analyses did not inform the base case for any of the interventions.

In TA534, the committee accepted the use of conditional response to inform week 52 outcomes (week 16 responders who lose response by week 52) and as such this was used in the upadacitinib and tralokinumab economic models. However, in TA681, the committee preferred the use of conditional discontinuation to inform week 52 outcomes (all cause discontinuation for people whose condition responded to treatment at week 16 but withdrew from treatment at week 52) and this was implemented in the abrocitinib economic model. The approach to resource use and costs in all of the economic models was largely the same and based on the approach accepted in TA534. However, in TA681, the committee preferred to exclude the cost of bathing products from the cost-effectiveness analyses and this approach was adopted in both the abrocitinib and tralokinumab models.

Across all three models, there was variation in the modelling of long-term discontinuation to incorporate key trial data relevant to each of the drugs and, where data were unavailable, dupilumab data from TA534 were used. Treatment waning from year two onwards was included in

all of the company models with different assumptions used in each of the different models. In all of company models, treatment waning for BSC was applied through loss of utility gain associated with response (return to baseline utility). However, the proportion of BSC patients losing response differed across the models. In the upadacitinib and tralokinumab model, all BSC patients lose response by year 5. In the abrocitinib model, up to 96% of BSC patients lost response by year 5. In TA534 the committee considered that by year 5, 97% of BSC patients would lose response. In TA681, the ERG preferred to assume that there is no treatment waning for patients who respond to BSC as it separated utilities from costs in the model (costs remained unchanged in the BSC health state). However, the committee for TA681 did not agree with the ERG as it potentially overestimated the quality of life of BSC patients and considered that BSC treatment waning lay between the ERG's approach and the company's approach based on TA534 (i.e. up to 97% of BSC losing response).

Given the requirements of the MTA and the need for a consistent approach to the clinical and cost-effectiveness analyses for abrocitinib, tralokinumab and upadacitinib, the EAG developed its own NMA and *de novo* cost-effectiveness model to take account of the committee's preferences for TA534 and TA681 in the treatment pathway under consideration for the adult and adolescent populations. No model presented by the companies facilitated this consistent evaluation of the treatments under consideration. Furthermore, the EAG has adopted a "drug class effect" approach as a way to address gaps in the data.

4 Assessment of clinical effectiveness

4.1 Method for reviewing effectiveness

A review of the evidence on the clinical effectiveness of abrocitinib, tralokinumab and upadacitinib in the treatment of moderate-to-severe atopic dermatitis (AD) was undertaken systematically following the general principles recommended in the PRISMA statement.[51] Flow diagrams illustrating the flow of information through the systematic review process is presented in Section 4.2.1.1, according to the PRISMA reporting guidelines.[51]

4.1.1 Identification of studies

During scoping, the Evidence Assessment Group (EAG) identified a systematic review reporting a network meta-analysis (NMA) of systemic treatments for moderate-to-severe AD that searched records up to August 2019.[48] The EAG considers the review to have been carried out systematically and following accepted systematic review methodology. The systematic review identified completed and ongoing studies evaluating all interventions and comparators of interest to the MTA outlined here.

The identified review evaluated systemic immunosuppressive and immunomodulatory therapies used in the management of AD, and therefore implemented broad search terms relating to interventions.[48] For the purposes of the current MTA, the EAG designed the search strategies to incorporate terms specific to the interventions of interest. Search strategies were designed to include Medical Subject Headings (MeSH) and free text terms for the condition and all interventions.

As the identified review retrieved studies on all interventions of interest to the MTA, the EAG's searches were restricted to records published from 1 August 2019.[48] Multiple electronic databases were searched, including MEDLINE (searched via OVID), EMBASE (searched via EMBASE), and CENTRAL. Search terms were tailored to the database searched and the platform used to carry out the search. Search filters developed and validated by the Scottish Intercollegiate Guidelines Network (SIGN) were used to identify RCTs in MEDLINE, and the strategy developed by Glanville *et al.*[52] was used to retrieve records in EMBASE. Full details of the terms used in the search are presented in Appendix 10.1. Electronic database searches were carried out on 8 July 2021 and an update search run 29 November 2021. No language restrictions were applied to the search strategy.

The EAG evaluated the studies identified in the systematic review against the inclusion criteria for this MTA, presented in Table 3. Bibliographies of retrieved studies (RCTs and other systematic reviews) identified as relevant were manually reviewed for potentially eligible studies. Ongoing clinical trials were identified by searching the clinical trial registries ClinicalTrials.gov and the EU Clinical Trials Register. In addition, clinical experts advising the EAG were contacted with a request for details of additional published and unpublished studies of which they had knowledge. Furthermore, submissions provided by companies were assessed for unpublished data and the companies were contacted with a request for relevant data not available within the submissions.

Based on the scoping search and the RCTs reported in the identified systematic review, the EAG considered that data on the clinical outcomes of interest to the MTA would likely not be available from RCTs for CsA. An additional search was therefore conducted, concurrent with the RCT search, for observational and non-comparative studies of CsA in moderate-to-severe AD. Search filters developed and validated by SIGN were used for the observational search.

4.1.2 Inclusion and exclusion criteria

Eligibility criteria for the review of clinical effectiveness were as specified in the decision problem and summarised in Table 3. Two reviewers independently screened all titles and abstracts retrieved from the database and trial registry searches. Full paper manuscripts of titles/abstracts that were deemed relevant were obtained and the relevance of each study assessed. Evidence submissions provided by the company for each of the interventions (abrocitinib, tralokinumab and upadacitinib) and committee papers for the comparators (dupilumab [TA534][12] and baricitinib [TA681][13]) were screened for unpublished data. Discrepancies were resolved by consensus, with involvement of a third reviewer when necessary.

4.1.3 Data abstraction strategy

Full papers were ordered for all included references. Data were extracted independently by two reviewers using a standardised data extraction form. Information extracted included details of the study's design and methodology, baseline characteristics of participants and data on outcomes of interest, both clinical effectiveness outcomes and AEs. Where there was incomplete information the companies of the interventions of interest were contacted for additional details. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Data extraction forms for the included studies are provided in Appendix 10.3.1.

4.1.4 Critical appraisal strategy

The quality of the clinical effectiveness studies was assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements were resolved by consensus and, if necessary, a third reviewer was consulted. The quality of RCTs was assessed according to the Cochrane Risk of Bias Tool, version 2, for randomised studies.[53] Details of quality assessment for each included study are presented in structured tables (Appendix 10.2.1) and, an overall assessment of study quality is provided as a narrative summary (Section 4.2.1.2). The possible effects of study quality on the clinical effectiveness data and review findings are discussed where relevant.

4.1.5 Methods of data synthesis

Details of results on clinical effectiveness for each included study are presented in structured tables in Appendix 10.2.

The data were analysed by the pre-specified subgroups based on age and line of therapy, in line with the populations in the economic model:

- adults with moderate-to-severe AD and inadequate response to topical treatments receiving first-line systemic treatment,
- adults with moderate-to-severe AD receiving second-line systemic treatment after inadequate response to CsA, or where CsA was not tolerated or was contraindicated;
- adolescents, irrespective of prior therapy.

The effectiveness of the interventions in subgroups based on skin colour was also captured and reported, where available, but no analysis of relative effectiveness versus the comparators of interest were conducted due to paucity of data.

The SLR did not identify any studies investigating the clinical effectiveness of each of the interventions (abrocitinib, tralokinumab, and upadacitinib) with the comparators of interest (dupilumab, baricitinib, and CsA) in the populations considered in the economic model (listed above). Therefore, network meta-analyses (NMAs) were conducted for each population, with results presented for comparisons with dupilumab, baricitinib and CsA but not comparing the interventions with each other. The methods used for the NMA followed the guidance described in the NICE Decision Support Unit's (DSU's) Technical Support Documents (TSDs) for Evidence Synthesis.[54, 55] NMAs were performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation using

OpenBUGS.[56] NMAs were conducted using three chains with results based on 50,000 iterations after a "burn in" of 50,000 iterations. Convergence was assessed by visual inspection of Brooks-Gelman-Rubin (BGR) diagnostic plots, which assesses convergence by comparing within- and between-chain variability. The BGR diagnostic should gradually shrink to one as convergence is approached.

Fixed effect (FE) and random effects (RE) models were carried out for all analyses. All networks were expected to be populated with the results from a small number of studies in a "star-shape" with few or no "loops". In simple networks with a paucity of trials it is likely there will be insufficient data to accurately estimate between study heterogeneity. The EAG attempted to minimise some differences in the patient populations across the trials by focusing on the pre-specified subgroups based on age and line of therapy. However, other differences across studies at the trial level were expected to potentially introduce heterogeneity into the network, such as strength of TCS used and washout period prior to enrolment. In a Bayesian RE NMA, there is a risk that the prior selected for the between-study heterogeneity will dictate the heterogeneity in the posterior distribution when the number of studies per comparison is low, as in the NMAs in this MTA.

In order to inform the prior estimate of the between-study heterogeneity, external evidence on the likely extent of this heterogeneity was incorporated. A predictive distribution for the degree of between-study heterogeneity was chosen from Turner *et al.* 2015 based on type of intervention comparison and outcome.[57] Turner 2015 presents prior distributions for between trial heterogeneity based on pair-wise meta-analyses but the priors in the paper can also be applied to NMA provided comparisons are within one category. The most relevant category of intervention comparison was deemed to be "pharmacological versus placebo/control", as the majority of the studies in the networks were placebo controlled. As the outcomes for the NMAs were EASI 50 + DLQI ≥4 and EASI 75, the most relevant outcome type was deemed to be the subjective outcome of "signs/symptoms reflecting continuation/end of condition". The predictive distribution for the between-study heterogeneity for this combination of intervention comparison and outcome was a mean and variance on the natural log scale of −2.06 and 1.51^2, respectively. Vague or uninformed prior distributions were used for the relative treatment effects d and trial-specific baselines.

Given the potential differences between the trials, the small number of trials expected in the networks, and the likely small number of patients from the trials (given the subpopulations required), the EAG has a preference for a RE model with an informed prior over a FE model. Model fit of the FE and RE analyses were compared based on deviance information criteria (DIC). However,

a difference in DIC of 5 or less was not considered significant and judged to indicate a similar model fit. That is, a FE model would have to have a DIC>5 lower than the RE DIC to be considered a better statistical fit. Model fit was also assessed by comparing the residual deviance, which is a measure of how similar (or not) the model would predict the data used for the analysis, with the number of unconstrained data points.

As all outcome data analysed were dichotomous, treatment effects are presented as odds ratios (OR) with 95% credible interval (CrI). The median ORs are presented in the clinical section, as these are easier to interpret and more applicable to individual patients, whereas the mean estimates are more informative on a population level and therefore inform the economic model (as log ORs).

Inconsistency in the NMAs was assessed where loops were present allowing a comparison of the direct and indirect effect estimates. The presence of inconsistency was assessed using the Bucher method for single loops of evidence as described in DSU TSD4.[58]

Based on TA534 and TA681, the EAG was aware there could be different censoring rules, around patients who receive rescue medication during treatment, in the trials used for the analysis of clinical effectiveness. For the purposes of the research presented here, the EAG defines the population for the primary analysis to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. That is, the primary NMAs are based on using all observed data, regardless of rescue medication use to determine response, where possible. A sensitivity analysis was planned, where feasible, where patients requiring rescue medication were considered non-responders and censored following initiation of rescue therapy.

For dichotomous outcomes where the number of patients experiencing an outcome (n), for example, the number of responders, was not reported but the proportion with a response (%) and total number of patients (N) were available, n was imputed by multiplying % and N and rounding to the nearest integer. Missing data were analysed as a treatment failure for all outcomes, that is, for EASI 50 + DLQI ≥4 and EASI 75, people lost to follow-up were considered not to have achieved response.

The low number of studies included in each comparison within the network precluded the evaluation of publication bias and/or small study effects. The potential limitations of the NMAs,

together with associated influence on the generated estimates of effect, are discussed in the strengths and limitations of the report (Section 4.3.3).

4.2 Results

4.2.1 Quantity and quality of research available

4.2.1.1 Quantity of research available

As noted in Section 4.1.1, the EAG identified a systematic review reporting an NMA of systemic treatments for moderate-to-severe AD that searched records up to August 2019.[48] The EAG considers the review to have been carried out systematically and to follow accepted systematic review methodology. The systematic review appraised completed and ongoing studies for all systemic therapies used in the management of AD, and captured studies on all interventions and comparators of interest to the MTA reported here. The EAG re-evaluated the studies included by the review against the inclusion criteria presented in Table 3.

Searches of electronic databases to update the search of the identified review (search date 1 August 2019 to 8 July 2021) retrieved 1,365 records (post deduplication) that were of possible relevance to the review (Figure 2). First-pass appraisal of the 1,365 unique records led to exclusion of 1,244 records. Full publications for 121 references from the EAGs' literature review were ordered, of which publications for two records (both conference abstracts) could not be obtained.[59, 60] Manual searching of the identified systematic review forming the basis of the update search identified 18 supplementary records for full-text appraisal.[61-78] The EAG's systematic literature review retrieved records for an additional seven systematic reviews that evaluated one or more systemic interventions of interest to the MTA:[79-85] one of the identified reviews is a "living" systematic review and as such is continually updated.[80] Cross referencing of bibliographies of the seven systematic reviews identified one additional record[86] to those retrieved by the EAG and the original review, giving a total of 138 full text publications screened for inclusion in the review. Additionally, two sets of committee papers outlining recommendations from NICE for the use of dupilumab[12] and baricitinib[13] in the management of AD were also identified by searching the NICE website. The EAG's literature search captured all studies presented in the committee papers for baricitinib and dupilumab. As noted in Section 2, the EAG had access to submissions to the Single Technology Appraisal (STA) process from the individual companies producing abrocitinib, tralokinumab and upadacitinib, with documents available including the original submission and responses to requests

for data from the EAG. The EAG's literature search identified all relevant studies reported in the company submissions.

Of the 138 full articles evaluated, 38 publications describing 23 studies were relevant to the review (including 4 errata; Table 4): citation details for conference abstracts identified during the EAG's literature review and related to full publications are provided for completeness. Six additional studies for which full text publications were not available at the time of writing were identified from searches of trial registries (ClinicalTrials.Gov and EU Clinical Trials Register). The six studies each evaluated one of abrocitinib, tralokinumab or upadacitinib, and relevant results were provided by the companies during clarification (Table 4). Summaries of the studies included in the review are presented by key characteristics of studies (Table 4). A list of publications screened but subsequently excluded (with reasons for exclusion) from the review is available in Appendix 10.4.

The update search of the literature carried out on 29 November 2021 identified an additional 377 unique records. Given that only 5 months had passed since the EAG's original search, the EAG limited its inclusion criteria to full publications of RCTs not previously found. Of the 377 titles and abstracts appraised, only one record identified a novel RCT.[87] The study compares dupilumab 300 mg Q2W versus placebo with clinical efficacy assessed at 16 weeks in Chinese patients. Patients were required to be aged ≥18 years old and have moderate-to-severe AD for ≥3 years which could not be adequately controlled with topical medications or for which topical treatment was inadvisable. Additional criteria for eligibility were EASI score ≥16, IGA score ≥3 and ≥10% BSA affected by AD. Based on the full-text publication, it is unclear whether people who had previously received systemic therapy were included, and, thus, data are not available for those having inadequate response to systemic therapy prior, or who cannot tolerate or are contraindicated to systemic therapy. Additionally, the study enrols only adults, and focuses on monotherapy. As data are not available by prior line of therapy, the study would not inform the EAG's analyses and has not been described in full.

Seven publications[62-68] describing four studies of CsA versus placebo were identified by the systematic review forming the basis of the EAG's literature review.[48] The published studies met the inclusion criteria of the EAG's systematic literature review for RCTs. However, because none of the studies of CsA reported data on the clinical outcomes of interest to the review and the studies were carried out 15 years ago or longer, the studies are not discussed further and study characteristics are not reported. As no RCT for CsA was available to inform an NMA, the EAG carried out a systematic

literature review of observational studies evaluating CsA in the treatment of AD (described in greater detail in Section 4.1).

The company submission for upadacitinib reported results from a search to identify observational studies on CsA that could inform an NMA. The company's review identified one study describing an indirect comparison of CsA with dupilumab plus TCS to generate an estimate of comparative clinical effectiveness for EASI 75.[88] The EAG considered the company's literature review to be robust and chose to carry out an update search to identify additional potentially relevant studies.

Searches of electronic databases to update the company's search of the identified review (search date 1 January 2019 to 8 July 2021) retrieved 746 records (post deduplication) that were of possible relevance to the review (Figure 3). First-pass appraisal of the 746 unique records led to exclusion of 743 records. Full publications for three references from the EAG's literature review were reviewed,[88-90] one of which was the study described in the company submission for upadacitinib (Ariens *et al*.).[88] One publication was identified as a Letter to the Editor detailing the drug survival of dupilumab and was excluded.[90] The second publication described a retrospective observational study with a primary outcome of drug survival of dupilumab and CsA when used to treat moderate-to-severe AD in adults (N=251), with EASI 75 captured as a secondary outcome (Dal Bello *et al*.).[89] Both full text publications report data on proportion of people achieving EASI 75 with dupilumab and with CsA and so both meet the EAG's inclusion criteria.[88, 89] However, in Ariens *et al*.,[88] the authors applied regression models to adjust data for people receiving CsA to those of people receiving dupilumab 300 mg Q2W with TCS from LIBERTY AD CHRONOS.[71] The authors repeated the analysis in reverse, that is, adjusting results from those treated with dupilumab from CHRONOS to those given CsA in the registry. No type of adjustment was reported in the second publication identified by the EAG.[89] Ariens *et al*.[88] reported the adjusted proportion of people achieving EASI 75 after 12–16 weeks of treatment with CsA to be 52%, compared with 75% as observed in the dupilumab group from CHRONOS. By contrast, Dal Bello *et al*.[89] reported achievement of EASI 75 at 16 weeks by 44.3% (66/149) of those in the dupilumab group compared with 24.5% (25/102) of people treated with CsA. The EAG acknowledges that there is a considerable difference in estimates for dupilumab between the two studies. As data reported by Ariens *at el*.[88] for dupilumab are derived from the RCT, CHRONOS, rather than a registry, and CHRONOS is included in the network to generate estimates of first-line treatment, the EAG considered the adjusted estimate for CsA reported by Ariens *et al*.[88] to be more the appropriate choice to inform an NMA of RCTs.

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature review of RCTs[51]

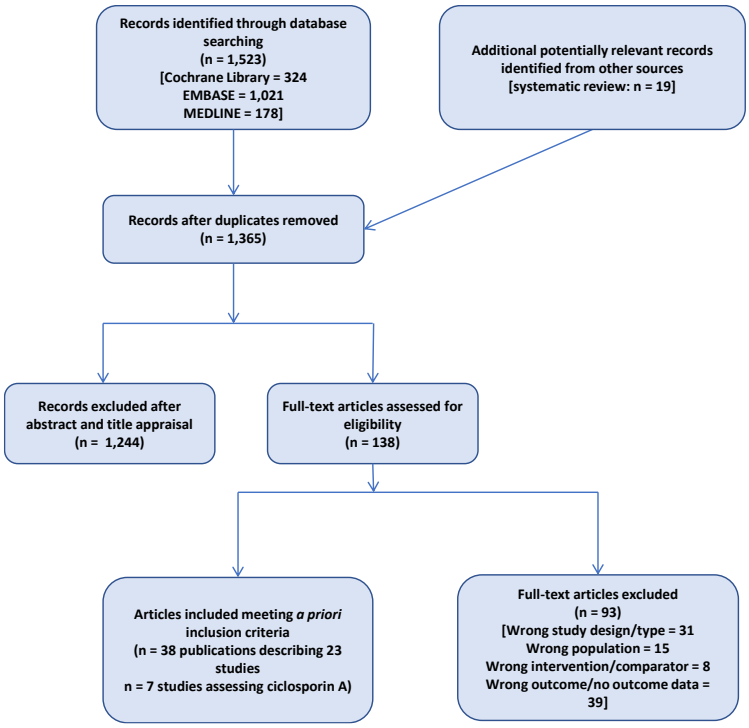
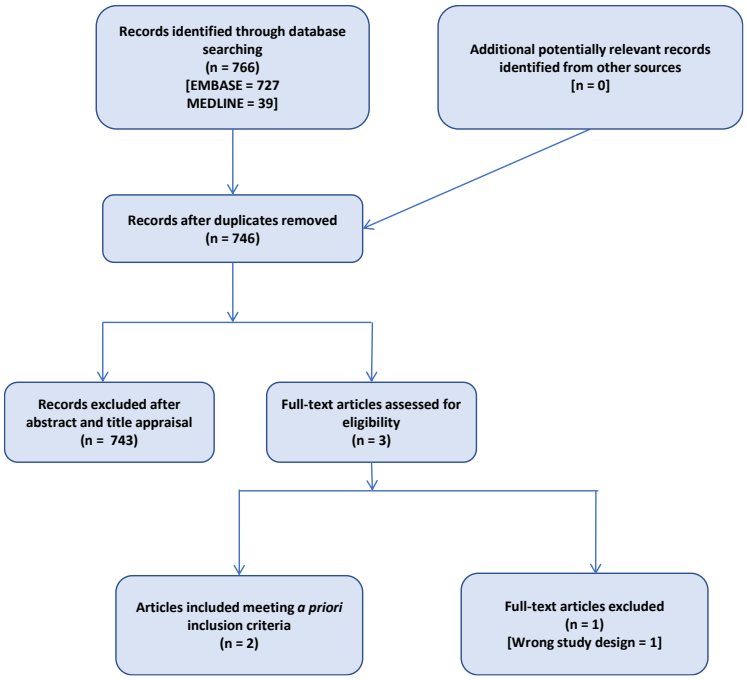


Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature review of observational studies of ciclosporin A[51]



4.2.1.1.1 Interventions to be assessed

As noted above, the EAG identified 23 studies (reported in 38 publications) of relevance to the MTA. Below, the EAG provides a summary of the key characteristics of the studies included in its review. The EAG considers it important to note that the identified studies predominantly include mixed populations of people with moderate-to-severe AD, with some studies comprising both adolescents and adults, as well as a combination of people receiving systemic therapy as a first-line or second-line regimen. Thus, data informing the NMAs for the populations and outcomes of interest to the MTA (described in Section 4.2.2) are predominantly derived from *post hoc* subgroups, which introduces bias and uncertainty around the robustness of the results of any analyses. Further discussion on the limitations in using *post hoc* subgroup data is available in Section 4.2.1.1.3.

For abrocitinib, tralokinumab and upadacitinib, where data were not available in the submissions to the STA process, data were supplied by the companies during a clarification stage. For dupilumab and baricitinib, the relevant data were primarily extracted from the committee papers

accompanying the NICE recommendations for their use in the NHS.[12, 13] The overview of the included studies, together with the accompanying quality assessment, pertain to the design and conduct of the RCT from which data are derived, and not the *post hoc* subgroups and subsequent analyses.

4.2.1.1.1.1 Abrocitinib

Six publications reporting on five studies evaluating abrocitinib at the recommended dose (200 mg or 100 mg orally, once daily) in the treatment of adolescents and adults with moderate-to-severe AD were included in the MTA (Table 4).[27-32] Of the five studies, four are Phase III randomised controlled trials (RCTs),[28-32] and one is a Phase IIb dose-ranging study.[27] All studies included a group receiving placebo. The EAG identified one ongoing RCT, JADE DARE, which compares abrocitinib versus dupilumab, both in combination with TCS.[91] Results for JADE DARE were provided by the company but unfortunately not in time to be incorporated in the analysis.

Three studies assessed clinical effectiveness of abrocitinib as a monotherapy, with one study focusing on an adult population (Phase IIb[27]), with the two remaining studies enrolling adolescents as well as adults (JADE MONO-1[28] and JADE MONO-2[29]). Of the two studies evaluating abrocitinib in combination with TCS, one study recruited adolescents only (JADE TEEN[30, 31]), and the second enrolled adults only (JADE COMPARE[32]) and included an active comparator group of dupilumab 300 mg Q2W with TCS. Topical therapies allowed in JADE TEEN and JADE COMPARE included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy. Use of rescue therapy was not permitted in any of the included Phase III RCTs evaluating abrocitinib.[28-32] Across the included studies, primary efficacy endpoints were assessed at 12 weeks. The treatment phase lasted 12 weeks in all studies with the exception of JADE COMPARE in which the treatment phase lasted 20 weeks.

4.2.1.1.1.2 Tralokinumab

Six studies were identified that included tralokinumab at the recommended dose (loading dose of 600 mg followed by 300 mg subcutaneously Q2W) either as a monotherapy or in combination with TCS and compared with placebo (Table 4):[35-37, 39, 92] results from the ECZTRA 1 and ECZTRA 2 RCTs were reported in the same publication.[35] The EAG identified one ongoing RCT, ECZTRA 8, that is located in Japan and compares tralokinumab in combination with TCS versus placebo.[38] Results for ECZTRA 8 are not yet available. The EAG notes that clinical practice on use of high potency TCS differs between Japan and England, with use of high potency TCS more common in Japan. Use of

different potency of TCS across studies could introduce clinical heterogeneity into any analyses. The EAG considers inclusion of results from ECZTRA 8 could increase heterogeneity and uncertainty into an NMA.

All included studies enrolled adults only, which aligns with the population for which the company sought a recommendation from NICE in their submission to the STA process. Results for three of the studies identified have yet to be published in peer-reviewed journals, including the key ECZTRA 7 study,[39] with the public record of the studies taken from the clinical trial registry ClinicalTrials.gov.[36] Additional details were available in the company submission to the STA process and were supplemented with information provided by the company on request.

ECZTRA 1 and ECZTRA 2 (reported in the same publication) are independent multicentre RCTs that were run in parallel and evaluated tralokinumab as a monotherapy.[35] In addition to ECZTRA 1 and ECZTRA 2, a Phase IIb study[92] and ECZTRA 5[36] also evaluated tralokinumab as a monotherapy, with the remaining two studies assessing tralokinumab in combination with TCS.[37-39] The objective of ECZTRA 5 was to assess whether tralokinumab affects the body's immune response to vaccines: clinical outcomes of interest, such as EASI 75, were captured as secondary outcomes. In response to the EAG's request for data for ECZTRA 5 for the subgroup of adults receiving tralokinumab monotherapy after inadequate response to, inability to tolerate, or contraindicated to CsA, the company declined to provide the data, commenting that, "*The number of ECZTRA 7-like patients in the ECZTRA 5 study was [redacted], just [redacted] of all randomised patients. The study was designed to assess whether treatment with tralokinumab can affect the body's immune response to vaccines. Given limited time, we have presented only the baseline characteristics of all patients for reference*." Similarly, data for the relevant subgroup from the Phase IIb study are not available, with the company replying, "*The Phase IIb dose ranging study was not powered to include analyses of an ECZTRA-7-like subgroup and efficacy was only assessed up to week 12*". Given the likely small number of events and patients forming the relevant subgroups for the Phase IIb study and ECZTRA 5, the EAG considers that the omission of the data is unlikely to have had a substantial impact on the results generated from the NMAs involving tralokinumab.

Of the two studies evaluating tralokinumab in combination with TCS, ECZTRA 3 and ECZTRA 7, ECZTRA 7 is a key study of relevance to the MTA, assessing treatment of patients with severe AD who had not had adequate control with, or had intolerance or contraindications to, CsA.[39] In

ECZTRA 7, efficacy and safety were assessed over a 26-week treatment phase, whereas all other studies assessed primary clinical outcomes at 16 weeks after start of treatment.

4.2.1.1.1.3 Upadacitinib

Six studies were included that assessed upadacitinib (30 mg or 15 mg orally, once daily) in adolescents and adults (Table 4):[40-42, 93, 94] results from the MEASURE UP1 and MEASURE UP2 RCTs were reported in the same publication.[40] Of the six studies, five were Phase III RCTs,[40-42, 94] with one study being a Phase IIb design.[93] MEASURE UP1, MEASURE UP2 and the Phase IIb study all evaluated upadacitinib as a monotherapy versus placebo, each assessing clinical effectiveness at 16 weeks of treatment. Additionally, HEADS UP[41] compared upadacitinib versus dupilumab as a monotherapy but with a treatment period of 24 weeks.

AD UP is the only study for which data are available on the clinical effectiveness of upadacitinib in combination with TCS, and reports outcomes after 16 weeks of treatment.[42] RISING UP is an RCT carried out in Japan for which data are not yet available.[94] In their response to the EAG's request for data from RISING UP, the company commented that, "*Results from the AD UP, MEASURE UP1, MEASURE UP2 and HEADS UP were prioritised for this response*". Given the likely low number of events and of patients in the relevant subgroup, together with the fact that clinical practice in Japan on use of TCS differs from that in England, the EAG considers that omission of the results from RISING UP are unlikely to have a substantial impact on the results of the NMA involving upadacitinib in combination with TCS.

4.2.1.1.2 Available treatment options

4.2.1.1.2.1 Baricitinib

Five studies (four publications) evaluating the efficacy and safety of baricitinib (4 mg or 2 mg orally, once daily) for the treatment of moderate-to-severe AD in adults were identified by the EAG's literature review (Table 4).[78, 95-97] BREEZE-AD1 and BREEZE-AD2 are two Phase III RCTs conducted in parallel that evaluated baricitinib monotherapy versus placebo and captured treatment response as 16 weeks, the results of which are available in the same publication.[95] A long-term extension study enrolling those with partial or full response from BREEZE-AD1 and BREEZE-AD2 was also identified (BREEZE-AD3).[98] Two additional Phase III studies, BREEZE-AD4[96] and BREEZE-AD7,[97] together with a Phase II study[78] compared baricitinib in combination with TCS versus placebo. Of note, BREEZE-AD4

enrolled adults with moderate-to-severe AD and a history of intolerance to, contraindication to, or inadequate response to CsA.

4.2.1.1.2.2 Dupilumab

Five RCTs (four publications[71, 75, 99, 100]) and one Phase IIb[76, 86] study compared dupilumab (300 mg Q2W given subcutaneously) with placebo in people with moderate-to-severe AD (Table 4). Together with the Phase IIb study, three RCTs evaluated dupilumab as a monotherapy, with one enrolling adolescents only (AD ADOL[99]), and two focussing on adults (SOLO 1[75] and SOLO 2[75]). SOLO 1 and SOLO 2 were of similar design and results were available in the same publication.[75] The remaining two RCTs — CAFÉ[100] and CHRONOS[71] — evaluated efficacy and safety of dupilumab in combination with TCS in an adult population. To be eligible for entry into CAFÉ, patients were required to have a history of intolerance, inadequate response or contraindication to CsA. All studies involved patients with moderate-to-severe AD whose disease was not adequately controlled with topical medications or for whom topical treatment was medically inadvisable and reported primary results after 16 weeks of treatment.

4.2.1.1.2.3 Ciclosporin A

As noted in Section 4.2.1.1, four studies evaluating clinical effectiveness of CsA versus placebo were identified,[62-68] but none of the studies reported data on the clinical outcomes of interest to the MTA. Of the studies retrieved from a systematic search of the observational literature, the EAG selected Ariens *et al*.[88] to inform an NMA of first-line treatments for moderate-to-severe AD. Ariens *et al.*[88] describes an indirect comparison of CsA versus dupilumab plus TCS to generate an estimate of comparative clinical effectiveness for EASI 50 and EASI 75. For effectiveness of CsA, the authors sourced patient level data from a registry of those treated with CsA at the University Medical Center, Utrecht, the Netherlands. Concomitant use of TCS was allowed as needed for patients treated with CsA. Effectiveness of dupilumab (300 mg Q2W) plus TCS was derived from the results of the CHRONOS RCT.[71] The EAG notes that the mean baseline EASI score in the group treated with CsA was considerably lower than that in the dupilumab group, with mean EASI scores of 19.3 (SD 8.4) and 33.6 (SD 13.3) for the CsA and dupilumab groups, respectively. The lower EASI score observed in the CsA group reflects feedback from the EAG's expert advisors that people seen in clinical practice are more likely to present with moderate, rather than severe, AD, whereas those enrolled in clinical trials predominantly have more severe AD.

As those receiving CsA were treated in clinical practice rather than as part of a clinical trial, there were no fixed clinic visits, and so the analysis of EASI 50 and EASI 75 was based on time periods rather than a strict number of weeks of treatment.[88] Data on EASI 50 and EASI 75 were collated for people treated between weeks 12 and 16, and between weeks 24 and 30. To facilitate the comparison with CsA, EASI 50 and EASI 75 scores from CHRONOS were those recorded at weeks 16 and 28 in the scheduled follow-up assessments. To derive the estimate of effect for achieving EASI 75, the authors used regression models to adjust data for people receiving CsA to those of people allocated to dupilumab 300 mg Q2W plus TCS in CHRONOS.[71] The authors also adjusted results from those treated with dupilumab from CHRONOS to those given CsA. Given that data from CHRONOS are derived from an RCT, the EAG used the results from the adjustment of people receiving CsA to those allocated to dupilumab in CHRONOS to inform the NMA for first-line treatment. The dependent variable was EASI 50 or EASI 75 (achieved or not achieved), and the focal regressor was a treatment indicator for CsA versus dupilumab use. Missing data were imputed by means of the last observation carried forward method for both populations. Additional regressors in the model were sex, baseline EASI, and baseline thymus and activation-regulated chemokine (TARC) level. Adjusted-weighting was carried out according to the baseline data.

4.2.1.1.3 Potential sources of heterogeneity and limitations of the available evidence base

4.2.1.1.3.1 Population and use of *post hoc* subgroup data

Inclusion criteria across included studies were predominantly comparable, with studies enrolling either adults or adolescents and adults with moderate-to-severe AD. Differences were noted in the level of baseline severity of AD required at baseline in terms of EASI score. Most studies specified an EASI score of ≥16 for eligibility, with three studies requiring a score of ≥12 and two of ≥20 (Table 4). Most studies also required baseline IGA score of ≥3, and ≥10% body surface area (BSA) involvement (Table 4). Duration of AD at enrolment ranged from at least 12 months to a minimum of 36 months. The EAG notes that the mean baseline EASI score was around 29 in most studies (baseline characteristics available in Appendix 10.3.1), which, based on the EASI score categories (available in Table 1), denotes severe AD. Clinical experts advising the EAG commented that the patients enrolled in the clinical studies have more severe AD than would typically be seen in clinical practice, with most patients presenting with disease that would be categorised as moderate severity. The primary outcome for clinical effectiveness for the MTA is the composite outcome of EASI 50 + DLQI ≥4. The EAG notes that some studies enrolled participants with a baseline DLQI score of 3, and, as such, these patients would not able to contribute to the composite outcome. The EAG notes that, based

on number of people included in analyses for EASI 50 + DLQI ≥4, most people enrolled in the studies had a baseline score of DLQI 4 and so the EAG considers the impact on the robustness of the outcome to be minimal.

Despite some differences in inclusion criteria relating to disease severity, mean baseline EASI score and the proportion of people with an IGA score of 3 or 4 were comparable across the included studies. Most studies required a documented history of inadequate response to topical or systemic therapies. Two studies (ECZTRA 7[39] and CAFÉ[100]) specified that people either had not been exposed to CsA and were not a candidate for CsA treatment, or had previous exposure to CsA and had an inadequate response.

Although baseline characteristics for the full trial populations are comparable, as noted earlier, most studies, the exceptions being ECZTRA 7[39] and CAFÉ[100], included a blended population and clinical data to inform the NMAs are derived from *post hoc* subgroups. The use of *post hoc* subgroups increases the comparability and applicability of the analyses, but also introduces bias and uncertainty to the results generated by the NMAs. The limitations and potential sources and types of heterogeneity for the populations of interest to the MTA are discussed in greater detail in the discussion of the interpretation of the results from the relevant NMA.

4.2.1.1.3.2 Use of TCS and rescue therapy

As expected, variation was noted across studies in the use of a washout period for TCS before randomisation to treatment, with some studies not including a washout period and, for those that did, the time allocated for washout varied (details available in Appendix 10.2.1). In studies evaluating treatment in combination with TCS, differences were noted in the type and potency of concomitant TCS (low or medium). In studies allowing use of rescue therapy, rescue treatment was given at the discretion of the investigator and typically comprised use of TCS or higher potency TCS in studies evaluating combination treatment, or systemic immunosuppressant. Notably, in BREEZE AD7 high- or ultra-high potency topical corticosteroids were permitted as rescue therapy. The use of rescue therapy was prohibited in trials evaluating abrocitinib (JADE COMPARE, JADE MONO-1 and MONO-2, and JADE TEEN).

In most studies, patients receiving topical rescue treatment continued treatment with the study drug. By contrast, those receiving systemic rescue therapy discontinued the study drug, either permanently or until a pre-determined period of time after the last dose of systemic rescue

treatment. The use of and the level of potency of topical rescue therapy may impact on the treatment and placebo response achieved in individual studies. Disparity in type of rescue therapy used across studies could potentially lead to clinical heterogeneity in observed placebo response, which may introduce bias and uncertainty into the NMA. The EAG evaluated the potential impact of placebo response on estimates of effect generated from the NMAs (discussed in Section 4.2.2).

4.2.1.1.3.3 Availability of data

In addition to most of the data informing the NMAs being derived from *post hoc* subgroups, the EAG notes that much of the data for baricitinib was unavailable at the time of writing. Results for studies evaluating baricitinib are not yet published in peer reviewed journals and data submitted to the STA process were redacted from the committee papers accompanying the recommendation by NICE. Lack of data for baricitinib on clinical outcomes of interest to the MTA precluded inclusion of baricitinib in most of the relevant NMAs. However, data on clinical effectiveness of baricitinib in combination with TCS was available for EASI 75, which allowed inclusion of baricitinib in an NMA. No randomised evidence was identified to inform the efficacy of CsA, which is the relevant comparator in the first-line setting. However, an observational study carrying out an indirect comparison of CsA with or without TCS versus dupilumab plus TCS (based on CHRONOS) was identified.[88] Based on the reported methods and the populations analysed, the EAG considers the observational study to represent the best available evidence to facilitate comparison of upadacitinib and dupilumab in the first-line setting.

Table 4. Summary of studies included in the systematic review of clinical effectiveness

Study	Population	Intervention(s)	Comparator	Duration of treatment and follow up	Additional information and related references
Interventions yet to be recommended by NICE for AD					
Abrocitinib (oral)					
Monotherapy					
Phase IIb[27]	Adults with moderate-to-severe AD (EASI score ≥12, IGA score of ≥3, and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical or systemic therapies.	Abrocitinib 200 mg (N=55) Abrocitinib 100 mg (N=56) Abrocitinib 30 mg (N=51) Abrocitinib 10 mg (N=49)	Placebo (N=56)	12-week treatment phase	Related conference abstract[61] Erratum to full publication[101]
JADE MONO-1[28]	Adolescents and adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical or systemic therapies.	Abrocitinib 200 mg (N=154) Abrocitinib 100 mg (N=156)	Placebo (N=77)	12-week treatment phase	Related conference abstracts[102, 103] JADE MONO-1 and JADE MONO-2 are independent multicentre RCTs that were run in parallel. Use of rescue medication was not permitted.
JADE MONO-2[29]		Abrocitinib 200 mg (N=155) Abrocitinib 100 mg (N=158)	Placebo (N=78)		
Combination with TCS					
JADE TEEN[30, 31]	Adolescents with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response	Abrocitinib 200 mg (N=94) Abrocitinib 100 mg (N=95)	Placebo (N=96)	12-week treatment phase	Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were

	to topical or systemic therapies.				allowed to use more than one topical therapy. At the time of writing, results from JADE TEEN are not available in a published peer-reviewed journal. Reported details have been extracted from conference abstracts and from information provided by the company during the MTA process. Use of rescue medication was not permitted.
JADE COMPARE[32]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical or systemic therapies.	Abrocitinib 200 mg (N=226) Abrocitinib 100 mg (N=238)	Dupilumab 300 mg Q2W (N=242) Placebo (N=131) Dupilumab: 600 mg loading dose	20-week treatment phase, with subsequent long-term extension	Related conference abstract[104] Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy. Use of rescue medication was not permitted.
Tralokinumab (subcutaneous injection)					
Monotherapy					
ECZTRA 1[35]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3 and ≥10% BSA involvement) for at least	Tralokinumab 300 mg (N=603) Tralokinumab: 600 mg loading dose	Placebo (N=199)	16-week treatment phase. Those achieving a clinical response at week 16 (defined as IGA of 0 or 1 or at least 75%	ECZTRA 1 and ECZTRA 2 are independent multicentre RCTs that were run in parallel.

ECZTRA 2[35]	12 months, documented history of inadequate response to topical or systemic therapies.	Tralokinumab 300 mg (N=593) Tralokinumab: 600 mg loading dose	Placebo (N=201)	reduction EASI score from baseline) moved onto maintenance treatment that continued until week 52. Patients in the tralokinumab arm who achieved EASI 75 or IGA 0/1 were re-randomised to receive tralokinumab 300 mg either Q2W or Q4W, or placebo. Patients in the placebo arm who achieved EASI 75 or IGA 0/1 continued to receive placebo. The remaining patients received open-label tralokinumab Q2W and had the option of adding TCS	
ECZTRA 5[36]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3 and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical therapies.	Tralokinumab 300 mg (N=107) Tralokinumab: 600 mg loading dose	Placebo (N=108)	16-week treatment phase followed by 14-week off-treatment follow-up period for the assessment of safety. Dependent on eligibility, people could transfer to an open-label, long-term trial at week 16 or later.	The objective of the study was to assess whether tralokinumab can affect the body's immune response to vaccines. At the time of writing, results from ECZTRA 5 are not available in a published peer-reviewed journal. Reported details have been extracted from the study entry on ClinicalTrials.gov and from information provided by the company during the MTA process.
Combination with TCS					

Phase IIb[92]	Adults with moderate-to-severe AD (EASI score ≥12, IGA score of ≥3 and ≥10% BSA involvement) for at least 12 months.	Tralokinumab 300 mg (N=52) Tralokinumab 150 mg (N=51) Tralokinumab 45 mg (N=50)	Placebo (N=51)	12-week treatment phase	Related conference abstract[105] Unclear from full publication whether those enrolled in the tralokinumab group were given a loading dose of tralokinumab
ECZTRA 3[37]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3 and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical therapies.	Tralokinumab 300 mg (N=252) Tralokinumab: 600 mg loading dose	Placebo (N=126)	16-week treatment phase After 16 weeks, people could continue in an extension phase in which, depending on response, people could receive one of tralokinumab 300 mg Q2W, tralokinumab 300 mg Q4W or placebo.	Related conference abstract[106] Concomitant TCS was mometasone furoate 0.1%.
ECZTRA 7[39]	Adults with moderate-to-severe AD (EASI score ≥20, IGA score of ≥3 and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical therapies and either no previous CsA exposure and not currently a candidate for CsA treatment or previous exposure to CsA and had an inadequate response	Tralokinumab 300 mg (N=[redacted]) Tralokinumab: 600 mg loading dose	Placebo (N=[redacted])	26-week treatment phase	Concomitant TCS was mometasone furoate 0.1%. At the time of writing, results from ECZTRA 7 are not available in a published peer-reviewed journal. Reported details have been extracted from the study entry on ClinicalTrials.gov and from information provided by the company during the MTA process.
Upadacitinib (oral)					
Monotherapy					

Phase IIb[93]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) for at least 12 months.	Upadacitinib 30 mg (N=42) Upadacitinib 15 mg (N=42) Upadacitinib 7.5 mg (N=42)	Placebo (N=41)	16-week treatment phase followed by 72-week double-blind, randomised withdrawal period	Conference abstract reporting longer-term follow up results[107]
HEADS UP[41]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) and with a history of inadequate response to topical therapies or for whom topical therapies were medically inadvisable.	Upadacitinib 30 mg (N=325)	Dupilumab 300 mg Q2W (N=325)	24-week treatment period followed by 12-week follow-up	At the time of writing, results from HEADS UP are not available in a published peer-reviewed journal. Reported details have been extracted from the information provided by the company during the MTA process and the study entry on ClinicalTrials.gov.
MEASURE UP1[40]	Adolescents and adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) and with a history of inadequate response to topical therapies or for whom topical therapies were medically inadvisable.	Upadacitinib 30 mg (N=285) Upadacitinib 15 mg (N=281)	Placebo (N=281)	16-week treatment phase followed by blinded extension period for up to 120 weeks of treatment. At week 16, people in the placebo group were randomised to upadacitinib 30 mg or 15 mg for the blinded extension period.	Erratum to full publication[108] MEASURE UP1 and MEASURE UP2 are independent multicentre RCTs that were run in parallel.
MEASURE UP2[40]		Upadacitinib 30 mg (N=282) Upadacitinib 15 mg (N=276)	Placebo (N=278)		
Combination with TCS					
AD UP[42]	Adolescents and adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3, and ≥10% BSA involvement) for at least 36 months.	Upadacitinib 30 mg (N=297) Upadacitinib 15 mg (N=300)	Placebo (N=304)	16-week treatment phase followed by blinded extension period for up to 120 weeks of treatment.	Related conference abstract[109] Erratum to full publication[110] Initial concomitant TCS was of medium potency (clinician choice), moving to low potency for 7 days once

					lesions became “clear” or “almost clear” or after 3 weeks, whichever occurred sooner.
RISING UP[94]	Adolescents and adults with moderate-to-severe AD and with a history of inadequate response to topical therapies or for whom topical therapies were medically inadvisable.	Upadacitinib 30 mg (N=?) Upadacitinib 15 mg (N=?)	Placebo (N=?)	16-week treatment phase followed by a long-term extension study.	Study carried out in Japan and enrolled 272 people. At the time of writing, results from RISING UP are not available in a published peer-reviewed journal. Reported details have been extracted from the study entry on ClinicalTrials.gov.
Interventions recommended as treatment options by NICE for the management of moderate-to-severe AD					
Baricitinib (oral)[13]					
Monotherapy					
BREEZE-AD1[95]	Adults with moderate-to-severe AD (EASI score ≥16, vIGA-AD score of ≥3 and ≥10% BSA involvement) for at least 12 months prior to screening, and documented history of inadequate response to topical or systemic therapies within 6 months before screening.	Baricitinib 4 mg (N=125) Baricitinib 2 mg (N=123) Baricitinib 1 mg (N=127)	Placebo (N=249)	16-week treatment phase and follow-up at 4 weeks after treatment	Related conference abstract[111] Long-term extension study enrolling those with partial or full response from BREEZE-AD1 and BREEZE-AD2 (BREEZE-AD3).[98] BREEZE-AD1 and BREEZE-AD2 are independent multicentre RCTs that were run in parallel.
BREEZE-AD2[95]		Baricitinib 4 mg (N=123) Baricitinib 2 mg (N=123) Baricitinib 1 mg (N=125)	Placebo (N=244)		
Combination with TCS					
Phase II[78]	Adults with moderate-to-severe AD (EASI score ≥12, and ≥10% BSA involvement)	Baricitinib 4 mg (N=38) Baricitinib 2 mg (N=37)	Placebo (N=49)	16-week treatment phase	Concomitant TCS was triamcinolone 0.1%.

	for at least 24 months prior to screening, and documented history of inadequate response to topical or systemic therapies.				
BREEZE-AD4[96]	Adults with moderate-to-severe AD (EASI score ≥16, vIGA-AD score of ≥3 and ≥10% BSA involvement) for at least 12 months and a history of inadequate response to topical therapy and a history of intolerance to, contraindication to, or inadequate response to CsA.	Baricitinib 4 mg (N=92) Baricitinib 2 mg (N=185) Baricitinib 1 mg (N=93)	Placebo (N=93)	5-week wash-out 52-week treatment period (followed by a 52-week double-blind long-term extension which included a down-titration sub-study for responders and re-randomisation for non-responders) 4-week post-treatment follow-up	At the time of writing, results from BREEZE AD4 are not available in a published peer-reviewed journal. Reported details have been extracted from the study entry on ClinicalTrials.gov. and data available in TA681.[13] Background TCS therapy with moderate potency and/or low-potency TCS.
BREEZE-AD7[97]	Adults with moderate-to-severe AD (EASI score ≥16, vIGA-AD score of ≥3 and ≥10% BSA involvement) for at least 12 months prior to screening, and documented history of inadequate response to topical or systemic therapies within 6 months before screening.	Baricitinib 4 mg (N=111) Baricitinib 2 mg (N=109)	Placebo (N=109)	16-week treatment phase and follow-up at 4 weeks after treatment	Patients were allowed to use concomitant TCS that were of moderate or low potency.
Dupilumab (subcutaneous injection)[12]					
Monotherapy					
Phase IIb[76, 86]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3 and ≥10%	Dupilumab 300 mg Q4W (N=65)	Placebo (N=61)	16-week treatment phase	N/A

	BSA involvement) for at least 36 months prior to screening, and documented history of inadequate response to topical or systemic therapies within 6 months before screening.	Dupilumab 300 mg Q2W (N=64) Dupilumab 300 mg QW (N=63) Dupilumab 200 mg Q2W (N=61) Dupilumab 100 mg Q4W (N=65) Dupilumab: 600 mg loading dose			
LIBERTY AD-ADOL[99]	Adolescents with moderate-to-severe AD for at least 12 months prior to screening, and inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable.	Dupilumab 300 mg Q4W (N=84) Dupilumab 200 mg or 300 mg Q2W (N=82)	Placebo (N=85)	16-week treatment phase	Related conference abstracts[31, 112, 113] In the dupilumab Q2W group, dose was weight-based, with those weighing <60 kg receiving 200 mg Q2W after a loading dose of 400 mg. Those weighing ≥60 kg received 300 mg Q2W after a loading dose of 600 mg.
LIBERTY AD SOLO-1[75]	Adults with moderate-to-severe AD (IGA score of ≥3 and ≥10% BSA involvement) for at least 36 months prior to screening, and documented history of inadequate response to topical or systemic therapies within 6 months before screening.	Dupilumab 300 mg Q2W (N=224) Dupilumab 300 mg QW (N=223) Dupilumab: 600 mg loading dose	Placebo (N=224)	16-week treatment phase People achieving an IGA score of 0 or 1 or EASI 75 at 16 weeks were re-randomised to dupilumab 300 mg at various intervals (QW, Q2W, Q4W, or Q8W) or to placebo (SOLO-CONTINUE)	Pooled analysis[114] Long-term extension SOLO-CONTINUE[115] Assessment of efficacy of dupilumab in different racial subgroups[45] SOLO-1 and SOLO-2 are independent multicentre RCTs that were run in parallel.
LIBERTY AD SOLO-2[75]		Dupilumab 300 mg Q2W (N=233) Dupilumab 300 mg QW (N=239)	Placebo (N=236)		

		Dupilumab: 600 mg loading dose			
Combination with TCS					
LIBERTY AD CAFE[100]	Adults with moderate-to-severe AD (EASI score ≥20, IGA score of ≥3 and ≥10% BSA involvement) for at least 12 months, documented history of inadequate response to topical therapies and either no previous CsA exposure and not currently a candidate for CsA treatment or previous exposure to CsA and an inadequate response	Dupilumab 300 mg Q2W (N=107) Dupilumab 300 mg QW (N=110) Dupilumab: 600 mg loading dose	Placebo (N=108)	16-week treatment phase	Initial concomitant TCS was of medium potency applied once daily to active lesions. Low-potency TCS could be applied to areas of thin skin.
LIBERTY AD CHRONOS[71]	Adults with moderate-to-severe AD (EASI score ≥16, IGA score of ≥3 and ≥10% BSA involvement) for at least 36 months prior to screening, and documented history of inadequate response to topical or systemic therapies within 6 months before screening.	Dupilumab 300 mg Q2W (N=106) Dupilumab 300 mg QW (N=319) Dupilumab: 600 mg loading dose	Placebo (N=315)	52-week treatment phase and 12 weeks of follow-up Efficacy at week 16 was the study's primary objective.	Topical therapies allowed during the trial included low or medium potency TCS and TCI. People were allowed to use more than one topical therapy. Initial concomitant TCS was of medium potency, moving to low potency for 7 days once lesions became "clear" or "almost clear".

Abbreviations: AD, atopic dermatitis; CsA, ciclosporin A; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; MTA, Multiple Technology Appraisal; N/A, not applicable; NICE, National Institute for Health and Care Excellence; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; TA, technology appraisal; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids.

4.2.1.2 *Quality of research available*

Most of the studies included in the assessment of clinical effectiveness are considered to be well-conducted and well-designed Phase III RCTs, and, as such, are at an overall low risk of bias (summary of quality assessment in Table 5). All studies are described as randomised, aside from the single observational study that provides evidence on CsA.[88] For most studies, the method of randomisation and allocation concealment for the included RCTs was deemed to be adequate. However, details on the methods used to generate the randomisation sequence were not available for five studies and so risk of allocation bias was judged to be unclear for these trials (Table 5).

Limited details were available in the full publications on the methods implemented to initially conceal allocation and to subsequently maintain masking of treatment from clinicians and participants. However, additional information was available from other sources, including clinical trial registries, the company submissions to the STA process, and committee papers for recommended treatment options (dupilumab and baricitinib). The tools used to assess severity of the signs and symptoms of AD, and therefore level of improvement, are subjective in nature and so most recorded outcomes are at increased risk of bias. Most of the included studies employed a double-blind process to mitigate against introducing bias into outcome assessment. However, for most studies described as double blind, it was unclear whether the outcome assessor was the treating clinician and, if not, whether the outcome assessor was masked to treatment. Follow-up at the end of treatment (12–16 weeks) was high across most studies, with several studies categorised as a low risk of attrition bias for the outcomes evaluated. No study was assessed as high risk of selective reporting, with results routinely reported for all prespecified outcomes.

The quality of the observational study[88] used to facilitate comparison of upadacitinib and dupilumab in the first-line setting was assessed using the Case–Control component of the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies.[116] Based on the NOS, the observational study scored a point for most aspects of selection, comparability and exposure. The EAG acknowledges that the NOS is not an ideal tool to assess quality as Ariens *et al*.[88] does not include a control group, with both groups receiving an active treatment. Data on patients receiving CsA were acquired from secure records and, with the exception of EASI 75, the groups had comparable baseline characteristics. As noted earlier (Section 4.2.1.1.2.3), the lower baseline EASI score of those receiving CsA reflects the patient population likely to present in clinical practice with moderate-to-severe AD, whereas people enrolled in clinical trials typically have more severe AD.

Overall, the EAG considers the data presented by Ariens *et al*.[88] to represent the most robust evidence available to inform the NMA.

As highlighted in Section 4.2.1.1, despite the low overall risk of bias of the studies, much of the data informing the analyses of comparative clinical effectiveness are derived from *post hoc* subgroups, which introduces uncertainty, the level of which cannot be quantified, into the analyses.

Table 5. Summary of risk of bias assessments of RCTs included in the review

Study	Sequence generation	Allocation concealment	Masking of participants and personnel	Masking of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
Abrocitinib							
Study B7451006[27]	✓	✓	✓	✓	X	✓	Some concerns
JADE MONO-1[28]	✓	✓	✓	✓	✓	✓	Low
JADE MONO-2[29]	✓	✓	✓	✓	✓	✓	Low
JADE TEEN[30]	?	?	✓	✓	✓	?	Some concerns
JADE COMPARE[32]	?	✓	✓	✓	✓	✓	Low
Tralokinumab							
Phase IIb[92]	?	?	✓	✓	✓	✓	Some concerns
ECZTRA 1[35]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 2[35]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 3[37]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 5[36]	?	✓	✓	✓	✓	✓	Low
ECZTRA 7[39]	✓	✓	✓	✓	✓	✓	Low
Upadacitinib							
Phase IIb[93]	✓	✓	✓	✓	✓	✓	Low
AD UP[42]	✓	✓	✓	✓	✓	?	Low
HEADS UP[41]	✓	✓	✓	✓	?	?	Some concerns
MEASURE UP1[40]	✓	✓	✓	✓	✓	?	Low
MEASURE UP2[40]	✓	✓	✓	✓	✓	?	Low

RISING UP[94]	?	?	✓	✓	?	?	Some concerns
Baricitinib							
Phase II[78]	✓	✓	✓	✓	X	✓	Some concerns
BREEZE-AD1[95]	✓	✓	✓	✓	✓	✓	Low
BREEZE-AD2[95]	✓	✓	✓	✓	✓	✓	Low
BREEZE-AD4[96]	✓	✓	✓	✓	✓	✓	Low
BREEZE-AD7[97]	✓	✓	✓	✓	✓	✓	Low
Dupilumab							
Phase IIb[76, 86]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD-ADOL[99]	?	✓	✓	✓	✓	✓	Low
LIBERTY AD CAFE[100]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD CHRONOS[71]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD SOLO-1[75]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD SOLO-2[75]	✓	✓	✓	✓	✓	✓	Low
Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.							

4.2.2 Assessment of clinical effectiveness

NMAs were conducted for the primary outcome EASI 50 + DLQI ≥4 and for EASI 75. Results for quality of life (captured as change from baseline in EQ-5D), use of rescue medication, the number of days free from TCS and safety outcomes are described narratively.

The primary NMAs were based on using all observed data, regardless of rescue medication use to determine response. Sensitivity analysis were conducted where patients requiring rescue medication were considered non-responder. Data based on this censoring rule were available for baricitinib, dupilumab, tralokinumab and upadacitinib, but not for CsA, and for abrocitinib rescue therapy was not allowed.

For abrocitinib, the primary analysis was based on the subgroup of second-line patients who have failed on CsA, in line with the populations defined for this MTA. This subgroup, which is referred to as the "restricted" population, was very small in all abrocitinib trials. Sensitivity analyses were therefore conducted using the "generalisable" population for abrocitinib. The generalisable population included patients who were previously treated with at least one systemic treatment for AD. This subgroup was slightly larger than the restricted population. The generalisable population may be more reflective of the population who are likely to receive abrocitinib in UK clinical practice, but this population is less comparable to the populations in the comparator trials than the restricted population.

The companies for abrocitinib, tralokinumab and upadacitinib explored the impact of differences in baseline risk (placebo response) on the results of the network meta-analyses (NMAs) in their evidence submission. However, the results of the baseline-risk adjustment analyses did not inform the any company's base case for any of the interventions. The EAG therefore explored as a sensitivity analysis differences in placebo response, where possible, and where variation in placebo response was observed. The methods detailed in NICE DSU TSD3 were followed, in which heterogeneity in baseline risk is accounted for by centering the placebo response at the mean placebo response.[117] However, the EAG is aware that NICE DSU TSD5 recommends a different approach.[118]

Given the small number of trials in the networks, the small number of patients from the trials, and the potential difference between the trials, the EAG had a preference for a RE model with informed prior over a FE model for the NMAs. Comparisons of the DIC between the RE and FE models show a

difference of less than 5 for all analyses, confirming the EAG's preference for RE model, as the model fit is "similar" between the two approaches. Therefore, a RE model with informed prior for the between-trial heterogeneity was chosen for the primary analysis, for all NMAs in all populations.

4.2.2.1 ~~Given the small number of trials in the networks, the small number of patients from the trials, and the potential difference between the trials, the EAG had a preference for a RE model with informed prior over a FE model for the NMAs. Comparisons of the DIC between the RE and FE models show a difference of less than 5 for all analyses, confirming the EAG's preference for RE model, as the model fit is "similar" between the two approaches. Therefore, a RE model with informed prior for the between-trial heterogeneity was chosen for the primary analysis, for all NMAs in all populations.~~ First-line systemic treatments – adult population

Upadacitinib is the only one of the interventions assessed in this MTA that is proposed as a first-line systemic therapy for adults having inadequate response to topical treatments.

NMA

The most relevant comparator in the first-line setting is CsA, however, no relevant RCTs of CsA were identified that could be linked in an NMA to the upadacitinib trials. In the broader search for evidence to inform a comparison with CsA, Ariens *et al.* was identified. As described in section 4.2.1, Ariens *et al*. provides the results of a regression analysis of patient level data for patients treated with dupilumab in the placebo controlled RCT CHRONOS and patients treated with CsA in daily practice at the Department of Dermatology and Allergology, University Medical Center (UMC) Utrecht, the Netherlands. Data for EASI 50 + ΔDLQI ≥4 were not available from Ariens *et al*. and so EASI 75 became the primary outcome for this population.

Concomitant use of TCS was permitted as needed for all patients treated with CsA. CsA effectiveness presented in Ariens *et al*. was therefore adjusted to data for dupilumab in combination with TCS from CHRONOS. Consequently, the EAG considered the appropriate comparator to be upadacitinib in combination with TCS from the AD UP trial. An NMA assessing upadacitinib versus CsA without concomitant TCS was not possible, but the results of the monotherapy trials for upadacitinib are presented alongside the combination therapy NMA results below for completeness.

Time of assessment in the CHRONOS and AD-UP trials was 16 weeks whereas EASI scores were available for the range between weeks 12 and 16 for CsA.

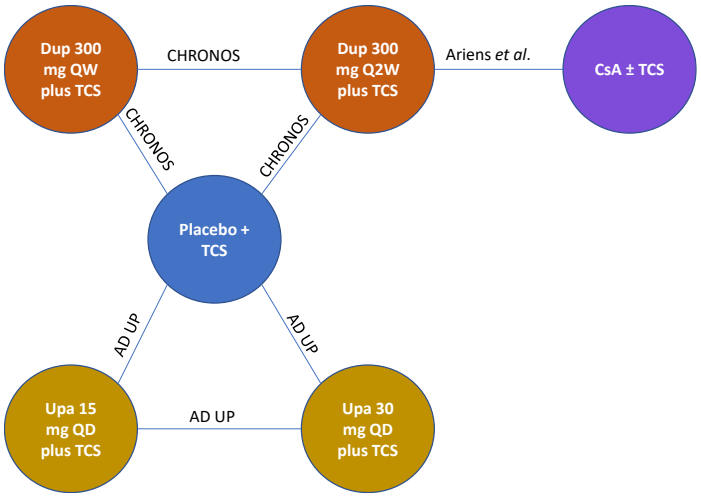
The primary analysis focused on the *post hoc* subgroup of patients in the upadacitinib trial, AD UP, for whom upadacitinib (or placebo) was their first-line systemic therapy. Of the CsA-treated patients in Ariens *et al*., 70% had no history of previous treatment with oral immunosuppressive drugs, though outcome data for this specific subgroup were not available and this cohort was therefore compared with the full population of the CHRONOS trial treated with dupilumab. Of the dupilumab treated patients in CHRONOS, 41% had previously received systemic immunosuppressants to treat AD. A sensitivity analysis was conducted using the full trial population for AD UP, 52-58% of which had previously received systemic therapy. The difference in prior systemic therapy introduces clinical heterogeneity into the analysis, which is likely to favour upadacitinib because those with prior treatment are more severe at baseline.

The dupilumab data from CHRONOS reported in the Ariens *et al*. analysis and in the committee papers for TA534 differ slightly; an additional two patients had a response (EASI 75) according to Ariens *et al*. compared with TA534. The difference may be due to different handling of missing data with a last observation carried forward (LOCF) analysis performed in cases of missing follow-up EASI values in Ariens *et al*., whereas the dupilumab data from CHRONOS in TA534 either included all observed data or censored patients who received rescue medication. In the primary analysis, the data from Ariens *et al*. (CsA versus dupilumab) and from CHRONOS (dupilumab versus placebo), were therefore analysed as two separate studies. However, in order to assess the possible impact of including the same dupilumab arm twice (once in CHRONOS and once in Ariens *et al*.), a sensitivity analysis was conducted, where the CsA arm from Ariens *et al*. was considered an additional arm of the CHRONOS study. A different sensitivity analysis was also conducted where patients requiring rescue medication were considered non-responders. These data were available for AD UP and CHRONOS but not for the observational CsA data.

EASI 75

The network of trials contributing to the NMA in the first-line adult population are presented in Figure 4.

Figure 4. Network plot first-line adult population, combination therapy, EASI 75



Abbreviations: CsA, cyclosporine A; Dup, dupilumab; OD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Upa, upadacitinib.

For the NMA in the first line adult population, the random and fixed effect models for the primary analysis and the sensitivity analyses were similar in terms of goodness of model fit (similar DIC), and the residual deviance were similar to the number of unconstrained data points in all analyses (Table 7).

The results of the NMA, presented in Table 6, showed that upadacitinib, dupilumab and CsA were all more effective than placebo, i.e., leading to more responders (patients reaching EASI 75). The difference versus placebo was statistically significant for upadacitinib (both doses) and dupilumab, but not for CsA. Results from the NMA were in agreement with findings from standard pair-wise analyses, in which all interventions analysed were found to be statistically significantly more effective than placebo. Upadacitinib was also shown to be more effective than CsA, with a larger OR for upadacitinib 30 mg ([redacted]) than for upadacitinib 15 mg ([redacted]), although neither was statistically significant.

Analysing the CsA data from Ariens[88] and dupilumab data from CHRONOS (as reported in TA534)[12] as one multi-arm trial resulted in similar results to the primary analysis but with narrower CrIs. Similarly, using the full trial population in AD UP rather than focusing on the first line population (patients who had not received CsA) had limited impact on the results compared with the primary

analysis. The sensitivity analysis using data where patients who received rescue therapy in AD UP and CHRONOS were censored also gave similar results to the primary analysis.

The placebo response in AD UP and CHRONOS were similar at [redacted] and [redacted], respectively. Therefore, no baseline risk adjustment sensitivity analysis was conducted for the first line adult population.

Table 6. Estimates of effect (EASI 75) of first line systemic treatments in combination with TCS in adults at 16 weeks, generated by NMA (RE) and standard pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)			
	Primary	Primary	Sensitivity		
		Chronos/Ariens separate studies	Chronos/Ariens Multi-arm trial	Upa – all lines of therapy	Rescue therapy censoring
Treatments versus placebo					
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300 mg Q2W + TCS	5.82 (3.56 to 9.52)	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300 mg QW + TCS	5.07 (3.62 to 7.11)	[redacted]	[redacted]	[redacted]	[redacted]
CsA + TCS	NA	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus CsA					
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus Upa 15 mg QD + TCS					
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CrI, credible interval; CsA, cyclosporine A; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; QW, every week; TCS, topical corticosteroid; Upa, upadacitinib

Table 7. Summary of NMA model characteristics

Characteristic	Primary analysis		Sensitivity analysis					
	Ariens/CHRONOS separate studies		Ariens/CHRONOS analysed as one study		All lines of therapy in AD UP		Censoring of patients receiving rescue therapy	
	RE	FE	RE	FE	RE	FE	RE	FE
Deviance information criterion	58.60	58.52	51.75	51.73	59.25	59.26	58.68	58.63
Total residual deviance	8.1	8.0	7.0	7.0	8.0	8.0	8.1	8.0
Number of data points	8	8	7	7	8	8	8	8

Abbreviations: FE, fixed effect model; RE, random effects model

No comparator data for CsA used without concomitant TCS were identified and therefore a NMA comparing upadacitinib and CsA used as monotherapies was not possible. However, data on the efficacy of upadacitinib as a monotherapy compared with placebo or dupilumab in the first-line setting were available and presented for completeness (Table 8). The results showed that upadacitinib monotherapy is statistically significantly more effective than placebo, in terms of both EASI 50 + ΔDLQI ≥4 and EASI 75, with a larger benefit in response assessed as EASI 75 than the composite outcome. In terms of EASI 75, upadacitinib monotherapy is also more effective than dupilumab, but the difference did not reach statistical significance.

Table 8. Estimates of effect (EASI 50 + ΔDLQI ≥4 and EASI 75) of upadacitinib monotherapy as a first line systemic treatment in adults at 16 weeks, generated by standard pair-wise meta-analysis[x]

Outcome	Upa 30 mg QD vs placebo OR (95% CI)	Upa 15 mg QD vs placebo OR (95% CI)	Upa 30 mg QD vs Dup 300mg Q2W OR (95% CI)
EASI 50 + ΔDLQI ≥4	[redacted]	[redacted]	NA
EASI 75	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; Upa, upadacitinib

Quality of life (EQ-5D)

In the upadacitinib trials Measure UP 1, Measure UP 2, and AD UP, EQ-5D-5L was captured throughout to measure the impact of upadacitinib therapy on general QoL. For each of the sub-populations, including the first-line population in the upadacitinib trials, EQ-5D data were provided

as the mean at baseline and week 16. The results show a larger improvement in EQ-5D from baseline to week 16 in patients treated with upadacitinib than for patients receiving placebo, irrespective of upadacitinib dose or if used as a monotherapy or in combination with TCS (Table 9).

Table 9. EQ-5D-5L at baseline and week 16 for adults receiving upadacitinib as a first line systemic therapy

Upadacitinib				
Monotherapy		Upa 30 mg QD	Upa 15 mg QD	Placebo
Measure UP 1	N*	(N=204)	(N=195)	(N=196)
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D-5L at week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Measure UP 2	N*	(N=178)	(N=164)	(N=169)
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D-5L at week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Combination therapy		Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS
	N*	(N=203)	(N=203)	(N=209)
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
AD UP	EQ-5D-5L at week 16, mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: QD, once daily; SD, standard deviation; TCS topical corticosteroid; Upa, upadacitinib
*N contributing to the data at week 16

Use of rescue medication

Use of rescue therapy was not captured for the CsA data in Ariens *et al*. and for CHRONOS rescue therapy use was only reported at 52 weeks. However, data on the use of rescue therapy were provided by the company for upadacitinib used in the first line setting either as a monotherapy (Measure UP 1, Measure UP 2, and Heads UP) and in combination with TCS (AD UP).

The proportion of people treated with upadacitinib as a first line monotherapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg (Table 10). A similar dose-related effect was not seen when upadacitinib was given in combination with TCS in AD UP. The rates were relatively similar for upadacitinib used as a monotherapy (Measure UP 1 and Measure UP 2) and combination therapy (AD UP), whereas patients given placebo as a monotherapy received substantially more rescue therapy than people given placebo with concomitant TCS. That is, the

difference in use of rescue medication between upadacitinib and placebo was substantially higher in the monotherapy trials (Measure UP 1 and Measure UP 2) than in the combination therapy trial (AD UP). Interestingly, the rate of patients needing rescue therapy in HEADS UP, the head-to-head trial of upadacitinib and dupilumab monotherapy, were similar for the two treatments and higher than the proportion in the other monotherapy trials.

The allowed rescue therapy was the same for the monotherapy and combination therapy upadacitinib trials; the first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. In AD UP, patients requiring rescue therapy mainly received high potency TCS. In Measure UP 1 and 2, where a larger proportion required rescue therapy, especially in the placebo arms, the most frequently used types of rescue therapy included TCS of varying potency (low, medium or high) and non-biologic systemic treatments. Similarly, patients who needed rescue therapy in Heads UP mainly received TCS of varying potency.

Table 10. Upadacitinib – first line adults – Use of rescue medication during the double-blind period

Proportion of people requiring use of rescue therapy during treatment n (%)				
Combination therapy	Upa 30 mg QD + TCS	Upa 15 mg QD + TCS	Placebo + TCS	
AD UP	(N=203)	(N=203)	(N=209)	NA
	[redacted]	[redacted]	[redacted]	NA
Monotherapy	Upa 30 mg QD	Upa 15 mg QD	Placebo	Dup 300mg Q2W
Measure UP 1	(N=211)	(N=200)	(N=201)	NA
	[redacted]	[redacted]	[redacted]	NA
Measure UP 2	(N=189)	(N=168)	(N=178)	NA
	[redacted]	[redacted]	[redacted]	NA
Heads UP	(N=298)	NA	NA	(N=288)
	[redacted]	NA	NA	[redacted]

Abbreviations: Dup, dupilumab; NA, not applicable; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Number of days free from TCS during treatment

Data on the number of days free from TCS during treatment were reported for the subgroup of the adult population of AD UP who received upadacitinib as a first-line systemic therapy in combination with TCS. In this subgroup of AD UP, upadacitinib therapy

[redacted]

(Table 11).

Table 11. Number of days free from TCS during treatment

AD UP Adult systemic naïve	Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS
Number of days free from TCS during treatment	(N=203)	(N=203)	(N=209)
Primary analysis Mean (95% CI)	[redacted]	[redacted]	[redacted]
All observed analysis Mean (95% CI)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.

4.2.2.2 Monotherapies as second-line treatment – adult population

NMA

NMAs of interventions used as monotherapies in the second-line setting (for patients who have failed on CsA) could be carried out for both EASI 50 + ΔDLQI ≥4 and EASI 75, and, although results are reported for both, the primary outcome for this appraisal is EASI 50 + ΔDLQI ≥4.

Although relevant trials for baricitinib used as a monotherapy were identified, the results of these were redacted and baricitinib could, therefore, not be included in the monotherapy networks assessing EASI 50 + ΔDLQI ≥4 or EASI 75. For upadacitinib, the dose finding trial reported by Guttmann-Yassky *et al.* in 2020, could have informed the NMA for EASI 75, as it provides the relevant outcome data at 16 weeks for upadacitinib 15 mg, 30 mg and for placebo. However, the company did not provide the relevant subgroup data for this trial at the clarification stage and it was therefore excluded from the analysis. Data for dupilumab were informed by the *post hoc* subgroup data from SOLO 1 and SOLO 2 presented in TA534. For both endpoints in the monotherapy NMA, results for SOLO 1 and SOLO 2 were reported pooled across both studies and so has been considered as a single study, referred to as "SOLO CAFÉ-like".

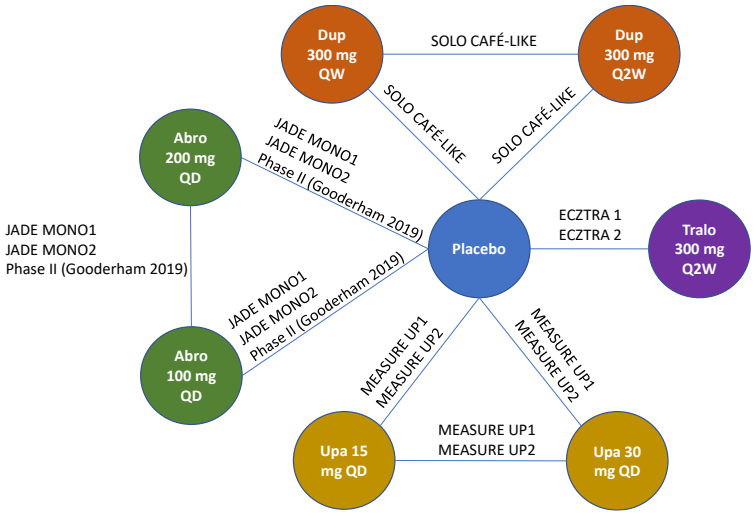
The primary analysis for the monotherapy NMAs was based on using all observed data, regardless of rescue medication use to determine response, with a sensitivity analysis conducted where patients requiring rescue medication were considered non-responders. Patients were not allowed rescue therapy in the abrocitinib trials.

The relevant subgroup in the abrocitinib studies, the restricted population, which was used for the primary analysis, was small with [redacted] people in each treatment arm. A sensitivity analysis using the generalisable population, which includes people who have had any prior systemic immunotherapy (not limited to prior CsA) was therefore also conducted. Due to variation across studies in placebo response, for both EASI 50 + ΔDLQI ≥4 and EASI 75, sensitivity analyses were also conducted to assess the impact of adjusting for these differences.

EASI 50 + ΔDLQI ≥4

The network of trials contributing to the NMA of monotherapies on EASI 50 + ΔDLQI ≥4 in the second line adult population is presented in Figure 5.

Figure 5. Network plot second line adult population, monotherapy, EASI 50 + ΔDLQI ≥4



Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; Tralo, tralokinumab; Upa, upadacitinib.

For the NMAs of EASI 50 + ΔDLQI ≥4, the RE and FE models for the primary and all sensitivity analyses were similar in terms of goodness of model fit (similar DIC) (Table 13). However, for both RE

and FE models, the residual deviance showed a relatively poor prediction of the data used in each analysis, especially for the sensitivity analysis using the generalisable abrocitinib population.

The primary analysis, which focused on response irrespective of rescue therapy use, showed that treatment with any of the interventions assessed (abrocitinib, dupilumab, tralokinumab or upadacitinib) led to a statistically significant improvement in EASI 50 + ΔDLQI ≥4 compared with placebo (Table 12). Results from the NMA were in agreement with findings from standard pair-wise analyses, in which all interventions analysed were found to be statistically significantly more effective than placebo. Although, for abrocitinib 200 mg the NMA resulted in a substantially higher OR compared with the underlying trial data.

A dose dependent numerical benefit was observed for upadacitinib 15mg ([redacted]) and upadacitinib 30mg ([redacted]) over dupilumab, however, the differences did not reach statistical significance (Table 12). Similarly, abrocitinib showed a dose dependent effect versus dupilumab with an OR of [redacted]) for abrocitinib 200mg, and for abrocitinib 100mg the OR was [redacted] ([redacted]). Neither analysis showed a statistically significant difference versus dupilumab. Tralokinumab therapy resulted in a lower response than dupilumab ([redacted]), although, as for the other interventions the difference was not statistically significant.

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials led to a smaller benefit of abrocitinib 200 mg, upadacitinib 15mg and 30 mg compared with dupilumab, whereas the benefit of dupilumab over tralokinumab therapy increased and it also became more beneficial than abrocitinib 100 mg. Though, none of the relative differences between the interventions and dupilumab were statistically significant.

The sensitivity analysis based on the generalisable population for abrocitinib show relatively similar results to the primary analysis, although the ORs for both doses of abrocitinib were more favourable and the 95% CrIs were narrower for the generalisable population as the sample sizes were larger.

There was variation in placebo response across the included trials, from no responders to a third of patients on placebo being responders at 12 or 16 weeks: treatment effectiveness was captured at 12 weeks in studies evaluating abrocitinib and at 16 weeks in all other studies. However, the largest variation in placebo response rates was in the abrocitinib trials, which had very low numbers of

included patients (6 patients in each of the placebo arms). The sensitivity analysis adjusting for heterogeneity in placebo response gave a lower DIC than the primary, unadjusted analysis, indicating a better model fit. However, the total residual deviance, for this analysis, was lower than the number of unconstrained data points, indicating that the model may be "overfitting" the data. That is, the model predicts the underlying trial data extremely well (and hence a lower DIC) but is likely to be less generalisable to the population of interest than the unadjusted analysis using observed data. The EAG is concerned that the results are unreliable for use in the cost effectiveness analyses and, in keeping with the companies approach, the EAG used the observed data to inform the primary cost effectiveness analysis. However, the results of the placebo response adjusted NMAs are presented in Appendix 10.5.

Table 12. Estimates of effect (EASI 50 + ΔDLQI ≥4) of second line systemic monotherapies in adults at 16 weeks, generated by NMA and standard pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)		
	Primary	Primary	Sensitivity Rescue therapy	Sensitivity Abrocitinib generalisable
Treatments versus placebo				
Abro 200 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dup 300 mg QW	[redacted]	[redacted]	NA	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus Dup 300 mg every 2 weeks				
Abro 200 mg QD	NA	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	NA	[redacted]	[redacted]	[redacted]
Tralokinumab	NA	[redacted]	[redacted]	[redacted]
Upa 30 mg QD	NA	[redacted]	[redacted]	[redacted]
Upa 15 mg QD	NA	[redacted]	[redacted]	[redacted]
Treatment doses versus each other				
Abro 200 mg QD vs abro 100 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD vs upa 15 mg QD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Table 13. Summary of NMA model characteristics

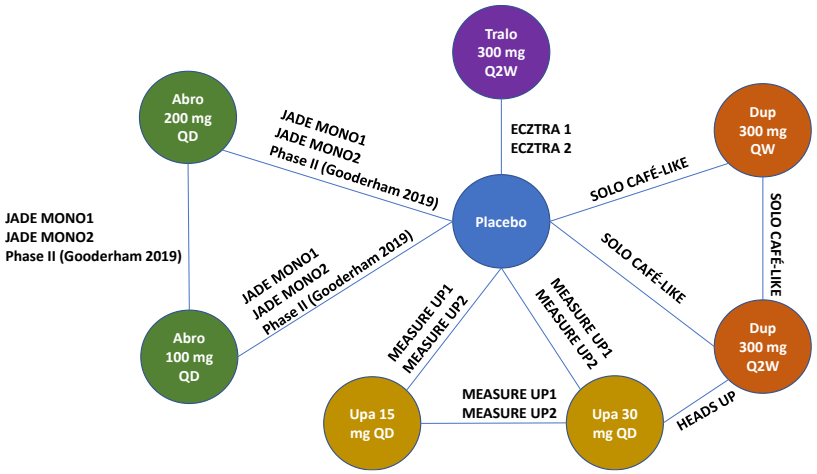
Characteristic	Primary analysis		Sensitivity analysis				
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population		Placebo risk adjustment
	RE	FE	RE	FE	RE	FE	RE
Deviance information criterion	121.1	120.7	111.4	111.1	130.1	130.4	115.8
Total residual deviance	25.0	26.4	23.6	25.0	27.7	30.4	20.2
Number of data points	22	22	21	21	22	22	22

Abbreviations: FE, fixed effect model; RE, random effects model.

EASI 75

The trials contributing to the NMA of monotherapies on EASI 75 in the second line adult population are presented in Figure 6. Unlike some of the networks in this report, this network includes one head-to-head trial of an active intervention versus a comparator (HEADS UP, upadacitinib versus dupilumab). This is likely to produce different results to a "star-shaped" network that relies only on indirect comparisons.

Figure 6. Network plot second line adult population, monotherapy, EASI 75



Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; Tralo, tralokinumab; Upa, upadacitinib.

For the primary analysis and all sensitivity analyses of EASI 75, the goodness of model fit of the FE and RE models were similar (Table 15), but the residual deviance for the RE models were considerably closer to the number of unconstrained data points than the FE models in all analyses, which reinforces the EAG's preference for the RE model.

Treatment with any of the interventions assessed (abrocitinib, dupilumab, tralokinumab or upadacitinib) led to a statistically significant OR in favour of active treatment compared with placebo (Table 14). Results from the NMA were broadly in agreement with findings from standard pair-wise analyses, in which all interventions analysed were found to be more effective than placebo. Although, for abrocitinib 200 mg and 100 mg, the NMA resulted in substantially higher ORs compared with the underlying trial data.

For the comparison with dupilumab, the results of the primary analysis for EASI 75 were similar to those for EASI 50 + ΔDLQI ≥4 for tralokinumab, which resulted in a lower improvement in response than dupilumab ([redacted]), and both dose of upadacitinib, which were more effective than dupilumab, though, the results were only statistically significant for upadacitinib 30 mg ([redacted]). The benefit of abrocitinib treatment (either dose) over dupilumab treatment was larger when response was assessed as EASI 75 than as EASI 50 + ΔDLQI ≥4, but the results did not reach statistical significance.

There was one loop in the NMA of EASI 75 consisting of upadacitinib 30 mg, dupilumab and placebo, for which the direct and indirect estimates of the ORs generated for the interventions were compared to assess possible inconsistency. The results of the inconsistency assessments demonstrated no evidence of statistically significant inconsistency (inconsistency estimate -0.88, 95% CI: -2.28 to 0.53).

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials led to a smaller benefit of each of the treatments compared with dupilumab, with the exception of tralokinumab; the benefit of dupilumab over tralokinumab therapy increased compared with the primary analysis. None of the relative differences between the interventions and dupilumab were statistically significant.

The sensitivity analysis based on the generalisable population for abrocitinib resulted in a markedly smaller benefit of treatment with abrocitinib 200 mg compared with dupilumab, than seen in the restricted population used in the primary analysis. The OR of the comparison of abrocitinib 100 mg versus dupilumab changed direction, favouring dupilumab in the generalisable population. The 95% CrIs for the comparisons of both abrocitinib doses were substantially narrower for the generalisable population likely due to the larger sample size.

There was variation in placebo response across the included trials, from no responders to just under a quarter of patients on placebo being responders at 16 weeks. The sensitivity analysis adjusting for differences in placebo response gave a marginally lower DIC than the primary, unadjusted analysis, however, the total residual deviance for this analysis, was lower than the number of unconstrained data points, indicating that the model may be "overfitting" the data. As such, the observed data were preferred to inform the primary cost effectiveness analysis. However, the results of the placebo response adjustment are presented in Appendix 10.5.

Table 14. Estimates of effect (EASI 75) of second line systemic monotherapies in adults at 16 weeks, generated by NMA and standard pair-wise meta-analysis

Comparison	Pair-wise analysis OR (95% CI)	NMA OR (95% CrI)		
	Primary	Primary	Sensitivity Rescue therapy	Sensitivity Abrocitinib generalisable
Treatments versus placebo				
Abro 200 mg QD	[redacted]	[redacted]	[redacted]	[redacted]

Abro 100 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dup 300 mg QW	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus Dup 300 mg every 2 weeks				
Abro 200 mg QD	NA	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	NA	[redacted]	[redacted]	[redacted]
Tralokinumab	NA	[redacted]	[redacted]	[redacted]
Upa 30 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD	NA	[redacted]	[redacted]	[redacted]
Treatment doses versus each other				
Abro 200 mg QD vs Abro 100 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD vs upa 15 mg QD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Table 15. Summary of NMA model characteristics

Characteristic	Primary analysis		Sensitivity analysis				
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population		Placebo risk adjustment
	RE	FE	RE	FE	RE	FE	RE
Deviance information criterion	127.6	133.2	119.2	123	137.8	142.2	123.3
Total residual deviance	24.6	33.6	23.5	30.4	24.1	32.5	22.6
Number of data points	24	24	23	23	24	24	24

Abbreviations: FE, fixed effect model; RE, random effects model.

Quality of life (EQ-5D)

EQ-5D data for people receiving monotherapy treatment for AD in the second line setting were available or provided by the companies for abrocitinib, dupilumab, tralokinumab and upadacitinib.

Data were reported as change from baseline, with the exception of upadacitinib, where data were provided at baseline and at week 16. In the upadacitinib and abrocitinib trials, general QoL was captured using EQ-5D-5L, whereas EQ-5D-3L was used in the dupilumab trials.

The results for dupilumab, tralokinumab and upadacitinib show a larger improvement in EQ-5D from baseline to week 16 in patients treated with active monotherapy than for patients receiving placebo. For upadacitinib this was irrespective of dose (Table 16). The results for abrocitinib, which are based on the restricted population and assessed after 12 weeks of treatment, are less clear; treatment with abrocitinib 200 mg, but not abrocitinib 100 mg, seems to result in an improvement in EQ-5D compared with placebo. However, the relevant sample sizes are very small.

Table 16. EQ-5D for adults receiving monotherapy in the second line setting

Trial	Outcome measure	Trial arm 1	Trial arm 2	Trial arm 3
Upadacitinib		Upa 30 mg QD	Upa 15 mg QD	Placebo
Measure UP 1 – second line	N*	(N=31)	(N=39)	(N=40)
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Measure UP 2 – second line	N*	(N=56)	(N=73)	(N=60)
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Abrocitinib		Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo
JADE MONO1 - restricted	N	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D-5L at Week 12, least square mean	[redacted]	[redacted]	[redacted]
JADE MONO2 - restricted	N	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D-5L at Week 12, least square mean	[redacted]	[redacted]	[redacted]
Tralokinumab		Tralokinumab Q2W	Placebo	
ECZTRA 1 - ECZTRA-7 like	N	224	62	NA
	Change from baseline in EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	NA
ECZTRA 2 - ECZTRA-7 like	N	193	58	NA
	Change from baseline in EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	NA
Dupilumab		Dupilumab 300mg	Dupilumab 300mg	Placebo QW

		Q2W	QW	
SOLO CAFÉ-like	N	104	96	88
	Change from baseline in EQ-5D at Week 16, least square mean (SE)	0.281 (0.0238)	0.318 (0.0236)	0.161 (0.0205)

Abbreviations: NA, not applicable; Q2W, every 2 weeks; QD, once daily; SD, standard deviation; SE, standard error; TCS topical corticosteroid; Upa, upadacitinib.

*N contributing to the data at week 16

Use of rescue medication

Data on the use of rescue therapy for monotherapies used in the second line setting were provided by the company for upadacitinib (Measure UP 1, Measure UP 2, and Heads UP) and for tralokinumab (ECZTRA 1 and ECZTRA 2). Data on the use of rescue medication needed with dupilumab monotherapy were available from SOLO 1 and SOLO2 but for the full trial populations rather than the subgroup of patients treated in the second line setting. Limited data were also available for baricitinib on the use of rescue therapy used in BREEZE AD1 and BREEZE AD2.

The use of rescue medication was markedly reduced in patients receiving active treatment (baricitinib, dupilumab, tralokinumab or upadacitinib) compared with placebo (Table 17). The proportion of people treated with upadacitinib in combination with TCS as a second line therapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg.

TCSs were the most common form of rescue medication in the upadacitinib and tralokinumab trials. In the upadacitinib trials this was followed by non-biologic systemic therapy, and in the tralokinumab trials by other topical therapies for people treated with tralokinumab and either systemic corticosteroids or immunosuppressants for people treated with placebo. The most common form of rescue therapy in the dupilumab trials was systemic corticosteroids.

Table 17. Use of rescue medication during the double-blind period for adults treated with monotherapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)				
Upadacitinib trials	Upa 30 mg QD	Upa 15 mg QD	Placebo	Dupilumab 300mg Q2W
Measure UP 1	(N=32)	(N=39)	(N=40)	NA
	[redacted]	[redacted]	[redacted]	NA

Measure UP 2	(N=58)	(N=75)	(N=64)	NA
	[redacted]	[redacted]	[redacted]	NA
Heads UP	(N=50)	NA	NA	(N=56)
	[redacted]	NA	NA	[redacted]
Dupilumab trials	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	
SOLO 1	N=224	N=223	N=224	NA
	47 (21.0%)	52 (23.3%)	115 (51.3%)	NA
SOLO 2	N=233	N=239	N=236	NA
	35 (15.0%)	49 (20.5%)	123 (52.1%)	NA
Tralokinumab trials	Tralokinumab Q2W	Placebo		
ECZTRA 1	(N=224)	(N=62)	NA	NA
	[redacted]	[redacted]	NA	NA
ECZTRA 2	(N=193)	(N=58)	NA	NA
	[redacted]	[redacted]	NA	NA
Baricitinib trials	Baricitinib 4 mg	Placebo		
BREEZE-AD1	NR	NR	NA	NA
	51 (40.8)	166 (66.7)	NA	NA
BREEZE-AD2	NR	NR	NA	NA
	72 (58.5)	187 (76.6)	NA	NA

Abbreviations: NA, not applicable; NR, not reported; Q2W, every 2 weeks; QD, once daily; Upa, upadacitinib.

4.2.2.3 Second-line systemic treatments in combination with TCS – adult population

NMA

For the NMAs of interventions used in combination with TCS in the second-line setting (patients who have failed on CsA) *post hoc* subgroups were used for all studies apart from the dupilumab trial CAFÉ and the tralokinumab study ECZTRA 7. However, the data for dupilumab were informed by the pooled results of CAFÉ and the relevant *post hoc* subgroup data from CHRONOS presented in TA534. The pooled data have been considered as a single study. Two baricitinib trials were relevant for inclusion in these analyses, BREEZE-AD4 and BREEZE AD7. The majority of the results from these trials were redacted but baricitinib could be included in the analysis of EASI 75 based on data from BREEZE-AD4.

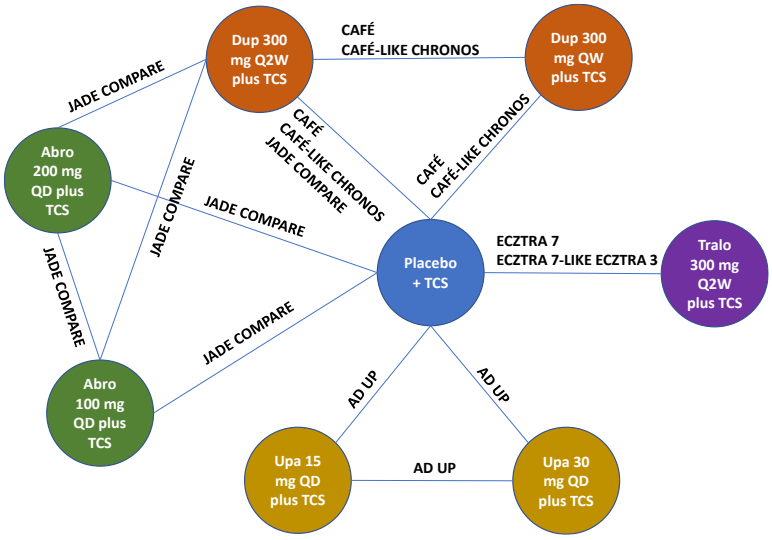
NMAs were possible to perform for both EASI 50 + ΔDLQI ≥4 and EASI 75, and although results are reported for both, the key outcome for this appraisal is EASI 50 + ΔDLQI ≥4.

The primary analysis for the combination therapy NMAs is based on using all observed data, regardless of rescue medication use to determine response, with a sensitivity analysis conducted where patients requiring rescue medication were considered non-responders. Sensitivity analysis were also conducted using the generalisable rather than restricted population for abrocitinib. A baseline risk-adjusted sensitivity analysis was conducted but the models did not converge despite attempts to increase convergence by thinning the sampling and increasing the number of model iterations. The lack of convergence could be due to the small number of patients in the abrocitinib trial. However, looking at a larger sample size, such as the ITT population, would not provide results of relevance to the population of interest to this report.

EASI 50 + ΔDLQI ≥4

The network of trials contributing to the NMA of combination therapies on EASI 50 + ΔDLQI ≥4 in the second line adult population is presented in Figure 7. Unlike some of the networks in this report, this network includes one head-to-head trial of an active intervention versus a comparator (JADE COMPARE, abrocitinib 200 mg and 100 mg versus dupilumab). This is likely to produce different results to a "star shaped" network that relies only on indirect comparisons.

Figure 7. Network plot second line adult population, combination therapy, EASI 50 + ΔDLQI ≥4



Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Tralo, tralokinumab; Upa, upadacitinib.

For the NMAs of EASI 50 + ΔDLQI ≥4, the RE and FE models for the primary and all sensitivity analyses were similar in terms of goodness of model fit (similar DIC) and residual deviance (Table 19).

The primary analysis showed that treatment with abrocitinib, dupilumab or upadacitinib led to a statistically significant improvement in EASI 50 + ΔDLQI ≥4 compared with placebo (

Table 18). Treatment with tralokinumab was also favoured over placebo treatment but the results were not statistically significant. The results from the NMA were in agreement with findings from standard pair-wise analyses, however, in the pair-wise analyses all interventions were found to be statistically significantly more effective than placebo.

When compared with dupilumab, there were no comparisons that were statistically significant. The largest relative treatment effects were for upadacitinib 30 mg with an OR of [redacted]) in favour of upadacitinib, and for tralokinumab ([redacted]) in favour of dupilumab. The OR of upadacitinib 15 mg, abrocitinib 100mg and 200 mg were closer to 1, favouring dupilumab for both of the lower doses and favouring abrocitinib for the higher dose.

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials had a limited impact on the comparison of abrocitinib 100mg or 200mg versus dupilumab. However, the benefit of upadacitinib 30mg over dupilumab was substantially smaller ([redacted]) than for the primary analysis, the benefit of dupilumab over tralokinumab was statistically significant ([redacted]), and although not statistically significant, dupilumab therapy was favoured over upadacitinib 15mg.

The sensitivity analysis based on the generalisable population for abrocitinib showed similar results to the primary analysis for upadacitinib 15mg, 30mg and tralokinumab, however, the benefit of dupilumab therapy over tralokinumab therapy reached statistical significance ([redacted]). For abrocitinib 100 mg and 200 mg, the direction of effect compared with dupilumab was the same as when using the restricted population (primary analysis) but the treatment effect favouring abrocitinib 200mg over dupilumab was larger and the treatment effect favouring dupilumab over abrocitinib 100mg was also more pronounced.

Placebo response varied between 25% and 61% in the studies contributing to the composite outcome. However, the models for the baseline risk-adjusted sensitivity analysis did not converge despite attempts to increase convergence by thinning the sampling and increasing the number of model iterations. Therefore, no results are presented for this sensitivity analysis. The lack of convergence could potentially be due to the small number of patients in the abrocitinib trial. However, looking at a larger sample size, such as the ITT population, would not provide results of relevance to the population of interest to this report.

Formatted: Font color: Auto

Formatted: Line spacing: 1.5 lines

Table 18. Estimates of effect (EASI 50 + ΔDLQI ≥4) of second line systemic treatments in combination with TCS in adults at 16 weeks, generated by NMA (RE) and standard pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)		
	Primary	Primary	Sensitivity Rescue therapy	Sensitivity Abrocitinib generalisable
Treatments versus placebo				
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	7.05 (4.22 to 11.77)	[redacted]	[redacted]	[redacted]
Dup 300 mg QW + TCS	6.60 (4.09 to 10.66)	[redacted]	NA	[redacted]
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus Dup 300 mg every 2 weeks				
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Treatment doses versus each other				
Abro 200 mg QD + TCS vs Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]

Upa 30 mg QD + TCS vs Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Table 19. Summary of NMA model characteristics

Characteristic	Primary analysis		Sensitivity analysis			
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population	
	RE	FE	RE	FE	RE	FE
Deviance information criterion	86.38	85.59	79.78	78.69	88.83	88.07
Total residual deviance	13.6	14.0	12.4	12.5	13.6	14.2
Number of data points	14	14	13	13	14	14

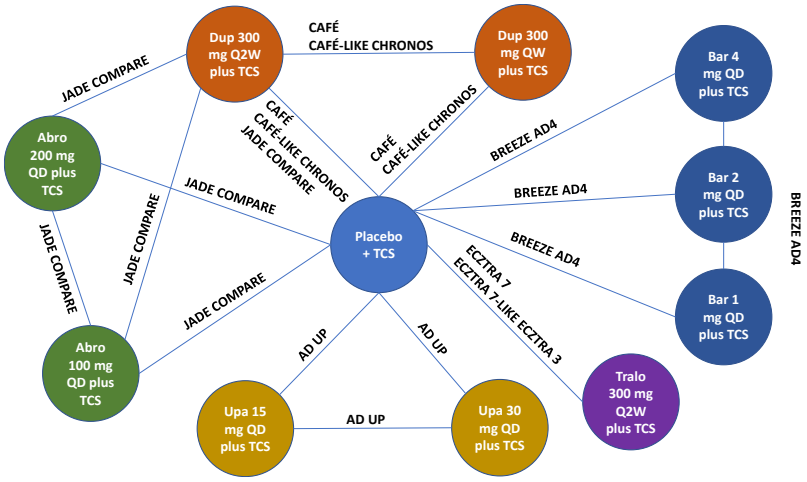
Abbreviations: FE, fixed effect model; RE, random effects model.

EASI 75

The trials contributing to the NMA of combination therapies on EASI 75 in the second line adult population are presented in Figure 8. Unlike some of the networks in this report, this network includes one head-to-head trial of an active intervention versus a comparator (JADE COMPARE, abrocitinib 200 mg and 100 mg versus dupilumab). This is likely to produce different results to a "star shaped" network that relies only on indirect comparisons.

The only available baricitinib data were based on patients requiring rescue medication being considered non-responder and censored from the analysis. These data have informed both the primary analysis, where the data for other therapies are based on using all observed data, regardless of rescue medication use to determine response (except for the abrocitinib trial in which rescue therapy was not allowed), whereas a more consistent dataset informs the rescue therapy sensitivity analysis.

Figure 8. Network plot second line adult population, combination therapy, EASI 75



Abbreviations: Abro, abrocitinib; Bar, baricitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Tralo, tralokinumab; Upa, upadacitinib.

For the NMAs of EASI 75, the RE and FE models for the primary and all sensitivity analyses were similar in terms of goodness of model fit (similar DIC) and residual deviance (Table 19).

The primary analysis showed that treatment with any of the interventions assessed, which for this outcome also included baricitinib 1mg, 2mg or 4mg, led to an improvement in EASI 75 compared with placebo (Table 20). The results versus placebo were statistically significant for abrocitinib 200 mg, dupilumab, and either dose of upadacitinib (15 mg or 30 mg), but not for abrocitinib 100 mg, tralokinumab, or baricitinib 1, 2, or 4 mg. Results from the NMA were broadly in agreement with findings from standard pair-wise analyses. Although, for abrocitinib 200 mg and 100 mg the NMA resulted in a substantially lower ORs, that is, the benefit over placebo was less pronounced compared with the underlying trial data. Also, in contrast to the NMA results, in the pair-wise analyses the comparisons of abrocitinib 100 mg and baricitinib 4mg with placebo were both statistically significant.

For the comparison with dupilumab, there were no comparisons that were statistically significant. Similar to the assessment of the EASI 50 + ΔDLQI ≥4, the largest relative treatment effects favouring the interventions were for upadacitinib 30 mg ([redacted]). However, the relative benefit of upadacitinib 30 mg was substantially smaller when response was assessed as

EASI 75 compared with the composite outcome. The NMA results also indicate that there may be a benefit of treatment with abrocitinib 200 mg over dupilumab, in terms of EASI 75 ([redacted]). The results for abrocitinib 100 mg, upadacitinib 15 mg and tralokinumab were similar for EASI 75 and EASI 50 + ΔDLQI ≥4; a large relative treatment effect favouring dupilumab was observed for tralokinumab ([redacted]) and the OR of upadacitinib 15 mg and abrocitinib 100 mg were closer to 1, favouring dupilumab for both.

Similarly, none of the comparisons versus baricitinib 2mg or 4 mg were statistically significant. Tralokinumab therapy led to a lower EASI 75 response than baricitinib 2 mg and 4 mg ([redacted]), although the difference was smaller than compared with dupilumab. A dose dependent benefit was observed for both upadacitinib and abrocitinib compared with baricitinib 4 mg and 2mg.

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials only had a very limited impact on the comparisons with dupilumab and the comparisons with baricitinib. In this sensitivity analysis, the benefit of dupilumab over tralokinumab was statistically significant ([redacted]). Similarly, there was little impact of the sensitivity analysis based on the generalisable population for abrocitinib; the benefit of dupilumab over tralokinumab reached statistically significance ([redacted]), and the credible intervals for the comparisons of either dose of abrocitinib versus dupilumab or baricitinib narrowed.

Placebo response varied between 8% and 49% in the studies contributing to EASI 75 analysis. However, the models for the baseline risk-adjusted sensitivity analysis did not converge despite attempts to increase convergence by thinning the sampling and increasing the number of model iterations. Therefore, no results are presented for this sensitivity analysis. The lack of convergence could potentially be due to the small number of patients in the abrocitinib trial. However, looking at a larger sample size, such as the ITT population, would not provide results of relevance to the population of interest to this report.

Table 20. Estimates of effect (EASI 75) of second line systemic treatments in combination with TCS in adults at 16 weeks, generated by NMA and standard pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)		
	Primary	Primary	Sensitivity Rescue therapy	Sensitivity Abrocitinib generalisable
Treatments versus placebo				
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Bar 1 mg + TCS	1.40 (0.68 to 2.90)	[redacted]	[redacted]	[redacted]
Bar 2 mg + TCS	1.83 (0.98 to 3.43)	[redacted]	[redacted]	[redacted]
Bar 4 mg + TCS	2.22 (1.11 to 4.44)	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	4.68 (2.86 to 7.65)	[redacted]	[redacted]	[redacted]
Dup 300 mg QW + TCS	3.97 (2.51 to 6.28)	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Treatments versus Bar 4 mg plus TCS				
Abro 200 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Treatments versus Bar 2 mg plus TCS				
Abro 200 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Treatments versus Dup 300 mg every 2 weeks				
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]	[redacted]

Upa 30 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]	[redacted]
Treatment doses versus each other				
Abro 200 mg QD + TCS vs Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS vs Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; Bar, baricitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Table 21. Summary of NMA model characteristics

Characteristic	Primary analysis		Sensitivity analysis			
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population	
	RE	FE	RE	FE	RE	FE
Deviance information criterion	116.5	115.3	108.8	107.4	119.4	118.7
Total residual deviance	17.8	17.8	16.6	16.3	17.9	18.6
Number of data points	18	18	17	17	18	18

Abbreviations: FE, fixed effect model; RE, random effects model.

Quality of life (EQ-5D)

EQ-5D data for people receiving combination therapy for AD in the second line setting were available or provided by the companies for abrocitinib, dupilumab, tralokinumab and upadacitinib. Data were reported as change from baseline, with the exception of upadacitinib, where data were provided at baseline and at week 16. In the upadacitinib and abrocitinib trials, general QoL was captured using EQ-5D-5L, whereas EQ-5D-3L was used in the dupilumab trials.

The results show a larger improvement in EQ-5D from baseline to week 16 (week 12 for abrocitinib) in patients treated with any of the active therapies in combination with TCS than for patients receiving placebo and TCS (Table 22). For upadacitinib and abrocitinib this was irrespective of dose. The results for abrocitinib, are based on the restricted population with low patient numbers in each treatment arm.

Table 22. EQ-5D for adults receiving combination therapy in the second line setting

Trial	Outcome	Trial arm 1	Trial arm 2	Trial arm 3	Trial arm 4
Upadacitinib		Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS	
AD UP – second line	N*	(N=56)	(N=57)	(N=53)	NA
	EQ-5D-5L at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	NA
	EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]	NA
Abrocitinib		Abrocitinib 200 mg QD plus TCS	Abrocitinib 100 mg QD plus TCS	Dupilumab 300 mg Q2W plus TCS	Placebo plus TCS
JADE Compare - restricted	N	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D-5L at Week 12, least square mean	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab		Tralokinumab Q2W plus TCS	Placebo plus TCS		
ECZTRA 3 – ECZTRA 7-like	N	N=119	N=62	NA	NA
	Change from baseline in EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	NA	NA
ECZTRA 7	N	N=138	N=137	NA	NA
	Change from baseline in EQ-5D-5L at Week 16, mean (SD)	[redacted]	[redacted]	NA	NA
Dupilumab		Dupilumab 300mg Q2W + TCS	Dupilumab 300mg QW + TCS	Placebo QW + TCS	
CAFÉ CHRONOS CAFÉ-like	N	130	163	169	NA
	Change from baseline in EQ-5D at Week 16, least square mean (SE)	0.194 (0.0212)	0.195 (0.0185)	0.119 (0.0187)	NA

Abbreviations: NA, not applicable; Q2W, every 2 weeks; QD, once daily; SD, standard deviation, SE, standard error; TCS topical corticosteroid; Upa, upadacitinib.

*N contributing to the data at week 16

Use of rescue medication

Data on the use of rescue therapy for each of the treatments used in combination with TCS in the second line setting were provided by the company for upadacitinib (AD UP) and for tralokinumab (ECZTRA 3 and ECZTRA 7). Data on the use of rescue medication needed with dupilumab combination therapy were available from CHRONOS and CAFE but for the full trial population for CHRONOS rather than the subgroup of patients treated in the second line setting.

The use of rescue medication was markedly reduced in patients receiving active treatment (dupilumab, tralokinumab or upadacitinib) compared with placebo (Table 23). The only exception was ECZTRA 1, in which a similar proportion of patients received rescue therapy in the tralokinumab and placebo arms of the trial. The proportion of people treated with upadacitinib as a second line monotherapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg.

TCS was the most common form of rescue medication in the dupilumab, tralokinumab and upadacitinib trials. In the dupilumab trial CHRONOS this was followed by systemic corticosteroids. In all other combination therapy trials the rates of other types of rescue therapy were low.

Table 23. Use of rescue medication during the double-blind period for adults treated with combination therapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)			
Upadacitinib trials	Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS
AD UP	(N=57)	(N=58)	(N=55)
	[redacted]	[redacted]	[redacted]
Dupilumab trials	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo QW + TCS
CHRONOS	N=106	N=319	N=315
	17 (16.0%)	64 (20.1%)	167 (53.0%)
Cafe	(N=107)	(N=110)	(N=108)
	4 (3.7%)	5 (4.5%)	19 (17.6%)
Tralokinumab trials	Tralokinumab Q2W plus TCS	Placebo plus TCS	
ECZTRA 3	(N=119)	(N=62)	NA
	[redacted]	[redacted]	NA
ECZTRA 7	(N=138)	(N=137)	NA
	[redacted]	[redacted]	NA

Abbreviations: NA, not applicable; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Number of days free from TCS during treatment

In the restricted subgroup of JADE COMPARE, the number of days free from TCS during treatment varied; patients in the dupilumab arm had [redacted] placebo, abrocitinib 200 mg and lastly abrocitinib 100mg (Table 24). In the generalisable population [redacted] abrocitinib 200 mg, [redacted] dupilumab and [redacted] abrocitinib 100mg and placebo, [redacted]

Tralokinumab and upadacitinib therapy [redacted]. Data on the number of days free from TCS during treatment were not reported for dupilumab and baricitinib in TA534 and TA681, respectively.

Table 24. Number of days free from TCS during the double-blind period for adult treated with combination therapy in the second line setting

Trial	Trial arm 1	Trial arm 2	Trial arm 3	Trial arm 4
Upadacitinib trial	Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS	
AD UP	(N=57)	(N=58)	(N=55)	NA
All observed analysis Mean (95% CI)	[redacted]	[redacted]	[redacted]	NA
Abrocitinib trial JADE COMPARE*	Abrocitinib 200 mg QD plus TCS	Abrocitinib 100 mg QD plus TCS	Dupilumab 300 mg Q2W plus TCS	Placebo plus TCS
Generalisable	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Restricted	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab trials	Tralokinumab Q2W	Placebo		
ECZTRA 7 Mean (SE)	[redacted]	[redacted]	NA	NA
ECZTRA-7 like ECZTRA-3 Mean (SE)	[redacted]	[redacted]	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

4.2.2.4 Adolescents

The companies for abrocitinib and upadacitinib are seeking a recommendation by NICE for the use of their drugs for the treatment of AD in adolescents. Of the treatment options for AD available in the NHS, baricitinib does not hold a marketing authorisation for use in adolescents and CsA is only for people aged 16 years and over, and is thereby not available for a large proportion of the adolescent population. Thus, neither baricitinib nor CsA is a relevant comparator for treatment of adolescents. Additionally, although dupilumab has only been assessed and recommended by NICE for an adult population, its marketing authorisation encompasses adolescents, and dupilumab is funded for use in adolescents under the NHS England Medicines for Children Policy as part of specialised commissioning.[119] An adolescent is eligible for treatment with dupilumab if they are seen within a specialised treatment centre and they meet the criteria set out within TA534, for use of dupilumab in adults.[119] Dupilumab is therefore the key comparator for the adolescent population.

NMA

Trial evidence was available for the use of upadacitinib and abrocitinib both as monotherapies (JADE MONO 1 and 2, MEASURE UP 1 and 2) and in combination with TCS (JADE TEEN and AD UP) in the adolescent population. However, comparator data for dupilumab were only identified as a monotherapy (AD ADOL) but no trial was identified assessing dupilumab in combination with TCS in an adolescent population. An NMA assessing abrocitinib and upadacitinib versus dupilumab, all in combination with TCS, was therefore not possible, but the results of the combination therapy trials for abrocitinib and upadacitinib are presented alongside the monotherapy NMA results below for completeness.

Data on the composite outcome EASI 50 + DLQI ≥4 was not presented in the dupilumab trial (AD ADOL) and therefore only EASI 75 could be assessed for this population.

The abrocitinib trials did not allow use of rescue medications, whereas the dupilumab and upadacitinib trials included in the NMA for the adolescent population did. However, the dupilumab trial only reported results where patients were censored if/when they received rescue therapy. So,

the primary analysis for the NMA in the adolescent population is based on upadacitinib data where patients were included in the analysis even if they required rescue medication, dupilumab data where patients were censored when they received rescue medication and abrocitinib data where patients did not receive rescue medication. A sensitivity analysis was conducted using upadacitinib data where patients were censored when receiving rescue medication, similar to the dupilumab study.

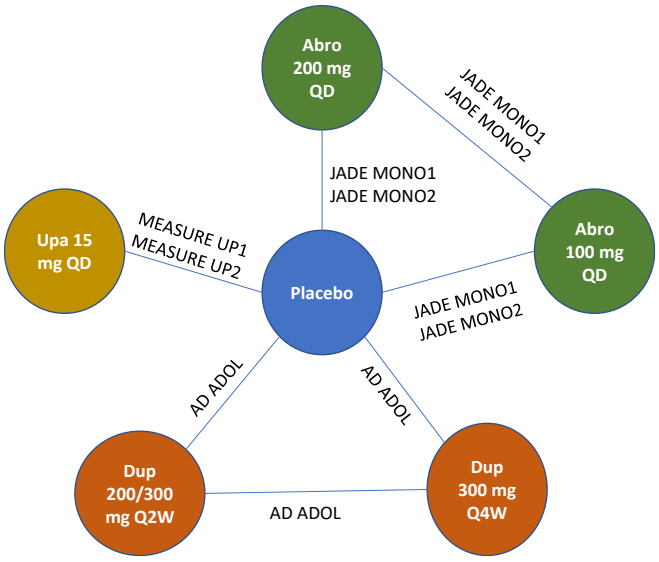
Due to variation in the placebo response between the trials included in the analysis, a sensitivity analysis adjusting for heterogeneity in placebo response was also conducted.

The NMA results are focused on the doses of the interventions recommended for adolescents, which are abrocitinib 100 and 200 mg and upadacitinib 15 mg.

EASI 75

The network of trials contributing to the NMA in the adolescent population are presented in Figure 9.

Figure 9. Network plot adolescent population, monotherapy, EASI 75



Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; Q4W, every 4 weeks; Upa, upadacitinib.

For the NMA in the adolescent population, the FE and RE models of the primary and sensitivity analyses were similar in terms of goodness of model fit (similar DIC, Table 26), but the residual deviance for the RE models were closer to the number of unconstrained data points in all analyses, which reinforces the EAG's preference for the RE model.

The primary analysis shows that treatment with abrocitinib (either dose), dupilumab, or upadacitinib 15 mg were associated with a statistically significant improvement in EASI 75 compared with placebo (Table 25). Results from the NMA were in agreement with findings from standard pair-wise analyses for each of the trial, in which all interventions analysed were found to be statistically significantly more effective than placebo. Although, for abrocitinib 200 mg and 100 mg, the NMA resulted in substantially higher ORs compared with the underlying trial data.

When compared with dupilumab, treatment with abrocitinib 200 mg (OR vs dupilumab [redacted]),abrocitinib 100 mg (OR vs dupilumab [redacted]) and upadacitinib 15 mg (OR vs dupilumab [redacted]) were all more effective than dupilumab. Although, these comparisons were not statistically significant.

Censoring patients receiving rescue therapy in the dupilumab and upadacitinib trials led to relatively similar ORs compared with the primary analysis and no statistically significant difference compared with dupilumab.

Placebo response varied from 0% to 22% in the studies contributing to the analysis for the adolescent population. The DIC for the sensitivity analysis adjusting for heterogeneity in placebo response, was markedly lower than the DIC for the primary analysis, indicating a better fitting model. However, similar to the sensitivity analysis conducted for the second-line adult monotherapy analysis, residual deviance for this NMA was lower than the number of data points used in the analysis, potentially indicating "overfitting" to the underlying data used in the model. As such, due to concerns around generalisability of the results of the sensitivity analysis, the NMAs based on the observed data were preferred to inform the cost effectiveness analyses. However, the results of the placebo response adjustment are presented in Appendix 10.5.

Table 25. Estimates of effect (EASI 75) of systemic monotherapies in adolescents at 16 weeks, generated by NMA (RE) and standard pair-wise meta-analysis

Comparison	Pair-wise analysis OR (95% CI)	NMA OR (95% CrI)	
	Primary	Primary	Sensitivity Rescue therapy
Treatments versus placebo			
Abro 200 mg QD	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	[redacted]	[redacted]	[redacted]
Dup 200 mg or 300 mg every 2 weeks	7.89 (3.24 to 19.21)	[redacted]	[redacted]
Upa 15	[redacted]	[redacted]	[redacted]
Treatments versus Dup 200 mg or 300 mg every 2 weeks			
Abro 200 mg QD	NA	[redacted]	[redacted]
Abro 100 mg QD	NA	[redacted]	[redacted]
Upa 15	NA	[redacted]	[redacted]
Treatments versus Abro 100 mg QD			
Abro 200 mg QD	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; QD, once daily; Upa, upadacitinib.

Table 26. Summary of NMA model characteristics

Characteristic	Primary analysis		Sensitivity analysis		
			Censoring of patients receiving rescue therapy		Placebo risk adjustment
	RE	FE	RE	FE	RE
Deviance information criterion	81.94	82.92	79.33	78.92	57.03
Total residual deviance	17.2	20.0	15.6	16.3	13.9
Number of data points	15	15	15	15	15

Abbreviations: FE, fixed effect model; RE, random effects model.

No data were identified on dupilumab used with concomitant TCS in an adolescent population. Therefore, a NMA comparing upadacitinib and abrocitinib with dupilumab, all in combination with TCS, was not possible. However, data on the efficacy of upadacitinib and abrocitinib in combination with TCS and compared with placebo in adolescents were available and presented for completeness (Table 27). The results showed that both upadacitinib and abrocitinib with TCS are statistically significantly more effective than placebo with TCS, in terms of EASI 75. However, the relative benefit

over placebo was substantially smaller when the interventions were used in combination with TCS than as monotherapies.

Table 27. Estimates of EASI 75 for upadacitinib in combination with TCS in adolescents at 16 weeks, generated by standard pair-wise meta-analysis

Outcome	Upa 15 mg QD + TCS vs placebo OR (95% CI)	Abro 200 mg QD + TCS vs placebo OR (95% CI)	Abro 100 mg QD + TCS vs placebo OR (95% CI)
EASI 75	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; EASI, Eczema Area and Severity Index; OR, odds ratio; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Quality of life (EQ-5D)

EQ-5D-5L data for adolescents receiving monotherapy or combination therapy for AD were provided by the companies for abrocitinib and upadacitinib. Data were reported as change from baseline to week 12 for abrocitinib and at baseline and week 16 separately for upadacitinib.

The results show a larger improvement in EQ-5D from baseline to week 12/16 in patients treated with upadacitinib or abrocitinib than for patients receiving placebo, irrespective of dose or if used as a monotherapy or in combination with TCS (Table 28). The results for abrocitinib are based on the full adolescent trial populations. Therefore, the number of patients in the analyses was not as low as for some of the other populations.

Table 28. EQ-5D for adolescents receiving monotherapy or combination therapy

Upadacitinib				
Monotherapy		Upa 30 mg QD	Upa 15 mg QD	Placebo
Measure UP 1	N	(N=42)	(N=42)	(N=40)
	EQ-5D at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Measure UP 2	N	(N=35)	(N=33)	(N=36)
	EQ-5D at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]
Combination therapy		Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS
AD UP	N	(N=37)	(N=39)	(N=40)
	EQ-5D at baseline, mean (SD)	[redacted]	[redacted]	[redacted]
	EQ-5D at Week 16, mean (SD)	[redacted]	[redacted]	[redacted]

Abrocitinib				
Monotherapy		Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo
JADE MONO1	N	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D at Week 12, least square mean	[redacted]	[redacted]	[redacted]
JADE MONO2	N	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D at Week 12, least square mean	[redacted]	[redacted]	[redacted]
Combination therapy		Abrocitinib 200 mg QD plus TCS	Abrocitinib 100 mg QD plus TCS	Placebo plus TCS
JADE TEEN	N	[redacted]	[redacted]	[redacted]
	Change from baseline in EQ-5D at Week 12, least square mean	[redacted]	[redacted]	[redacted]

Abbreviations: SD, standard deviation; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

Use of rescue medication

Rescue therapy was not permitted in the abrocitinib trials, including JADE MONO 1, JADE MONO 2, and JADE TEEN.

The proportion of people treated with upadacitinib requiring use of rescue therapy during the first 16 weeks of treatment were dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg. The rates were relatively similar for upadacitinib used as a monotherapy (Measure UP 1 and Measure UP 2) and combination therapy (AD UP), whereas patients given placebo as a monotherapy received substantially more rescue therapy than people given placebo with concomitant TCS. That is, the difference in use of rescue medication between upadacitinib and placebo was substantially higher in the monotherapy trials (Measure UP 1 and Measure UP 2) than in the combination therapy trial (AD UP).

The allowed rescue therapy was the same for the monotherapy and combination therapy upadacitinib trials; the first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. In AD UP, patients requiring rescue therapy mainly received high potency TCS. In Measure UP 1 and 2, where a larger proportion required rescue therapy, especially in the placebo

arms, the most frequently used types of rescue therapy included TCS of varying potency (low, medium or high) and non-biologic systemic treatments.

Dupilumab data in the adolescent population were only available from AD ADOL, where dupilumab was used as a monotherapy. Similar to the data for upadacitinib, AD ADOL showed that a substantially smaller proportion of patients treated with dupilumab needed to use rescue medication compared with placebo.

Table 29. Use of rescue medication during the double-blind period for adults treated with combination therapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)			
Upadacitinib trials	Upa 30 mg QD	Upa 15 mg QD	Placebo
Measure UP 1	(N=42)	(N=42)	(N=40)
	[redacted]	[redacted]	[redacted]
Measure UP 2	(N=35)	(N=33)	(N=36)
	[redacted]	[redacted]	[redacted]
AD UP	(N=37)	(N=39)	(N=40)
	[redacted]	[redacted]	[redacted]
Dupilumab trials	Dupilumab 200/300 Q2W	Dupilumab 300 Q4W	Placebo
AD ADOL	82	84	85
	17 (20.7)	27 (32.1%)	50 (58.8)

Abbreviations: Q2W, every 2 weeks; Q4W, once every four weeks; QD, once daily; Upa, upadacitinib.

Number of days free from TCS during treatment

Data on the number of days free from TCS during treatment were reported for JADE TEEN and for the adolescent population of AD UP in which abrocitinib and upadacitinib, respectively, were used in combination with TCS. In the adolescent subgroup of AD UP, upadacitinib therapy [redacted] in JADE TEEN, abrocitinib therapy [redacted] (Table 30).

Table 30. Number of days free from TCS during the double-blind period for adolescents

Trial	Trial arm 1	Trial arm 2	Trial arm 3
Upadacitinib trials	Upa 30 mg QD +TCS	Upa 15 mg QD +TCS	Placebo plus TCS

AD UP Mean (95% CI)	N=37 [redacted]	N=39 [redacted]	N=40 [redacted]
Abrocitinib trials	Abrocitinib 200 mg QD plus TCS	Abrocitinib 100 mg QD plus TCS	Placebo plus TCS (N=96)
JADE TEEN Mean	82 [redacted]	88 [redacted]	82 [redacted]

Abbreviations: QD, once daily; TCS, topical corticosteroid, Upa, upadacitinib.

4.2.2.5 Safety

The safety of the interventions and comparators during treatment up to 16 weeks, are reported for the full trial populations and not separated by line of therapy. The EAG has focused on serious adverse events (SAE) and on specific adverse events (irrespective of severity) in line with those included in TA534 and TA681; injection site reaction (for dupilumab and tralokinumab), conjunctivitis and allergic conjunctivitis, upper respiratory tract infections, acne, and oral herpes.

These are not necessarily the most common adverse events for each of the treatments, but each has been found to be associated with at least one of the treatments and were considered the most important to include by the EAG's clinical experts.

In terms of both SAE and the specific adverse events of any severity, the numbers were generally small, indicating that short-term use of these interventions, as monotherapy and in combination with TCS, were well tolerated. The results are therefore not discussed separately for monotherapy and combination therapy, or for adults and adolescents. AE data from individual studies are provided in Appendix 10.3.1.

Abrocitinib

The short-term data (16 weeks) showed a dose-related increase in acne events with abrocitinib compared with placebo,

[redacted]

[redacted]

Tralokinumab

The overall frequency of SAEs during randomised treatment (16 weeks) was low, with slightly lower incidence with tralokinumab compared with placebo. Among the most frequent AEs in the initial treatment period were URTI, conjunctivitis (allergic and infectious), and injection-site reactions. The results of the trials indicate that tralokinumab therapy is associated with higher rates of conjunctivitis and of injection-site reactions than patients who received placebo, and potentially with a lower rate of oral herpes than placebo. There was no consistent trend across studies towards URTI being more common among patients treated with tralokinumab (± TCS) than among those receiving placebo.

Upadacitinib

Upadacitinib therapy was associated with slightly higher rates of [redacted] compared with placebo. The company for upadacitinib reports that there is a reasonable possibility that these AEs are related to upadacitinib treatment. The overall frequency of SAEs during randomised treatment (16 weeks) was low and relatively even between upadacitinib and placebo.

Dupilumab

There appeared to be increased rates of conjunctivitis and allergic conjunctivitis with dupilumab compared with placebo. Dupilumab therapy was also associated with higher rates of injection-site reactions compared with placebo. The rates of SAEs were slightly lower with dupilumab than placebo across the dupilumab trials.

Baricitinib

In the company submission it is reported that the rates of SAEs were lower with baricitinib 4 mg than with placebo across most BREEZE-AD trials. Some unredacted data are only available for BREEZE-AD 4 and BREEZE-AD 7, both of which had low numbers of SAEs, and for BREEZE-AD 4 the number was lower with baricitinib than placebo.

4.2.2.6 Subgroup by skin colour

In the full-text publications identified by the EAG, clinical effectiveness of interventions that are the focus of the MTA was not reported by racial subgroup. One publication was identified,[45] which was cited as a related publication (Table 4), that reported clinical effectiveness of dupilumab by racial subgroup, as self-reported by the patient, based on evidence derived from three RCTs (SOLO-1, SOLO-2, and CHRONOS). The racial subgroups considered, from a total number of 2,058 people enrolled across the studies, were White (1,429 [69.4%]), Asian (501 [24.3%]) and Black/African American (128 [6.2%]). The authors reported that baseline demographics and disease characteristics were generally well balanced across treatment groups and among racial subgroups. The authors focused on mean change from baseline for the outcomes assessed, commenting that continuous outcomes are the most sensitive for subgroup analyses. Across the cohorts, dupilumab 300 mg Q2W, with or without TCS, statistically significantly improved mean change (least squares) in EASI score from baseline:[45]

- White: -25.35 (standard error [SE] 0.69) with dupilumab versus -14.91 (SE 0.70) with placebo, p <0.0001;
- Asian: -24.23 (standard error [SE] 1.62) with dupilumab versus -10.97 (SE 1.66) with placebo, p <0.0001;
- Black/African/American: -20.02 (standard error [SE] 2.72) with dupilumab versus -11.88 (SE 1.95) with placebo, p=0.0161.

Clinical improvements were noted for other measures of the signs and symptoms of AD for the White and Asian cohorts, including IGA, POEM, Peak Pruritus NRS, and DLQI, with differences between dupilumab 300 mg Q2W and placebo reaching statistical significance for all outcomes. Level of improvement was reported to be comparable to that achieved for the full trial populations of SOLO-1, SOLO-2 and CHRONOS. For the Black/African American racial subgroup, dupilumab 300 mg Q2W was associated with a statistically significant improvement over placebo for only weekly Peak Pruritus NRS, DLQI, and POEM, in addition to EASI 75. Effectiveness of dupilumab 300 mg QW was also evaluated. Dupilumab 300 mg QW was associated with statistically significant improvements over placebo in most outcomes evaluated for the three cohorts. The authors commented that results for the Black/African American cohort be interpretated with caution due to the small sample size informing the analysis. Overall, the authors considered dupilumab to be clinically effective in treating AD, irrespective of racial subgroup.

4.3 Discussion

4.3.1 Summary of key results

The comparative clinical effectiveness of abrocitinib, tralokinumab and upadacitinib at their recommended dose or doses, both as monotherapy and in combination with TCS, versus treatment options available in the NHS for moderate-to-severe AD, was evaluated in the positions in the treatment pathway proposed by the individual companies.

Due to a lack of data for some interventions for EASI 50 + ΔDLQI ≥4, which is the primary outcome of interest to the MTA, the EAG also evaluated clinical effectiveness in achieving EASI 75. Estimates of comparative clinical effectiveness for abrocitinib, tralokinumab and upadacitinib versus treatment options available in the NHS were derived from NMAs as direct evidence for these comparisons was limited: some studies included dupilumab as an active comparator, but only as monotherapy.

Experts advising the EAG commented that, in clinical practice for the management of AD, all systemic therapies are likely to be used in combination with TCS rather than as monotherapies. However, monotherapy will still be relevant for a proportion of patients who cannot tolerate or do not want to use TCSs. Although comparisons of relevant treatments in combination with TCS are of most importance to this MTA, comparisons of monotherapies were explored for all populations, where possible. The EAG's primary analyses are based on using all observed data, regardless of rescue medication as receipt of rescue therapy more closely reflects clinical practice in England.

Experts advising the EAG commented that, in clinical practice for the management of AD in adults, abrocitinib, tralokinumab and upadacitinib are likely to be used as alternatives to dupilumab and baricitinib, which are NICE-recommended treatment options after inadequate response, inability to tolerate, or contraindication to first-line systemic therapy.

For the NMAs there were considerable amounts of uncertainty and the vast majority of results were not statistically significant. However, there were consistent trends across the outcomes (EASI 50 + ΔDLQI ≥4 and EASI 75), interventions (combination therapy or monotherapy), and populations (adults in the first- or second line setting, and adolescents) which are summarised below.

Abrocitinib

The NMA results indicate that treatment of adults in the second line setting with abrocitinib 200 mg leads to a better response, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than dupilumab

treatment. The benefit in favour of abrocitinib 200 mg was larger when both treatments were used as monotherapies (EASI 50 + ΔDLQI ≥4, [redacted], EASI 75, [redacted]) and less pronounced when used in combination with TCS (EASI 50 + ΔDLQI ≥4, [redacted], EASI 75, [redacted]). The effect was also greater when response was assessed as EASI 75 compared with when assessed as EASI 50 + ΔDLQI ≥4. The effectiveness of abrocitinib was dose dependent. As for abrocitinib 200 mg, the benefit of abrocitinib 100 mg compared with dupilumab was greatest for adults in the second line setting using both treatments as monotherapies and when assessing response as EASI 75 ([redacted]). The effectiveness of abrocitinib 100 mg compared with dupilumab favoured dupilumab when the two treatments were used in combination with TCS (assessed as EASI 50 + ΔDLQI ≥4 [[redacted]], or EASI 75 [[redacted]]). The effectiveness of abrocitinib 100 mg and dupilumab was similar to dupilumab when used as monotherapies and response assessed as EASI 50 + ΔDLQI ≥4 ([redacted]). Abrocitinib 200 mg and 100 mg with concomitant TCS were both more effective than baricitinib 4 mg with TCS in terms of EASI 75 (abrocitinib 200 mg [redacted]), abrocitinib 100 mg [redacted]) for adults in the second line setting and in the adolescent population both doses of abrocitinib were more effective than dupilumab, also in terms of EASI 75 (abrocitinib 200 mg [redacted]), abrocitinib 100 mg [redacted]).

Rescue therapy was not permitted in the abrocitinib trials, unlike the trials for the other interventions included in the MTA. However, the use of systemic rescue therapy was low in the studies for the interventions where it was allowed. The lack of rescue therapy may lead to lower absolute response rates (in all trial arms) in the abrocitinib trials compared with clinical practice. However, it is unclear how the lack of rescue therapy may affect the relative treatment effect and therefore what impact the difference in rescue therapy has had on the results of the primary analysis. Sensitivity analysis censoring patient who needed rescue therapy in the trials informing the other interventions in the networks (dupilumab, tralokinumab, and upadacitinib) had limited impact on the effectiveness of abrocitinib (either dose) on EASI 75 in the adolescent population and on EASI 50 + ΔDLQI ≥4 or EASI 75 in the adult population when all treatments given in combination with TCS in the second line setting. However, for adults given the treatments as monotherapies in the second

line setting, the effectiveness of abrocitinib versus dupilumab (assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75) decreased substantially when patients receiving rescue therapy were censored.

The restricted population, which was used for the primary analysis of adults in the second line setting, is in line with the populations used for dupilumab and baricitinib, however, it constituted a very small proportion of the abrocitinib trial populations and hence there is substantial uncertainty around the assessment of abrocitinib. The sensitivity analysis based on expanding the population receiving abrocitinib from those receiving only CsA as the first systemic therapy (restricted population) to include those who had received any type of systemic therapy at first-line (generalisable population), was also uncertain and the 95% CrIs were wide, partly because the sample size of the generalisable population was still small. The sensitivity analysis gave similar results to the primary analysis for the composite outcome and EASI 75 for abrocitinib used in combination with TCS and for abrocitinib monotherapy when response was assessed as EASI 50 + ΔDLQI ≥4. However, for EASI 75 the benefit of abrocitinib monotherapy compared with dupilumab monotherapy was substantially reduced, favouring dupilumab over abrocitinib 100 mg but still favouring abrocitinib 200 mg over dupilumab.

Tralokinumab

The NMA results indicate that treatment of adults in the second line setting with tralokinumab leads to a better response treatment, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than placebo but an inferior response to dupilumab treatment and baricitinib 4 mg treatment (only available for EASI 75). The benefit in favour of dupilumab over tralokinumab was larger when both treatments were used in combination with TCS (EASI 50 + ΔDLQI ≥4 [redacted], EASI 75 [redacted]) and less pronounced when used as monotherapies (EASI 50 + ΔDLQI ≥4 [redacted], EASI 75 [redacted]). Sensitivity analysis censoring patient who required rescue therapy in the dupilumab, tralokinumab and upadacitinib trials informing the networks had limited impact on the effectiveness of tralokinumab compared with dupilumab or baricitinib on EASI 50 + ΔDLQI ≥4 or EASI 75 in the adult population when all treatments given in combination with TCS or as monotherapies in the second line setting.

Upadacitinib

The NMA results indicate that treatment of adults in the second line setting with upadacitinib 30 mg is more effective than dupilumab treatment when assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75. The benefit in favour of upadacitinib 30 mg over dupilumab was relatively similar for EASI 50 + ΔDLQI ≥4 ([redacted]) or EASI 75 ([redacted]) when both treatments were used as monotherapies. For upadacitinib 30 mg treatment in combination with TCS the benefit over dupilumab was substantially larger when response was assessed as EASI 50 + ΔDLQI ≥4 ([redacted]), and smaller when assessed as EASI 75 ([redacted]), compared with the results for upadacitinib 30 mg as a monotherapy.

The effectiveness of upadacitinib was dose dependent with upadacitinib 15 mg consistently being less effective than upadacitinib 30 mg. Compared with dupilumab, upadacitinib 15 mg was more effective than dupilumab when both were given as monotherapies (assessed as EASI 50 + ΔDLQI ≥4, [redacted], or EASI 75[redacted]) but broadly similar effectiveness or even favouring dupilumab when given in combination with TCS (EASI 50 + ΔDLQI ≥4, [redacted], or EASI 75[redacted]). Upadacitinib 30 mg and 15 mg were both more effective than baricitinib 4 mg in terms of EASI 75 for adults in the second line setting (upadacitinib 30 mg [redacted], upadacitinib 15 mg [redacted]) and more effective than CsA for adults in the first line setting (upadacitinib 30 mg [redacted], upadacitinib 15 mg [redacted]). In the adolescent population upadacitinib 15 mg was also more effective than dupilumab ([redacted]26), also in terms of EASI 75.

Sensitivity analysis censoring patient who required rescue therapy in the dupilumab, tralokinumab and upadacitinib trials informing the networks had limited impact on the effectiveness of upadacitinib 30 mg and 15 mg compared with dupilumab, irrespective of outcome (EASI 50 + ΔDLQI ≥4 or EASI 75), population (first- or second line adults or adolescent population), and if used as monotherapy or in combination with TCS. However, for the NMA of treatments in combination with TCS, the results for EASI 50 + ΔDLQI ≥4 differed substantially between the primary analysis and the sensitivity analysis censoring patients who received rescue therapy.

Placebo response

For all but the network for the first line adult population, there was relatively large variability in placebo response for the treatments in each network. This indicates that there may be imbalances in prognostic factors, treatment effect modifiers or differences in the conduct between the trials. If the difference is due to imbalance in treatment effect modifiers this can have an impact on the relative efficacy of the treatments. All companies explored the impact of differences in baseline risk (placebo response) on the results of their NMAs. However, the results of the baseline-risk adjustment analyses did not inform the base case for any of the interventions. The EAG also attempted to adjust for heterogeneity in placebo response rates, however, this was not possible for all networks and outcomes. Models assessed either did not converge on the posterior distribution or were considered by the EAG to overfit the underlying data. The EAG is concerned that the results produced are unreliable for use in the cost effectiveness analyses and, in keeping with the companies approach, the EAG considers the analyses based on the observed data to be the most appropriate to inform the cost effectiveness analyses.

Other outcomes

Quality of life measured using EQ-5D, showed that treatment with abrocitinib, tralokinumab and upadacitinib for 12 to 16 weeks leads to an improvement in general quality of life compared with placebo irrespective of dose, concomitant TCS or place in the treatment pathway (for adolescents, as a first-line or second-line systemic treatment for adults). The size of the benefit varied and, although based on direct evidence, there was substantial uncertainty around the results.

As mentioned previously rescue medication wasn't allowed in the abrocitinib trials but for tralokinumab and upadacitinib use of rescue medication was lower than for patients given placebo. Use of rescue medication was also lower when tralokinumab and upadacitinib were used in combination with TCS compared to when used as monotherapies.

The trials assessing abrocitinib, tralokinumab and upadacitinib with concomitant TCS, generally showed a higher number of days free from TCS with active therapy compared with placebo. The exception was for the restricted population for abrocitinib where the patient numbers were very low.

The incidence of both serious adverse events (SAE) and specific adverse events (injection site reaction, conjunctivitis, upper respiratory tract infections, acne, and oral herpes) of any severity

were generally low, indicating that short-term use of these interventions, as monotherapy and in combination with TCS, were well tolerated.

4.3.2 Generalisability

Clinical experts advising the EAG commented that, based on baseline EASI scores, the patients enrolled in the RCTs identified as relevant to the MTA have more severe AD than would typically be seen in clinical practice, with most patients presenting with disease in clinical practice categorised as moderate severity. No analysis was possible to explore potential differences in effectiveness of abrocitinib, tralokinumab and upadacitinib based on disease severity. As such, the efficacy of these interventions seen in patients with more severe AD in the clinical trials may be different to the effect in patients with more moderate AD in clinical practice.

Evidence informing the NMAs is predominantly derived from *post hoc* subgroups for the populations relevant to the MTA. As discussed in Section 4.3.3, there are limitations associated with using *post hoc* subgroups that have an impact on the robustness of the results from the NMA.

For adults, the *post hoc* subgroups informing the EAG's preferred analyses for second-line systemic treatment are clinically homogenous in terms of people having inadequate response to, not being able to tolerate, or being contraindicated to CsA, and in line with the population underpinning the recommendation for baricitinib and dupilumab. Both dupilumab and baricitinib are recommended by NICE for patients whose disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable. While the populations analysed in the MTA represent a subgroup of the population likely to be treated in clinical practice they are "equally" representative of the populations used for decision making with dupilumab and baricitinib.

For the analysis of first-line systemic treatment, data for upadacitinib informing the NMA were supplied by the company in response to a request from the EAG for data on the subgroup of adults who were naïve to systemic therapy in the relevant studies. Thus, the EAG considers the population to be generalisable to the patient population who would likely be eligible for first-line treatment. However, the population informing the comparator, CsA, was not limited to those who were naïve to systemic therapy. It is unclear how this difference in the populations may affect the results of the analysis and the generalisability of the results to the systemic naïve patients in clinical practice.

For adolescents, the EAG considers the populations enrolled in the various studies to be generalisable to the adolescents in England who would likely be eligible for treatment with abrocitinib or upadacitinib. However, the EAG notes that comparisons with dupilumab were only possible for abrocitinib and upadacitinib monotherapy, whereas both treatments are likely to be used in combination with TCS by the majority of adolescents. Based on the results of the adult populations, it is possible that both upadacitinib and abrocitinib will be more efficient when used in combination with TCS than when used as monotherapies also for adolescents.

4.3.3 Strengths and limitations

A strength of the MTA is that a systematic literature review has been carried out to identify the relevant evidence. The systematic review was carried out in line with established methods and principles. The RCTs identified by the EAG as relevant to the MTA were considered to be well-designed and well-conducted, and, generally, at a low-risk of bias. However, only two RCTs provided direct evidence for a single population of interest to the MTA, with most RCTs predominantly including mixed populations of people with moderate-to-severe AD. Some studies comprised both adolescents and adults, as well as a combination of people receiving systemic therapy as a first-line or second-line regimen. Thus, data informing the NMAs for the populations and outcomes of interest to the MTA are primarily derived from *post hoc* subgroups, which introduces bias and uncertainty around the results generated by the NMAs, and is a considerable limitation that impacts on the robustness and confidence in the estimates of effect for clinical effectiveness. Use of *post hoc* subgroups reduces the sample size for analysis and also breaks the randomisation component of an RCT. While breaking randomisation can cause an imbalance in observed baseline characteristics these were not apparent to the EAG based on the information supplied by the companies (Appendix 10.3.1). However, there remains the potential imbalances in the unobserved baseline characteristics.

However, the strength of the analyses is that the populations informing the comparison in the second line setting are clinically homogenous in terms of people having inadequate response to, not being able to tolerate, or being contraindicated to CsA.

Methodological heterogeneity between the trials in the networks is likely to have contributed to the uncertainty in the results. Sources of methodological heterogeneity included variation across studies in the use of a washout period for TCS before randomisation to treatment, the type and potency of concomitant TCS used in studies evaluating treatment in combination with TCS, and the type and potency of rescue medication used. These differences, especially the disparity in use of and potency

of rescue therapy used across studies, may lead to clinical heterogeneity in observed placebo response, which, consequently, may introduce bias and uncertainty into the NMA. Although variation was observed in the placebo response across several of the networks, sensitivity analysis adjusting for differences in placebo response was either not possible (due to lack of convergence) or the data were overfitted. Therefore, the unadjusted analyses were used to inform the economic model. The disparity in data available for the primary analysis and sensitivity analysis based on censoring of patients who needed rescue therapy is also likely to have introduced some bias in the results. However, despite the lack of consistency in the available data for some of the analyses, the difference between the primary analysis and the rescue therapy sensitivity analysis was small for the majority of comparisons.

The EAG considers it important to note that the sample sizes informing the NMAs equate to a small proportion of the overall trial populations from which the subgroups are created, particularly for abrocitinib. The effect of small sample size on the results of the NMA is apparent in the wide 95% CrIs, which indicate considerable uncertainty around the true estimate of comparative effectiveness.

In addition to most of the data informing the NMAs being derived from *post hoc* subgroups, the EAG notes that much of the data for baricitinib were unavailable at the time of writing. Results for studies evaluating baricitinib are not yet published in peer reviewed journals and data submitted to the STA process were redacted from the committee papers accompanying the recommendation by NICE. Lack of data for baricitinib on clinical outcomes of interest to the MTA precluded inclusion of baricitinib in most of the relevant NMAs. Additionally, no randomised evidence was identified to inform the efficacy of CsA, which is the relevant comparator in the first-line setting. Thus, results for the comparison with upadacitinib in the first-line setting are derived from observational data, which is associated with the bias inherent in observational studies and the results should be interpreted with caution.

Another limitation of the MTA are the data gaps; for the adolescent population and the adult population in the first-line setting data to inform only EASI 75 could be assessed as data on EASI 50 + ΔDLQI ≥4 were not available. In addition, for the adolescent population relevant comparisons could only be made for abrocitinib and upadacitinib as monotherapies although the interventions are likely to be primarily used with concomitant TCS in clinical practice.

The analyses in this MTA focused on the efficacy and safety of patients after 12 to 16 weeks of treatment. 16 weeks is the timepoint when response, in terms of EASI 50 + ΔDLQI ≥4, is evaluated for dupilumab and baricitinib to determine if treatment should be continued or stopped. However, the EAG notes that longer term follow-up data for efficacy and safety of these treatments is important and that it is lacking for most of them. It is therefore unclear if the level of response seen in the data will be maintained after 16 weeks.

5 Assessment of cost-effectiveness

5.1 Systematic review of existing cost-effectiveness evidence

5.1.1 Methods

A systematic literature review (SLR) was undertaken in July 2021 to identify published economic evaluations of biologic treatments of moderate-to-severely active atopic dermatitis (AD). A separate search was conducted to identify studies reporting health-related quality of life (HRQoL) data in patients with moderate-to-severely active AD.

Multiple electronic databases were searched including MEDLINE, EMBASE, the International Network of Agencies for Health Technology Assessment (INAHTA) and the Cost-Effectiveness Analysis (CEA) Registry. Further to the database searches, health technology appraisal (HTA) websites including Canadian Agency for Drugs and Technologies in Health (CADTH), National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) were searched to identify relevant appraisals. In addition, experts in the field were contacted with a request for details of relevant published and unpublished studies and reference lists of key identified studies were also reviewed for any potentially relevant studies.

The Centre for Reviews and Dissemination (CRD) databases were not be searched as the CRD stopped adding records to the Health Technology Assessment (HTA) database in March of 2018 and the Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluations Database (NHS EED) in March of 2015. The EAG considers it unlikely that relevant studies will be missed from the CRD databases as the INAHTA has taken over the responsibility for the production of the HTA database. During protocol development, clinical experts also advised that they are unaware of any economic evaluations or HRQoL studies published prior to March of 2015 that will be of relevance to this review.

The search strategy for economic evaluations combined terms capturing the interventions or comparators of interest, the target condition (AD) and health economic terms (adapted from the CADTH search filter for economic evaluations). The search strategy for HRQoL data was not restricted by treatment, and combined terms capturing the target population with HRQoL terms (adapted from Arber *et al.* 2017[120]).

Limits were applied to the search strategies to remove animal studies. Additionally, a start date of 2014 was applied to the search strategies as clinical experts advised the EAG that clinical practice started to change following the publication of the first dupilumab randomised controlled trial (RCT) in 2014, with the most marked changes in UK clinical practice taking place after approval of dupilumab by NICE in 2018. As such, a start date of 2014 is considered to be inclusive. No language (to assess volume of foreign language studies available), setting or country restrictions were applied to the search strategies. Full details of the search strategies are presented in Appendix 10.1.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using pre-defined eligibility criteria. The inclusion and exclusion criteria for each review are outlined in Table 31 for economic evaluations and Table 32 for studies reporting HRQoL data. For the economic evaluation search, systematic reviews identified as potentially relevant were manually reviewed for potentially eligible studies then only primary sources were included. Additionally, for both searches the EAG reviewed the companies' submissions (including results of their SLRs) for additional references.

Table 31. Eligibility criteria: economic evaluations

Criteria	Inclusion	Exclusion
Population	Patients with moderate-to-severe AD and aged ≥12 years.	• Patients with mild to moderate AD; • Paediatric patients (aged <12 years); • Patients suffering from other dermatological conditions; • AD affecting the hands.
Interventions	The interventions below will be considered as monotherapy or in combination with TCS: • Abrocitinib; • Baricitinib; • CsA; • Dupilumab; • Tralokinumab; • Upadacitinib.	None.
Comparators	Specified interventions versus each other or BSC. Where interventions are evaluated as a monotherapy, the intervention will be compared with other monotherapies and not in combination with TCS, and vice versa. BSC may include: emollients, low to mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or TCIs.	None.
Outcomes	• Costs per unit of outcome (e.g. ICERs)	None.

	• QALYs; • LYG.	
Study design	Economic evaluations: • Cost-utility analyses • Cost-effectiveness analyses • Cost-minimisation analyses • Cost-benefit analyses • Cost-consequence analyses.	• Budget impact analysis; • Commentaries and letters; • Systematic and non-systematic reviews; • Study protocols with no results.
Limits	• Publications after January 1, 2014 • Publications in English (numbers of relevant non-English studies will be reported).	• Publications prior to 1 January 2014; • Non-English studies (numbers of relevant non-English studies will be reported).

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

Table 32. Eligibility criteria: studies reporting HRQoL data

Criteria	Inclusion	Exclusion
Population	Patients with moderate-to-severe AD and aged ≥12 years.	• Patients with mild to moderate AD; • Paediatric patients (aged <12 years); • Patients suffering from other dermatological conditions; • AD affecting the hands.
Interventions	None.	None.
Comparators	None.	None.
Outcomes	• Preference-based multi-attribute utility values (e.g. EQ-5D, HUI-3, SF-6D) • Direct utility elicitation tools (TTO, standard gamble, rating scale) • Generic health-related quality of life questionnaires (e.g. SF-36, SF-12).	Outcomes not listed.
Study design	Studies reporting original HRQoL data.	• Commentaries and letters; • Systematic and non-systematic reviews; • Study protocols with no results.
Limits	• Publications after January 1, 2014 • Publications in English (numbers of relevant non-English studies will be reported).	• Publications prior to 1 January 2014; • Non-English studies (numbers of relevant non-English studies will be reported).

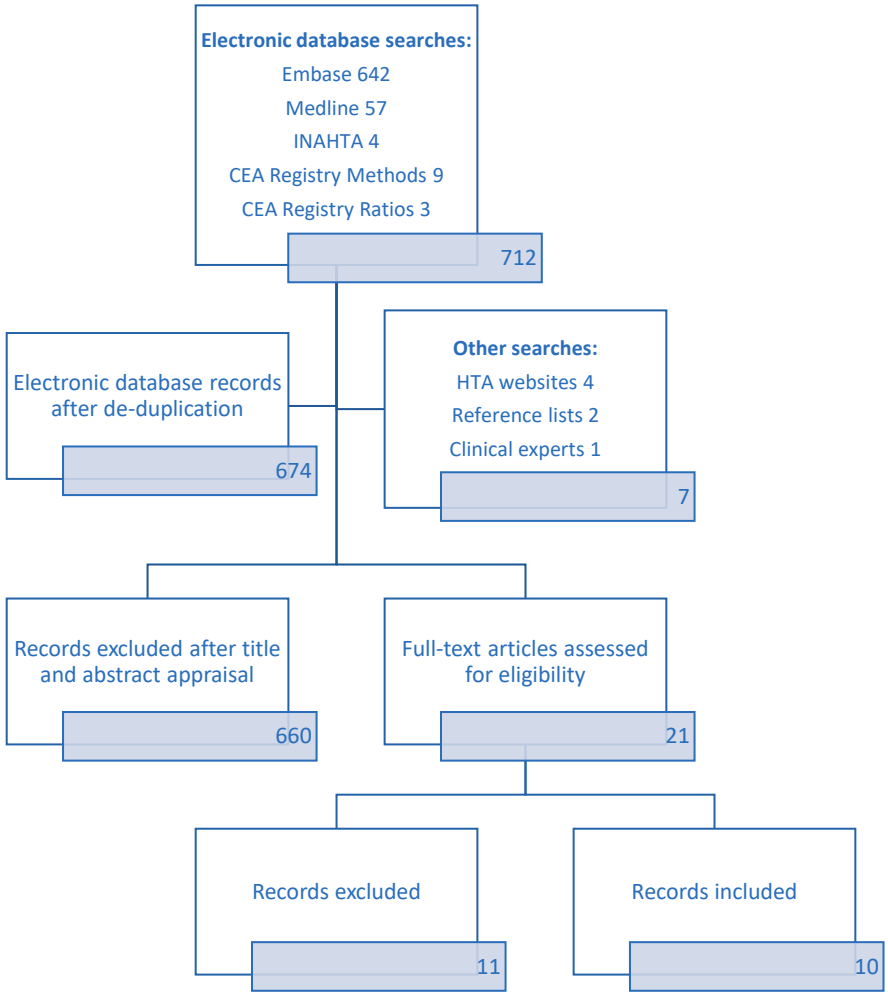
Abbreviations: AD, atopic dermatitis; EQ-5D, EuroQol 5 Dimensions; HRQoL, health-related quality of life; HUI, health utilities index; SF-6D, short-form 6-dimension; SF-12, 12-item short-form health survey; TTO, time trade-off

5.1.2 *Results – economic evaluations*

The electronic database searches identified 712 potential publications. Upon removal of duplicates, 674 publications were screened against the eligibility criteria. Of these, 14 publications were

included and further assessed against the same eligibility criteria with 7 additional studies separately identified from HTA websites, reference lists and clinical experts. Overall, 10 publications were included, 4 were UK full-text publications (2 NICE technology appraisals[12, 13] and 2 SMC appraisals[121, 122]), 5 were non-UK full-text publications[123-127] and 1 was a non-UK abstract.[128] The PRISMA flow diagram presented in Figure 10 details the inclusion and exclusions of studies at each stage of the review.

Figure 10. PRISMA diagram for economic evaluations



Of the interventions of interest to this review, all 10 publications included standard care, 7 included dupilumab only (monotherapy or with topical corticosteroids [TCS]),[12, 121, 123-126, 128] 2 included baricitinib only (monotherapy or with TCS)[13, 122] and 1 included abrocitinib, baricitinib, dupilumab, tralokinumab, and upadacitinib.[127] However, the definition of standard care was not consistent across the studies.

The type of economic evaluation in each of the 10 included publications was a cost-utility analysis, where the incremental cost-effectiveness ratio (ICER) was expressed as the cost per quality-adjusted life-year (QALY) gained. The most common type of model structure was a short-term decision tree, which modelled induction of treatment, followed by a long-term Markov model, which modelled the maintenance phase of treatment. However, in 5 of the publications, a Markov model structure was solely used with either model cycle length adjusted to 4-months in the first year or the use of tunnel states to account for short-term treatment induction phase.[13, 122, 125-127]The time horizon used in 9 of the publications was lifetime,[12, 13, 121-126, 128] with one publication implementing a 5-year time horizon.[127] Model cycle lengths ranged from 4 months to 1 year, although 1 study implemented a 4-week cycle length.[13] The time horizon for models with a short-term decision tree component, was typically 52 weeks, but one study limited the decision tree component to 16 weeks.[124]

Response to treatment was assessed at week 16 in 9 of the publications (insufficient detail on response provided in abstract by Fanelli *et al.*, 2020[128]). Treatment response was primarily based on percentage change in baseline (Eczema Area and Severity Index) EASI scores. However, across included publications, the threshold for change in baseline EASI scores varied, with 9 studies opting for a minimum of 50% or more improvement in EASI score compared with baseline (EASI 50) or 75% or more improvement in EASI score compared with baseline (EASI 75). In addition to treatment response of EASI 50, 3 of the included publications defined treatment response to also include an improvement in the Dermatology Life Quality Index (DLQI) of at least 4, resulting in a composite outcome of EASI 50 plus DLQI >4 at week 16.

Modelling of long-term treatment response post week 16 varied in the included publications. Long-term response was estimated from responders at week 16, either as a conditional response probability or as a conditional discontinuation (preferred NICE TA681[13]). After year 2, all studies used treatment discontinuation in combination with various treatment waning assumptions applied to estimate the proportion of patients per cycle who transition to best supportive care (BSC).

A summary of the 10 extracted publications is provided in Table 33 and detailed data extractions can be found in Appendix 10.2.

Table 33. Summary of included economic evaluations

Study	Population	Model type	Intervention/ comparator	Outcomes
CADTH 2020[123]	Patients aged 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable.	Short-term 1-year decision tree followed by a long-term maintenance Markov model. The Markov-model included annual cycles with half-cycle correction.	Intervention: dupilumab plus SOC. Comparator: SOC, assumed to be topical therapy (type of topical treatments not listed in study).	Treatment response at week 16 based on EASI 50, with scenario using EASI 75. Treatment response at week 52 based on conditional response for responders at week 16. Treatment discontinuation applied annually for dupilumab patients in long-term model.
Kuznik *et al*. 2017.[124]	Adult patients with moderate-to-severe AD	Short-term (16-week) decision tree followed by a lifetime horizon Markov model. A 4-month cycle length was used for the Markov model.	Intervention: dupilumab plus emollients. Comparator: SOC, assumed to be emollients as required.	Treatment response at week 16 based on EASI 75. Treatment response at week 52 based on conditional discontinuation (previously responding patients discontinued by 52 weeks).
Fanelli *et al*. 2020[128] (abstract)	Adolescents (aged 12-17) with uncontrolled moderate-to-severe AD	Short-term 1-year decision tree followed by a lifetime horizon Markov model.	Intervention: dupilumab. Comparator: current supportive care.	Not reported.
Zimmermann, *et al*. 2018[125]	Adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable.	Lifetime Markov model with 4-month cycles.	Intervention: dupilumab. Comparator: usual care (emollients).	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Treatment discontinuation applied annually for dupilumab and usual care patients in long-term model.

NICE TA534, 2018[12]	Adult patients with moderate-to-severe AD who are contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.	Short-term 1-year decision tree followed by a long-term Markov model.	Intervention: dupilumab Comparator: BSC, which includes emollients, low-to-mid potency topical corticosteroids, and rescue therapy which may include higher potency topical corticosteroids, oral corticosteroids, topical calcineurin inhibitors, phototherapy or psychological support.	Treatment response at week 16 based on composite outcome for EASI 50 + DLQI ≥4. Treatment response at week 52 based on conditional response to treatment at week 16. Treatment discontinuation applied annually for dupilumab patients in long-term model. Assumptions around loss of response also included for both arms of the model.
NICE TA681, 2021[13]	Adult patients with moderate-to-severe AD who have previously failed one or more systemic therapies.	A four-state, lifetime Markov model. The model cycle length was 4 weeks.	Intervention: baricitinib in combination with topical corticosteroids. Comparators: dupilumab and BSC, which includes emollients, low-to-mid potency topical corticosteroids, phototherapy, psychological support and rescue therapy.	Treatment response at week 16 based on composite outcome for EASI 50 + DLQI ≥4. Treatment response at week 52 based on all cause discontinuations applied to responders at week 16. Treatment discontinuation applied annually for dupilumab and BSC patients in long-term model.
Healthcare Improvement Scotland SMC2011	Patients who have had an inadequate response to existing systemic immunosuppressants such	Short-term 1-year decision tree followed by a long-term (lifetime) Markov model with annual cycles.	Intervention: dupilumab. Comparator: BSC (not defined).	Treatment response at week 16 based on composite outcome for EASI 50 + DLQI ≥4.

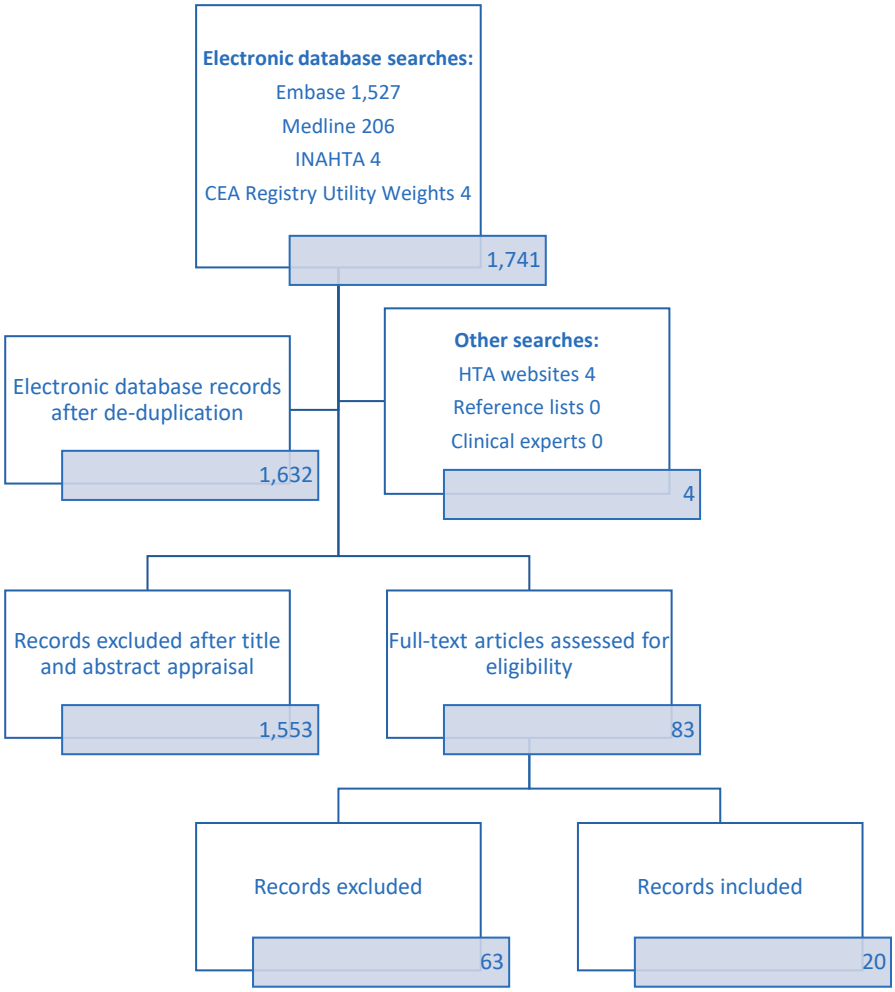
(2018) & SMC2232 (2019)[121, 129]	as ciclosporin, or in whom such treatment is considered unsuitable.			Treatment discontinuation applied annually for dupilumab patients in long-term model.
Healthcare Improvement Scotland SMC2337, 2021[122]	Adult patients with moderate-to-severe AD who are candidates for systemic therapy who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.	Lifetime 4-state Markov model.	Intervention: baricitinib . Comparators: dupilumab, BSC (not defined).	Treatment response at week 16 based on EASI 75. Treatment response at week 52 based on conditional response for responders at week 16. After year 1, all cause discontinuation rate at week 52 was used to calculate a constant rate of discontinuation.
Institute for Clinical and Economic Review, 2017[126]	Adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable.	Lifetime Markov model with 4-month cycles.	Intervention: dupilumab. Comparator: usual care (emollients).	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Treatment discontinuation applied annually for dupilumab and usual care patients in long-term model.
Institute for Clinical and Economic Review, 2021[127]	Patients with moderate-to-severe atopic dermatitis.	5-year Markov model with 4-month cycles.	Interventions: - abrocitinib; 200 mg once daily - baricitinib 2 mg once daily; - tralokinumab 300 mg Q2W; - upadacitinib 30 mg once daily. Comparators: SOC (emollients), dupilumab 300 mg Q2W.	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Treatment specific per-cycle treatment discontinuation rates (all cause) for the first year after initial treatment and then for all subsequent years over the model time horizon where data was available was used in the model.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NICE, National Institute of Health and Care Excellence; SMC, Scottish Medicines Consortium.

5.1.3 Results – Health-related quality of life

The electronic database searches identified 1,741 potential publications. Upon removal of duplicates, 1,632 publications were screened against the eligibility criteria. Of these, 79 publications were included and further assessed against the same eligibility criteria with 4 additional studies separately identified from HTA websites. Following this, 20 publications were included. The PRISMA flow diagram presented in Figure 11 details the inclusion and exclusions of studies at each stage of the review.

Figure 11. PRISMA diagram for studies reporting HRQoL data



Of the 20 included publications, 4 were HTA submissions,[12, 13, 121, 122] 12 were full-text publications[86, 125, 130-139] and 4 were abstracts[140-143]. The 4 HTA submissions include 2 NICE technology appraisals and 2 SMC technology appraisals (each including 1 appraisal for dupilumab and 1 appraisal for baricitinib). The 20 publications represent 16 unique studies (3 studies were reported in abstract and full-text form[130, 135, 136] and 1 study was reported in 2 publications[86, 138]). Although the HTA submissions to NICE and SMC for the same drug are based on the same study data, they are considered separately in this review as different methods and processes were used to analyse and assess the EQ-5D data provided by the company (thus, different results are reported).

Of the 20 included publications, 15 reported EQ-5D data [12, 13, 86, 121, 122, 125, 130-134, 137, 138, 141, 142]and 1 reported EQ-5D data and time trade-off (TTO) data.[139] The remaining 4 publications reported SF-6D data or TTO data[135, 136, 140, 143]. Of the 16 publications which reported EQ-5D data, 9 collected EQ-5D-5L data[13, 122, 130-132, 134, 139, 141, 142] and 4 collected EQ-5D-3L data. [12, 86, 137, 138] The remaining 3 publications did not clearly specify which levels of the EQ-5D were used.[121, 125, 133] Of the 9 publications which collected EQ-5D-5L data, 2 mapped EQ-5D-5L responses to EQ-5D-3L[13, 122] responses using the Van Hout 2021 algorithm.[144]

The majority of publications reported heath state utility values (HSUVs) according to severity (based on the PO-SCORAD score, SCORAD score, or self-reported severity) or response (based on improvements in the EASI score, or EASI + DLQI score). A summary of the 20 included publications (16 unique studies) is provided in Table 34 and detailed data extractions can be found in Appendix 10.2.

Table 34. Summary of included HRQoL studies in patients with moderate-to-severely active AD

Study	Author, Year	Country	Measure	Valuation	HSUVs according to
1	Andersen, 2020[130]	Europe (France, Germany, the UK) and the USA	EQ-5D-5L	Unclear (respective weights)	Severity and country
	Nyberg, 2018 (abstract)[142]	Europe (France, Germany, the UK) and the USA	EQ-5D-5L	Unclear	Severity and country
2	Hsieh, 2021[131]	Taiwan	EQ-5D-5L	UK weights	Severity
3	Kwatra, 2021[132]	US	EQ-5D-5L	Unclear	Comorbidity
4	Misery, 2018[133]	France	EQ-5D	Unclear	Severity
5	Girolomoni, 2021[134]	EU5 (France, Germany, Italy, Spain, and the UK)	EQ-5D-5L	Unclear	Comorbidity
6	Retzler, 2019[135]	UK	TTO	TTO	Regimen intensity

	Retzler, 2018 (abstract)[143]	Unclear	TTO	TTO	Regimen intensity
7	Silverberg, 2019[136]	USA	SF-6D	US weights	Severity
	Silverberg, 2019 (abstract) [140]	USA	SF-6D	Unclear	Severity
8	Simpson, 2017[137]	Multiple study locations	EQ-5D-3L	Unclear	Response and treatment
9	Simpson, 2016[86]	Multiple study locations	EQ-5D-3L	UK weights	Treatment
	Simpson, 2016[138]	Multiple study locations	EQ-5D-3L	UK weights	Overall only
10	Song, 2019[139]	Korea	EQ-5D-5L and TTO	Korean weights	Response
11	Vietri, 2017 (abstract)[141]	France, Germany, the UK	EQ-5D-5L	Unclear	Severity
12	Zimmerman, 2018[125]	USA	EQ-5D	Unclear	Severity and response
13	SMC2011, 2018[121]	Multiple study locations	EQ-5D	Unclear	Response and treatment
14	SMC2237, 2021[122]	Multiple study locations	EQ-5D-5L mapped to EQ-5D-3L	UK weights	Response
15	NICE TA534, 2018[12]	Multiple study locations	EQ-5D-3L	UK weights	Response and treatment
16	NICE TA681, 2021[13]	Multiple study locations	EQ-5D-5L mapped to EQ-5D-3L	UK weights	Response

Abbreviations: 5D, 5 dimension; 6D, 6 dimension; 3L, 3 level; 5L, 5 level; AD, atopic dermatitis; EQ, EuroQol; EU, European Union; HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence; SF, short-form; SMC, Scottish Medicines Consortium; UK, United Kingdom; USA, United States of America

5.2 Independent economic assessment

5.2.1 Methods

5.2.1.1 Populations

As described in Section 2.1, the population relevant to the multiple technology assessment (MTA) are those with moderate-to-severe AD, irrespective of previous treatment and of age, with a subgroup of interest being those for whom systemic therapies have been inadequately effective, not tolerated or contraindicated.

As per guidance from NICE, the Evidence Assessment Group (EAG) has considered each of the companies proposed positions in the treatment pathway as part of the assessment for the cost-effectiveness analysis. Thus, clinical data in the network meta-analysis (NMA) were analysed by pre-specified subgroups based on age and line of therapy and TCS use (described further in Section 4.1.5). As such, the populations considered in the economic model are as follows:

- Adults who are eligible for systemic treatment (ciclosporin [CsA]) on inadequate response to topical treatments (referred to hereafter as the adult first-line systemic treatment population)
- Adults who achieve inadequate response to, cannot tolerate, or are contraindicated to CsA – monotherapy and combination therapy (referred to hereafter as the adult second-line systemic treatment population.
- Adolescents, irrespective of prior therapy.

As noted in Section 4.1, trials assessing AD treatments in the adolescent population included a mix of patients at all lines of systemic treatment. Due to small numbers in the trials that include adolescents, a robust subgroup analyses by line of treatment for this population is not possible, as such adolescents are considered in the model irrespective of prior line of therapy. Furthermore, due to limitations in the clinical evidence, discussed in Section 4.2.2, combination therapy data are unavailable for the adolescent population and monotherapy data are unavailable for the adult first-line systemic treatment population. Section 5.2.1.5 provides further detail on available treatment effectiveness data and Section 5.2.1.2 provides further details on the interventions and proposed positions in the treatment pathway for the cost-effectiveness analysis.

5.2.1.1.1 Baseline characteristics

In each of the companies economic models, baseline characteristics were taken from the key trials for the drugs, which is appropriate for a single technology appraisal (STA) model. However, for an MTA model a consistent approach using common assumptions and baseline characteristics is required. Due to the heterogeneity of baseline characteristics of those enrolled across the key trials of interest for abrocitinib, tralokinumab and upadacitinib, the EAG sought to select trials that most closely reflect the populations of interest to the MTA model. The EAG consulted with its clinical experts who considered that the upadacitinib trials were appropriate to inform the baseline characteristics in the EAG economic model. Table 35 presents the baseline characteristics used for each population in the economic model along with the source upadacitinib trial.

Table 35. Baseline characteristics by population

Population	Baseline characteristics	Trial
First-line systemic treatment – adults, combination therapy	Mean age: [redacted] % male: [redacted] Mean weight: [redacted]	AD UP
Second-line systemic treatment – adults, monotherapy	Mean age: [redacted] % male: [redacted] Mean weight: [redacted]	Measure UP 1 and 2
Second-line systemic treatment – adults, combination therapy	Mean age: [redacted] % male: [redacted] Mean weight: [redacted]	AD UP
Adolescents, monotherapy	Mean age: [redacted] % male: [redacted] Mean weight: [redacted]	Measure UP 1 and 2

Abbreviations: kg, kilogram.

5.2.1.2 Interventions and comparators

The interventions of interest as part of this MTA are abrocitinib, tralokinumab and upadacitinib. As per the final protocol,[49] the EAG has considered each of the companies proposed position in the treatment pathway as part of the assessment for the cost-effectiveness analysis. As such, the interventions are compared with the recommended treatment in the proposed position of the treatment pathway. Table 36 presents the proposed product position for each of the interventions and relevant comparators. The recommended first-line systemic treatment for adults is CsA. As noted previously, CsA does not hold a marketing authorisation for use in adolescents as a first-line systemic treatment. However, dupilumab is funded for use in adolescents under the NHS England Medicines for Children Policy and is included as the comparator for the adolescent population position. Recommended second-line systemic treatments for adults include dupilumab and baricitinib.

It should be noted that each of the treatments are considered as a monotherapy and in combination with TCS in the cost-effectiveness analyses. However, as described in Section 4.1, results are only available from the NMA for combination therapy for the adult first-line systemic treatment population, while results for monotherapy are available for the adolescent population and for baricitinib for the adult second-line systemic treatment population. Table 36 presents an overview of the interventions and comparators by population included in the economic model.

Table 36. Interventions and comparators by population

Population	Intervention	Comparator
Adults		
First-line systemic therapy for those having inadequate response to topical treatments	Upadacitinib + TCS	CsA + TCS
Second-line systemic therapy for those who achieve inadequate response to, cannot tolerate, or are contraindicated to CsA	Abrocitinib (+/- TCS)	Dupilumab (+/- TCS) Baricitinib + TCS
	Tralokinumab (+/- TCS)	
	Upadacitinib (+/- TCS)	
Adolescents		
Adolescents, irrespective of prior therapy	Abrocitinib	Dupilumab
	Upadacitinib	

Abbreviations: CsA, ciclosporin; TCS, topical corticosteroids.

Table 37 presents an overview of the treatment regimens and the EAG approach to inclusion of the different treatment regimens in the model.

Table 37. Treatment regimens

Treatment	Dose	Administration and frequency	SmPC guidance*	EAG approach
Abrocitinib	200 mg	Oral tablet, once daily.	Recommended starting dose for most adults.	As both doses are recommended in the draft SmPC, each are evaluated separately in the cost-effectiveness analysis over a lifetime horizon.
	100 mg	Oral tablet, once daily.	Recommended starting dose for patients aged 65 years and over and other patients who may benefit from a lower starting dose.	
Baricitinib	4 mg	Oral tablet, once daily.	Recommended starting dose for patients.	In TA681,[13] the committee considered 4 mg was the licensed dose relevant for most patients and was used as the basis for the recommendation. For consistency, the EAG only considers the 4 mg dose.
	2 mg	Oral tablet, once daily.	Appropriate for patients aged 75 years and over and those with a history of chronic or recurrent infections. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily.	
CsA	5 mg/kg for first six weeks, followed by 3 mg/kg thereafter.	Oral tablet, once daily for a maximum of one year.	Recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses. However, due to the variability of this condition,	The EAG's clinical experts advised there is no clinical consensus on the appropriate CsA regimen, as this is individualised as per SmPC guidance. As

			treatment must be individualised.	such, the accepted dose in TA534 is included in the EAG base case. Alternative dosing explored in scenario analyses.
Dupilumab	300 mg with an initial loading dose of 600 mg.	Subcutaneous injection, once every two weeks.	Recommended dose for adults and adolescents weighing >60kg.	Included as per SmPC recommendation.
Tralokinumab	300 mg with an initial loading dose of 600 mg.	Subcutaneous injection, once every two weeks.	Recommended dose and frequency for all patients. At prescriber's discretion, frequency of dose can be reduced to once every four weeks for patients who achieve clear or almost clear skin after 16 weeks of treatment.	The base case assumed that all patients stay on Q2W dosing. A scenario analysis was run where a proportion of responders (assumed to be the proportion achieving EASI 75 or more) move to once every four weeks dosing.
Upadacitinib	15 mg	Oral tablet, once daily.	The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. Recommended dose of upadacitinib is 15 mg for adolescents weighing at least 30 kg and patients ≥ 65 years of age, the recommended dose is 15 mg once daily. - A dose of 30 mg once daily may be appropriate for patients with high disease burden or inadequate response to 15 mg once daily. - The lowest effective dose for maintenance should be considered.	For the EAG base case, both doses evaluated for adults and only the 15 mg dose evaluated for adolescents.
	30 mg	Oral tablet, once daily.		

Abbreviations: CsA, ciclosporin; EAG, Evidence Assessment Group; EASI, Eczema Area and Severity Index; kg, kilogram; mg, milligram;

5.2.1.3 Model structure

To assess the cost-effectiveness of abrocitinib, tralokinumab and upadacitinib for the treatment of moderate-to-severe AD, a hybrid economic model was developed, comprising a short-term (1 year) decision tree component, to capture the treatment induction phase and treatment response assessments, followed by a long-term (lifetime), three-state Markov model. The comparator in the analysis for first-line systemic treatment is CsA and for second-line systemic treatment, the comparators are dupilumab and baricitinib. All treatments in the model are evaluated as both monotherapies and in combination with TCS. The development of the model structure was informed by published models identified in the SLR, supplied company submissions and the approaches accepted for TA534[12] and TA681.[13]

Due to the different proposed treatment pathway positions of the drugs by their respective companies, the EAG has developed two short-term decision tree models to reflect the differences in first- and second-line systemic treatment. Each component of the model is discussed in turn below.

Short-term decision tree – first-line systemic treatment (adults)

Upadacitinib is the only treatment that has a proposed position in the first-line systemic treatment pathway and as such will be compared against CsA. Currently, CsA is recommended to only be given for a maximum of one year, after which all patients discontinue to BSC.

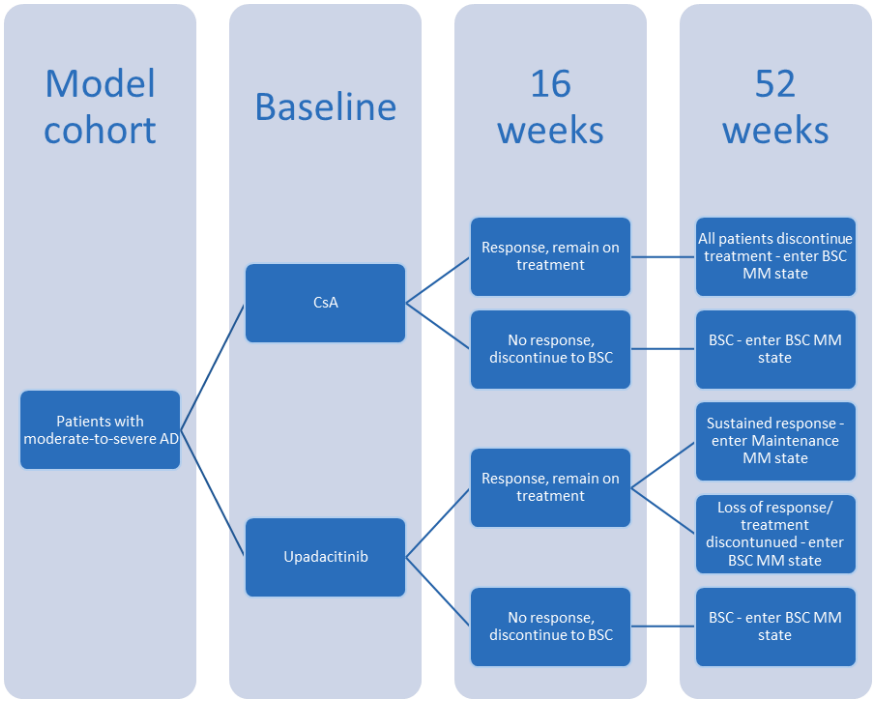
Figure 12 presents the model schematic for first-line systemic treatment for adults. All patients enter the first-line systemic treatment, short-term decision tree model, starting treatment on either upadacitinib or CsA and remain on treatment for 16 weeks (treatment induction phase). At week 16, response to treatment is assessed, defined as achieving EASI 50 + (C)DLQI≥4. In both arms of the model, responders at week 16 remain on treatment until week 52. Non-responders at week 16 discontinue treatment and receive BSC.

Between week 16 and 52, responders may lose response to treatment or discontinue treatment for other reasons and will enter the long-term Markov model in the BSC health state. Upadacitinib responders who sustain their response between week 16 and 52 and are still on treatment enter the long-term Markov model in the maintenance health state. For patients on CsA, the maximum recommended treatment duration is 12 months. As such, all CsA patients still on treatment at week 52 discontinue to BSC in the long-term Markov model. Sustained response for the intervention at

week 52 is based on conditional discontinuation data, defined as the proportion of patients discontinuing treatment at week 52 from those who achieve response at week 16.

In the short-term model, the BSC health state is composed of responders and non-responders and these proportions are informed by week 16 data response data (Section 4.1 and Section 5.2.1.5). This approach was accepted in TA681 as an appropriate way to capture the waxing and waning nature of response to BSC treatment.

Figure 12. First-line systemic treatment short-term decision tree model structure – adults



Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CsA, ciclosporin; MM, Markov model.

Short-term decision tree – second-line systemic treatment (adults) / adolescents (all lines of treatment)

Figure 13 presents the model schematic for second-line systemic treatment (adults) and adolescents. As noted in Section 5.2.1.1, trials assessing AD treatments in the adolescent population included a mix of patients at all lines of systemic treatment. Due to small numbers in the trials that

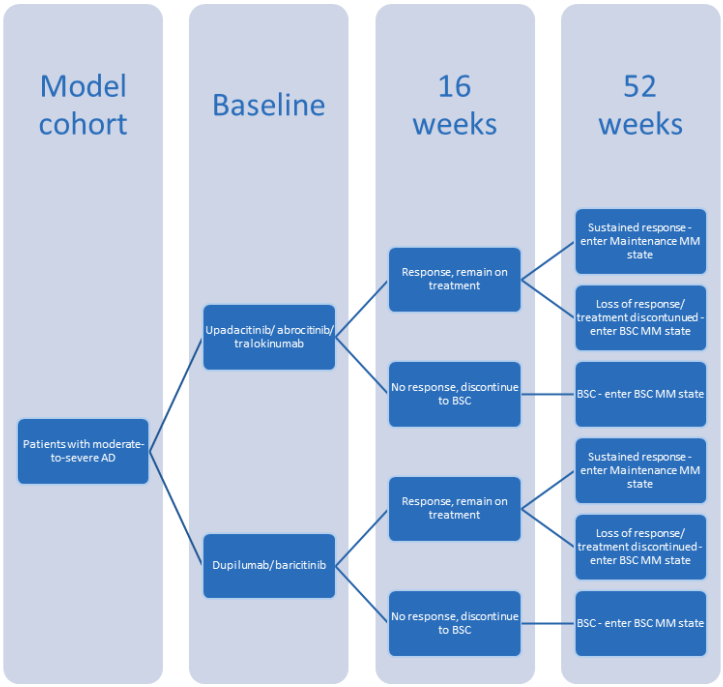
included adolescents, a robust subgroup analyses by line of treatment for this population is not possible, as such adolescents are considered in the model irrespective of prior line of therapy. Additionally, CsA does not hold a marketing authorisation for use in adolescents as a first-line systemic treatment. Thus, dupilumab is the comparator for treatments in an adolescent population position, as it is funded for use in adolescents under the NHS England Medicines for Children Policy.

Adult patients enter the short-term, decision tree model, starting treatment on one of the five second-line systemic treatments (abrocitinib, baricitinib, dupilumab, tralokinumab, or upadacitinib). Adolescent patients enter the model on either abrocitinib, dupilumab, or upadacitinib. Patients remain on treatment for 16 weeks (treatment induction phase), after which point response to treatment is assessed, defined as achieving EASI 50 + (C)DLQI ≥4. Responders at week 16 remain on treatment until week 52. Non-responders at week 16 discontinue treatment and receive BSC.

Between week 16 and 52, responders may lose response to treatment or discontinue treatment for other reasons and will enter the long-term Markov model in the BSC health state. Responders who sustain their response between week 16 and 52 and are still on treatment enter the long-term Markov model in the maintenance health state. Sustained response at week 52 is based on conditional discontinuation data, defined as the proportion of patients discontinuing treatment at week 52 from those who achieve response at week 16.

In the short-term model, the BSC health state is composed of responders and non-responders and these proportions are informed by week 16 data response data (Section 4.1 and Section 5.2.1.5). As mentioned previously, this approach was accepted in TA681 as an appropriate way to capture the waxing and waning nature of response to BSC treatment.

Figure 13. Second-line systemic treatment short-term decision tree model structure (adults)/adolescents (all lines of treatment)

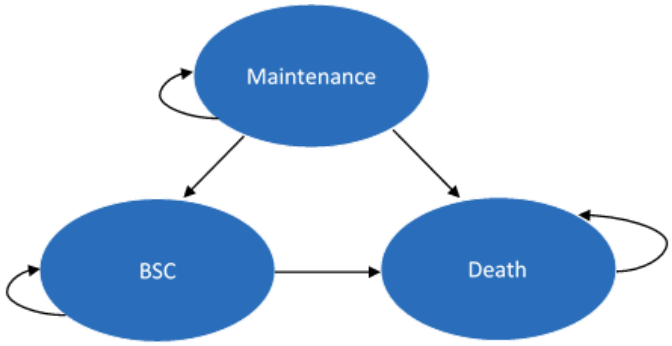


Abbreviations: AD, atopic dermatitis; BSC, best supportive care; MM, Markov model.

Long-term Markov model

At the end of each of the short-term decision trees (start of year 2), patients enter a long-term three-health state Markov model. Health states in the model consisted of maintenance, BSC and death. Figure 14 presents the model schematic.

Figure 14. Long-term Markov model schematic



Abbreviations: BSC, best supportive care.

Patients who have maintained a response at week 52 and still on treatment enter the Markov model in the maintenance health state and remain there until loss of response (via treatment waning) or if they discontinue treatment for any reason (all cause discontinuation). If patients lose response or discontinue treatment, they transition to the BSC health state.

Patients that have discontinued treatment to BSC in the short-term decision tree enter the Markov model in the BSC health state and remain there until death. As with the BSC health state in the short-term decision tree model, the Markov model BSC health state is composed of responders and non-responders and these proportions are informed by week 16 data response data (Section 4.1 and Section 5.2.1.5), in line with approach accepted in TA681.[13]

At any time in the model, patients can transition to the death state. As treatment for AD is not expected to affect mortality, transitions to the death state are informed by general population mortality rates.

In the long-term model, an annual cycle length has been implemented and half cycle correction applied.

5.2.1.4 Time horizon, perspective and discounting

The time horizon of the model is lifetime (up to a maximum age of 100 years). The perspective of the analysis is the NHS in England. Costs and QALYs have been discounted at 3.5%, as per the NICE

reference case. Scenarios were conducted limiting the time horizon to 5 years after the mean age and 75 years of age for the adult analyses and 18 years of age for the adolescent analyses.

5.2.1.5 Treatment effectiveness

The primary treatment outcome assessed in the model is response to treatment at Week 16, defined using a composite outcome of EASI 50 + DLQI ≥ 4. In TA534[12] and TA681,[13] the composite outcome was preferred by the committee as it was deemed to be sensitive to changes in treatment outcomes and more clinically relevant than EASI 75. As a result of the committee decision in TA534, the composite outcome was carried forward in TA681 and in each of the company economic models submitted as part of the MTA.

Log odds ratios from the NMA, described Section 4.1, were used to estimate Week 16 treatment response probabilities used in the EAG economic model. However, as noted in Section 4.2.1, there were several data limitations in the NMA that meant outcome data (composite or EASI 75) were unavailable for some of the populations. Table 38 presents an overview of the NMA outcome data available for each population.

Table 38. Treatment response outcome data availability by population and type of treatment

Population	Monotherapy		Combination therapy	
	EASI 50 +DLQI ≥4	EASI 75	EASI 50 +DLQI ≥4	EASI 75
Adults - first-line systemic treatment	✗	✗	✗	✓
Adults - Second-line systemic treatment*	✓	✓	✓	✓
Adolescents	✗	✓	✗	✗

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index
*Only EASI 75 outcome available for baricitinib as combination therapy for the adult second-line systemic population.

The composite outcome from the NMA was obtained for the adult second-line systemic subgroup for both monotherapy and combination therapy analyses and EASI 75 was explored in scenario analyses. However, the EAG was unable to obtain composite outcome data for baricitinib as these data are redacted in TA681 (and the company declined to provide them to the EAG). Furthermore, EASI 75 data for baricitinib were only available as combination therapy for the adult second-line systemic population. Therefore, any comparisons with baricitinib in the adult second-line systemic treatment subgroup will be presented as scenario analyses.

The composite outcome could not be obtained for treatments relevant to the adolescent and adult first-line systemic treatment subgroups for both monotherapy and combination therapy analyses. However, the EASI 75 outcome was available for the adolescent subgroup for the monotherapy analyses and adult first-line systemic treatment subgroup for the combination analyses and as such this outcome is used for the base case in these populations.

The committee for TA534 and TA681 considered that in clinical practice, dupilumab and baricitinib will likely be used as combination therapies rather than monotherapies and this view is reflected by the EAG's clinical experts when considering the three new treatments under consideration. Thus, for the adult first-line systemic treatment subgroup, the combination analyses are likely to be more relevant than the monotherapy analyses. Furthermore, upadacitinib is the only treatment where the company has proposed its use in the adult first-line systemic treatment subgroup. For the adolescent population, the EAG's clinical experts explained that they would be treated in the same way as adults, thus combination therapy is more relevant than monotherapy.

As the combination therapy analyses are more relevant for clinical practice, the EAG considered missing monotherapy data is not critical for decision-making for the adult first-line systemic treatment subgroup. However, for the adolescent population monotherapy analyses may potentially underestimate the effectiveness of the treatments when used in combination with TCS in clinical practice. Therefore, adolescent monotherapy analyses may reflect a conservative view of cost-effectiveness. The EAG has included treatment response outcomes one-way sensitivity analyses to capture the uncertainty around the estimates, but in particular the upper bound estimate for the adolescent population may be useful to help understand what the cost-effectiveness of combination therapy might be for this population.

Implementation of NMA outputs

To calculate the probability of response at Week 16 for each of the treatments, a baseline level of treatment response for patients who would have otherwise been on BSC was needed for the economic model. In TA534, TA681 and the company models, placebo response from the key trials of the drug under consideration was used. However, as placebo response varies in each of the trials, the EAG consulted with its clinical experts to select a trial which had baseline characteristics that were representative of the population who would be treated in the NHS.

Baseline characteristics used in the model are described Section 5.2.1.1.1. For the adolescent and the second-line adult monotherapy analyses, the EAG's clinical experts considered that the upadacitinib Measure UP 1 & 2 trials were appropriate to use for the baseline characteristics of the model and placebo response. As the populations in Measure UP 1 & 2 were considered comparable, for each subgroup the EAG pooled placebo trial data. For the adult first- and second-line combination analyses, the upadacitinib AD-UP trial was considered appropriate to use for the baseline characteristics and placebo response by the EAG's experts. Table 39 presents the baseline Week 16 treatment response by population used in the economic model. It should be noted that the baseline treatment response is also used for the weighted average of responders and non-responders in the BSC health state to estimate costs and QALYs.

Table 39. Baseline BSC treatment response at Week 16 used in the economic model

Population	Baseline response	Source
Monotherapy		
Adults - Second-line systemic treatment	[redacted]	Pooled placebo response data from Measure UP 1 ([redacted]) and Measure UP 2 ([redacted]).
Adolescents	[redacted]	Pooled placebo response data from Measure UP 1 ([redacted]) and Measure UP 2 ([redacted]).
Combination therapy		
Adults - first-line systemic treatment	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16
Adults - Second-line systemic treatment	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16

Abbreviations: BSC, best supportive care

The baseline Week 16 treatment response was converted into log-odds to be applied to the log-odds ratios from the NMA (representing treatment versus placebo) to estimate baseline-adjusted log-odds for each treatment. The baseline-adjusted log-odds for each treatment were then exponentiated and transformed to calculate the probability of patients responding to treatment at Week 16. Table 40 presents the Week 16 treatment response probabilities for each subgroup. Please refer to Appendix 10.7 for the log-odds ratios from the NMA and Week 16 treatment response probabilities based on EASI 75 for the adult second-line systemic treatment subgroup scenario analyses.

Table 40. Week 16 treatment response probabilities

Intervention	Monotherapy	Combination therapy
Adult First-line systemic treatment - EASI 75		
CsA	N/A	[redacted]

Upadacitinib - 15 mg	N/A	[redacted]
Upadacitinib - 30 mg	N/A	[redacted]
Adult Second-line systemic treatment - EASI 50 +DLQI ≥4		
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]
Baricitinib	N/A	N/A
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]
Adolescents - EASI 75		
Abrocitinib - 100 mg	[redacted]	N/A
Abrocitinib - 200 mg	[redacted]	N/A
Dupilumab	58.5%	N/A
Upadacitinib - 15 mg	[redacted]	N/A

Abbreviations: CsA, ciclosporin; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; N/A, not available.

As mentioned in Section 4.2.1.1, the log-odds ratios for each treatment are based on the all-observed data from the trials, that is, patients were not censored from the analysis upon receipt of rescue treatment. Furthermore, for the abrocitinib analyses in the adult second-line systemic treatment analyses, the EAG used data from the relevant JADE trials for patients who previously failed or were intolerant to ciclosporin (referred to by the company as the restricted population in the abrocitinib company submission). The EAG considers that the abrocitinib restricted population more closely reflects the definition of the adult second-line systemic treatment population, as described in Section 4.2.2. However, the patient numbers informing the abrocitinib restricted population are small. As mentioned in Section 4.2.2, the NMA sensitivity analysis based on the generalisable population for abrocitinib (defined by the company as patients who were previously treated with at least one systemic treatment for AD) show relatively similar results to the primary analysis. Nonetheless, the EAG performed a scenario analysis exploring log-odds ratios based on data from the relevant JADE trials for the generalisable population.

As mentioned in Section 4.2.2, the EAG ran a sensitivity analysis in the NMA where patients were censored for rescue therapy. The sensitivity analysis had a substantial impact on the treatment effect for dupilumab in the adult second-line systemic treatment monotherapy analyses and for upadacitinib 15 mg in the adolescent monotherapy analyses. As such, the EAG explored a scenario implementing the log-odds ratios based on the NMA for rescue therapy censoring for the adult

second-line systemic treatment monotherapy analyses. Data for this scenario are presented in Appendix 10.7.

For the EAG base case, the results from the NMA using the observed data from studies were used, consistent with TA534, TA681 and the companies submissions. However, the EAG ran a sensitivity analysis in the NMA exploring an adjustment for potential baseline heterogeneity in placebo response. As discussed in Section 4.2.2, the EAG's sensitivity analysis failed to converge for the first- and second-line adult analyses for combination treatment. However, the adolescent and adult second-line monotherapy sensitivity analyses did converge. As such, the EAG explored a scenario implementing the log-odds ratios based on the placebo response adjustment NMA for the adult second-line systemic treatment and adolescent monotherapy analyses. Data for this scenario are presented in Appendix 10.7.

5.2.1.5.1 Week 52 treatment response outcomes

By the end of the time horizon in the short-term decision tree model (Week 52), a proportion of responders to treatment at Week 16 may not continue on to long-term maintenance treatment. In TA534, the committee preferred Week 52 treatment response outcomes to be modelled using conditional response data, defined as the proportion of Week 16 responders who were still responding to treatment at Week 52. However, in TA681 the committee considered that loss of response is not the only reason for treatment discontinuation in Week 16 responders and that sustained response at 52 weeks should be based on all cause stopping rate for people whose condition responded to treatment at Week 16 but withdrew from treatment at Week 52 (conditional discontinuation).

Of the company submissions supplied to the EAG, the abrocitinib model was the only one to use conditional discontinuation data to estimate the proportion of responders still on treatment at Week 52. As noted earlier, the upadacitinib model was developed prior to the publication of TA681 and therefore the company's base case used conditional response data to model Week 52 outcomes, as per TA534. However, the tralokinumab model also based Week 52 outcomes on conditional response data, which was used to inform an NMA for response to treatment at Week 52, though the recommendations for TA681 had recently been published prior to the company's submission to NICE.

In clinical practice, patients may achieve response at Week 16 but cannot tolerate longer term treatment due to adverse events or other reasons and as such discontinue treatment. Therefore, basing Week 52 outcomes based on loss of effectiveness potentially overestimates the proportion of patients who go on to long-term maintenance treatment. As such, the EAG has used conditional discontinuation data, consistent with TA681, to estimate the probability of Week 16 responders transitioning to long-term maintenance treatment at Week 52. The EAG requested conditional discontinuation data from the companies for abrocitinib, tralokinumab and upadacitinib, as well as extracting relevant data from TA534. It should be noted that discontinuation data in TA681 were redacted and the company declined to provide them to the EAG.

Based on the data supplied by the companies, it precluded carrying out an NMA for Week 52 conditional discontinuation for the treatments of interest. In the studies evaluating abrocitinib and upadacitinib, on completion of the 16-week treatment phase, those receiving placebo or active comparator and achieving response in the parent trial were re-randomised to a dose of the investigational treatment evaluated, that is either abrocitinib or upadacitinib. Thus, there are no data available in the longer term for placebo, which means that there is no common comparator across the studies to provide a connected network suitable for analysis. Additionally, the data supplied by the company on conditional discontinuation of abrocitinib was for the whole trial population, which is predominantly formed of those receiving first-line systemic treatment. In addition, data for baricitinib are redacted in TA681 and so could not be included.

In lieu of NMA results for conditional discontinuation at Week 52, the EAG implemented the available conditional discontinuation data in the model, but assumptions were made where data gaps existed. Table 41 presents an overview of available conditional discontinuation data at Week 52 and EAG assumptions for each treatment considered in the model. Please refer to Appendix 10.7.1 for conditional discontinuation data for the EASI 75 scenario analyses.

The company for tralokinumab only provided conditional discontinuation data for monotherapy administered once every two weeks (Q2W) and once every four weeks (Q4W) based on EASI 75 at Week 52. As such, the EAG assumed conditional discontinuation data for tralokinumab monotherapy was the same as the combination therapy and composite outcome due to lack of data. It should be noted that the company for tralokinumab provided annual treatment discontinuation data based on the composite outcome for tralokinumab from the ECZTEND study for the ECZTRA-7 like population in their clarification response. The all-cause treatment discontinuation rate for the ECZTRA-7 like

population in ECZTEND for patients who achieved EASI 50 + DLQI ≥4 in the parent study was [redacted] and [redacted] for the EASI 75 outcome. However, in ECZTEND TCS use was optional and Q4W dosing was not an option. Furthermore, ECZTEND also included patients from ECZTRA 4, 5 and 6. To maintain a consistent approach with the estimation of conditional discontinuation across treatments, the EAG only considered the ECZTRA-7 like data from ECZTEND in a scenario analysis.

For dupilumab and tralokinumab, conditional discontinuation was assumed to be the same for monotherapy and combination therapy as the type of monoclonal antibody appears to be more important than the addition of TCS when considering sustained treatment response. For abrocitinib, the EAG assumed the same conditional discontinuation as upadacitinib as they are both JAK inhibitors. However, in the adolescent population, as only upadacitinib 15 mg is applicable, the conditional discontinuation rate has been assumed for abrocitinib 200 mg. The company for abrocitinib did provide conditional discontinuation data from JADE EXTEND for the adolescent population, but as an overall percentage rather than supplying patient numbers as requested by the EAG. The EAG is therefore unclear how many adolescent patients from JADE MONO-1/2 entered EXTEND and therefore inform the company's estimates of conditional discontinuation. For completeness, the company estimated that conditional discontinuation for adolescent patients on monotherapy from EXTEND was [redacted] for abrocitinib 200mg and [redacted] for abrocitinib 100 mg.

Table 41. Conditional discontinuation data

Treatment	Conditional discontinuation at Week 52	Source/ assumptions
Monotherapy – Adults, EASI 50 + DLQI ≥4		
Abrocitinib 100 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Abrocitinib 200 mg	[redacted]	Assumed to be the same as upadacitinib 30 mg.
Dupilumab	3.7%	Assumed to be the same as dupilumab combination therapy
Tralokinumab Q2W	[redacted]	ECZTRA 2. Conditional discontinuation data based on those achieving EASI 75 for the ECZTRA 7-like population (n/N = [redacted])
Tralokinumab Q4W	[redacted]	Pooled data based on those achieving EASI 75 for the ECZTRA 7-like population from ECZTRA 1 (n/N = [redacted]) and ECZTRA 2 (n/N = [redacted]).
Upadacitinib 15 mg	[redacted]	Pooled data from Measure UP 1 (n/N = 1/28) and Measure UP 2 (n/N = 1/52). Only second-line systemic treatment reported.

Upadacitinib 30 mg	[redacted]	Pooled data from Measure UP 1 (n/N = 1/25) and Measure UP 2 (n/N = 2/43). Only second-line systemic treatment reported.
Combination therapy – Adults, EASI 50 + DLQI ≥4		
Abrocitinib 100 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Abrocitinib 200 mg	[redacted]	Assumed to be the same as upadacitinib 30 mg.
Dupilumab	3.7%	TA534. Estimate accepted by the committee. Data based on annual discontinuation in CHRONOS, defined as non-completers in the 52-week treatment period among responders at week 16.
Tralokinumab Q2W	[redacted]	Assumed to be the same as tralokinumab Q2W monotherapy.
Tralokinumab Q4W	[redacted]	Assumed to be the same as tralokinumab Q4W monotherapy.
Upadacitinib 15 mg	[redacted]	AD UP. Data are based on second-line systemic treatment subgroup only (n/N = 6/47).
Upadacitinib 30 mg	[redacted]	AD UP. Data are based on second-line systemic treatment subgroup only (n/N = 3/54).
Monotherapy – Adolescents (EASI 75)		
Abrocitinib 100 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Abrocitinib 200 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Dupilumab	5.1%	TA534. Data based on annual discontinuation in CHRONOS, defined as non-completers in the 52-week treatment period among EASI 75 responders at week 16 (n/N = 4/78).
Upadacitinib 15 mg	[redacted]	Pooled data from Measure UP 1 (n/N = 6/32) and Measure UP 2 (n/N = 2/22).

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; Q2W, once every two weeks; Q4W, once every four weeks.

5.2.1.5.2 Long-term treatment discontinuation

No long-term (year 2 onwards) treatment discontinuation data are available for any of the treatments considered in the model. In TA534, the annual treatment discontinuation rate for dupilumab (3.7%) was based on the observed probability of week 16 responders discontinuing treatment by week 52, which was accepted by the committee. In TA681, the Evidence Review Group (ERG) preferred the use of all-cause discontinuation data observed between week 16 and 52 to model a single discontinuation rate across both the 16 to 52 week and post 52-week periods for baricitinib (data are redacted). However, it should be noted that in both TA534 and TA681, the

annual discontinuation data based on conditional discontinuations is for the period between week 16 and week 52 and therefore represents 36-week data and not 52-week data.

The company for tralokinumab followed the same approach to long-term treatment discontinuation accepted in TA534 and TA681 in their economic model. Specifically, 56-week conditional treatment discontinuation data for tralokinumab from the full trial population in ECZTEND (which includes patients from ECZTRA 1,2 and 3 as well as from ECZTRA 4, 5 and 6) were used in the model. The annual rate of discontinuation from tralokinumab due to adverse events or lack of efficacy in ECZTEND was 2.3% among patients who achieved EASI 50 & ΔDLQI ≥ 4 at week 16 in their parent study.

In the upadacitinib model, the company used 52-week treatment discontinuation data (based on response status at week 16) from AD UP to model annual discontinuations. The annual rate of treatment discontinuation for upadacitinib 15 mg and 30 mg was [redacted] and [redacted], respectively, but this was based responders to EASI 75 and non-responders in the intention-to-treat population in AD UP. It should be noted that upadacitinib conditional discontinuation data from AD UP in the EAG base case is also based on the 52-week data cut but specifically for responders to the composite outcome and EASI 75 for scenario analyses. In the abrocitinib model, the company used the conditional discontinuation data at Week 52, converted to an annual probability to inform the long-term treatment discontinuation rate.

For consistency, the EAG has adopted the approach accepted in TA534 and TA681 for long-term treatment discontinuation for the base case. Specifically, it is assumed for the economic model that the long-term treatment discontinuation rate is equal to the conditional discontinuation rate for each treatment presented in Table 41. The EAG recognises that using conditional discontinuation data does not represent an annual rate, but rather a 36-week rate. However, there is a lack of long-term data on treatment discontinuation to suggest whether or not rates are likely to increase for patients with a long-term response to treatment. Furthermore, as discussed in Section 5.2.1.6, the EAG has assumed that treatment waning also results in treatment discontinuation. Nonetheless, the EAG explored a scenario where conditional discontinuation data is converted to an annual rate for completeness. Additionally annual treatment discontinuation data from ECZTEND for the ECZTRA-7 like population was only considered in scenario analyses due to limitations with the data, discussed in Section 5.2.1.5.1.

5.2.1.6 Treatment waning

Over time, patients may lose response to treatment, whether on active treatment with biologics or BSC. In TA534, assumptions around treatment effect waning were included in the company's economic model and accepted by the committee. The TA534 final appraisal decision (FAD) states, "*In the dupilumab maintenance state, the company assumed that 2% of the benefit would be lost in year 2, 5% in year 3, 7% in year 4, and 8% in year 5 and beyond. It used these estimates to adjust down the proportion of people who continued to have dupilumab (that is, those who lost the benefit of dupilumab moved to the best supportive care state and then accrued the utility associated with that state)*".

In the company submissions for abrocitinib, tralokinumab and upadacitinib and in TA681, treatment waning assumptions were influenced by the approach in TA534 due to a lack of data in the key trials for the drugs. However, as outlined in Table 118 and described below, the assumptions and implementation of active treatment waning in TA534 have been interpreted in various ways by the companies for baricitinib (TA681), abrocitinib, tralokinumab and upadacitinib.

Active treatment waning proportions in the abrocitinib and upadacitinib models were taken from TA534. In the abrocitinib model, by year 5 and beyond 8% of patients on active treatment would lose response. However, between year 2 and 5 in the upadacitinib model, up to 8% of patients experienced treatment waning and from year 6 up to year 10, a further 1% per year were assumed to lose response, with no further waning beyond year 10. For the tralokinumab base case, it was assumed that between 2-3% of patients would lose treatment response annually up to year 4, with 1% losing treatment response annually from year 5 onwards.

The implementation of active treatment waning in the tralokinumab and upadacitinib models was similar to TA534, with patients discontinuing to BSC upon treatment waning. However, in the upadacitinib model, when patients on active treatment move to the BSC health state upon treatment waning, they first incur utility of BSC non-responders then gradually return to the baseline utility following BSC non-responders treatment waning rates (See Appendix 10.8 for details on BSC treatment waning). In TA681 and the abrocitinib model, patients on active treatment were assumed to incur a utility loss. In TA681, patients returned to baseline utility upon treatment waning and in the abrocitinib model, non-responder utilities were applied to patients who lost response.

For the MTA model, the EAG has adopted the active treatment waning approach accepted in TA534. Specifically, the EAG has assumed that in years 2, 3, 4 and 5 onwards, 2%, 5%, 7% and 8% of patients will lose response to active treatment and discontinue to BSC. Thus, as soon as patients no longer achieve EASI 50 + DLQI ≥4, they are considered non-responders. The EAG acknowledges that there may be overlap between the proportion of patients losing response to treatment and long-term all-cause treatment discontinuation, as lack of efficacy is included as a reason to stop treatment. However, due to lack of data, the size of the overlap between treatment waning and all-cause discontinuation is unknown and as such the EAG approach can be considered conservative. The EAG included long-term all cause treatment discontinuation and treatment waning proportions in one-way sensitivity analysis (OWSA) to determine if these parameters are key drivers of cost-effectiveness and results are presented in Section 5.2.2. Furthermore, the EAG included a scenario analysis where no active treatment effect waning was assumed.

Unlike TA534, TA681 and the company economic models, BSC is not a comparator in the EAG model but a single health state that patients transition to due to lack or loss of response to treatment or treatment discontinuation for other reasons. As described in Section 5.2.1.3, BSC is modelled as a weighted average of responders and non-responders to BSC to reflect the waxing and waning nature of AD and thus captures treatment effectiveness fluctuations. As such, the EAG has assumed no additional treatment waning for the BSC health state, which is in line with the ERG's preferred approach in TA681 (see Appendix 10.8). The committee for TA681 considered that the ERG's approach represented different patients moving in and out of disease control over time, but treatment waning would be between the ERG's approach (no waning, BSC modelled as a single health state of 50% responders and 50% non-responders) and the company's approach based on TA534 (up to 97% of BSC patients lose response). However, the committee for TA681 did not give further direction on how to model treatment waning in the BSC health state. To explore the uncertainty around BSC waning, baseline placebo response has been included in the OWSA (which informs the BSC health state), as well as scenarios exploring shorter time horizons.

Further information on the BSC treatment waning assumptions adopted in TA534 and TA681, and assumptions used in the company models can be found in Appendix 10.8.

5.2.1.7 Mortality

Treatments for moderate-to-severe AD are not expected to affect mortality. In TA534, TA681 and the companies' submissions, all-cause mortality was estimated using the Office of National Statistics

(ONS) National Life Tables for England and Wales.[145] As such, the EAG has also used ONS National Life Tables for England and Wales to estimate age-adjusted all-cause mortality in the economic model.

5.2.1.8 Adverse events

Adverse events (AEs) included in the EAG's economic model are in line with those included in TA534 and TA681 and were considered the most important to include by the EAG's clinical experts. In TA534, the most frequent and serious AEs reported in the dupilumab trials were included and these were injection site reaction, allergic conjunctivitis, infectious conjunctivitis and oral herpes. TA681 also included the most frequent and serious AEs reported in the baricitinib trials, as well as those from TA534, with the only addition to the included AEs being upper respiratory tract infection. The company for tralokinumab only included the TA534 AEs in their economic model. In the abrocitinib and upadacitinib models, AEs with an incidence of >5% in the intervention trials, dupilumab trials, TA534 and TA681 were included but no detail was provided for the severity of the AEs. Furthermore, the company for upadacitinib excluded oral herpes from included AEs as clinical advice suggested that patients with oral herpes would self-medicate with over-the-counter medication. However, in TA534 the cost associated with oral herpes was for a GP visit and the EAG considers it should be included in the cost-effectiveness analysis. Please refer to Appendix 10.9 for a comparison of AEs included in TA534, TA681 and the company models.

The EAG's approach to AEs is generally in line with TA534, TA681 and the company models and includes serious AEs with an incidence of >5% in any treatment arm. The EAG reviewed and extracted data on AEs from publications included in the clinical SLR, company submissions and appendices, company clarification responses and committee papers from TA534 and TA681. The available clinical study reports (CSRs) for abrocitinib, tralokinumab and upadacitinib studies were also searched for the AEs of interest where there was missing data. As the EAG included specific AEs which may not be applicable or captured for all treatments in the model, an NMA on individual AEs was not deemed to be appropriate.

The AEs included in the EAG's economic model are injection site reaction, allergic conjunctivitis, infectious conjunctivitis, oral herpes, upper respiratory tract infection and acne. In the upadacitinib model skin infections were included and in the abrocitinib model folliculitis, headache, nausea, pharyngitis and nasopharyngitis but these were excluded from the EAG model as the severity of these events could not be determined, these AEs are easily treated, and a cost to the NHS is rarely

incurred. The EAG considered that the definition of infectious conjunctivitis in the companies' models is based on the Medical Dictionary for Regulatory Activities (MedDRA) term 'conjunctivitis' (system organ class of infections and infestations), which is likely to reflect infectious conjunctivitis. To maintain consistency across the analysis, the EAG extracted data for conjunctivitis to inform the AE rate for infectious conjunctivitis.

Data on AEs for CsA were unavailable. In TA534, the committee accepted assuming zero AEs for CsA in the short-term as treatment is only given for one year before patients move to BSC and this assumption has been carried forward in the EAG economic model.

AEs for BSC were based on placebo data from AD-UP. As mentioned in Section 5.2.1.1.1, baseline characteristics from the upadacitinib trials were deemed to be representative of the population who would be treated in clinical practice in England according to the EAG's clinical experts. The EAG has assumed the BSC AE rate for monotherapy is the same as combination therapy because in clinical practice BSC includes TCS.

Table 42 presents the 16-week AE rates included in the EAG economic model. Weekly and annual rates of AEs were calculated from the 16-week data for the short- and long-term model. The rates of AEs were used to estimate the costs to treat an AE only as it was assumed that the health-related quality of life data collected in the trials and used in the model would capture the acute impact of AEs. The EAG's approach is in line with TA534 and TA681, as well as the approach adopted in the company models for abrocitinib, tralokinumab and upadacitinib. Please refer to Section 5.2.1.11.6 for AE costs used in the economic model.

Table 42. 16-week adverse event rates

Treatment	Injection site reaction	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Source/ assumptions
Monotherapy - Adults							
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE MONO 1, MONO 2 and Silverberg 2020[146]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE MONO 1, MONO 2 and Silverberg 2020[146]
Dupilumab	10.97%	3.01%	4.30%	3.66%	2.80%	0.00%	Pooled data from SOLO1 and SOLO2
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ECZTRA 1, ECZTRA 2 and Wollenberg 2021[35]
Upadacitinib 15 mg	0.00%	0.21%	0.62%	2.49%	6.85%	5.44%	Pooled data from Measure UP 1 and Measure UP 2
Upadacitinib 30 mg	0.00%	0.41%	1.02%	4.49%	9.18%	16.46%	Pooled data from Measure UP 1 and Measure UP 2
Combination therapy - Adults							
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE COMPARE
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE COMPARE
Baricitinib	0.00%	0.00%	0.00%	3.60%	2.70%	3.60%	BREEZE AD 7 (Reich 2020)[97]
BSC	0.00%	0.33%	1.65%	1.65%	6.93%	1.98%	Placebo data from AD UP
CsA	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Assumption accepted in TA534[12]
Dupilumab	5.53%	10.60%	5.53%	2.76%	3.69%	0.00%	Pooled data from CHRONOS and CAFE
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ECZTRA 3 and Silverberg 2021[37]
Upadacitinib 15 mg	0.00%	0.00%	1.15%	3.83%	7.66%	9.58%	AD UP
Upadacitinib 30 mg	0.00%	0.77%	0.77%	8.85%	7.31%	13.85%	AD UP
Monotherapy - Adolescents							
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE TEEN

Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	JADE TEEN
BSC	0.00%	0.00%	0.00%	0.00%	2.56%	0.00%	AD UP
Dupilumab	8.54%	3.66%	4.88%	0.00%	12.20%	0.00%	AD ADOL (Simpson 2019[99])
Upadacitinib 15 mg	0.00%	1.33%	0.00%	0.00%	14.67%	13.33%	Pooled data from Measure UP 1 and Measure UP 2
Abbreviations: BSC, best supportive care; CsA, ciclosporin; mg, milligram.							

5.2.1.9 Flares

During treatment for moderate-to-severe AD, patients may experience acute exacerbations of symptoms, called flares. The rate of flare can vary depending on the treatment received by a patient but treatments for flare are similar.

Flare rate was not an endpoint in the key studies described in Section 4.2.1. In TA534 and TA681, the receipt of rescue medication was accepted as a proxy for flare. Furthermore, the companies for tralokinumab and upadacitinib used receipt of rescue medications from their key trials to inform the rate of flare used in their economic models. However, the company for abrocitinib had data on protocol defined flares from REGIMEN and this was used to inform their economic model.

The EAG requested 16-week data on the receipt of rescue medication (used as a proxy for flare, in line with TA534 and TA681) or rate of flare. Each company supplied the requested data, presented in Table 43 and this has been used in the EAG's economic model. The flare rate for dupilumab were extracted from TA534 and data for baricitinib were obtained from Reich 2020.[97] Like with AEs, the flare rate for BSC was based on placebo data from AD-UP. However, unlike the data for AEs, flare data is split by first- and second-line systemic treatment. As mentioned in Section 5.2.1.1.1, baseline characteristics from the upadacitinib trials were deemed to be representative of the population who would be treated in clinical practice in England according to the EAG's clinical experts. The EAG has assumed the BSC flare rate for monotherapy is the same as combination therapy because in clinical practice BSC includes TCS.

For abrocitinib, receipt of rescue medication in JADE COMPARE, MONO 1 and MONO 2 was prohibited. However, protocol defined flare data at 40-weeks from REGIMEN were available for abrocitinib (reported in the company submission) and this was used to inform the annual rate of flare for both adults (second-line systemic treatment) and adolescents for monotherapy and combination therapy, in line with the company's preferred approach. Additionally, the annual rate of flare for abrocitinib was used to calculate a weekly rate of flare to be used in the short-term part of the economic model.

Table 43. Treatment specific flare rates

Treatment	Rate of flare			Source/ assumptions
	16-week	Weekly	Annual	
Monotherapy - Adults				

Abrocitinib 100 mg	N/A	1.06%	42.60%	Receipt for rescue medication was not permitted in JADE MONO 1/2. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
Abrocitinib 200 mg	N/A	0.40%	18.90%	Receipt for rescue medication was not permitted in JADE MONO 1/2. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
Dupilumab	17.94%	1.23%	47.53%	16-week data from SOLO1 (n/N = 47/224) & SOLO2 (n/N = 35/233), reported in TA534 (pooled n/N = 82/457).
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	Pooled 16-week data ECZTRA 7-like population from ECZTRA 1 (n/N = [redacted]) & ECZTRA 2 (n/N = [redacted]).
Upadacitinib 15 mg – **second-line**	[redacted]	[redacted]	[redacted]	Pooled 16-week data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted]).
Upadacitinib 30 mg – **second-line**	[redacted]	[redacted]	[redacted]	Pooled 16-week data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted]).
Combination therapy - Adults				
Abrocitinib 100 mg	N/A	1.06%	42.60%	Receipt for rescue medication was not permitted in JADE COMPARE. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
Abrocitinib 200 mg	N/A	0.40%	18.90%	Receipt for rescue medication was not permitted in JADE COMPARE. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
Baricitinib	5.41%	0.35%	16.58%	16-week data from BREEZE-AD7 (n/N = 6/111)[97]
BSC – **First-line**	[redacted]	[redacted]	[redacted]	16-week placebo data from AD-UP (n/N = [redacted])
BSC – **Second-line**	[redacted]	[redacted]	[redacted]	16-week placebo data from AD-UP (n/N = [redacted])
CSA	[redacted]	[redacted]	[redacted]	Assumed to be the same as first-line upadacitinib 15/30 mg (flare rate is the same for both doses). Treatment with CSA is only given for a maximum of

				one year, after which, all patients move to BSC.
Dupilumab	N/A	0.34%	16.04%	52-week data from CHRONOS, reported in TA534 (n/N = 17/106).
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	Pooled 16-week data from ECZTRA 7 (n/N = [redacted]) and ECZTRA 7-like population from ECZTRA 3 (n/N = [redacted])
Upadacitinib 15 mg – **First line**	[redacted]	[redacted]	[redacted]	16-week data from AD-UP (n/N = [redacted])
Upadacitinib 30 mg – **First line**	[redacted]	[redacted]	[redacted]	16-week data from AD-UP (n/N = [redacted])
Upadacitinib 15 mg – **Second line**	[redacted]	[redacted]	[redacted]	16-week data from AD-UP (n/N = [redacted])
Upadacitinib 30 mg – **Second line**	[redacted]	[redacted]	[redacted]	16-week data from AD-UP (n/N = [redacted])
Monotherapy - Adolescents				
Abrocitinib 100 mg	N/A	1.06%	42.60%	Receipt for rescue medication was not permitted in JADE MONO 1/2. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
Abrocitinib 200 mg	N/A	0.40%	18.90%	Receipt for rescue medication was not permitted in JADE MONO 1/2. 40-week data from REGIMEN used in long-term model, taken from the company submission. Annual data used to calculate weekly rate.
BSC	[redacted]	[redacted]	[redacted]	Pooled 16-week placebo data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted]).
Dupilumab	20.73%	1.44%	53.12%	16-week data from AD ADOL (n/N = 17/82)[99]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	Pooled 16-week data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted]).

Abbreviations: BSC, best supportive care; mg, milligram; N/A, not available

The rate of flare was applied in the short-term model by converting the available treatment specific data into weekly rates. For the long-term model, annual rates of flare were estimated from the 16-week data, except for dupilumab and abrocitinib where annual flare data were already available. Flare rates were used to estimate the costs to treat a flare only as it was assumed that the health-related quality of life data collected in the trials and used in the model would capture the acute impact of flares. The EAG's approach is in line with TA534 and TA681, as well as the approach

adopted in the company models for abrocitinib, tralokinumab and upadacitinib. Please refer to Section 5.2.1.11.5 for flare costs used in the economic model.

5.2.1.10 Health-related quality of life

For each of the drugs considered in the MTA, their key trials all collected EQ-5D-5L data, which in the companies' submissions were mapped to the EQ-5D-3L using the van Hout crosswalk algorithm,[144] as per the NICE reference case.[147] Each of the companies developed regression models to estimate utility values to be used in their models. They also estimated baseline, responder and non-responder values, according to subgroup and measure of response. The companies for abrocitinib and tralokinumab estimated utility values by type of therapy (combination therapy or monotherapy). Disutility values associated with AEs and flares were not included in the companies' models as per TA534 and TA681. Please refer to Table 118 for an overview of the companies approaches and assumptions accepted in TA534 and TA681.

Treatment-specific utility values were adopted by the companies for abrocitinib and tralokinumab, as this approach was accepted in TA534 and TA681. Furthermore, in TA534 it was accepted that non-responders on dupilumab accrued the average utility of a dupilumab non-responder and BSC non-responder (0.82) at week 16 after starting treatment, and after week 52 accrued the utility value of BSC non-responders (0.77). The TA534 approach was adopted by the companies for abrocitinib and tralokinumab. However, in the abrocitinib model utility values were used to capture the benefit of early response to systemic treatment prior to the week 16 assessment point. In the upadacitinib model, utility values were not treatment-specific, thus no weighting of systemic treatment non-responder and BSC non-responder values was implemented. However, utility values were used to capture the benefit of early response to upadacitinib treatment prior to the week 16 assessment point.

Due to the variation in the approach to utilities across the companies models, TA681 and TA534, a consistent and conservative approach to utilities for all treatments is adopted in the MTA model. It is worth noting that unlike in TA534, TA681 and the companies models, BSC is not a comparator in the EAG's model. As mentioned previously, BSC is modelled as an average of responders and non-responders to BSC treatment to capture the waxing and waning nature of response. The implication of BSC as a comparator in the previous models is that it was reasonable to assume that being on systemic treatment but not achieving response was still likely to result in an improvement in HRQoL over and above BSC in the short term, hence the assumption being accepted in TA534.

However, as the three new drugs are only being compared against currently available systemic treatments in the MTA model and BSC is only a health state and not an independent comparator, the EAG took a conservative approach to use treatment-specific baseline utilities for week 0 to 16, treatment-specific responder utility values for those who achieve and maintain response to treatment and the weighted average utility of responders and non-responders to BSC for non-responders to treatment and those who discontinue treatment (Table 44 and Table 45).

As such, the benefit of systemic treatment remains only for those who respond to treatment. Given the remit of the MTA and the approach to the BSC, the EAG considers this a necessary deviation from the approach accepted in TA534 and can be considered conservative.

The EAG investigated the utility regressions and resulting utility values from each of the company submissions to assess the suitability of the data for the MTA model but found that that definition of the populations used to estimate utilities in each of the companies' models was not aligned with definitions used in the EAG analysis (see Section 4.1.5 and 5.2.1.1). Furthermore, monotherapy and combination therapy specific utility values were not available in the upadacitinib company submission. Thus, from each of the companies the EAG requested health state utility values based on the relevant subgroups from the key trials, by response category (composite and EASI 75), dose (where applicable) and type of therapy (monotherapy and combination therapy). Additionally, the EAG requested data on the number of observations at each assessment point to gauge the size of the datasets informing the utility regressions and aid choice of which utilities should inform the drug class estimates.

All three companies provided the requested utility data to the EAG in time for the development of the economic model. The utility data provided by the company for abrocitinib was subject to several issues which made the suitability for use in the MTA model limited. Utility data for abrocitinib in the adolescent population using the EASI 75 measure of response were not provided, which is relevant for the adolescent analyses. The company did provide utility data for adult second-line systemic population for both the composite and EASI 75 outcomes and monotherapy and combination therapy. The abrocitinib utility analyses use data from the full trial populations of the relevant JADE trials and apply the baseline characteristics of relevant populations (generalisable and restricted) to generate utility values. However, as mentioned in Section 4.2.1.1, a fundamental issue with the JADE trial programme is that most of the trial populations aren't relevant to the decision problem (patients are predominantly naïve to systemic treatment). Thus the patient numbers informing the

post hoc subgroups that are relevant to this appraisal are small and potentially may result in unreliable estimates of utility.

The companies for tralokinumab and upadacitinib provided complete data for the populations that are relevant to proposed position in the pathway for their drugs. The utilities provided warranted further examination by the EAG in light of other available data.

As part of the HRQoL SLR (Section 5.1.3), the EAG extracted utility data from TA534 and TA681 for dupilumab and baricitinib. The baricitinib values were available for the composite outcome and combination therapy for the adult second-line systemic treatment, but in the MTA analyses outcome data for baricitinib are only available for EASI 75. Additionally, the committee for TA681 concluded that, given the flaws with the company's utility values, the utility values from TA534 were preferable. From TA534, utility values for dupilumab were available for monotherapy and combination therapy for the adult second-line systemic treatment population, but no data were available for adolescents.

As such, to account for limitations associated with missing data, uncertainty due to small numbers and relevance of the populations for utility values, the EAG decided to adopt a drug class approach for utility values in the model. The drug class approach was considered to be appropriate as the drugs considered in the economic model fall into two classes: Janus Kinase (JAK) inhibitors (abrocitinib, baricitinib and upadacitinib); and monoclonal antibodies (dupilumab and tralokinumab). The EAG considers that health related quality of life is unlikely to be affected by different treatments within a drug class but there could be differences across different drug classes due to the mode of action and administration of treatment. As such, company's utility values for tralokinumab were used to inform the base case for the monoclonal antibody drug class and upadacitinib utility values were used for the JAK inhibitors.

The EAG employed a simplification for JAK inhibitors, using available high and low dose and mapping values to high and low dose treatments. For the scenario analyses that included baricitinib, there was uncertainty around whether 4 mg can be considered a high dose JAK inhibitor (a 2 mg dose is available but not recommended for treatment of AD). Additionally, both doses of abrocitinib and upadacitinib are more effective than baricitinib 4 mg. As such, the EAG explored two scenarios for the baricitinib analyses using either high dose or low dose JAK inhibitors utility values (see Section

5.2.2.4). Notably, analyses that include baricitinib are only considered in a scenario and not the EAG base case due to lack of the composite outcome for baricitinib.

With regards to CsA, utility values were assumed to be the same as upadacitinib 15 mg or 30 mg (depending on the comparison). In the adolescent population, as there are no monoclonal antibody utility values, the EAG assumed the tralokinumab monotherapy adult second-line systemic treatment utility values for dupilumab monotherapy.

The weighted utility values for BSC responders and non-responders were based on the upadacitinib placebo utility values for the relevant population as baseline characteristics and BSC response status reflect the upadacitinib trials. Table 44 and Table 45 presents the utility values used in the economic model. Please refer to Appendix 10.10 for an overview of the companies' regression models used to estimate the utility values used in the EAG base case analysis and EASI 75 utilities for the adult second-line systemic treatment population. The EAG also explored a scenario where utility values for TA534 (presented in Appendix 10.10.2) were used for all the populations.

Table 44. Drug class utility values

Health state	JAK inhibitor – low dose	JAK inhibitor – high dose	Monoclonal antibody	Source/ assumptions
Adult first-line systemic treatment, combination therapy - EASI 75				
Baseline	[redacted]	[redacted]	-	AD UP CSA assumed to be the same as JAK inhibitors.
Responder	[redacted]	[redacted]	-	
Adult second-line systemic treatment, monotherapy - EASI 50 + DLQI ≥4				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – Measure UP 1 & 2 Monoclonal antibody – ECZTRA 7-like subgroup from ECZTRA 1 & 2
Responder	[redacted]	[redacted]	[redacted]	
Adult second-line systemic treatment, combination therapy - EASI 50 + DLQI ≥4				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – AD UP Monoclonal antibody – ECZTRA 7 and ECZTRA 7-like subgroup from ECZTRA 3
Responder	[redacted]	[redacted]	[redacted]	
Adolescents, monotherapy - EASI 75				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – Measure UP 1 & 2 Monoclonal antibody – ECZTRA 7-like subgroup from ECZTRA 1 & 2
Responder	[redacted]	[redacted]	[redacted]	

Abbreviations: CSA, ciclosporin; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

Table 45. BSC utility values

BSC	Utility value	Source/ assumptions
Adult first-line systemic treatment, combination therapy - EASI 75		
Responder	[redacted]	AD UP. Combination data used as patients in the BSC likely to get TCS as a subsequent treatment.
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]
Adult second-line systemic treatment, monotherapy - EASI 50 + DLQI ≥4		
Responder	[redacted]	Measure UP 1 and 2
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]
Adult second-line systemic treatment, combination therapy - EASI 50 + DLQI ≥4		
Responder	[redacted]	AD UP
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]
Adolescents, monotherapy		
Responder	[redacted]	Measure UP 1 and 2
Non-responder	[redacted]	
Weighted average	[redacted]	Responders to BSC = [redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

Disutilities associated with AEs have not been included in the EAG's economic model in line with TA534, TA681 and the companies' models. It has been assumed that due to the frequency of capturing EQ-5D data in the upadacitinib and tralokinumab trials, the impact of AEs on HRQoL will be captured in the data.

Utility values in the model are adjusted for age based on UK population norms using the multiplicative method detailed in Ara and Brazier 2010.[148] The general population EQ-5D regression calculation used to estimate the multiplier in the model is as follows:

*General Population, EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2*

The age multiplier was the calculated by taking the general population utility value for age at time *t* in the model and dividing it by the general population utility value for the baseline age of the relevant subgroup.

5.2.1.11 Resource use and costs

The following cost categories are included in the model:

- Drug acquisition costs (Section 5.2.1.11.1);
- Drug administration costs (Section 5.2.1.11.2);
- Concomitant medication costs (Section 5.2.1.11.3);
- Health care resource use costs (monitoring costs) (Section 5.2.1.11.4);
- Costs of managing flares (Section 5.2.1.11.5);
- Costs of managing AEs (Section 5.2.1.11.6).

The economic analysis is conducted from an NHS and personal social services perspective and therefore only includes costs that would be incurred by the NHS and personal social services. Costs are reported in pound sterling for a 2019/20 cost year. Drug costs have been sourced from the British National Formulary (BNF) and electronic drug marketing tool (eMIT), while service costs have been sourced from the National Schedule of NHS Costs and Personal Social Services Research Unit (PSSRU).

5.2.1.11.1 Drug acquisition costs

The drug acquisition costs included in the model are given in Table 46. The BNF was used to inform the cost of CsA, dupilumab, baricitinib, tralokinumab and upadacitinib 15mg. Company submissions were used to inform the cost of upadacitinib 30mg and abrocitinib 100 mg and 200 mg in the absence of publicly available costs. Confidential patient access schemes (PAS) are in place for all drugs, except CsA. Please refer to the confidential appendix for drug acquisition costs including PAS discounts.

Treatments costs for treatment induction (Weeks 1-16) and per year are given in Table 47. The BNF was used to inform the dosing schedules for dupilumab, baricitinib and upadacitinib, while SmPC guidance were used to inform the dosing schedules for abrocitinib.

For weight-based dosing of CsA, baseline weight reported in adults in the AD UP study of 77.2 kg is used in the model. As described in Section 5.2.1.2, the recommended dose range for CsA is 2.5 to 5 mg/kg/day and treatment is individualised.[149] According to the EAG's clinical experts, there is no clinical consensus on a typical CsA dose for patients with moderate-to-severe AD and depends largely on the treating clinician. In TA534, the dose accepted by the committee was 5mg/kg for 6 weeks followed by 3mg/kg for 46 weeks (maximum treatment duration of one year) and this has been used for the EAG base case. After one year of treatment with CsA, patients discontinue to BSC

for the remainder of the model time horizon. The following alternative CsA doses are explored in sensitivity analysis:

- Clinical expert opinion – 3mg/kg for 16 weeks followed by 5mg/kg for 36 weeks;
- Ariens *et al.* 2019[88] – 5mg/kg for 3 weeks followed by 2mg/kg for 48 weeks.

The treatments under consideration can be given as monotherapies or in combination with TCS. The costs associated with TCS can be found in Section 5.2.1.11.3 (concomitant medication costs).

The recommended treatment regimen as per the SmPC for tralokinumab is 300 mg Q2W and this is used for the base case. A scenario for tralokinumab was explored where a percentage of patients switched to Q4W treatment regimen. The tralokinumab treatment switching scenario was explored as the SmPC for tralokinumab states that at the prescriber's discretion, frequency of dose can be reduced to Q4W for patients who achieve clear or almost clear skin after 16 weeks of treatment. Data on the number of patients entering maintenance phase by dose in ECZTRA 3 (ECZTRA 7-like subgroup) for combination therapy and pooled data on the ECZTRA-7 like population from ECZTRA 1 and ECZTRTA 2 for monotherapy were extracted from the tralokinumab company submission to calculate the proportion of patients who switched to the Q4W regimen. For the monotherapy analysis, [redacted] switched from Q2W to Q4W and for combination therapy [redacted] switched and these data have been used in the scenario, presented in Section 5.2.2.4. The percentage of tralokinumab patients switching to Q4W dosing in the EAG's scenario is similar the [redacted] assumed the company's submission, which was used for the company's base case analysis.

Table 46. Drug acquisition costs

Treatment	Pack size	List price	
		Pack cost	Cost per unit
Oral			
CsA, 100mg capsules	30	£41.59	£1.39
CsA, 50mg capsules	30	£21.80	£0.73
CsA, 25mg capsules	30	£11.14	£0.37
CsA, 10mg capsules	60	£12.75	£0.21
Baricitinib, Olumiant 2mg and 4mg tablets (Eli Lilly and Company Ltd)	28	£805.56	£28.77
Upadacitinib, Rinvoq 15mg modified-release tablets (AbbVie Ltd)	28	£805.56	£28.77
Upadacitinib, Rinvoq 30mg modified-release tablets (AbbVie Ltd)	28	[redacted]	[redacted]

Abrocitinib, CIBINQO 100mg and 200mg tablets (Pfizer)	28	[redacted]	[redacted]
Subcutaneous injection			
Dupilumab, Dupixent 300mg/2ml solution for injection pre-filled pens or syringes (Sanofi)	2	£1,264.89	£632.45
Tralokinumab, Adtralza 150 mg pre-filled syringes (Leo Pharma UK)	4	£1,070.00	£267.50

Abbreviations: CsA, ciclosporin; NA, not applicable; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous

Table 47. Drug acquisition costs per year according to dose

Treatment	Dose	List price	
		Weeks 1-16	Annual
Oral			
CsA	5mg/kg for 6 weeks followed by 3mg/kg for 46 weeks	£449.80	£1,242*
Baricitinib	4 mg once daily	£3,222	£10,508
Upadacitinib	15 mg once daily	£3,222	£10,508
Upadacitinib	30 mg once daily	[redacted]	[redacted]
Abrocitinib	100 mg or 200 mg once daily	[redacted]	[redacted]
Subcutaneous injection			
Dupilumab	Loading: 600 mg (two 300 mg injections) Maintenance: 300 mg (one 300 mg injection) Q2W	£5,692	£16,444†
Tralokinumab	Loading: 600 mg (four 150 mg injections) Maintenance: 300 mg (two 150 mg injections) Q2W	£4,815	£13,910†
Tralokinumab	Maintenance: 300 mg (two 150 mg injections) Q4W^	NA	£6,995†

Abbreviations: CsA, ciclosporin; NA, not applicable; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous
*Total cost in year 1 as CsA treatment is limited to 1 year
^Patients who respond to treatment at week 16 may reduce dose frequency from Q2W to Q4W for maintenance treatment.
†Annual cost in subsequent years (that is, excluding the loading dose)

5.2.1.11.2 Drug administration costs

Based on the resource use assumptions from previous technology appraisals (TA534 and TA681) and verified with the EAG's clinical experts, it is assumed that patients treated with subcutaneous (SC) formulations (dupilumab and tralokinumab) receive training on how to self-administer treatment. It is assumed that each patient only receives one self-injection training session, requiring 30 minutes of patient contact with a hospital-based Band 6 nurse at a cost of £62.50 (PSSRU 2020,[150] note: each hour spent with a client requires 2.5 paid hours). This cost is incurred when the SC treatment is prescribed (that is, the first model cycle).

Leo Pharma has indicated that training on how to self-administer tralokinumab will be provided to the NHS free of charge. As such, no administration costs are incurred by tralokinumab-treated patients in the base case analysis.

Orally administered drugs (CsA, baricitinib, upadacitinib and abrocitinib) are assumed to incur no administration costs in the model.

5.2.1.11.3 Concomitant medication costs

Based on the resource use assumptions accepted in TA681 and verified with the EAG's clinical experts, it is assumed that patients receive concomitant medications, consisting of:

- emollient products;
- mid-potency background TCS (mometasone 0.1% ointment); and,
- Topical calcineurin inhibitors (TCI) (protopic 0.1% ointment).

When TA534 was published, bathing products were frequently used in clinical practice to manage the symptoms of moderate-to-severe AD. Following RCT evidence[151] suggesting bathing products offer no benefits, there has been a significant reduction in the use of bathing products and most NHS trusts no longer prescribe them. Furthermore, the committee for TA681[13] preferred to exclude the costs of bathing products from the cost-effectiveness analysis for baricitinib. As such, the cost of bathing products are excluded in the economic model.

Based on the resource use assumptions accepted from previous technology appraisals (TA534 and TA681) and verified with the EAG's clinical experts, it is assumed that:

- The weekly cost of emollients is derived by averaging the weekly cost of the most commonly prescribed emollients;
- Responders to systemic treatment have a 50% reduction of resource use for concomitant emollients and TCS compared to non-responders; and,
- Responders do not require TCI.

Based on feedback from the EAG's clinical experts, it is assumed that there is no reduction in use of emollients and TCS for patients who discontinue systemic maintenance treatment and go on to BSC.

The concomitant medication costs included in the model are summarised in Table 48. Further details on the sources used to inform concomitant medication costs can be found in Appendix 10.11. As

mentioned in Section 5.2.1.3, costs for the BSC health stated are weighted by the proportion of responders and non-responders to BSC at the week 16 assessment point. The weighted concomitant costs applied to BSC in the base case analysis are given in Table 49.

Table 48. Concomitant medication costs included in the model

Medication	Cost	Source	Responders to systemic treatment		Non-responders		Responders to BSC	
			Amount per week*	Cost per week	Amount per week*	Cost per week	Amount per week*	Cost per week
TCI								
Protopic 0.1% ointment (cost per 60g, g per week)	£45.56	BNF[152]	0.00	£0.00	1.75	£1.33	0.00	£0.00
TCS								
Mometasone 0.1% ointment (cost per 100g, g per week)	£2.58	eMIT[153]	56.70	£1.46	112.04	£2.89	112.04	£2.89
Emollient (cost per pack, packs per week)								
Aveeno cream	£6.47	BNF[152]	0.50	£3.24	1.00	£6.47	1.00	£6.47
Cetraben ointment	£5.39		0.50	£2.70	1.00	£5.39	1.00	£5.39
Dermol cream	£6.63		0.50	£3.32	1.00	£6.63	1.00	£6.63
Diprobase ointment	£5.99		0.50	£3.00	1.00	£5.99	1.00	£5.99
Epaderm ointment	£12.42		0.25	£3.11	0.50	£6.21	0.50	£6.21
Hydromol ointment	£8.31		0.25	£2.08	0.50	£4.16	0.50	£4.16
White soft paraffin 50% / Liquid paraffin 50% ointment	£4.32		0.50	£2.16	1.00	£4.32	1.00	£4.32
Oilatum cream	£5.28		0.25	£1.32	0.50	£2.64	0.50	£2.64
Total cost per week			**£4.08**		**£9.45**		**£8.12**	
Total cost per year			**£212.66**		**£492.83**		**£423.49**	

Abbreviations: BSC, best supportive care; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

*Sourced from TA534

Table 49. Concomitant medication cost applied to BSC in the base case

Response status	Annual cost	Weekly cost	Proportion
First-line systemic treatment – Adults, monotherapy			
Responder	£423.49	£8.12	[redacted]
Non-responder	£492.83	£9.45	[redacted]
Weighted cost	£469.94	£9.01	-
Second-line systemic treatment – Adults, monotherapy			
Responder	£423.49	£8.12	[redacted]
Non-responder	£492.83	£9.45	[redacted]
Weighted cost	£478.96	£9.18	-
Second-line systemic treatment – Adults, combination			
Responder	£423.49	£8.12	[redacted]
Non-responder	£492.83	£9.45	[redacted]
Weighted cost	£464.05	£8.89	-
Adolescents, monotherapy			
Responder	£423.49	£8.12	[redacted]
Non-responder	£492.83	£9.45	[redacted]
Weighted cost	£482.80	£9.25	-

Abbreviations: BSC, best supportive care.

5.2.1.11.4 Health care resource use costs (monitoring costs)

In the model, health care resource use depends on:

- the stage of treatment (induction vs maintenance);
- the treatment response (responder vs non-responder); and,
- the treatment received (BSC and CsA are associated with more visits and test than biologics).

Based on feedback from the EAG's clinical experts, adolescents typically follow the same treatment pathway as adults and therefore healthcare resource use is assumed to be the same for adults and adolescents.

Health care resource use in the economic model is based on the ERG estimates for TA534 and the company estimates for TA681, which were accepted by their relevant appraisal committees and have been verified by the EAG's clinical experts. The types of visits and tests considered in the economic model include:

- outpatient visits to a dermatologist;
- outpatient visits to a dermatology nurse;
- visits to a general practitioner (GP);
- visits to accident and emergency (A&E);
- hospital admissions;
- hospital day case visits;
- full blood counts (FBCs) (an additional test for patients on CsA, JAKis or BSC);
- phototherapy (an additional service for patients who are non-responders to BSC); and,
- psychological support (an additional service for patients who are non-responders to BSC).

When any systemic treatment is initiated, patients are assumed to visit their dermatologist twice during the induction period. These visits are in addition to the ongoing monitoring a dermatologist will provide. The ongoing health care resource use data applied in the economic model, according to response status, is given in Table 50. Further details on the sources used to inform monitoring costs can be found in Appendix 10.11.

Health care resource use is stratified by induction (weekly frequency in year 1) and maintenance (annual frequency in year 2+) to ensure that the right frequency of visits or tests is captured in the appropriate period in the short- and long-term models. It is assumed that resource use in the induction phase of the short-term model is based on non-responders until the initial treatment assessment point (Table 51). This is a deviation from the approach in TA681, where responder resource use estimates were applied in the treatment induction phase (weeks 0-16). However, the EAG considered that assuming non-responder resource use until treatment response is assessed at week 16 is a conservative assumption for all treatment arms.

It should be noted that for patients on JAK inhibitors, additional FBC monitoring is required. In TA681, the committee accepted that 4 FBCs per annum would be required for patients on baricitinib. Furthermore, in the company submissions for abrocitinib and upadacitinib, 4 FBCs per annum were assumed for the base case analyses. As such, the EAG has assumed that patients on treatment with a JAK inhibitor incur the costs of 4 FBCs per annum (including the induction period).

Table 50. Ongoing health care resource use

Visit/test	Unit cost	Number per annum			Cost per annum			Number per week			Cost per week		
		Responder (MAB)	Responder (BSC/ JAKi)	Non-responder (BSC)	Responder (MAB)	Responder (BSC/ JAKi)	Non-responder (BSC)	Responder (MAB)	Responder (BSC/ JAKi)	Non-responder (BSC)	Responder (MAB)	Responder (BSC/ JAKi)	Non-responder (BSC)
Dermatologist outpatient consultation	£124.83	4.320	4.320	6.000	£539.27	£539.27	£748.98	0.083	0.083	0.115	£10.34	£10.34	£14.35
Dermatologist nurse visit	£31.25	0.350	0.350	0.460	£10.94	£10.94	£14.38	0.007	0.007	0.009	£0.21	£0.21	£0.28
GP consultation	£39.00	6.150	6.150	12.810	£239.85	£239.85	£499.59	0.118	0.118	0.246	£4.60	£4.60	£9.57
A&E visit	£170.98	0.021	0.021	0.082	£3.59	£3.59	£14.02	0.000	0.000	0.002	£0.07	£0.07	£0.27
Hospitalisation	£1,611.14	0.017	0.017	0.130	£27.39	£27.39	£209.45	0.000	0.000	0.002	£0.52	£0.52	£4.01
Day case	£439.00	0	0.000	0.200	£0	£0	£87.80	0	0.000	0.004	£0	£0.00	£1.68
FBC	£2.58	0	4.000	4.000	£0	£10.32	£10.32	0	0.077	0.077	£0	£0.20	£0.20
Phototherapy	£107.24	0	0.000	0.060	£0	£0	£6.43	0	0.000	0.001	£0	£0.00	£0.12
Psychological support	£324.88	0	0.000	0.070	£0	£0	£22.74	0	0.000	0.001	£0	£0.00	£0.44
Total cost					**£821.03**	**£831.35**	**£1,613.71**				**£15.74**	**£15.93**	**£30.93**

Abbreviations: A&E, accident and emergency; BSC, best supportive care; FBC, full blood count; GP, general practitioner; JAKi, Janus Kinase inhibitor; MAB, monoclonal antibody.

Table 51. Monitoring costs applied to non-responders before the initial assessment point

Visit/ test	Unit cost	Number per annum	Number per week	Cost per week
Dermatologist outpatient consultation	£124.83	6.000	0.115	£14.35
Dermatologist nurse visit	£31.25	0.460	0.009	£0.28
GP consultation	£39.00	12.810	0.246	£9.57
A&E visit	£170.98	0.082	0.002	£0.27
Hospitalisation	£1,611.14	0.130	0.002	£4.01
Day case	£439.00	0.200	0.004	£1.68
Total cost				**£30.17**

Abbreviations: A&E, accident and emergency; BSC, best supportive care; FBC, full blood count; GP, general practitioner

It is assumed that non-responders to systemic treatment incur the health care resource use costs associated with BSC when they transition to the BSC health state. As mentioned in Section 5.2.1.3, costs in the BSC health state are weighted by the proportion of responders and non-responders to BSC at the week 16 assessment point. The weighted monitoring costs applied to BSC in the base case analysis are given in Table 52.

Table 52. Health care resource cost applied to BSC in the base case

Population	BSC responders	BSC non-responders	Weighted annual cost	Weighted weekly cost
First-line systemic treatment – Adults, monotherapy	[redacted]	[redacted]	£1,355.42	£25.98
Second-line systemic treatment – Adults, monotherapy	[redacted]	[redacted]	£1,457.24	£27.93
Second-line systemic treatment – Adults, combination therapy	[redacted]	[redacted]	£1,288.96	£24.70
Adolescents, monotherapy	[redacted]	[redacted]	£1,500.47	£28.76

Abbreviations: BSC, best supportive care.

CsA requires additional monitoring for potentially severe side-effects including nephrotoxicity.[154] Thus, regular monitoring of blood pressure, renal function, FBC and liver function is recommended.[152] The company for TA534 considered CsA as a comparator in scenario analysis. To reflect the increased burden of CsA monitoring in this scenario analysis, 15 FBCs were costed in the first year of treatment, as per the BNF requirement that, in psoriasis and atopic dermatitis serum creatinine should be monitored every 2 weeks for first 3 months then every month. This results in around 8 FBCs for weeks 1-16 (months 1-4), followed by around 7 FBCs for weeks 17-52 (months 5-12). It is likely that some of these tests will be combined with routine dermatology appointments and GP visits. As such, 6 additional nurse visits are costed in the induction period (8 FBCs in the

induction phase minus the 2 dermatologist visits in the induction phase). The additional monitoring costs associated with CsA are summarised in Table 53.

Table 53. Additional monitoring for CsA

Visit/ test	Unit cost	Weeks 1-16		Weeks 17-52	
		Number	Cost	Number	Cost
Dermatologist nurse visit	£31.25	6	£187.50	0	£0.00
FBC	£2.58	8	£20.64	7	£18.06
Total cost		**£208.14**		**£18.06**	

Abbreviations: CsA, ciclosporin; FBC, full blood count

5.2.1.11.5 Costs of managing flares

The treatments used and associated costs to manage a flare are given in Table 54. These treatments are generally in line with those accepted in TA534 and TA681 and are in line with the companies' economic models. Data on flare treatment distributions were obtained from TA534 for dupilumab and Reich 2020[97] for baricitinib. The companies for tralokinumab and upadacitinib supplied data on flare treatment distributions upon request from the EAG. No data on flare treatment distributions were available for abrocitinib as receipt of rescue medication was prohibited in the JADE COMPARE, MONO 1 and MONO 2 trials. As such, the company for abrocitinib assumed the flare treatment distribution from TA534. However, the EAG has assumed the flare treatment distribution data for adult second-line systemic treatment and adolescents for abrocitinib 100 mg and 200 mg (monotherapy and combination therapy) are the same as upadacitinib 15 mg and 30 mg (monotherapy and combination therapy), as both treatments are the same drug class (JAK inhibitors). Furthermore, adolescent flare treatment distribution data for upadacitinib 15 mg were also assumed for dupilumab, as data from AD ADOL[99] were unavailable.

The flare treatment distribution for BSC was based on placebo data from AD-UP, split by first and second line. As mentioned in Section 5.2.1.1.1, baseline characteristics from the upadacitinib trials were deemed to be representative of the population who would be treated in clinical practice in England according to the EAG's clinical experts.

The costs associated with flare treatments are multiplied by the distributions of flare treatments (Table 55) to estimate a treatment-specific flare cost. The treatment-specific flare costs are then multiplied by the treatment specific rate of flare (Table 43 in Section 5.2.1.9) to estimate weekly and

annual treatment-specific flare costs for the short- and long-term parts of the economic model. In the short-term part of the model, it is assumed that non-responders to systemic treatment incur the flare costs associated with BSC.

In scenario analysis, the EAG explored using flare treatment distributions from TA534 to estimate a single cost of flare treatment for patients on systemic treatment and BSC.

Table 54. Flare medication costs

Medication	Cost per pack	Packs per flare	Cost per flare	
TCS potent				
Betamethasone valerate cream	£2.71	1	£2.71	£16.83
Cutivate 0.005% ointment	£4.24	3.33	£14.12	
TCS very potent				
Eumovate 0.05% ointment	£5.44	1	£5.44	£13.34
Dermovate 0.05% cream	£7.90	1	£7.90	
Systemic steroid				
Prednisolone 5mg	£0.40	1	£0.40	£0.40
TCI				
Protopic 0.1% ointment	£45.56	0.4	£18.22	£18.22

Abbreviations: TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

Table 55. Distribution of flare medications

Treatment	TCS potent	TCS very potent	Systemic steroid*	TCI‡	Cost of flare treatment	Source
Monotherapy - Adults						
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 30 mg
Dupilumab	0.0%	0.0%	15.9%	0.0%	£0.06	TA534
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ECZTRA 7-like population from ECZTRA 1 & 2
Upadacitinib 15 mg – **second-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.
Upadacitinib 30 mg – **second-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.
Combination therapy - Adults						

Abrocitinib 100 - mg – **first-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
Abrocitinib 200 mg – **first-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 30 mg
Abrocitinib 100 - mg – **second-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
Abrocitinib 200 mg – **second-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 30 mg
Baricitinib	0.0%	66.7%	33.3%	0.0%	£9.03	BREEZE-AD7 (Reich 2020[97])
BSC – **first-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Placebo data from AD UP
BSC – **second-line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Placebo data from AD UP
CSA	0.0%	80.0%	20.0%	0.0%	£10.75	Assumed to be the same as upadacitinib 30 mg
Dupilumab	42.0%	23.0%	29.0%	0.0%	£10.25	TA534. For TCIs, rate was reported as 0% in TA534, however EAG's experts considered TCI use would be the same as BSC.
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from ECZTRA 7 and ECZTRA 7-like population from ECZTRA 3
Upadacitinib 15 mg – **first line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP
Upadacitinib 30 mg – **first line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP
Upadacitinib 15 mg – **second line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP
Upadacitinib 30 mg – **second line**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP
Monotherapy - Adolescents						
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg

Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib as data for dupilumab are only available for adult combination therapy
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.

Abbreviations: : BSC, best supportive care; mg, milligram; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

*Category includes systemic corticosteroids, immunosuppressants, non-biologic systemics based on clinical expert opinion to the EAG that it would be reasonable to combine them in the same cost category

‡In the data provided by the company, some topical treatments were classed as "other" and these have been costed in the MTA model as TCIs as the EAG's clinical experts considered "other" topical treatments are likely to be high cost.

5.2.1.11.6 Costs of managing AEs

The unit cost to manage each AE in the model is given in Table 56. These unit costs and sources are generally in line with those applied in TA534 and TA681.

In the short-term model it is assumed that non-responders to systemic treatment incur the AE costs associated with BSC and that CsA-treated patients incur no AE costs as CsA treatment is limited to 1 year and patients are likely to discontinue CsA should any AEs develop.

The unit costs associated with each AE (Table 56) are multiplied by the weekly (short-term model) and annual (long-term model) proportion of patients experiencing each AE calculated based on 16-week data reported in Table 42 in Section 5.2.1.8 to estimate weekly and annual treatment-specific AE costs (Table 57).

Table 56. Adverse event unit costs

AE	Unit cost	Source[150, 152, 155]
Injection site reaction	£124.83	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D
Allergic conjunctivitis	£39.00	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications

Infectious conjunctivitis	£53.33	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications. £39.00 (80% weight from TA681) National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 130, ophthalmology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D. £110.66 (20% weight from TA681)
Oral herpes	£39.00	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications (£39.00) 1-week Aciclovir 5% cream (£6.77, BNF)
Upper respiratory tract infection	£39.00	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications
Acne	£248.43	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications (£39.00) National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D (£124.83) 3 months Epiduo (£19.53 per month, BNF) and oral lymecycline (£8.67 per month, BNF)

Abbreviations: AE, adverse event; GP, General Practitioner; NHS, National Health Service

Table 57. Treatment-specific AE costs

Treatment	Weekly cost	Annual cost
Monotherapy - Adults		
Abrocitinib 100 mg	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Dupilumab	£1.57	£70.54
Tralokinumab	[redacted]	[redacted]
Upadacitinib 15 mg	£1.25	£60.01
Upadacitinib 30 mg	£3.57	£144.55
Combination therapy – Adults		
Abrocitinib 100 mg	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Baricitinib	£0.81	£39.64
BSC	£0.64	£31.75
CsA	-	-
Dupilumab	£1.22	£57.54
Tralokinumab	[redacted]	[redacted]
Upadacitinib 15 mg	£2.12	£95.40
Upadacitinib 30 mg	£3.09	£130.57
Monotherapy - Adolescents		

Abrocitinib 100 mg	£0.84	£40.35
Abrocitinib 200 mg	£1.29	£60.99
BSC	£0.06	£3.17
Dupilumab	£1.49	£67.84
Upadacitinib 15 mg	£2.95	£123.34
Abbreviations: AE, adverse event; BSC, best supportive care; CsA, ciclosporin; mg, milligram.		

5.2.1.12 List of assumptions

Table 58. List of assumptions used on model

EAG base case assumptions	Justification
Baseline characteristics and placebo response from upadacitinib trials	EAG's clinical experts considered that the upadacitinib trials were appropriate to inform the baseline characteristics and response in the EAG economic model
BSC modelled as a single health state, weighted by responders and non-responders	Preferred approach in TA681.
1st line CsA patients discontinue to BSC.	Simplification as patients likely to get dupilumab after discontinuing treatment.
The primary treatment outcome assessed in the model is response to treatment at Week 16, defined using a composite outcome of EASI 50 + DLQI ≥ 4.	In TA534 and TA681, the composite outcome was preferred by the committee as it was deemed to be sensitive to changes in treatment outcomes and more clinically relevant than EASI 75.
Conditional discontinuation data for tralokinumab monotherapy assumed to be the same as the combination therapy and composite outcome.	Lack of composite outcome and combination therapy conditional discontinuation data from ECZTRA 7 and ECZTRA 7-like population for tralokinumab.
Conditional discontinuation for abrocitinib and baricitinib assumed to be same as upadacitinib.	Lack of data on conditional discontinuation for abrocitinib and baricitinib, as such assumed a JAK inhibitor class effect.
Long-term treatment discontinuation rate is equal to the conditional discontinuation rates.	In line with the approach accepted in TA534 and TA681. Same in the abrocitinib and upadacitinib company models.
Active treatment waning results in discontinuation to BSC	Approach accepted by the committee in TA534.
No treatment waning assumptions applied to the BSC health state.	As BSC is modelled as a single health state, weighted by responders and non-responders, it captures the waxing and waning nature of a patient's response to BSC treatment for moderated to severe AD.
No AEs assumed for CsA.	Data on AEs for CsA were unavailable. In TA534, the committee accepted assuming zero AEs for CsA in the short-term as treatment is only given for one year before patients move to BSC.

AEs for BSC assumed based on placebo safety data from the upadacitinib trials.	To maintain alignment with the source for baseline characteristics and placebo response in the model.
BSC flare rate for monotherapy is the same as combination therapy.	In clinical practice BSC includes TCS.
Flare treatment distribution data for adult second-line systemic treatment and adolescents for abrocitinib 100 mg and 200 mg (monotherapy and combination therapy) are the same as upadacitinib 15 mg and 30 mg (monotherapy and combination therapy).	In the JADE trial programme for abrocitinib, rescue treatment was not permitted as such there is no data to inform the flare rate. Upadacitinib data were assumed for abrocitinib as both treatments are the same drug class (JAK inhibitors).
Adolescent flare treatment distribution data for upadacitinib 15 mg were assumed for dupilumab.	Data from AD ADOL[99] for dupilumab were unavailable.
Utilities based on drug class implemented for the base case.	To account for limitations associated with missing data, uncertainty due to small numbers and relevance of the populations for utility values.
Disutilities associated with AEs have not included in the base case.	In line with TA534, TA681 and the companies' models. It has been assumed that due to the frequency of capturing EQ-5D data in the upadacitinib and tralokinumab trials, the impact of AEs on HRQoL will be captured in the data.
Utility values for CsA were assumed to be the same as upadacitinib 15 mg or 30 mg (depending on the comparison).	Lack of utility data for CsA.
CsA dose based on TA534.	The recommended dose range for CsA is 2.5 to 5 mg/kg/day and treatment is individualised.[149] According to the EAG's clinical experts, there is no clinical consensus on a typical CsA dose for patients with moderate-to-severe AD and depends largely on the treating clinician. In TA534, the dose accepted by the committee was 5mg/kg for 6 weeks followed by 3mg/kg for 46 weeks (maximum treatment duration of one year)
No administration costs for tralokinumab	Company has indicated that training on how to self-administer tralokinumab will be provided to the NHS free of charge.
Resource use in the induction phase of the short-term model is based on non-responders until the initial treatment assessment point.	In TA681, responder resource use estimates were applied in the treatment induction phase (weeks 0-16). However, the EAG considered that a conservative assumption for all treatment arms is to assume non-responder resource use until treatment response is assessed at week 16.
Responders on maintenance treatment who discontinue to BSC have no reduction in resource use of emollients and TCS.	According the EAG's clinical experts, emollients and TCS are key components of BSC and no reduction in use should be assumed if a patient loses response to systemic treatment.
Costs of bathing products excluded from the model.	RCT evidence suggests bathing products offer no benefits and most NHS trusts no longer prescribe them.[151] Furthermore, the committee for TA681[13] preferred to exclude the costs of bathing products

Monitoring costs are the same for adults and adolescents	Based on feedback from the EAG's clinical experts, adolescents typically follow the same treatment pathway as adults and therefore healthcare resource use is assumed to be the same for adults and adolescents.
Non-responders to systemic treatment incur AE costs associated with BSC.	Once systemic treatment is stopped and BSC is initiated, AE profile will reflect treatments given in BSC.

Abbreviations: AD, atopic dermatitis; AE, adverse event; BSC, best supportive care; CsA, ciclosporin; DLQI, Dermatology Life Quality Index; EAG, Evidence Assessment group; EASI, Eczema Area and Severity Index; HRQoL, health related quality of life; kg, kilogram; mg, milligram; NHS, National Health Service; RCT, randomised controlled trial; TCS, topical corticosteroids

5.2.2 Results

A summary of the cost-effectiveness results is presented in Table 59. As abrocitinib and upadacitinib have different doses, the EAG has ordered these first in the presentation of results. Detailed deterministic and probabilistic results as well as one-way sensitivity and scenario analyses are presented in Sections 5.2.2.1 to 5.2.2.4. The EAG notes that incremental QALYs were relatively small and incremental costs were relatively large for each treatment in each population resulting in the sensitive ICERs.

Table 59. Summary of cost effectiveness results

Population	Deterministic ICER	Probabilistic ICER	Probability intervention is cost-effective at the WTP threshold	
			£20,000	£30,000
Adult first-line systemic treatment population, combination therapy – EASI 75				
Upadacitinib 15 mg + TCS vs CsA + TCS	£82,148	£78,889	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs CsA + TCS	£148,451	£152,043	[redacted]	[redacted]
Adult second-line systemic treatment population, monotherapy – EASI 50 + DLQI ≥4				
Abrocitinib 100 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]
Abrocitinib 200 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]
Upadacitinib 15 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]
Upadacitinib 30 mg vs dupilumab	£66,324	£66,361	[redacted]	[redacted]
Tralokinumab vs dupilumab	£406,187*	£388,870*	[redacted]	[redacted]
Adult second-line systemic treatment population, combination therapy – EASI 50 + DLQI ≥4				
Abrocitinib 100 mg + TCS vs dupilumab + TCS	£169,431*	£156,267*	[redacted]	[redacted]
Abrocitinib 200 mg + TCS vs dupilumab + TCS	Dominant	Dominant	[redacted]	[redacted]

Upadacitinib 15 mg + TCS vs dupilumab + TCS	£181,499*	£185,453*	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs dupilumab + TCS	£129,209	£123,337	[redacted]	[redacted]
Tralokinumab + TCS vs dupilumab + TCS	£219,181*	£232,282*	[redacted]	[redacted]
Adolescents, monotherapy – EASI 75				
Abrocitinib 100 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]
Abrocitinib 200 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]
Upadacitinib 15 mg vs dupilumab	Dominant	Dominant	[redacted]	[redacted]

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; WTP, willingness to pay.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

5.2.2.1 Deterministic results

List price ICERs are presented in Table 60 for the adult first-line systemic treatment, Table 61 to Table 62 for the adult second-line systemic treatment and Table 63 for the adolescent populations. Please refer to Appendix 10.12 for disaggregated results.

Table 60. Deterministic base case results: adults first-line systemic treatment population, combination therapy – EASI 75 – (list prices)

Results per patient	Upadacitinib 15 mg + TCS (1)	Upadacitinib 30 mg + TCS (2)	CsA + TCS (3)	Incremental value	
				(1-3)	(2-3)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER				£82,148	£148,451

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids.

Table 61. Deterministic base case results: adults second-line systemic treatment, monotherapy – EASI 50 + DLQI ≥4 (list price)

Results per patient	Abro 100 mg (1)	Abro 200 mg (2)	Upa 15 mg (3)	Upa 30 mg (4)	Tralo (5)	Dup (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER							Dominant	Dominant	Dominant	£66,324	£406,187*

Abbreviations: Abro, abrocitinib; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; Dup, dupilumab; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; Tralo, tralokinumab; Upa, upadacitinib.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 62. Deterministic base case results: adults second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list price)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,431*	Dominant	£181,499*	£129,209	£219,181*

Abbreviations: Abro, abrocitinib; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; Dup, dupilumab; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 63. Deterministic base case results: adolescents, monotherapy – EASI 75 – (list prices)

Results per patient	Abrocitinib 100 mg (1)	Abrocitinib 200 mg (2)	Upadacitinib 15 mg (3)	Dupilumab (4)	Incremental value		
					(1-4)	(2-4)	(3-4)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					Dominant	Dominant	Dominant

Abbreviations: EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year

5.2.2.2 Probabilistic results

The EAG conducted a probabilistic sensitivity analysis (PSA) to assess the impact of the combined uncertainty from all parameters in the model. This was performed by sampling from distributions of the uncertain parameters 1,000 times, to generate the equivalent number of sampled ICERs.

Conditional discontinuation data, utility values, adverse events and flare rates were varied using a beta distribution. Costs were varied using a gamma distribution. Variation for the Week 16 treatment response was based on 1,000 CODA samples from the NMA (please see Section 4.1.5 for NMA methods).

List price probabilistic ICERs are presented in Table 64 for the adult first-line systemic treatment, Table 65 to Table 66 for the adult second-line systemic treatment and Table 67 for the adolescent populations. For the cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), please refer to Appendix 10.14. It should be noted that for each population and intervention, PSA were run separately due to the structure of the model and therefore the sampling from parameter distributions for the comparator provide slightly different mean estimates for each pairwise comparison. However, total costs and QALYs for the comparator are similar for the PSA results. Additionally, the EAG notes that incremental QALYs were relatively small and incremental costs were relatively large for each treatment in each population resulting in the sensitive ICERs.

Table 64. Probabilistic base case results: adults first-line systemic treatment population, combination therapy – EASI 75 – (list prices)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	PSA ICER	Deterministic ICER
CsA + TCS	[redacted]	[redacted]	-	-	-	-
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£78,889	£82,148
CsA + TCS	[redacted]	[redacted]	-	-	-	-
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£152,043	£148,451

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids.

Table 65. Probabilistic base case results: adults second-line systemic treatment, monotherapy – EASI 50 + DLQI ≥4 (list price)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	PSA ICER	Deterministic ICER
Dupilumab	[redacted]	[redacted]	-	-	-	-
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Dupilumab	[redacted]	[redacted]	-	-	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Dupilumab	[redacted]	[redacted]	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Dupilumab	[redacted]	[redacted]	-	-	-	-
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£66,361	£66,324
Dupilumab	[redacted]	[redacted]	-	-	-	-
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£388,870*	£406,187*

Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 66. Probabilistic base case results: adults second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list price)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	PSA ICER	Deterministic ICER
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-
Abrocitinib 100 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£156,267*	£169,431*
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-
Abrocitinib 200 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£185,453*	£181,499*
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£123,337	£129,209
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£232,282*	£219,181*

Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 67. Probabilistic base case results: adolescents, monotherapy – EASI 75 – (list prices)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	PSA ICER	Deterministic ICER
Dupilumab	[redacted]	[redacted]	-	-	-	-
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Dupilumab	[redacted]	[redacted]	-	-	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Dupilumab	[redacted]	[redacted]	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

5.2.2.3 One-way sensitivity analysis

One-way sensitivity analysis was conducted by varying key model parameters between the upper and lower values of the expected value used in the deterministic base case. The key model parameters include:

- week 16 response;
- conditional discontinuation (used to inform the week 52 response and annual discontinuation);
- treatment waning;
- utility values;
- monitoring / health care resource use (frequency);
- adverse events (frequency);
- flares (frequency); and,
- age.

The response at week 16 was varied for each treatment using the 95% (credible interval) CrI estimated by the NMA. The response to BSC at week 16 was also varied as this parameter is used to weight costs and utilities when patients discontinue active treatment and transition to BSC.

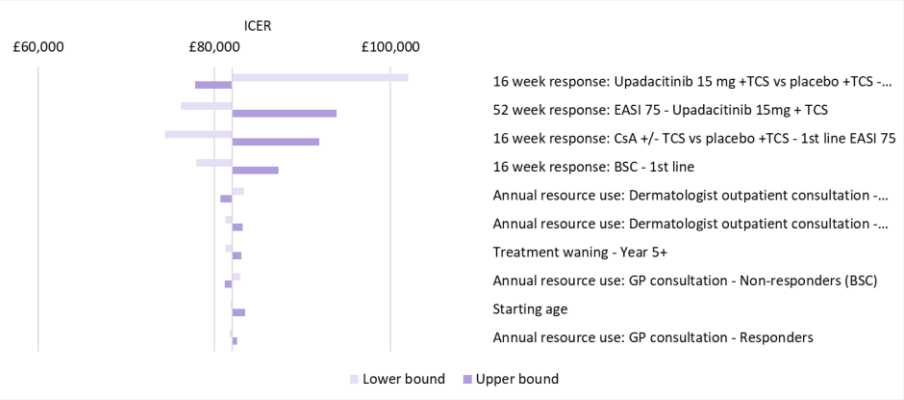
Conditional discontinuation rates, adverse event rates and flare rates were varied individually for each treatment by their 95% (confidence intervals) CIs. No estimates of precision were available for

treatment waning, utility or monitoring / health care resource use, and therefore the SE was assumed to equal +/- 20% of the mean value. Utility values were varied individually for each treatment, while treatment waning and monitoring / health care resource use parameters were varied simultaneously for the intervention and comparator. Age data (including variation) for the *post hoc* subgroups was presented by treatment arm rather than an overall mean. As such the EAG calculated a mean age for each subgroup (presented in Section 5.2.1.1.1) and this was varied by +/- 20% of the mean value. Drug acquisition costs and service costs were not varied as these are assumed to be fixed values. Alternative discount rates and time horizons were explored in scenario analysis (see Section 5.2.2.4).

The below subsections present the results of the OWSA for the top 10 parameters for the adult first-line systemic treatment population, adult second-line systemic treatment population and adolescents.

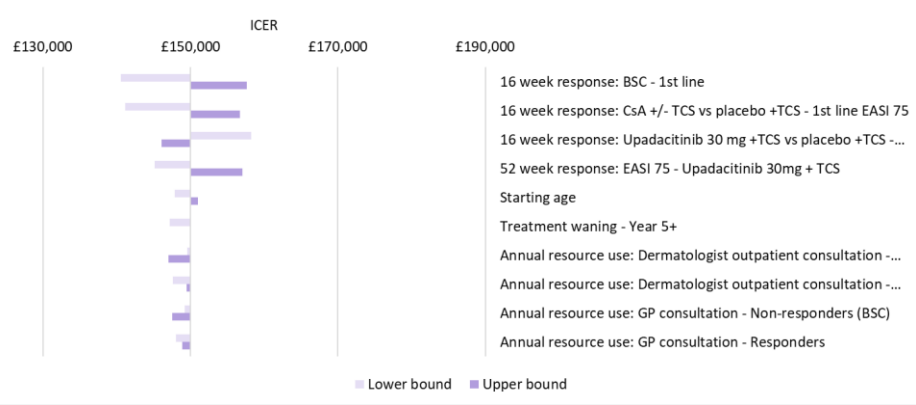
Adults first-line systemic treatment population

Figure 15. Tornado diagram for upadacitinib 15mg + TCS vs CsA + TCS: adult first-line - EASI 75 – combination therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

Figure 16. Tornado diagram for upadacitinib 30mg + TCS vs CsA + TCS: adult first-line – EASI 75 – combination therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

Table 68. OWSA results: adults first-line - EASI 75 – combination therapy (list prices)

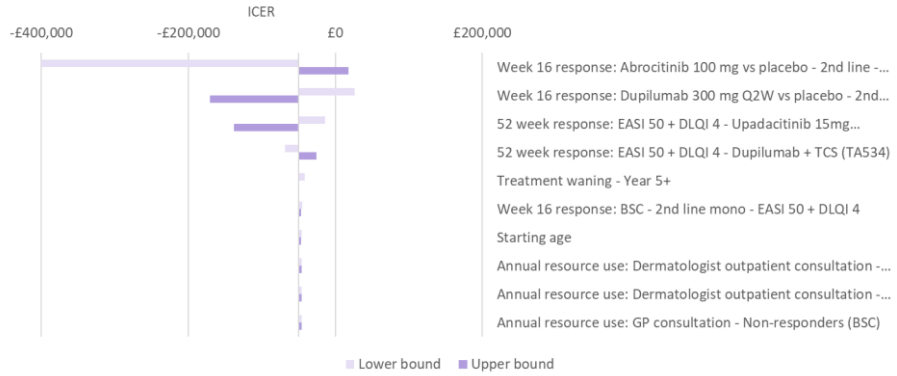
Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
Upadacitinib 15mg + TCS vs CsA + TCS **Base case ICER: £82,148 (NE quadrant)**					
1	16-week response: Upadacitinib 15 mg +TCS vs placebo +TCS - 1st line EASI 75	£102,063	£77,818	NE	NE
2	52-week response: EASI 75 - Upadacitinib 15mg + TCS	£76,203	£93,860	NE	NE
3	16-week response: CsA +/- TCS vs placebo +TCS - 1st line EASI 75	£74,390	£91,954	NE	NE
4	16-week response: BSC - 1st line	£77,932	£87,304	NE	NE
5	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£83,343	£80,696	NE	NE
6	Annual resource use: Dermatologist outpatient consultation - Responders	£81,287	£83,193	NE	NE
7	Treatment waning - Year 5+	£81,288	£83,073	NE	NE
8	Annual resource use: GP consultation - Non-responders (BSC)	£82,945	£81,179	NE	NE
9	Starting age	£81,921	£83,484	NE	NE
10	Annual resource use: GP consultation - Responders	£81,765	£82,613	NE	NE

Upadacitinib 30mg + TCS vs CsA + TCS Base case ICER: £148,451 (NE quadrant)					
1	16-week response: BSC - 1st line	£140,596	£157,665	NE	NE
2	16-week response: CsA +/- TCS vs placebo +TCS - 1st line EASI 75	£141,164	£156,684	NE	NE
3	16-week response: Upadacitinib 30 mg +TCS vs placebo +TCS - 1st line EASI 75	£158,239	£146,063	NE	NE
4	52-week response: EASI 75 - Upadacitinib 30mg + TCS	£145,162	£157,040	NE	NE
5	Starting age	£147,872	£151,044	NE	NE
6	Treatment waning - Year 5+	£147,222	£149,902	NE	NE
7	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£149,602	£147,053	NE	NE
8	Annual resource use: Dermatologist outpatient consultation - Responders	£147,622	£149,457	NE	NE
9	Annual resource use: GP consultation - Non-responders (BSC)	£149,219	£147,518	NE	NE
10	Annual resource use: GP consultation - Responders	£148,082	£148,898	NE	NE

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; NE, north-east; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids

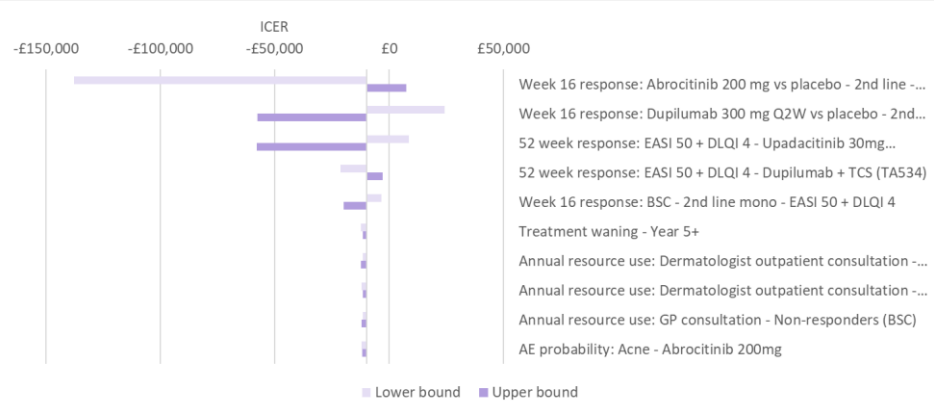
Adults second-line systemic treatment population – monotherapy

Figure 17. Tornado diagram for abrocitinib 100mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)



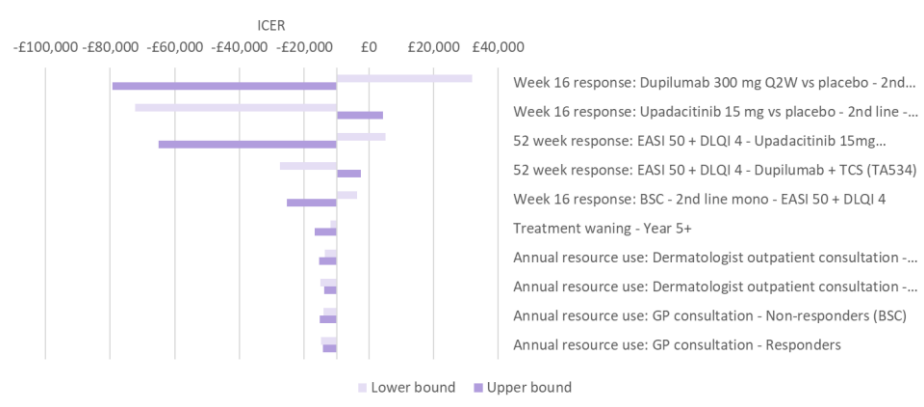
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 18. Tornado diagram for abrocitinib 200mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)



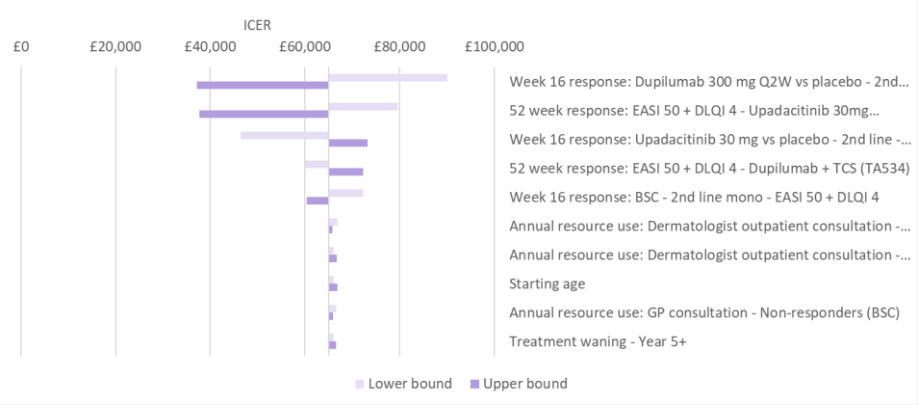
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 19. Tornado diagram for upadacitinib 15mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)



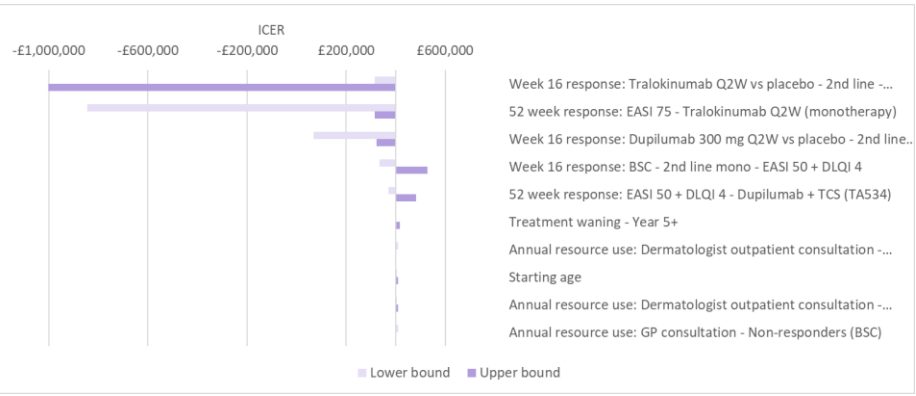
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 20. Tornado diagram for upadacitinib 30mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 21. Tornado diagram for tralokinumab vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Table 69. OWSA results: adults second-line – EASI 50 + DLQI ≥4 – monotherapy (list prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
Abrocitinib 100mg vs dupilumab **Base case ICER: -£45,732 (SE quadrant)**					

1	Week 16 response: Abrocitinib 100 mg vs placebo - 2nd line - EASI 50 + DLQI 4	-£32,170,528‡	£18,028	Dominant	NE
2	Week 16 response: Dupilumab 300 mg Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£26,428	-£170,378	NE	Dominant
3	52-week response: EASI 50 + DLQI 4 - Upadacitinib 15mg (monotherapy)	-£14,214	-£138,040	Dominant	Dominant
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	-£68,161	-£25,980	Dominant	Dominant
5	Treatment waning - Year 5+	-£41,805	-£49,204	Dominant	Dominant
6	Week 16 response: BSC - 2nd line mono - EASI 50 + DLQI 4	-£45,328	-£46,737	Dominant	Dominant
7	Starting age	-£45,377	-£46,352	Dominant	Dominant
8	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	-£45,429	-£46,100	Dominant	Dominant
9	Annual resource use: Dermatologist outpatient consultation - Responders	-£45,950	-£45,467	Dominant	Dominant
10	Annual resource use: GP consultation - Non-responders (BSC)	-£45,530	-£45,977	Dominant	Dominant
Abrocitinib 200mg vs dupilumab Base case ICER: -£11,853 (SE quadrant)					
1	Week 16 response: Abrocitinib 200 mg vs placebo - 2nd line - EASI 50 + DLQI 4	-£137,841	£7,556	Dominant	NE
2	Week 16 response: Dupilumab 300 mg Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£24,074	-£57,595	NE	Dominant
3	52-week response: EASI 50 + DLQI 4 - Upadacitinib 30mg (monotherapy)	£8,543	-£57,768	NE	Dominant
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	-£21,416	-£2,860	Dominant	Dominant
5	Week 16 response: BSC - 2nd line mono - EASI 50 + DLQI 4	-£3,316	-£19,881	Dominant	Dominant
6	Treatment waning - Year 5+	-£12,337	-£11,539	Dominant	Dominant
7	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	-£11,495	-£12,288	Dominant	Dominant
8	Annual resource use: Dermatologist outpatient consultation - Responders	-£12,111	-£11,540	Dominant	Dominant
9	Annual resource use: GP consultation - Non-responders (BSC)	-£11,614	-£12,143	Dominant	Dominant
10	AE probability: Acne - Abrocitinib 200mg	-£11,968	-£11,711	Dominant	Dominant

Upadacitinib 15mg vs dupilumab **Base case ICER: -£14,484 (Dominant, SE quadrant)**					
1	Week 16 response: Dupilumab 300 mg Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£31,819	-£79,393	NE	Dominant
2	Week 16 response: Upadacitinib 15 mg vs placebo - 2nd line - EASI 50 + DLQI 4	-£72,351	£4,363	Dominant	NE
3	52-week response: EASI 50 + DLQI 4 - Upadacitinib 15mg (monotherapy)	£5,075	-£65,014	NE	Dominant
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	-£27,466	-£2,531	Dominant	Dominant
5	Week 16 response: BSC - 2nd line mono - EASI 50 + DLQI 4	-£3,649	-£25,340	Dominant	Dominant
6	Treatment waning - Year 5+	-£11,900	-£16,771	Dominant	Dominant
7	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	-£13,720	-£15,412	Dominant	Dominant
8	Annual resource use: Dermatologist outpatient consultation - Responders	-£15,034	-£13,816	Dominant	Dominant
9	Annual resource use: GP consultation - Non-responders (BSC)	-£13,974	-£15,103	Dominant	Dominant
10	Annual resource use: GP consultation - Responders	-£14,729	-£14,187	Dominant	Dominant
Upadacitinib 30mg vs dupilumab **Base case ICER: £66,324 (NE quadrant)**					
1	Week 16 response: Dupilumab 300 mg Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£89,947	£37,125	NE	NE
2	52-week response: EASI 50 + DLQI 4 - Upadacitinib 30mg (monotherapy)	£79,574	£37,739	NE	NE
3	Week 16 response: Upadacitinib 30 mg vs placebo - 2nd line - EASI 50 + DLQI 4	£46,438	£73,249	NE	NE
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£60,086	£72,219	NE	NE
5	Week 16 response: BSC - 2nd line mono - EASI 50 + DLQI 4	£72,270	£60,366	NE	NE
6	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£66,765	£65,788	NE	NE
7	Annual resource use: Dermatologist outpatient consultation - Responders	£66,006	£66,709	NE	NE
8	Starting age	£66,096	£66,764	NE	NE

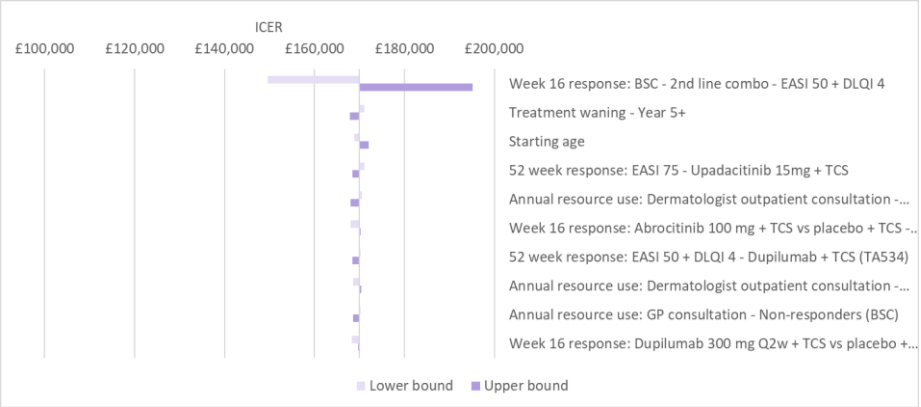
9	Annual resource use: GP consultation - Non-responders (BSC)	£66,618	£65,966	NE	NE
10	Treatment waning - Year 5+	£65,997	£66,613	NE	NE
Tralokinumab Q2W vs dupilumab **Base case ICER: £406,187 (SW quadrant)**					
1	Week 16 response: Tralokinumab Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£315,613	-£1,680,731	SW	Dominant
2	52-week response: EASI 75 - Tralokinumab Q2W (monotherapy)	-£843,885	£314,995	Dominant	SW
3	Week 16 response: Dupilumab 300 mg Q2W vs placebo - 2nd line - EASI 50 + DLQI 4	£67,576	£322,750	NE	SW
4	Week 16 response: BSC - 2nd line mono - EASI 50 + DLQI 4	£335,272	£526,999	SW	SW
5	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£371,502	£482,686	SW	SW
6	Treatment waning - Year 5+	£397,247	£415,428	SW	SW
7	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£409,906	£401,672	SW	SW
8	Starting age	£403,966	£409,997	SW	SW
9	Annual resource use: Dermatologist outpatient consultation - Responders	£403,510	£409,438	SW	SW
10	Annual resource use: GP consultation - Non-responders (BSC)	£408,668	£403,176	SW	SW

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NMA, network meta-analysis; NW, north-west; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; Q2W, twice weekly; SE, south-east; SW, south-west; TCS, topical corticosteroids.

‡ For this scenario, the 95% CrI for the odds ratio was [redacted], resulting in the probability of response at Week 16 varying from [redacted]. Furthermore, for the lower bound result, incremental QALYs were small, resulting in a highly sensitive ICER.

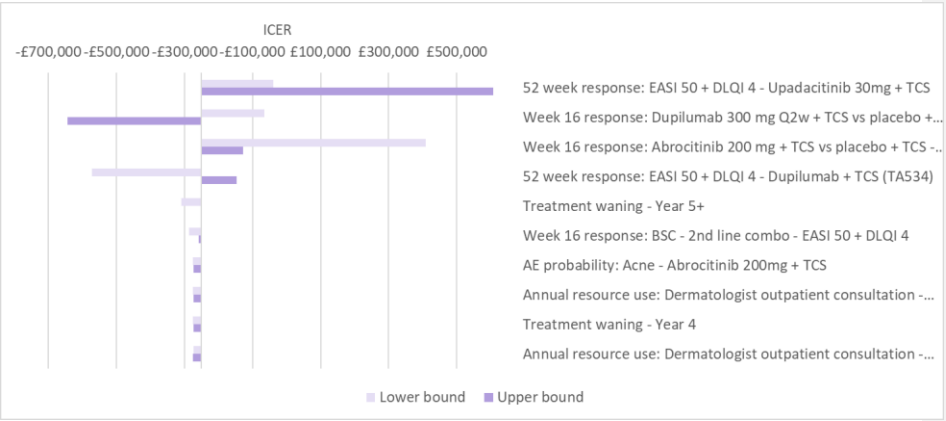
Adults second-line systemic treatment population – combination therapy

Figure 22. Tornado diagram for abrocitinib 100mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)



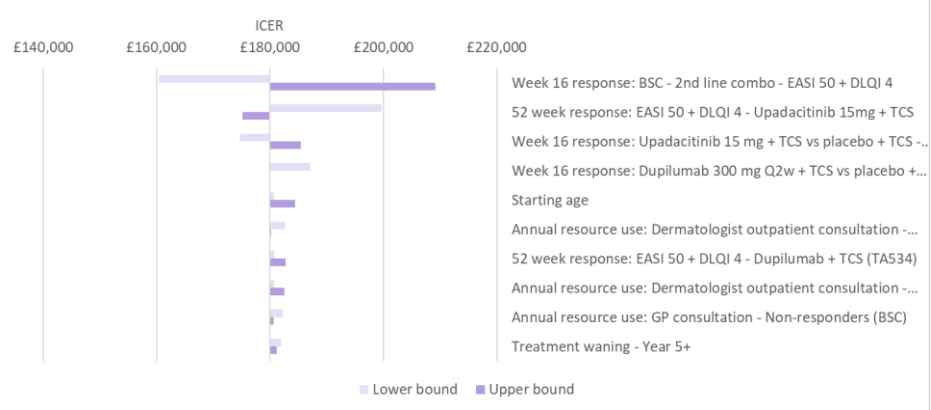
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 23. Tornado diagram for abrocitinib 200mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)



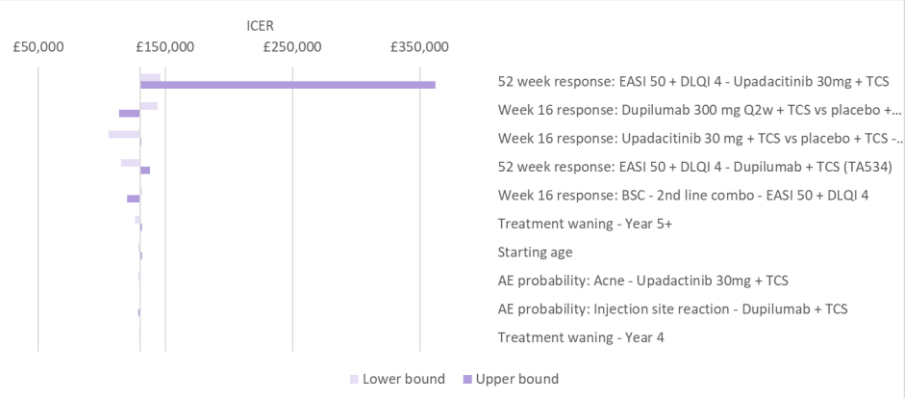
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 24. Tornado diagram for upadacitinib 15mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)



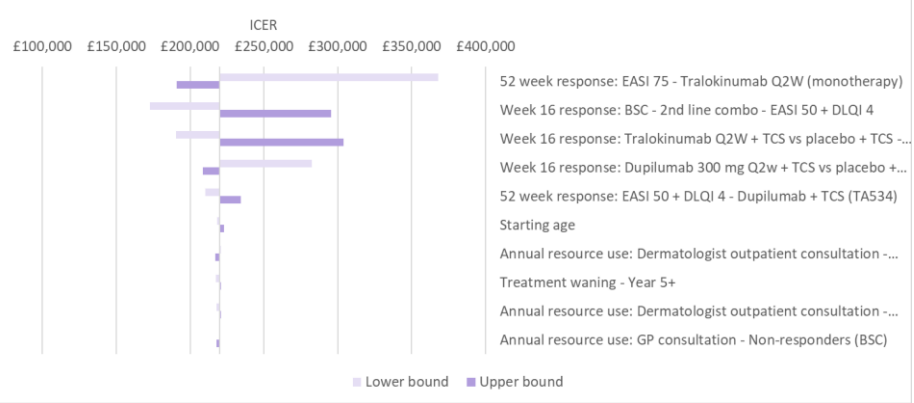
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 25. Tornado diagram for upadacitinib 30mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Figure 26. Tornado diagram for tralokinumab + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

Table 70. OWSA results: adults second-line – EASI 50 + DLQI ≥4 – combination therapy (list prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
Abrocitinib 100mg + TCS vs dupilumab + TCS Base case ICER: £169,431 (SW quadrant)					
1	Week 16 response: BSC - 2nd line combo - EASI 50 + DLQI 4	£149,714	£195,202	SW	SW
2	Treatment waning - Year 5+	£171,126	£167,883	SW	SW
3	Starting age	£168,809	£172,032	SW	SW
4	52-week response: EASI 75 - Upadacitinib 15mg + TCS	£171,037	£168,492	SW	SW
5	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£170,559	£168,062	SW	SW
6	Week 16 response: Abrocitinib 100 mg + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£168,003	£170,250	SW	SW
7	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£170,291	£168,390	SW	SW
8	Annual resource use: Dermatologist outpatient consultation - Responders	£168,619	£170,417	SW	SW
9	Annual resource use: GP consultation - Non-responders (BSC)	£170,183	£168,518	SW	SW

10	Week 16 response: Dupilumab 300 mg Q2w + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£168,356	£169,731	SW	SW
Abrocitinib 200mg + TCS vs dupilumab + TCS Base case ICER: -£274,603 (SE quadrant)					
1	52-week response: EASI 50 + DLQI 4 - Upadacitinib 30mg + TCS	-£39,895	£606,690	Dominant	SW
2	Week 16 response: Dupilumab 300 mg Q2w + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	-£64,873	-£644,350	Dominant	Dominant
3	Week 16 response: Abrocitinib 200 mg + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£408,224	-£127,133	SW	Dominant
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	-£571,336	-£145,966	Dominant	Dominant
5	Treatment waning - Year 5+	-£309,970	-£249,677	Dominant	Dominant
6	Week 16 response: BSC - 2nd line combo - EASI 50 + DLQI 4	-£286,745	-£258,803	Dominant	Dominant
7	AE probability: Acne - Abrocitinib 200mg + TCS	-£275,470	-£273,576	Dominant	Dominant
8	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	-£275,328	-£273,723	Dominant	Dominant
9	Treatment waning - Year 4	-£275,267	-£273,782	Dominant	Dominant
10	Annual resource use: Dermatologist outpatient consultation - Responders	-£274,081	-£275,237	Dominant	Dominant
Upadacitinib 15mg + TCS vs dupilumab + TCS Base case ICER: £181,499 (SW quadrant)					
1	Week 16 response: BSC - 2nd line combo - EASI 50 + DLQI 4	£160,464	£209,202	SW	SW
2	52-week response: EASI 50 + DLQI 4 - Upadacitinib 15mg + TCS	£199,644	£175,109	SW	SW
3	Week 16 response: Upadacitinib 15 mg + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£174,637	£185,410	SW	SW
4	Week 16 response: Dupilumab 300 mg Q2w + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£187,066	£179,948	SW	SW
5	Starting age	£180,768	£184,403	SW	SW
6	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£182,626	£180,132	SW	SW
7	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£180,706	£182,761	SW	SW

8	Annual resource use: Dermatologist outpatient consultation - Responders	£180,688	£182,484	SW	SW
9	Annual resource use: GP consultation - Non-responders (BSC)	£182,251	£180,587	SW	SW
10	Treatment waning - Year 5+	£182,010	£181,127	SW	SW
Upadacitinib 30mg + TCS vs dupilumab + TCS Base case ICER: £129,209 (NE quadrant)					
1	52-week response: EASI 50 + DLQI 4 - Upadacitinib 30mg + TCS	£146,109	£362,171	NE	SW
2	Week 16 response: Dupilumab 300 mg Q2w + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£143,764	£113,684	NE	NE
3	Week 16 response: Upadacitinib 30 mg + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£105,414	£131,274	NE	NE
4	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£114,862	£137,990	NE	NE
5	Week 16 response: BSC - 2nd line combo - EASI 50 + DLQI 4	£131,567	£119,949	NE	NE
6	Treatment waning - Year 5+	£126,046	£131,751	NE	NE
7	Starting age	£128,758	£131,393	NE	NE
8	AE probability: Acne - Upadactinib 30mg + TCS	£128,503	£129,953	NE	NE
9	AE probability: Injection site reaction - Dupilumab + TCS	£129,478	£128,880	NE	NE
10	Treatment waning - Year 4	£128,985	£129,486	NE	NE
Tralokinumab Q2W + TCS vs dupilumab + TCS Base case ICER: £219,181 (SW quadrant)					
1	52-week response: EASI 75 - Tralokinumab Q2W (monotherapy)	£367,800	£191,098	SW	SW
2	Week 16 response: BSC - 2nd line combo - EASI 50 + DLQI 4	£172,828	£295,267	SW	SW
3	Week 16 response: Tralokinumab Q2W + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£190,415	£303,687	SW	SW
4	Week 16 response: Dupilumab 300 mg Q2w + TCS vs placebo + TCS - 2nd line - EASI 50 + DLQI 4	£282,247	£208,423	SW	SW
5	52-week response: EASI 50 + DLQI 4 - Dupilumab + TCS (TA534)	£210,361	£234,495	SW	SW
6	Starting age	£218,188	£223,031	SW	SW
7	Annual resource use: Dermatologist outpatient consultation - Non-responders (BSC)	£220,871	£217,128	SW	SW

8	Treatment waning - Year 5+	£217,643	£220,848	SW	SW
9	Annual resource use: Dermatologist outpatient consultation - Responders	£217,964	£220,659	SW	SW
10	Annual resource use: GP consultation - Non-responders (BSC)	£220,308	£217,812	SW	SW

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; Q2W, twice weekly; SW, south-west; TCS, topical corticosteroids

Adolescents

The key drivers in the adolescent population include the week 16 response and the week 52 response. As noted in Section 5.2.1.5.1, the week 52 response represents all cause discontinuation for people whose condition responded to treatment at week 16 but withdrew from treatment at week 52. Additionally, the upadacitinib week 52 response is used to inform the abrocitinib week 52 response. The BSC non-responder HSUV is another key driver and lower non-responder BSC utility values favour dupilumab. As noted in Section 5.2.1.10, the overall BSC utility value is derived by weighting the BSC non-responder and responder values by the proportion of responders to BSC. An example of how the upper and lower values impact model results are provided in Table 71 for upadacitinib 15mg vs dupilumab.

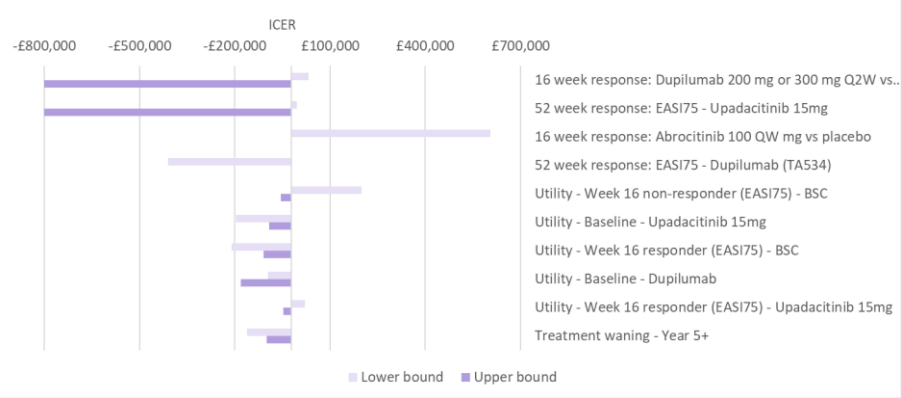
Table 71. Example varying the BSC non-responder HSUV in OWSA (adolescent population, upadacitinib 15mg vs dupilumab)

Analysis	Non-responder BSC utility	% of BSC responders	Overall BSC utility	ICER	QALYs upa	QALYs dup	Inc QALYs
Lower	[redacted]	[redacted]	[redacted]	£1,095,5175*	[redacted]	[redacted]	[redacted]
Base	[redacted]	[redacted]	[redacted]	-£91,977	[redacted]	[redacted]	[redacted]
Upper	[redacted]	[redacted]	[redacted]	-£50,315	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; dup, dupilumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; upa, upadacitinib

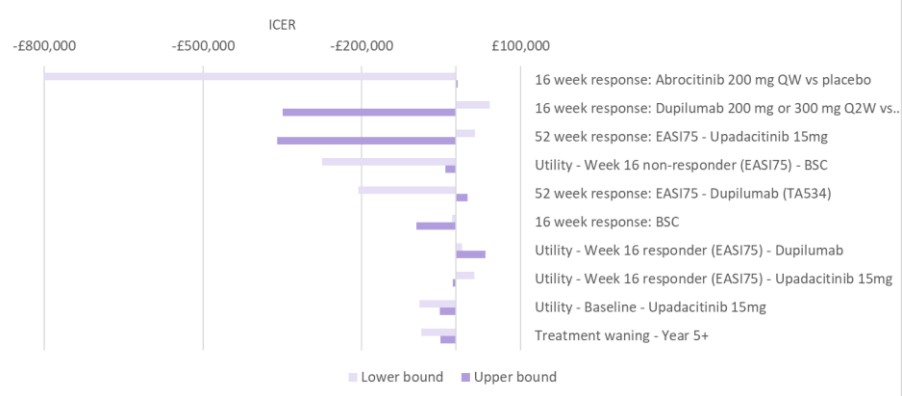
* This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup)

Figure 27. Tornado diagram for abrocitinib 100mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)



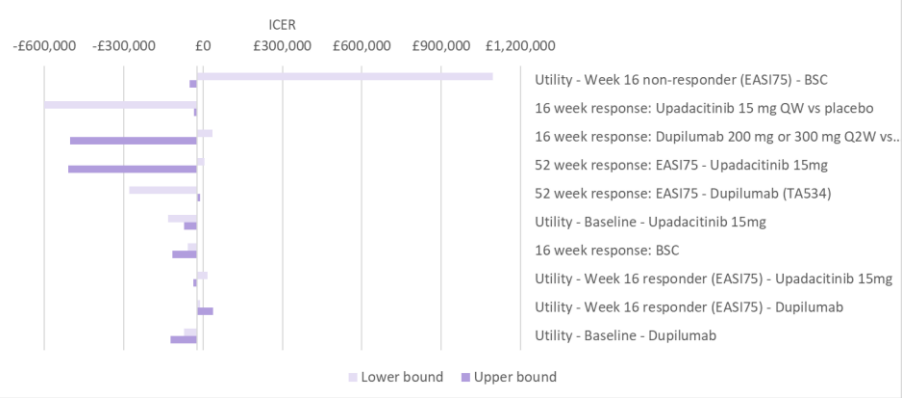
Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly.

Figure 28. Tornado diagram for abrocitinib 200mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; OD, once daily; Q2W, twice weekly.

Figure 29. Tornado diagram for upadacitinib 15mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)



Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; OD, once daily; Q2W, twice weekly.

Table 72. OWSA results: adolescents - EASI 75 – monotherapy (list prices)

Rank	Parameter	Lower bound ICER	Upper bound ICER	Lower bound quadrant	Upper bound quadrant
Abrocitinib 100mg vs dupilumab **Base case ICER: -£125,454 (dominant, SE quadrant)**					
1	16-week response: Dupilumab 200 mg or 300 mg Q2W vs placebo	£31,749	-£883,309	NE	Dominant
2	52-week response: EASI75 - Upadacitinib 15mg	-£5,786	-£852,933	Dominant	Dominant
3	16-week response: Abrocitinib 100 QW mg vs placebo	£605,384	-£22,839	SW	Dominant
4	52-week response: EASI75 - Dupilumab (TA534)	-£411,468	-£24,143	Dominant	Dominant
5	Utility - Week 16 non-responder (EASI75) - BSC	£199,998	-£55,930	SW	Dominant
6	Utility - Baseline - Upadacitinib 15mg	-£197,883	-£92,953	Dominant	Dominant
7	Utility - Week 16 responder (EASI75) - BSC	-£211,288	-£109,026	Dominant	Dominant
8	Utility - Baseline - Dupilumab	-£95,384	-£182,303	Dominant	Dominant
9	Utility - Week 16 responder (EASI75) - Upadacitinib 15mg	£20,265	-£47,267	SW	Dominant
10	Treatment waning - Year 5+	-£161,862	-£100,758	Dominant	Dominant
Abrocitinib 200mg vs dupilumab **Base case ICER: -£66,519 (dominant, SE quadrant)**					

1	16-week response: Abrocitinib 200 mg QW vs placebo	-£13,817,123‡	-£18,446	Dominant	Dominant
2	16-week response: Dupilumab 200 mg or 300 mg Q2W vs placebo	£41,403	-£349,681	NE	Dominant
3	52-week response: EASI75 - Upadacitinib 15mg	£14,161	-£360,519	NE	Dominant
4	Utility - Week 16 non-responder (EASI75) - BSC	-£274,931	-£42,125	Dominant	Dominant
5	52-week response: EASI75 - Dupilumab (TA534)	-£206,791	-£312	Dominant	Dominant
6	16-week response: BSC	-£29,698	-£96,625	Dominant	Dominant
7	Utility - Week 16 responder (EASI75) - Dupilumab	-£10,293	£33,802	Dominant	SW
8	Utility - Week 16 responder (EASI75) - Upadacitinib 15mg	£13,142	-£27,781	SW	Dominant
9	Utility - Baseline - Upadacitinib 15mg	-£90,485	-£53,087	Dominant	Dominant
10	Treatment waning - Year 5+	-£87,426	-£51,679	Dominant	Dominant
Upadacitinib 15mg vs dupilumab **Base case ICER: -£91,977 (dominant, SE quadrant)**					
1	Utility - Week 16 non-responder (EASI75) - BSC	£1,095,517	-£50,315	SW	Dominant
2	16-week response: Upadacitinib 15 mg QW vs placebo	-£682,775	-£34,477	Dominant	Dominant
3	16-week response: Dupilumab 200 mg or 300 mg Q2W vs placebo	£35,487	-£502,556	NE	Dominant
4	52-week response: EASI75 - Upadacitinib 15mg	£4,841	-£511,419	NE	Dominant
5	52-week response: EASI75 - Dupilumab (TA534)	-£279,375	-£12,228	Dominant	Dominant
6	Utility - Baseline - Upadacitinib 15mg	-£131,921	-£71,341	Dominant	Dominant
7	16-week response: BSC	-£58,191	-£116,307	Dominant	Dominant
8	Utility - Week 16 responder (EASI75) - Upadacitinib 15mg	£16,769	-£36,912	SW	Dominant
9	Utility - Week 16 responder (EASI75) - Dupilumab	-£12,696	£38,437	Dominant	SW
10	Utility - Baseline - Dupilumab	-£72,952	-£123,952	Dominant	Dominant

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NMA, network meta-analysis; OWSA, one-way sensitivity analysis; QD, once daily; QALY, quality-adjusted life year; Q2W, twice weekly; SW, south-west.

‡For this scenario, incremental QALYs are very small ([redacted]) and are primarily driven by higher baseline utility for abrocitinib.

5.2.2.4 Scenario analyses

A number of scenarios were performed to test the impact of alternative modelling assumptions and data sources. Table 73 outlines the scenarios undertaken in each population.

Table 73. List of scenarios

Scenario	Base case	Population			
		Adults first-line (combination therapy, EASI 75)	Adults second-line (monotherapy, EASI 50 + DLQI ≥4)	Adults second-line (combination therapy, EASI 50 + DLQI ≥4)	Adolescents (monotherapy, EASI 75)
Alternative response outcome - EASI 75, int. vs dupilumab	EASI 50 + DLQI ≥4, int. vs dupilumab	✗	✓	✓	✗
Alternative response outcome - EASI 75, int. vs baricitinib	EASI 50 + DLQI ≥4, int. vs baricitinib	✗	✗	✓	✗
Alternative NMA – patients censored for rescue therapy	Patients responding and receiving rescue medication are considered responders	✓	✓	✓	✓
Alternative NMA – abrocitinib generalisable population	Abrocitinib restricted population	✗	✓	✓	✗
Alternative Tralo annual discontinuation data – CS (full population in ECZTEND)	ECZTRA 7-like population in ECZTRA 1 and ECZTRA 2	✗	✓	✓	✗
Alternative Tralo annual discontinuation data – MTA CQ (ECZTRA 7-like population in ECZTEND)	ECZTRA 7-like population in ECZTRA 1 and ECZTRA 2	✗	✓	✓	✗
Proportion of patients transition from Tralo Q2W to Q4W at Week 16	No patients transition to Q4W	✗	✓	✓	✗

Alternative CsA dose - Ariens 2019	CsA dose as per TA534	✓	×	×	×
Alternative CsA dose – clinical expert opinion	CsA dose as per TA534	✓	×	×	×
No active treatment waning	Active treatment waning as per TA534	✓	✓	✓	✓
Alternative discount rate – costs and benefits discounted at 1.5% per year	Costs and benefits discounted at 3.5% per year	✓	✓	✓	✓
Reduced time horizon – 5 years from mean age	100 years of age	✓	✓	✓	×
Reduced time horizon - 75 years of age	100 years of age	✓	✓	✓	✓
Reduced time horizon - 18 years of age	100 years of age	×	×	×	✓
TA534 combined scenario (utility values, conditional discontinuation, flare treatment)	Treatment or class specific utility values	✓	✓	✓	✓
TA534 utility values only	Class specific utility values	✓	✓	✓	✓
Annual discontinuation rates adjusted for 36-week rates	No adjustment (52-week rates assumed)	✓	✓	✓	✓

Abbreviations: CQ, clarification question; CS, company submission; CsA, ciclosporin; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; NMA, network meta-analysis; Q2W, twice weekly; Q4W, every 4 weeks

Adults first-line systemic treatment population

In all scenarios (presented in Table 74), the resultant ICERs are above £30,000 per QALY gained and therefore conclusions are unlikely to change. The scenarios which led to the largest increases in the ICER include using TA534 inputs (combined scenario and utility values).

Table 74. Scenario analysis results: adults first-line systemic treatment population, combination therapy – EASI 75 – (list prices)

Results per patient	Upadacitinib 15 mg + TCS (1)	Upadacitinib 30 mg + TCS (2)	CsA + TCS (3)	Incremental value	
				(1-3)	(2-3)
Base case					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER				£82,148	£148,451
NMA – censored for rescue therapy					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£81,943	£149,206
No active treatment waning					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£78,175	£144,307
CsA dose - Ariens 2019					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£82,771	£148,741
CsA dose - clinical expert opinion					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£81,545	£148,170
Discount rate - costs and benefits 1.5%					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£80,674	£146,659
Time horizon - limit to 5 years from mean age					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-		£87,193	£157,980
Time horizon - limit to age 75					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		[redacted]		£82,148	£148,441
TA534 scenario					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER	-			£114,525	£233,182
TA534 utility values					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-			£122,667	£232,014
Annual discontinuation rates adjusted for 36-week rates					
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER				£85,616	£150,051

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NMA, network meta-analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids

Adults second-line systemic treatment population – monotherapy

Results of the scenario analyses are presented in Table 75. Except for tralokinumab, the ICERs in for the scenario exploring the alternative EASI 75 response definition are more in favour of dupilumab than the base case analysis.

Other scenarios with large impacts on the ICER include reducing the time horizon to 75 years of age, using TA534 inputs (combined scenario and utility values) and censoring patients who receive rescue therapy. The alternative NMAs were generally more in favour of the interventions than the base case analysis. Enabling a proportion of patients from tralokinumab Q2W to tralokinumab Q4W also had a large impact in favour of tralokinumab.

Table 75. Scenario analysis results: adults second-line systemic treatment population, monotherapy - EASI 50 + DLQI ≥4 – (list prices)

Results per patient	Abrocitinib 100 mg (1)	Abrocitinib 200 mg (2)	Upadacitinib 15 mg (3)	Upadacitinib 30 mg (4)	Tralokinumab (5)	Dupilumab (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Base case											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER							Dominant	Dominant	Dominant	£66,324	£406,187*
EASI 75 response definition											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER							Dominant	£7,354	Dominant	£72,901	£470,051*
NMA - abrocitinib generalisable population											

Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER							Dominant	Dominant	Dominant	£66,221	£404,342*
NMA – censored for rescue therapy											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			-				Dominant	Dominant	Dominant	£56,072	£364,771*
Alternative tralokinumab annual discontinuation data – CS (2.3%)											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER			-				NA	NA	NA	NA	£831,456*
Alternative tralokinumab discontinuation data – MTA CQ (6.2%)											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER			-				NA	NA	NA	NA	£392,675
Proportion of patients transition from tralokinumab Q2W to Q4W at Week 16 ([redacted])											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER			-				NA	NA	NA	NA	£407,709*
No active treatment waning											

Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£64,991	£377,337*
Discount rate - costs and benefits 1.5%											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£66,023	£398,381*
Time horizon - limit to 5 years from mean age											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£67,718	£461,296
Time horizon - limit to age 75											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£66,330	£406,270
TA534 scenario											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£304,614	£299,795*
TA534 utility values											

Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£321,223	£236,033*
Annual discontinuation rates adjusted for 36-week rates											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominant	Dominant	Dominant	£65,541	£393,673*

Abbreviations: EASI, Eczema Area and Severity Index; CQ, clarification question; CS, company submission; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NA, not applicable; NMA, network meta-analysis; Q2W, twice weekly; Q4W, every 4 weeks; QALY, quality-adjusted life year

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup)

Adults second-line systemic treatment population – combination therapy

Data were not available for baricitinib using the EASI 50 + DLQI ≥ 4 response definition, and so it was not included in the base case analysis and results using EASI 75 are presented as a scenario. There was uncertainty around whether baricitinib 4 mg can be considered a high dose JAK inhibitor (a 2 mg dose is available but not recommended for treatment of AD). Additionally, both doses of abrocitinib and upadacitinib are more effective than baricitinib 4 mg. As such, the EAG explored two scenarios for the baricitinib analyses using either high dose or low dose JAK inhibitors utility values. Results for baricitinib using the EASI 75 response definition with high or low dose JAK inhibitor utilities are provided in Table 76.

The results of the scenario analyses are presented in Table 77. Except for dupilumab, all treatments produce more QALYs using the EASI 75 response definition than the EASI 50 + DLQI ≥ 4 response definition. Furthermore, the ICERs in this scenario are generally more in favour of dupilumab than the base case analysis.

Other scenarios with large impacts on the ICER include reducing the time horizon to 75 years of age and using TA534 inputs (combined scenario and utility values). Removing treatment waning also had a large impact on abrocitinib.

Table 76. Deterministic base case results vs baricitinib: adults second-line systemic treatment population, combination therapy - EASI 75 – (list prices)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Bar 4 mg + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
High dose JAKi utilities for baricitinib											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						Dominated†	£81,431	Dominated†	£187,893	£551,116

Low dose JAKi utilities for baricitinib											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£183,004	£62,242	£138,506	£144,557	£117,828

Abbreviations: Abro, abrocitinib; Bar, baricitinib; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Bar)

†Intervention dominated by Bar (Bar is less expensive and more effective than the intervention)

Table 77. Scenario analysis results: adults second-line systemic treatment population, combination therapy - EASI 50 + DLQI ≥4 – (list prices)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Base case											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,431*	Dominant	£181,499*	£129,209	£219,181*
EASI 75 response definition											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£152,130*	Dominant	£165,090*	£126,037	£204,059*
NMA - abrocitinib generalisable population											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,202*	Dominant	£181,386*	£128,483	£218,113*

NMA – censored for rescue therapy											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,534*	Dominant	£182,497*	£124,066	£216,629*
Alternative tralokinumab annual discontinuation data – CS (2.3%)											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER	-						NA	NA	NA	NA	£269,624*
Alternative tralokinumab discontinuation data – MTA CQ (6.2%)											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER	-						NA	NA	NA	NA	£215,823*
Proportion of patients transition from tralokinumab Q2W to Q4W at Week 16 ([redacted])											
Total costs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
QALYs	NA	NA	NA	NA	[redacted]	[redacted]	NA	NA	NA	NA	[redacted]
ICER	-						NA	NA	NA	NA	£245,837*
No active treatment waning											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£176,400*	Dominant	£184,383*	£112,827	£214,597*
Discount rate - costs and benefits 1.5%											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£170,879*	Dominant	£182,003*	£126,396	£217,654*

Time horizon - limit to 5 years from mean age											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£161,896*	Dominant	£180,649*	£139,734	£229,440*
Time horizon - limit to age 75											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,370*	Dominant	£181,457*	£129,302	£219,179*
TA534 scenario											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£1,739,794	Dominant	£3,679,383*	£533,979	£223,893*
TA534 utility values											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£238,940*	£608,448*	£256,341*	£3,454,647	£204,552*
Annual discontinuation rates adjusted for 36-week rates											
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£168,099*	Dominant	£178,701*	£127,134	£215,807*

Abbreviations: Abro, abrocitinib; CQ, clarification question; CS, company submission; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; Dup, dupilumab; ICER, incremental cost-effectiveness ratio; mg, milligram; NA, not applicable; NMA, network meta-analysis; Q2W, twice weekly; Q4W, every 4 weeks; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Adolescents

The scenarios with the largest impact on the ICER include reducing the time horizon to 18 years of age and using TA534 inputs (combined scenario and utility values). In all other scenarios, the interventions continue to dominate dupilumab.

Table 78. Scenario analysis results: adolescents, monotherapy - EASI 75 - (list prices)

Results per patient	Abrocitinib 100 mg (1)	Abrocitinib 200 mg (2)	Upadacitinib 15 mg (3)	Dupilumab (4)	Incremental value		
					(1-4)	(2-4)	(3-4)
Base case							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					Dominant	Dominant	Dominant
NMA - censored for rescue therapy							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-			Dominant	Dominant	Dominant
No active treatment waning							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-			Dominant	Dominant	Dominant
Discount rate - costs and benefits 1.5%							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-			Dominant	Dominant	Dominant
Time horizon - limit to age 75							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-			Dominant	Dominant	Dominant
Time horizon - limit to age 18							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER		-			Dominant	Dominant	Dominant
TA534 scenario							

Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-				£61,356	£106,593	£87,617
TA534 utility values							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-				£219,440*	£267,817*	£248,853*
Annual discontinuation rates adjusted for 36-week rates							
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-				Dominant	Dominant	Dominant

Abbreviations: EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NMA, network meta-analysis; QALY, quality-adjusted life year

5.2.2.5 Model validation

A senior health economist was responsible for the specification and development of the MTA model. A principal health economist was responsible for validating model assumptions and performing a detailed quality assurance of the MTA model. A third health economist, not involved in the MTA project, performed an independent review of the MTA model, including face validity checks and black and white box testing of the model.

The EAG's clinical experts were involved with validating key assumptions in the model to ensure clinical validity of model inputs and outputs as well as peer review of the report.

5.2.3 Discussion

5.2.3.1 Summary of key results

The purpose of this MTA was to assess the cost-effectiveness of abrocitinib, tralokinumab and upadacitinib individually as monotherapy and in combination with TCS for treatment of moderate-to-severe AD. In the MTA, as requested by NICE, the cost effectiveness of abrocitinib, tralokinumab and upadacitinib has been evaluated for the proposed position in the treatment pathway for moderate-to-severe AD as presented by the companies in their submissions to the STA process. All results shown in this report are based on list prices for all drugs. For results and discussion including confidential PAS discounts for all drugs (except CsA as it does not have a PAS discount), please refer to the confidential appendix to the MTA report.

The company for upadacitinib was the only one to have a proposed position for the entire indication, that is for adolescents irrespective of prior treatment and adults as both first- and second-line systemic treatment. Upadacitinib is available in two doses, 15 mg and 30 mg. Upadacitinib 15 mg is approved for use in adolescents and both doses are approved for adults. In the adolescent population, upadacitinib 15 mg dominates dupilumab. In the adult first-line systemic treatment population, compared with CsA with TCS, upadacitinib 15 mg and 30 mg in combination with TCS are associated with probabilistic ICERS of £78,889 and £152,043. In the adult second-line systemic treatment population, upadacitinib 15 mg as monotherapy dominates dupilumab and in combination with TCS is less costly and less effective than dupilumab (south-west quadrant ICER of £185,453). Upadacitinib 30 mg as monotherapy and in combination with TCS is more expensive and more effective than dupilumab, with probabilistic ICERs of £66,361 and £123,337 respectively for the adult second-line systemic treatment population.

The company's proposed positions in the treatment pathway for abrocitinib were for adolescents and adult second-line systemic treatment. Abrocitinib is available in two doses, 100 mg and 200 mg, with both approved for use in adolescents and adults. In the adolescent population, abrocitinib 100 mg and 200 mg dominate dupilumab. In the adult second-line systemic treatment population, abrocitinib 100 mg in combination with TCS is less costly and less effective than dupilumab in combination with TCS (south-west quadrant probabilistic ICER of £156,267). However, as a monotherapy for both doses and as combination therapy with the 200 mg dose, abrocitinib is less costly and more effective than dupilumab in the adult second-line systemic treatment population.

The probabilistic ICERs for abrocitinib 100 mg and 200 mg and for 200 mg in combination with TCS are all dominant.

The proposed position in the treatment pathway by the company for tralokinumab was for the adult second-line systemic population. Compared with dupilumab as a monotherapy and combination therapy, tralokinumab was less expensive and less effective, resulting in south-west quadrant probabilistic ICERs of £388,870 for monotherapy and £232,282 for combination therapy.

For all treatments in the adolescent and adult first-line combination therapy and second-line systemic monotherapy and combination therapy populations (except for abrocitinib 100 mg + TCS and tralokinumab + TCS), probabilistic ICERs were consistent with deterministic ICERs. The EAG notes that in all analyses, incremental QALYs were relatively small for each treatment resulting in sensitive ICERs. Furthermore, the sensitivity in the ICERs were seen in the OWSA and scenarios (discussed below) with changes in magnitude but rarely direction of results.

The EAG cautions the interpretation of the cost-effectiveness results presented in the MTA report as they are based on list prices for abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib as all have confidential patient access scheme (PAS) discounts in place. As such, the cost-effectiveness results presented in the confidential appendix to the MTA report, which includes applicable PAS discounts for the interventions, are more relevant for decision-making.

In the OWSA for all populations, the key drivers of cost-effectiveness were Week 16 response probabilities and conditional discontinuation probabilities (used to inform the week 52 response and annual discontinuation), which are as expected as these are the key effectiveness estimates in the model. In particular, the NMA for Week 16 response was associated with substantial uncertainty, notably for abrocitinib due to small numbers informing the network.

The EAG conducted a range of scenarios to test the impact on the ICER of alternative assumptions and data inputs for key parameters. In the adult second-line systemic treatment population, baricitinib is also a comparator, but it could not be included in the EAG base case analyses as response data using the composite outcome were not made available to the EAG. However, EASI 75 response data were available for baricitinib combination therapy. Furthermore, using the EASI 75 outcome, baricitinib was less effective than both doses of abrocitinib and upadacitinib and as such there was uncertainty around the appropriateness of considered it as a high dose JAK inhibitor (a 2 mg dose is available but not recommended for AD treatment). Thus, the EAG conducted two

scenarios comparing the three new drugs against baricitinib as combination therapy using the EASI 75 response outcome and either high or low dose JAK inhibitor utility values for baricitinib.

When compared with baricitinib as a high dose JAK inhibitor in combination with TCS, abrocitinib 200 mg, upadacitinib 30 mg and tralokinumab (all in combination with TCS) are more costly and more effective (deterministic ICERs of £81,431, £187,893 and £551,116, respectively). Both abrocitinib 100 mg and upadacitinib 15 mg (all in combination with TCS) are dominated by baricitinib. Compared with baricitinib as a low dose JAK inhibitor, both doses of abrocitinib and upadacitinib as well as tralokinumab were all more expensive and more effective, resulting in deterministic ICERs of £183,004 and £62,242 for abrocitinib 100 mg and 200 mg, £138,506 and £144,557 for upadacitinib 15 mg and 30 mg and £117,828 for tralokinumab. However, as mentioned previously, the results are based on list prices for interventions and results based on inclusion of confidential PAS discounts are more appropriate for decision making.

The EAG explored the use of the EASI 75 response outcome for comparisons against dupilumab in the adult second-line systemic treatment population. For both the monotherapy and combination therapy analyses (except for monotherapy abrocitinib 200 mg), ICERs were consistent with the base case, although total QALYs were higher for all treatments (except dupilumab combination therapy). For monotherapy abrocitinib 200 mg, when using the EASI 75 outcome, the ICER changed from dominant to £7,354.

Focus on the composite outcome for the EAG base case analyses was informed by the recommendations of TA534 and TA681, where the committee considered that EASI 50 and an improvement in the DLQI of at least 4 are sensitive to changes in treatment outcomes and more clinically relevant than an EASI 75. The EAG's clinical experts fed back that EASI 50 + ΔDLQI ≥4 does inform their assessment of response to treatment, but they went on to caution that the subjective nature of the DLQI, as a patient-assessed tool that is open to recall bias, is also borne in mind and, consequently, their preference to assess clinical effectiveness is change in EASI by 75%. Furthermore, the EAG's clinical experts considered EASI 75 is much harder to achieve compared to the composite outcome.

The majority of the QALYs generated for each treatment are derived from occupation in the BSC health state and over a lifetime most patients end up on BSC. Patients on BSC will experience periods of response and relapse and data on the disease course is limited. As such, the EAG explored

a scenario reducing the time horizon of the model to five years for the adult analyses, which had a substantial impact on the results in the second-line population analyses. For both monotherapy and combination therapy for all interventions, ICERs were consistent with the base case results. For the adolescent analyses, reducing the time horizon to 18 years of age resulted in the ICERs for all treatments remaining dominant.

Across all populations, using parameter utility values, conditional discontinuation and flare treatment estimates from TA534 had a substantial impact on the ICERs, in particular, using utility values from TA534 was a key driver of cost-effectiveness. However, the TA534 scenario did not change the direction of the results, except for all treatments in the adolescent population (changed from dominant compared with dupilumab to north-east quadrant ICERs). However, the TA534 scenario should be considered as illustrative as data from the key trials for each of the three new drugs are available and can be considered as more appropriate for the base case compared to values in TA534 that just reflect dupilumab only.

Most of the other scenarios across all populations resulted in a change in the magnitude of the ICER, but not in the direction of the results.

5.2.3.2 Generalisability of results

The perspective of the cost effectiveness analysis reflects the NHS in England and thus results are generalisable to the patients in the England with moderate-to-severe atopic dermatitis. To ensure consistency with current clinical practice, the EAG has used relevant NICE guidance (TA534 and TA680) to inform key assumptions and parameters within the MTA model. Furthermore, the EAG consulted with its clinical experts to determine the trials which are most representative of the patient population in England to inform the baseline characteristics and effectiveness used in the model.

5.2.3.3 Strengths and limitations of analysis

The primary strength of the EAG's analysis of the three new drugs compared with current practice for each of the sub-populations is that the results have been produced using a consistent approach to the cost-effectiveness analysis. Specifically, common assumptions have been used across all comparators, such that results facilitate a consistent basis for decision making. Furthermore, the EAG has utilised available trial data for each of the interventions to ensure results are as robust as possible.

As expected, the EAG's base case cost-effectiveness results for each of the three new drugs differs from the each of the companies' own base case results. The base case results presented by the companies are not based on list price but include their PAS discounts. In the current MTA report, list price results are presented and the EAG's confidential appendix presents results for all interventions and comparators with PAS discounts simultaneously applied (except for CsA which does not have a PAS discount). As such, the EAG's and companies' results are not comparable. Nonetheless, there are other fundamental differences between the EAG's approach and each of the companies approaches which would drive differences in cost-effectiveness. Namely, the EAG has defined the populations under consideration to reflect the NICE final scope and the treatment pathway more closely for the topic compared with the population definitions used by the companies in their submissions. Furthermore, the EAG has specified a single NMA for each population for all relevant treatments to produce consistent effectiveness estimates to use in the MTA model. In the MTA model, the EAG has implemented drug class-based utilities which is deviation from the companies approaches and also uses conditional discontinuation rather than conditional response for Week 52 outcomes, which is another difference in the approach adopted compared with the approach used in the upadacitinib model.

Despite the strengths of the EAG's approach, there were several limitations with the analyses that required assumptions to be made where possible and where not possible omissions within the analysis. The most significant limitation with the analysis is that the composite outcome of EASI 50 + DLQI ≥4 could not be obtained for the adolescent and adult first-line systemic treatment populations due to a paucity of data for dupilumab informing the adolescent NMA and CsA data informing the adult first-line systemic treatment NMA. Furthermore, even though combination therapy data were available for abrocitinib and upadacitinib, only monotherapy could be assessed for the adolescent population as combination data for dupilumab were unavailable to inform the NMA. Conversely, only combination therapy could be assessed for the adult first-line systemic treatment population as monotherapy data were unavailable.

The EAG considered the feasibility of estimating an "adjustment factor" to estimate combination therapy outcomes based on monotherapy outcomes (and vice versa) to fill the data gaps. Treatment response data presented in Section 5.2.1.5 suggest that combination therapy is more effective than monotherapy for adults in the second line systemic treatment subgroup. However, there isn't a consistent trend in terms of inflation of benefit when comparing combination therapy and monotherapy across the treatments. Additionally, the populations considered in the MTA are

heterogenous and an adjustment factor based on one population for one treatment may not reflect the true outcomes for population where data are unavailable. Therefore, the EAG found that there was not a robust method to estimate the missing data.

As the combination therapy analyses are more relevant for clinical practice, the EAG considered missing monotherapy data is unlikely to be critical for decision-making for the adult first-line systemic treatment subgroup. However, for the adolescent population monotherapy analyses may potentially underestimate the effectiveness of the treatments when used in combination with TCS in clinical practice. Therefore, adolescent monotherapy analyses may reflect a conservative view of clinical effectiveness.

Another significant limitation with the analysis is that comparisons with baricitinib could only be included in scenario analysis. In TA681, baricitinib was assessed in the adult second-line systemic population using the composite outcome but data were redacted, and the company did not provide these data for inclusion in the MTA NMA analyses. As such, only EASI 75 data for baricitinib combination therapy could be included in the NMA for the adult second-line systemic treatment population and as this is not the primary outcome, was limited to a scenario. The downstream implication of a lack of base case result for the three new drugs compared with baricitinib is that incremental analysis of dupilumab and baricitinib against each of the three new drugs could not be presented and any recommendations for the adult second-line systemic population based on the primary composite outcome are limited to comparisons with dupilumab.

Analyses exploring increasing or decreasing dose for abrocitinib and upadacitinib were not possible as efficacy data based on titrating dose are unavailable. However, the SmPC guidance for both abrocitinib and upadacitinib does take into consideration circumstances where moving to the lower or higher dose of each drug may be beneficial and this is likely to happen in clinical practice.

Another consideration for clinical practice that could not be explored in the current analyses was treatment sequencing. Currently there is a lack of clinical data on the effectiveness of sequences of AD treatments, especially changing drug class (e.g. starting on a Janus kinase [JAK] inhibitor and then moving to a monoclonal antibody). As such, more clinical data is needed to understand how patients respond to subsequent lines of systemic treatment and the resulting cost-effectiveness of treatment sequences.

6 Assessment of factors relevant to the NHS and other parties

The Evidence Assessment Group (EAG) considers that all factors relevant to the National Health Service (NHS) and other parties are captured within the clinical and cost-effectiveness analyses. However, the EAG acknowledges that the outcome of the multiple technology assessment (MTA) may result in potentially more treatment options being made available to patients with moderate-to-severe atopic dermatitis (AD) and thus the cost-effectiveness of treatment sequencing becomes a relevant consideration.

As stated in the final protocol for the MTA, there is a lack of clinical data on the effectiveness of sequences of AD treatments. Furthermore, in agreement with the National Institute of Health and Care Excellence (NICE), the remit of the initial phase of the MTA prior to the first Appraisal Committee Meeting (ACM) is to compare each of the treatments against current treatment options to obtain a view on the cost-effectiveness of the new drugs. As such, the EAG considers that further analysis of the cost effectiveness of treatment sequences, based on assumptions in lieu of clinical data, can be provided for discussion at the second ACM if considered appropriate by the committee.

7 Discussion

7.1 Statement of principal findings

In the MTA, the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib at their recommended dose or doses versus treatment options available in the NHS for moderate-to-severe AD, was evaluated in the positions in the treatment pathway proposed by the individual companies.

The proposed positions are:

- Abrocitinib:
  - Second-line systemic therapy for adolescents;
  - Second-line systemic therapy for adults.
- Tralokinumab:
  - Second-line systemic therapy for adults.
- Upadacitinib:
  - Adolescents;
  - First-line systemic therapy for adults;
  - Second-line systemic therapy for adults.

The EAG has focused on outcomes of clinical effectiveness that inform the economic evaluation of this MTA. In line with preferences expressed by the NICE Committee for dupilumab and baricitinib in TA534 and TA681,[12, 13] a composite outcome of reduction in Eczema Area and Severity Index (EASI) score of 50% and improvement in Dermatology Life Quality Index (DLQI) of at least four points (EASI 50 + ΔDLQI ≥4) is the primary clinical outcome for the MTA. Clinical experts fed back that the patient-reported DLQI component of EASI 50 + ΔDLQI ≥4 renders the composite outcome open to recall bias. In addition, data on EASI 50 + ΔDLQI ≥4 were not available for all comparisons in all populations and, consequently, improvement in EASI by 75% was also evaluated.

The EAG's experts advised that, in clinical practice, systemic therapies are likely to be predominantly given concomitantly with TCS. However, treatment with systemic treatments as a monotherapy are relevant for a proportion of patients who cannot tolerate or do not want to use TCSs. Therefore, clinical effectiveness of abrocitinib, tralokinumab and upadacitinib was evaluated when given as a monotherapy and when administered with concomitant TCS.

The primary clinical effectiveness analysis included patients who received rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. That is, the primary NMAs were based on using all observed data, regardless of rescue medication use to determine response, where possible.

Experts advising the EAG commented that, in clinical practice for the management of AD in adults, abrocitinib, tralokinumab and upadacitinib are likely to be used as alternatives to dupilumab and baricitinib, which have been assessed as treatment options after inadequate response, inability to tolerate, or contraindication to first-line CsA. For abrocitinib, tralokinumab and upadacitinib, the primary analyses of adults in the second line setting were based on the subgroup of patients which aligned with the populations informing the efficacy of dupilumab, baricitinib. For abrocitinib in particular, this subgroup had a very small sample size.

There were considerable amounts of uncertainty and the vast majority of results for EASI 50 + ΔDLQI ≥4 and EASI 75 were not statistically significant. However, there were consistent trends across the outcomes (EASI 50 + ΔDLQI ≥4 and EASI 75), interventions (combination therapy or monotherapy), and populations (adults in the first- or second-line setting, and adolescents).

Treatment with abrocitinib 200 mg leads to a better response, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than dupilumab treatment, whereas there was less of a difference if effectiveness between dupilumab and the lower dose of abrocitinib (100 mg) with some comparisons showing a benefit in favour of dupilumab and others in favouring abrocitinib 100 mg. Both doses of abrocitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second line setting) and in the adolescent population both doses of abrocitinib were more effective than dupilumab (EASI 75). The sensitivity analyses based on expanding the population receiving abrocitinib from those that had failed/not tolerated CsA as the first systemic therapy (restricted population) to include those who were previously treated with at least one systemic treatment for AD (generalisable population), gave similar results to the primary analysis for the composite outcome and EASI 75 for abrocitinib used in combination with TCS and for abrocitinib monotherapy when response was assessed as EASI 50 + ΔDLQI ≥4. However, for EASI 75 the benefit of abrocitinib monotherapy compared with dupilumab monotherapy was substantially reduced, favouring dupilumab over abrocitinib 100 mg but still favouring abrocitinib 200 mg over dupilumab.

Although significantly better than placebo, tralokinumab treatment was numerically, but not statistically significantly, less effective than treatment with either dupilumab or baricitinib 4 mg (response assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75).

Similar to abrocitinib, treatment with upadacitinib 30 mg led to a better response, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than dupilumab treatment, whereas there was less of a difference if effectiveness between dupilumab and the lower dose of upadacitinib (15 mg) with some comparisons showing a benefit in favour of dupilumab and others favouring upadacitinib 15 mg. Both doses of upadacitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second line setting). In the adolescent population upadacitinib 15 mg was more effective than dupilumab (EASI 75).

Rescue therapy was not permitted in the abrocitinib trials. Though, sensitivity analysis censoring patient who needed rescue therapy in the trials informing the dupilumab, tralokinumab, and upadacitinib had limited impact for most comparisons. However, for adults given the treatments as monotherapies in the second line setting, the efficacy of abrocitinib versus dupilumab (assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75) decreased substantially when patients receiving rescue therapy were censored, and for the NMA of treatments in combination with TCS, the results for EASI 50 + ΔDLQI ≥4 differed substantially for upadacitinib between the primary analysis and the sensitivity analysis censoring patients who received rescue therapy.

For all but the network for the first line adult population, there were variability in placebo response for the treatments in each network. This indicates that there may be imbalances in treatment effect modifiers between the trials, which can have an impact on the relative efficacy of the treatments. The EAG attempted to adjust for the difference in placebo response rates, however, this was not possible for all networks and outcomes. The models for EASI 50 + ΔDLQI ≥4 and EASI 75 for the second line systemic treatments in combination with TCS did not converge and therefore no results could be presented for these, which means that substantial uncertainly remains which could not be adjusted for. The baseline adjusted models for the NMAs of the treatments used as monotherapies in the second line setting and in the adolescent population did converge and had a better statistical fit than for the unadjusted data. However, the data for these seemed to be overfitted. As the clinical results were produced to inform the health economic model, but results adjusted for baseline differences could not be produced for all outcomes and populations feeding in to the base case, the EAG has a strong preference for the unadjusted analyses.

The National Institute of Health and Care Excellence (NICE) typically considers interventions a cost-effective use of the National Health Service (NHS) resources if the incremental cost-effectiveness ratio (ICER) sits within a £20,000 – £30,000 threshold. The decision rule is reversed if an intervention is less costly and less effective, such that if the ICER is greater than the £20,000 – £30,000 threshold, it can be considered a cost-effective use of NHS resources.

For the adolescent population analyses, both doses of abrocitinib and upadacitinib 15 mg could be considered cost-effective uses of NHS resources. The probability of being cost-effective at the £30,000 threshold was estimated to be [redacted] and [redacted] for abrocitinib 100 mg and 200 mg and [redacted] for upadacitinib 15 mg.

For the adult second-line monotherapy population, both doses of abrocinitinib, upadacitinib 15 mg and tralokinumab could be considered cost-effective uses of NHS resources, with the probability of being cost-effective at the £30,000 threshold estimated as [redacted] and [redacted] for abrocitinib 100 mg and 200 mg, [redacted] for upadacitinib 15 mg and [redacted] for tralokinumab. For the adult second-line combination therapy population, both doses of abrocitinib, upadacitinib 15 mg and tralokinumab could be considered cost-effective uses of NHS resources. The probability of being cost-effective at the £30,000 threshold was estimated to be [redacted] and [redacted] for abrocitinib 100 mg and 200 mg, [redacted] for upadacitinib 15 mg and [redacted] for tralokinumab.

For the adult first-line systemic treatment population, upadacitinib may not be considered a cost-effective use of NHS resources, with the probability of being cost-effective at the £30,000 threshold for the 15 mg and 30 mg dose estimated as [redacted] and [redacted], respectively.

The EAG cautions the interpretation of the cost-effectiveness results presented in the multiple technology assessment (MTA) report as they are based on list prices for abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib but all have confidential patient access scheme (PAS) discounts in place. As such, the cost-effectiveness results presented in the confidential appendix to the MTA report, which includes applicable PAS discounts for the interventions, are more relevant for decision-making.

The key drivers of cost-effectiveness for all populations were Week 16 response probabilities and conditional discontinuation probabilities (used to inform the week 52 response and annual discontinuation), which are as expected as these are the key effectiveness estimates in the model. In

particular, the NMA for Week 16 response was associated with substantial uncertainty, in particular for abrocitinib due to small numbers informing the network.

The majority of the quality-adjusted life-years (QALYs) generated for each treatment are derived from occupation in the best supportive care (BSC) health state and over a lifetime most patients end up on BSC. Patients on BSC will experience periods of response and relapse and data on the disease course is limited. Reducing the time horizon of the model to five years for the adult analyses resulted in ICERs consistent with the base case. For the adolescent analyses, ICERs remained dominant when the time horizon was reduced to 18 years of age.

In the adult second-line systemic treatment population, baricitinib is also a comparator, but it could not be included in the EAG base case analyses as response data using the composite outcome were not made available to the EAG. However, EASI 75 response data were available for baricitinib combination therapy. Thus, the EAG conducted a scenario comparing the three new drugs against baricitinib as combination therapy using the EASI 75 response outcome. Furthermore, using the EASI 75 outcome, baricitinib was less effective than both doses of abrocitinib and upadacitinib and as such there was uncertainty around the appropriateness of considered it as a high dose JAK inhibitor (a 2 mg dose is available but not recommended for AD treatment). Thus, the EAG conducted two scenarios comparing the three new drugs against baricitinib as combination therapy using the EASI 75 response outcome and either high or low dose JAK inhibitor utility values for baricitinib. Under both scenarios for baricitinib, none of the three interventions could be considered cost-effective uses of NHS resources. However, as mentioned previously, the results are based on list prices for interventions and results based on inclusion of confidential PAS discounts are more appropriate for decision making.

The EAG explored the use of the EASI 75 response outcome for comparisons against dupilumab in the adult second-line systemic treatment population. For both the monotherapy and combination therapy analyses (except for monotherapy abrocitinib 200 mg), ICERs were consistent with the base case, although total QALYs were higher for all treatments (except dupilumab combination therapy). For monotherapy abrocitinib 200 mg, when using the EASI 75 outcome, the ICER changed from dominant to £7,354.

Focus on the composite outcome for the EAG base case analyses was informed by the recommendations of TA534 and TA681, where the committee considered that EASI 50 and an

improvement in the DLQI of at least 4 are sensitive to changes in treatment outcomes and more clinically relevant than an EASI 75. The EAG's clinical experts fed back that EASI 50 + ΔDLQI ≥4 does inform their assessment of response to treatment, but they went on to caution that the subjective nature of the DLQI, as a patient-assessed tool that is open to recall bias, is also borne in mind and, consequently, their preference to assess clinical effectiveness is change in EASI by 75%. As such, the EASI 75 scenario can be seen as a conservative view of cost-effectiveness as treatment response is based on a higher threshold of skin clearance.

Across all populations, using parameter utility values, conditional discontinuation and flare treatment estimates from TA534 had a substantial impact on the ICERs, in particular, using utility values from TA534 was a key driver of cost-effectiveness. However, the TA534 scenario did not change the direction of the results, except for all treatments in the adolescent population (changed from dominant compared with dupilumab to north-east quadrant ICERs). However, the TA534 scenario should be considered as illustrative as data from the key trials for each of the three new drugs are available and can be considered as more appropriate for the base case compared to values in TA534 that just reflect dupilumab only.

Most of the other scenarios across all populations resulted in a change in the magnitude of the ICER, but not in the direction of the results.

7.2 Strengths and limitations of the assessment

The primary strength of the EAG's analysis of the three new drugs compared with current practice for each of the sub-populations is that the results have been produced using a consistent approach to the clinical and cost-effectiveness analysis. Specifically, common assumptions have been used across all comparators, such that results facilitate a consistent basis for decision making. Furthermore, the EAG has utilised available trial data for each of the interventions in the model to ensure results are as robust as possible.

A strength of the EAG's clinical analysis is that the trial populations informing the comparisons in the first- and second-line settings were consistently defined across all interventions and in line with the clinical data informing TA534 and TA681. The second line population was defined as patients who achieved inadequate response to, could not tolerate, or were contraindicated to CsA. However, in some studies contraindication to CsA was not captured, and for abrocitinib the definition of the population eligible for treatment at second line meant a very small sample size could be included in

the primary analysis as the majority of patients in the trials had not received prior systemic therapy or failed/not tolerated systemic therapies other than CsA. That is, the majority of patients in the abrocitinib trials were eligible for first-line systemic therapy according to the EAG's definition; the population eligible for first-line systemic therapy was patients who were eligible for systemic treatment on inadequate response to topical treatments and who had not received prior systemic therapy.

In terms of the clinical data used, the EAG's approach differed from the companies to some extent. The clinical data informing the company's base case for tralokinumab were aligned with TA534 and TA681 and included patients who had inadequate control with, or intolerance or contraindications to CsA. However, the clinical data informing the base case for abrocitinib were for patients who were previously treated with at least one systemic treatment for AD (the generalisable population). For upadacitinib, the data informing the base case for the second-line population included people who had previously received CsA, irrespective of response to it and not including those for whom CsA was not tolerated or contraindicated. For the population corresponding to the EAG's definition of the first-line population, the company for upadacitinib used clinical data for people who were candidates for conventional systemic treatment, which included patients who were not systemic therapy naïve and thus overlapped with the second line population.

Although the consistent definitions of the first- and second-line populations is a strength of the analysis, the evidence informing the NMAs for these populations was predominantly derived from *post hoc* subgroups. The use of *post hoc* subgroups reduces the sample size for analysis and also breaks the randomisation component of an RCT. A consequence of breaking randomisation is the potential creation of imbalances in both observed and unobserved baseline characteristics. The use of *post hoc* subgroups introduces bias and uncertainty around the results generated by the NMAs, and is a considerable limitation that impacts on the robustness and confidence in the estimates of effect for clinical effectiveness, which is propagated to the cost effectiveness analysis.

As expected, the EAG's base case cost-effectiveness results for each of the three new drugs differs from the each of the companies' own base case results. The base case results presented by the companies are not based on list price but include their PAS discounts. In the current MTA report, list price results are presented and the EAG's confidential appendix presents results for all interventions and comparators with PAS discounts simultaneously applied (except for ciclosporin [CsA] which does not have a PAS discount). As such, the EAG's and companies' results are not comparable.

Nonetheless, there are other fundamental differences between the EAG's approach and each of the companies approaches which would drive differences in cost-effectiveness. As described above, the EAG has defined the populations under consideration to reflect the NICE final scope and the treatment pathway more closely for the topic compared with the population definitions used by the companies in their submissions. Furthermore, the EAG has specified a single NMA for each population for all relevant treatments to produce consistent effectiveness estimates to use in the MTA model. Additionally, the EAG has implemented drug class-based utilities which is deviation from the companies approaches and also uses conditional discontinuation rather than conditional response for Week 52 outcomes, which is another difference in the approach adopted compared with the approach used in the upadacitinib model.

Despite the strengths of the EAG's approach, there were several limitations with the analyses that required assumptions to be made where possible and where not possible omissions within the analysis. The most significant limitation with the analysis is that the composite outcome of EASI 50 + DLQI ≥4 could not be obtained for the adolescent and adult first-line systemic treatment populations due to a paucity of data for dupilumab informing the adolescent NMA and CsA data informing the adult first-line systemic treatment NMA. Furthermore, even though combination therapy data were available for abrocitinib and upadacitinib, only monotherapy could be assessed for the adolescent population as combination data for dupilumab were unavailable to inform the NMA. Conversely, only combination therapy could be assessed for the adult first-line systemic treatment population as monotherapy data were unavailable. As the combination therapy analyses are more relevant for clinical practice, the EAG considered missing monotherapy data is unlikely to be critical for decision-making for the adult first-line systemic treatment subgroup. However, for the adolescent population monotherapy analyses may potentially underestimate the relative effectiveness of the treatments when used in combination with TCS in clinical practice. Therefore, adolescent monotherapy analyses may reflect a conservative view of clinical effectiveness.

Another significant limitation with the analysis is that comparisons with baricitinib could only be included in scenario analysis. In TA681, baricitinib was assessed in the adult second-line systemic population using the composite outcome but data were redacted, and the company did not provide these data for inclusion in the MTA NMA analyses. As such, only EASI 75 data for baricitinib combination therapy could be included in the NMA for the adult second-line systemic treatment population and as this is not the primary outcome, was limited to a scenario. The downstream implication of a lack of base case result for the three new drugs compared with baricitinib is that

incremental analysis of dupilumab and baricitinib against each of the three new drugs could not be presented and any recommendations for the adult second-line systemic population based on the primary composite outcome are limited to comparisons with dupilumab.

Another limitation of the analysis for upadacitinib is the lack of RCT data for CsA in the first line setting. Thus, results for the comparison of upadacitinib and CsA in the first-line setting are derived from observational data, which is associated with the bias inherent in observational studies and the clinical and cost effectiveness results for upadacitinib versus CsA should be interpreted with caution.

Analyses exploring increasing or decreasing dose for abrocitinib and upadacitinib were not possible as efficacy data based on titrating dose are unavailable. However, the SmPC guidance for both abrocitinib and upadacitinib does take into consideration circumstances where moving to the lower or higher dose of each drug may be beneficial and this is likely to happen in clinical practice.

Another consideration for clinical practice that could not be explored in the current analyses was treatment sequencing. Currently there is a lack of clinical data on the effectiveness of sequences of AD treatments, especially changing drug class (e.g. starting on a Janus kinase [JAK] inhibitor and then moving to a monoclonal antibody). As such, more clinical data is needed to understand how patients respond to subsequent lines of systemic treatment and the resulting cost-effectiveness of treatment sequences.

7.3 Uncertainties

The generalisability of the clinical data informing the analysis is a key area of uncertainty. Clinical experts advising the EAG commented that, based on baseline EASI scores, the patients enrolled in the RCTs identified as relevant to the MTA have more severe AD than would typically be seen in clinical practice, with most patients presenting with disease in clinical practice categorised as moderate severity. No analysis was possible to explore potential differences in efficacy of abrocitinib, tralokinumab and upadacitinib based on disease severity. As such, the efficacy of these interventions seen in patients with more severe AD in the clinical trials may be different to the effect in patients with more moderate AD in clinical practice.

A key uncertainty in the cost-effectiveness analysis is around the long-term effectiveness of treatments for maintaining response, which is a key driver of cost-effectiveness in the MTA model. All of the key trials for each of the new drugs only report short-term data on treatment response and discontinuation. As such, the EAG made assumptions about long-term response in the MTA model

based on available short-term data conditional treatment discontinuation data, which is subject to a substantial amount of uncertainty but has been appropriately explored in sensitivity and scenario analyses.

Related to the uncertainty about long-term effectiveness of treatments is the question of how clinical similar treatments for moderate-to-severe AD are to each other. For the NMAs there were considerable amounts of uncertainty, and the vast majority of results were not statistically significant. There are several reasons for the large uncertainty (wide 95% CrIs) in the clinical results, including the use of *post hoc* subgroups and small sample sizes, especially for abrocitinib. The EAG is aware that non-significant results from NMAs have been used to substantiate an assumption of clinical equivalence. However, the EAG does not consider this appropriate in this MTA given the magnitude of uncertainty in the results. Additionally, direct evidence from the trials of abrocitinib and upadacitinib demonstrate a statistically significant difference between the lower and higher doses; as such it is not clinical plausible to consider that they would all have the same effectiveness as a comparator. Thus, the EAG could not reliably assume that treatments were clinically equivalent.

7.4 Other relevant factors

The EAG acknowledges that the outcome of the MTA may result in potentially more treatment options being made available to patients with moderate-to-severe AD, but there is a lack of clinical data on the effectiveness of sequences of AD treatments. Nonetheless, the cost-effectiveness of treatment sequencing may become a relevant consideration in the future.

8 Conclusions

8.1 Implications for service provision

As a result of this multiple technology assessment (MTA) more treatments for moderate-to-severe atopic dermatitis (AD) may be made available to patients. However, currently there is a lack of clinical data on the effectiveness of sequences of AD treatments, especially changing drug class (e.g. starting on a Janus kinase [JAK] inhibitor and then moving to a monoclonal antibody). As such, more clinical data is needed to understand how patients respond to subsequent lines of systemic treatment and the resulting cost-effectiveness of treatment sequences.

8.2 Suggested research priorities

Although abrocitinib has a marketing authorisation for the treatment of moderate-to-severe AD in adults and adolescents aged 12 years and over and who are candidates for systemic therapy, the company has positioned abrocitinib as a treatment option for adolescents and for adults in the second-line setting, where second-line systemic therapy captures those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy, which, for the MTA, was limited to ciclosporin (CsA). However, the majority of patients in the abrocitinib trials were systemic therapy naïve and not relevant for the company's proposed positioning of abrocitinib. More clinical data, in the form of confirmatory RCT evidence in the second-line setting is therefore needed.

The remit of this MTA was to assess abrocitinib, tralokinumab and upadacitinib against current treatments in the companies' proposed positions in the treatment pathway. However, where there are multiple new treatments in a proposed position (for instance, second-line systemic treatment for adults), comparing the new drugs against one another in addition to current practice in an incremental cost-effectiveness analysis would be beneficial to provide a robust view on which treatments are the most cost-effective. Furthermore, the incremental cost-effectiveness analysis could feed into further analyses around cost-effective treatment pathways. As noted in Section 8.1 the impact of this MTA is that more treatments for moderate-to-severe AD may be made available to patients. However, currently there is a lack of clinical data on the effectiveness of sequences of AD treatments, thus more research in this area is required to perform robust analyses of the cost-effectiveness of treatment sequences.

The UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR) is a currently ongoing observational study seeking to understand the safety, effectiveness and health economic implications of systemic immune-modulators in people with AD. Enrolment onto A-STAR for all patients starting these biologic treatments will provide useful real-world evidence to inform future clinical and cost-effectiveness studies of systemic treatments for AD.

9 References

1. Kapur S, Watson W, Carr S. Atopic dermatitis. *Allergy Asthma Clin Immunol* 2018; **14**: 52.
2. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy* 2014; **2014**: 354250.
3. Cork MJ, Danby SG, Ogg GS. Atopic dermatitis epidemiology and unmet need in the United Kingdom. *J Dermatolog Treat* 2020; **31**: 801-9.
4. Patient. Atopic Dermatitis and Eczema. 2021. Available from: https://patient.info/doctor/atopic-dermatitis-and-eczema#nav-0. Date accessed: 24 Sep 2021.
5. Al-Shobaili HA, Ahmed AA, Alnomair N, Alobead ZA, Rasheed Z. Molecular Genetic of Atopic dermatitis: An Update. *Int J Health Sci (Qassim)* 2016; **10**: 96-120.
6. Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci* 2009; **122**: 1285-94.
7. Baurecht H, Irvine AD, Novak N, Illig T, Buhler B, Ring J, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol* 2007; **120**: 1406-12.
8. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441-6.
9. Figueras-Nart I, Palomares-Gracia O. Atopic Dermatitis: From Physiopathology to the Clinics. 2019. Available from: https://www.intechopen.com/chapters/69553. Date accessed: 30 Sep 2021.
10. British Association of Dermatologists. Atopic eczema. 2020. Available from: https://www.bad.org.uk/shared/get-file.ashx?id=69&itemtype=document. Date accessed: 31 Mar 2021.
11. Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ* 2018; **361**: k1786.
12. National Institute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA534]. 2018. Available from: https://www.nice.org.uk/guidance/TA534/chapter/1-Recommendations. Date accessed: 18 Oct 2021.
13. National Institute for Health and Care Excellence (NICE). Baricitinib for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA681]. 2021. Available from: https://www.nice.org.uk/guidance/TA681. Date accessed: 18 Oct 2021.
14. Koszoru K, Borza J, Gulacsi L, Sardy M. Quality of life in patients with atopic dermatitis. *Cutis* 2019; **104**: 174-7.
15. Zink AGS, Arents B, Fink-Wagner A, Seitz IA, Mensing U, Wettemann N, et al. Out-of-pocket Costs for Individuals with Atopic Eczema: A Cross-sectional Study in Nine European Countries. *Acta Derm Venereol* 2019; **99**: 263-7.
16. Schofield J, Grindlay D, Williams H. Skin Conditions in the UK: a Health Care Needs Assessment. 2009. Available from: https://www.nottingham.ac.uk/research/groups/cebd/documents/hcnaskinconditionsuk2009.pdf. Date accessed: 30 Sep 2021.
17. National INstitute for Health and Care Excellence (NICE). Eczema. 2021. Available from: https://pathways.nice.org.uk/pathways/eczema. Date accessed: 29 Oct 2021.
18. Gooderham MJ, Bissonnette R, Grewal P, Lansang P, Papp KA, Hong CH. Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document. Section II: Tools for Assessing the Severity of Atopic Dermatitis. *J Cutan Med Surg* 2018; **22**: 10S-6S.

19. Harmonising Outcomes for Eczema. Core outcomes for trials. 2021. Available from: http://www.homeforeczema.org/research/index.aspx. Date accessed: 30 Jun 2021.
20. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**: 27-33.
21. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol* 2017; **177**: 1316-21.
22. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbe A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol* 2019; **181**: 761-9.
23. Primary Care Dermatology Society. Eczema - atopic aczema. 2019. Available from: http://www.pcds.org.uk/clinical-guidance/atopic-eczema. Date accessed: 1 Jun 2021.
24. NHS. Atopic eczema. 2021. Available from: https://www.nhs.uk/conditions/atopic-eczema/treatment/. Date accessed: 31 Mar 2021.
25. Berth-Jones J, Exton LS, Ladoyanni E, Mohd Mustapa MF, Tebbs VM, Yesudian PD, et al. British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018. *Br J Dermatol* 2019; **180**: 1312-38.
26. Scottish Intercollegiate Guidelines Network. Management of atopic eczema in primary care 2011. Available from: https://www.sign.ac.uk/media/1063/sign125.pdf. Date accessed: 29 Oct 2021.
27. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. *JAMA dermatology* 2019; **155**: 1371-9.
28. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet* 2020; **396**: 255-66.
29. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology* 2020; **156**: 863-73.
30. Eichenfield L, Flohr C, Sidbury R, Szalai Z, Galus R, Yao Z, et al. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): results From the Phase 3 JADE TEEN study. *Journal of allergy and clinical immunology* 2021; **147**: AB146-.
31. Eichenfield LF, Silverberg JI, Gadkari A, Guillemin I, Chen Z, Bansal A, et al. 15013 Dupilumab improves signs, symptoms, and quality of life in adolescents with moderate to severe atopic dermatitis. *Journal of the American Academy of Dermatology* 2020; **83**: AB26-.
32. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. *New England journal of medicine* 2021; **384**: 1101-12.
33. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. *Allergy* 2020; **75**: 54-62.
34. ClinicalTrials.gov. Tralokinumab monotherapy for adolescent subjects with moderate to severe atopic sermatitis - ECZTRA 6 (ECZema TRAlokinumab Trial no. 6). 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03526861. Date accessed: 2 Jun 2021.
35. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British journal of dermatology* 2021; **184**: 437-49.
36. ClinicalTrials.gov. Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis - ECZTRA 5 (ECZema TRAlokinumab Trial No. 5) (ECZTRA 5). 2021. Available from:

https://clinicaltrials.gov/ct2/show/NCT03562377?term=tralokinumab&cond=Atopic+Dermatitis&draw=2&rank=7. Date accessed.
37. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *British journal of dermatology* 2021; **184**: 450-63.
38. ClinicalTrials.gov. Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis (ECZTRA 8). 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04587453. Date accessed: 21 Oct 2021.
39. ClinicalTrials.gov. Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A (ECZTRA 7). 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03761537?term=tralokinumab&draw=2&rank=5. Date accessed: 2 Jun 2021.
40. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet (London, England)* 2021; **397**: 2151-68.
41. ClinicalTrials.gov. A study to compare safety and efficacy of upadacitinib to dupilumab in adult participants with moderate to severe atopic dermatitis (Heads Up). 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03738397. Date accessed: 2 Jun 2021.
42. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (London, England)* 2021; **397**: 2169-81.
43. National Institute for Health and Care Excellence (NICE). Abrocitinib, tralokinumab and upadacitinib for treating moderate to severe atopic dermatitis. Final scope. 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10856/documents/final-scope. Date accessed: 2 Nov 2021.
44. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *Br J Dermatol* 2002; **147**: 920-5.
45. Alexis AF, Rendon M, Silverberg JI, Pariser DM, Lockshin B, Griffiths CEM, et al. Efficacy of Dupilumab in Different Racial Subgroups of Adults With Moderate-to-Severe Atopic Dermatitis in Three Randomized, Placebo-Controlled Phase 3 Trials. *Journal of drugs in dermatology : JDD* 2019; **18**: 804-13.
46. National Institute for Health and Care Excellence (NICE). Resource impact report: Baricitinib for treating moderate to severe atopic dermatitis (TA681). 2021. Available from: https://www.nice.org.uk/guidance/ta681/resources/resource-impact-report-pdf-9021362653. Date accessed: 11 Oct 2021.
47. National Institute for Health and Care Excellence (NICE). Resource impact report: Dupilumab for treating moderate to severe atopic dermatitis (TA534). 2018. Available from: https://www.nice.org.uk/guidance/ta534/resources/research-impact-report-pdf-4909806541. Date accessed: 11 Oct 2021.
48. Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev* 2020; **9**: CD013206.
49. BMJ-TAG. Abrocitinib, tralokinumab and upadacitinib for treating moderate to severe atopic dermatitis. Protocol for Multiple Technology Appraisal. 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10856/documents/final-protocol. Date accessed: 2 Nov 2021.

50. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 (Process and methods [PMG9]). 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Date accessed: 30 Jun 2021.
51. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.
52. Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Info Libr J* 2019; **36**: 264-77.
53. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898.
54. Dias S WN, Sutton AJ, Ades AE,. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. 2012. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD1-Introduction.final_.08.05.12.pdf. Date accessed: 3 Jun 2021.
55. Dias S, Welton NJ, J. SA, E. AA. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011.
56. OpenBUGS v3.2.3 rev1012. 2014.
57. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015; **34**: 984-98.
58. Dias S WN, Sutton AJ, et al. NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials. 2011.
59. Reich K, Szepietowski JC, Smith CH, Irvine AD, Ogg G, Tsianakas A, et al. Safety of dupilumab in moderate-tosevere atopic dermatitis patients inadequately controlled with, intolerant to, or inadvisable for cyclosporine-a: laboratory findings from the liberty-ad-café trial. *Journal of the dermatology nurses' association* 2020; **12**.
60. Zheng YI, Li C. Efficacy and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults. *Journal of the Dermatology Nurses' Association* 2020; **12**.
61. Gooderham M, Forman S, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. The Janus kinase 1 (JAK1) inhibitor PF-04965842 reduces signs and symptoms of moderate to severe atopic dermatitis (AD). . *Journal of Investigative Dermatology* 2018; **138**: S94.
62. Sowden JM, Berth-Jones J, Ross JS, Motley RJ, Marks R, Finlay AY, et al. Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991; **338**: 137-40.
63. Allen BR. *A multicentre double blind placebo controlled crossover to assess the eJicacy and safety of cyclosporin A in adult patients with severe refractory atopic dermatitis.* WolJ K , editors(s). Royal Society of Medicine International Congress & Symposium Series. Vol. 192. Athens, Greece: Cyclosporin A and the skin: proceedings, satellite symposium to the 2nd congress of the European Academy of Dermatology & Venereology.1991. p. 29-37.
64. Berth Jones J. Cyclosporin in severe adult atopic dermatitis - a multi-centre, double-blind, placebo-controlled crossover study. *British Journal of Dermatology* 1991; **125**: 16.
65. Munro CS, Levell NJ, Shuster S, Friedmann PS. Maintenance treatment with cyclosporin in atopic eczema. *Br J Dermatol* 1994; **130**: 376-80.
66. Salek MS, Finlay AY, Luscombe DK, Allen BR, Berth-Jones J, Camp RD, et al. Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 1993; **129**: 422-30.
67. van Joost T, Heule F, Korstanje M, van den Broek MJ, Stenveld HJ, van Vloten WA. Cyclosporin in atopic dermatitis: a multicentre placebo-controlled study. *Br J Dermatol* 1994; **130**: 634-40.
68. Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm Venereol* 1990; **70**: 323-9.

69. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**: 130-9.
70. Bieber T, Thaci D, Graham N, Pirozzi G, Teper A, Ren H, et al. Dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a 12-week, randomized, double-blind, placebo-controlled study. . *Journal of Allergy and Clinical Immunology* 2014; **133**: AB404.
71. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *The Lancet* 2017; **389**: 2287-303.
72. Blauvelt A, Simpson EL, Tyring SK, Purcell LA, Shumel B, Petro CD, et al. Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol* 2019; **80**: 158-67 e1.
73. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019; **143**: 155-72.
74. Hamilton J, Ren H, Weinstein SP, Pirozzi G, Graham N, Radin A. Dupilumab improved all domains of Eczema Area and Severity Index (EASI) and 5-D pruritus scale in adults with atopic dermatitis in a phase 2 study. *Journal of Investigative Dermatology* 2014; **134**: S104.
75. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med* 2016; **375**: 2335-48.
76. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016; **387**: 40-52.
77. Tsianakas A, Luger TA, Radin A. Dupilumab treatment improves quality of life in adult patients with moderate-to-severe atopic dermatitis: results from a randomized, placebo-controlled clinical trial. *Br J Dermatol* 2018; **178**: 406-14.
78. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2019; **80**: 913-21 e9.
79. Arora CJ, Khattak FA, Yousafzai MT, Ibitoye BM, Shumack S. The effectiveness of Janus kinase inhibitors in treating atopic dermatitis: A systematic review and meta-analysis. *Dermatol Ther* 2020; **33**: e13685.
80. Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B, et al. Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis. *JAMA Dermatol* 2020; **156**: 659-67.
81. Kerschbaumer A, Smolen JS, Nash P, Doerner T, Dougados M, Fleischmann R, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. *RMD Open* 2020; **6**.
82. Lam M, Zhu JW, Maqbool T, Adam G, Tadrous M, Rochon P, et al. Inclusion of Older Adults in Randomized Clinical Trials for Systemic Medications for Atopic Dermatitis: A Systematic Review. *JAMA Dermatol* 2020; **156**: 1240-5.
83. Seger EW, Wechter T, Strowd L, Feldman SR. Relative efficacy of systemic treatments for atopic dermatitis. *J Am Acad Dermatol* 2019; **80**: 411-6 e4.
84. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. *Allergy* 2021; **76**: 1053-76.
85. Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *J Eur Acad Dermatol Venereol* 2021; **35**: 1797-810.

86. Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *J Am Acad Dermatol* 2016; **75**: 506-15.
87. Zhao Y, Wu L, Lu Q, Gao X, Zhu X, Yao X, et al. The efficacy and safety of dupilumab in Chinese patients with moderate-to-severe atopic dermatitis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2021.
88. Ariens LFM, Gadkari A, Van Os-Medendorp H, Ayyagari R, Terasawa E, Kuznik A, et al. Dupilumab versus cyclosporine for the treatment of moderate-to-severe atopic dermatitis in adults: Indirect comparison using the Eczema Area and severity index. *Acta Dermato-Venereologica* 2019; **99**: 851-7.
89. Dal Bello G, Maurelli M, Schena D, Girolomoni G, Gisondi P. Drug survival of dupilumab compared to cyclosporin in moderate-to-severe atopic dermatitis patients. *Dermatologic Therapy* 2020; **33**.
90. Spekhorst LS, Ariëns LFM, van der Schaft J, Bakker DS, Kamsteeg M, Oosting AJ, et al. Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: Results from the BioDay registry. *Allergy: European Journal of Allergy and Clinical Immunology* 2020; **75**: 2376-9.
91. Nct. Study of Abrocitinib Compared With Dupilumab in Adults With Moderate to Severe Atopic Dermatitis on Background Topical Therapy. *https://clinicaltrials.gov/show/NCT04345367* 2020.
92. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *The Journal of allergy and clinical immunology* 2019; **143**: 135-41.
93. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *Journal of allergy and clinical immunology* 2020; **145**: 877-84.
94. ClinicalTrials.gov. A study to evaluate safety of upadacitinib in combination with topical corticosteroids in adolescent and adult participants with moderate to severe atopic dermatitis (Rising Up). 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03661138. Date accessed: 22 Apr 2021.
95. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *British Journal of Dermatology* 2020; **183**: 242-55.
96. ClinicalTrials.gov. A Long-term Study of Baricitinib (LY3009104) With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis That Are Not Controlled With Cyclosporine or for Those Who Cannot Take Oral Cyclosporine Because it is Not Medically Advisable (BREEZE-AD4). 2018. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03428100. Date accessed: 18 Oct 2021.
97. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: a Randomized Clinical Trial. *JAMA dermatology* 2020; **156**: 1333-43.
98. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, Delozier AM, et al. Long-term Efficacy of Baricitinib in Adults with Moderate to Severe Atopic Dermatitis Who Were Treatment Responders or Partial Responders: An Extension Study of 2 Randomized Clinical Trials. *JAMA Dermatology* 2021; **157**: 691-9.
99. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: a Phase 3 Randomized Clinical Trial. *JAMA dermatology* 2020; **156**: 44-56.

100. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *British journal of dermatology* 2018; **178**: 1083-101.
101. Erratum: efficacy and safety of oral Janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial (JAMA Dermatology (2019) 155: 12 (1371-1379) DOI: 10.1001/jamadermatol.2019.2855). *JAMA dermatology* 2020; **156**: 104-.
102. Simpson EL, Sinclair R, Forman S, Wollenberg A, Asch R, Cork M, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: results from the phase III, JADE MONO-1 study. *British journal of dermatology* 2020; **183**: e105-e6.
103. Silverberg J, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: results from the phase III JADE MONO-2 study. *British journal of dermatology* 2020; **183**: e100-.
104. Thac-i D, Bieber T, Simpson EL, Silverberg JI, Paul C, Sinclair R, et al. A phase III study to investigate the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adults with moderate-to-severe atopic dermatitis. *British journal of dermatology* 2021; **184**: e72-e3.
105. Tralokinumab, an anti-interleukin-13 monoclonal antibody, reduces Staphylococcus aureus colonization of the skin and systemic levels of inflammatory biomarkers in atopic dermatitis patients. *Journal of the American Academy of Dermatology* 2019; **81**: AB139-.
106. Alexis AF, Zirwas M, Pinter A, Adam DN, Chiricozzi A, Pink AE, et al. Progressive and sustained improvements in the extent and severity of atopic dermatitis with tralokinumab in combination with topical corticosteroids as needed in moderate-to-severe atopic dermatitis. *British journal of dermatology* 2021; **184**: e82-e3.
107. Upadacitinib treatment withdrawal and retreatment in patients with moderate-to-severe atopic dermatitis from a phase 2b, randomized, controlled trial. *Journal of the American Academy of Dermatology* 2019; **81**: AB294-.
108. Erratum: Department of Error (The Lancet (2021) 397(10290) (2151–2168), (S0140673621005882), (10.1016/S0140-6736(21)00588-2)). *The Lancet* 2021; **397**: 2150.
109. Reich K, Teixeira HD, De Bruin-Weller M, Bieber T, Soong W, Kabashima K, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis: results from the pivotal phase III, randomized, double-blind, placebo-controlled AD Up study. *British journal of dermatology* 2021; **184**: e59-e60.
110. Erratum: Department of Error (The Lancet (2021) 397(10290) (2169–2181), (S0140673621005894), (10.1016/S0140-6736(21)00589-4)). *The Lancet* 2021; **397**: 2336.
111. Wollenberg A, Manuel Carrascosa J, Lacour J, Reich K, Eichenfield L, Rubel D, et al. Summary of efficacy, impact on work productivity and activity, and safety of baricitinib in moderateto-severe atopic dermatitis from two monotherapy phase III trials. *British journal of dermatology* 2020; **183**: 66-.
112. Paller A, Blauvelt A, Pariser D, Worrell R, Soong W, Hong C, et al. Dupilumab for adolescents with moderate-to-severe atopic dermatitis: results from a phase 3, randomized, double-blinded trial. *Australasian journal of dermatology* 2019; **60**: 69-.
113. Dupilumab for adolescents with moderate-to-severe atopic dermatitis: results from a phase 3, randomized, double-blinded trial. *Journal of the American Academy of Dermatology* 2019; **81**: AB195-.
114. Thaci D, L Simpson E, Deleuran M, Kataoka Y, Chen Z, Gadkari A, et al. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). *Journal of dermatological science* 2019; **94**: 266-75.

115. Worm M, Simpson EL, Thaci D, Bissonnette R, Lacour J-P, Beissert S, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. *JAMA dermatology* 2020; **156**: 131-43.
116. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2021. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Date accessed: 01 Dec 2021.
117. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013; **33**: 618-40.
118. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 5: the baseline natural history model. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013; **33**: 657-70.
119. England N. Early Access to Medicines Scheme – Dupilumab in the treatment of adolescent patients ≥12 to <18 years of age with severe atopic dermatitis who have responded inadequately to at least one systemic therapy or where the available systemic therapies are not recommended or are not tolerated. 2019.
120. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. Performance of Ovid Medline Search Filters to Identify Health State Utility Studies. *Int J Technol Assess Health Care* 2017; **33**: 472-80.
121. Health Improvement Scotland (HIS). SMC2232 Dupilumab 200mg and 300mg solution for injection in pre-filled syringe (Dupixent®). 2019. Available from: https://www.scottishmedicines.org.uk/media/4976/dupilumab-dupixent-abbreviated-final-december-2019-for-website.pdf. Date accessed: Aug 2021.
122. Health Improvement Scotland (HIS). SMC2337 Baricitinib 2mg and 4mg film-coated tablets (Olumiant®). 2018. Available from: https://www.scottishmedicines.org.uk/media/6030/baricitinib-olumiant-final-may-2021-for-website.pdf. Date accessed: Aug 2021.
123. Anonymous. CADTH Drug Reimbursement Review Dupilumab (Dupixent). 2018.
124. Kuznik A, Bego-Le-Bagousse G, Eckert L, Gadkari A, Simpson E, Graham CN, et al. Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. *Dermatology and therapy* 2017; **7**: 493-505.
125. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic evaluation of dupilumab for moderate-to-severe atopic dermatitis: A cost-utility analysis. *J. Drugs Dermatol.* 2018; **17**: 750-6.
126. Institute for Clinical and Economic Review (ICER). Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. 2017. Available from: https://icer.org/wp-content/uploads/2020/10/MWCEPAC_ATOPIC_EVIDENCE_REPORT_051217.pdf. Date accessed: August 2021.
127. Institute for Clinical and Economic Review (ICER). JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value. 2021. Available from: https://icer.org/wp-content/uploads/2020/12/ICER_Atopic-Dermatitis_Draft-Evidence-Report_051421.pdf. Date accessed: 4 Nov 2021.
128. Fanelli F, Pedone MP, Serra A, Bitonti R, Furneri G. PBI11 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Atopic Dermatitis in Adolescent Patients in Italy. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2020; **23**: S412.
129. Health Improvement Scotland (HIS). SMC2011 Dupilumab 300mg solution for injection in pre-filled syringe (Dupixent®). 2018. Available from: https://www.scottishmedicines.org.uk/media/3751/dupilumab-dupixent-final-august-2018-for-website.pdf. Date accessed: Aug 2021.

130. Andersen L, Nyeland ME, Nyberg F. Higher self-reported severity of atopic dermatitis in adults is associated with poorer self-reported health-related quality of life in France, Germany, the U.K. and the U.S.A. *Br. J. Dermatol.* 2020; **182**: 1176-83.
131. Hsieh B-J, Shen D, Hsu C-J, Chan TC, Cho Y-T, Tang C-H, et al. The impact of atopic dermatitis on health-related quality of life in Taiwan. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2021.
132. Kwatra SG, Gruben D, Fung S, DiBonaventura M. Psychosocial Comorbidities and Health Status Among Adults with Moderate-to-Severe Atopic Dermatitis: A 2017 US National Health and Wellness Survey Analysis. *Advances in therapy* 2021; **38**: 1627-37.
133. Misery L, Seneschal J, Reguiai Z, Merhand S, Héas S, Huet F, et al. Patient burden is associated with alterations in quality of life in adult patients with atopic dermatitis: Results from the ECLA study. *Acta Derm.-Venereol.* 2018; **98**: 713-4.
134. Girolomoni G, Luger T, Nosbaum A, Gruben D, Romero W, Llamado LJ, et al. The Economic and Psychosocial Comorbidity Burden Among Adults with Moderate-to-Severe Atopic Dermatitis in Europe: Analysis of a Cross-Sectional Survey. *Dermatology and therapy* 2021; **11**: 117-30.
135. Retzler J, Smith A, Reaney M, Rout R, Hudson R. Process utilities for topical treatment in atopic dermatitis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2019; **28**: 2373-81.
136. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Health Utility Scores of Atopic Dermatitis in US Adults. *The journal of allergy and clinical immunology. In practice* 2019; **7**: 1246-52.e1.
137. Simpson EL. Dupilumab Improves General Health-Related Quality-of-Life in Patients with Moderate-to-Severe Atopic Dermatitis: Pooled Results from Two Randomized, Controlled Phase 3 Clinical Trials. *Dermatol. Ther.* 2017; **7**: 243-8.
138. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NMH, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *Journal of the American Academy of Dermatology* 2016; **74**: 491-8.
139. Song HJ, Park H, Park S-Y, Lee E-K, Ha S-Y, Park S-Y, et al. Estimation of Health Utilities Based on the Response to Treatment in Atopic Dermatitis: a Population-based Study. *Clinical therapeutics* 2019; **41**: 700-13.
140. Silverberg J, Gelfand J, Margolis D, Boguniewicz M, Fonacier L, Grayson M, et al. Societal burden of atopic dermatitis in the US population. *J. Am. Acad. Dermatol.* 2019; **81**: AB125.
141. Vietri J, Nyberg F, Varol N. The impact of severity of atopic dermatitis on patient-reported outcomes of adults with moderate-to-severe atopic dermatitis. *J. Am. Acad. Dermatol.* 2017; **76**: AB254.
142. Nyberg F, Hansen JB, Andersen L. Greater severity of atopic dermatitis (AD) is associated with poorer patientreported outcomes among adults with moderate-to-severe AD. *Pharmacoepidemiol. Drug Saf.* 2018; **27**: 334.
143. Retzler J, Smith AB, Reaney M, Rout R, Hudson R. PROCESS UTILITIES FOR TOPICAL TREATMENT IN ATOPIC DERMATITIS. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2018; **21**: S433.
144. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 2012; **15**: 708-15.
145. National life tables: UK, 1980-1982 to 2017-2019 2020 [Internet]. 2020. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

146. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatol* 2020; **156**: 863-73.
147. NICE. Guide to the methods of technology appraisal 2013. 2013.
148. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**: 509-18.
149. electronic Medicines Compendium (eMC). Neoral Soft Gelatin Capsules. Summary of Product Characteristics. 2021. Available from: https://www.medicines.org.uk/emc/product/1034/smpc#gref. Date accessed: 4 Nov 2021.
150. Curtis L, Burns A. Unit Costs of Health and Social Care 2020, Personal Social Services Research Unit, University of Kent, Canterbury. 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/. Date accessed: March 2021.
151. Santer M, Rumsby K, Ridd MJ, Francis NA, Stuart B, Chorozoglou M, et al. Adding emollient bath additives to standard eczema management for children with eczema: the BATHE RCT. *Health Technol Assess* 2018; **22**: 1-116.
152. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. 2021. Available from: https://bnf.nice.org.uk/. Date accessed: Aug 2021.
153. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2021. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: March 2021.
154. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018; **32**: 850-78.
155. NHS Improvement. National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. 2020. Available from: https://www.england.nhs.uk/national-cost-collection/. Date accessed: Aug 2021.
156. Bieber T, Simpson EL, Silverberg JI, Thaci D, Paul C, Pink AE, et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. *The New England journal of medicine* 2021; **384**: 1101-12.
157. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 2287-303.
158. Correction (Journal of the American Academy of Dermatology (2020) 83(5) (1282–1293), (S019096222031152X), (10.1016/j.jaad.2020.06.054)). *Journal of the American Academy of Dermatology* 2020.
159. Alexis A, Soong W, De Bruin-Weller M, Barbarot S, Weidinger S, Ionita I, et al. ABROCITINIB VERSUS DUPILUMAB: TIME TO IMPROVEMENT BY BODY REGION (JADE COMPARE). *Annals of Allergy, Asthma and Immunology* 2020; **125**: S15.
160. Andres SR, Dolores CCM. Dupilumab for treating moderate to severe atopic dermatitis. *European Journal of Clinical Pharmacy* 2020; **22**: 44-51.
161. Armstrong A. 382 Dupilumab treatment provides continued improvements in signs and symptoms through week 100 in patients with moderate-to-severe atopic dermatitis who did not achieve ≥75% reduction in eczema area and severity index at week 16. *Journal of investigative dermatology* 2020; **140**: S49-.
162. Armstrong A, Blauvelt A, Simpson EL, Chen Z, Ardeleanu M, Rossi AB, et al. Dupilumab treatment provides improvements in signs of AD at Week 100 in adult patients with moderate-to-severe AD who did not achieve =75-percent reduction in Eczema Area and Severity Index at Week 16. *Journal of Clinical and Aesthetic Dermatology* 2021; **14**: S12.

163. Armstrong A, Blauvelt A, Simpson EL, Chen Z, Ardeleanu M, Rossi AB, et al. Dupilumab treatment provides improvements in signs of atopic dermatitis (AD) at week 100 in adult patients with moderate-to-severe AD who did not achieve ≥ 75% reduction in Eczema Area and Severity Index at week 16. *British Journal of Dermatology* 2021; **184**: e68-e9.
164. Beck LA. Eosinophil Count and Serum Immunoglobulin E Levels in Atopic Dermatitis: analysis of Upadacitinib Phase 2 Study Findings. *Journal of allergy and clinical immunology* 2019; **143**: AB125-.
165. Beck LA, Silverberg JI, Grebe K, Hong F, Parmentier J, Teixeira H, et al. Eosinophil Count and Serum Immunoglobulin E Levels in Atopic Dermatitis: Analysis of Upadacitinib Phase 2 Study Findings. *Journal of Allergy and Clinical Immunology* 2019; **143**: AB125.
166. Beck LA, Silverberg JI, Weidinger S, Grebe KM, Hong F, Parmentier J, et al. Eosinophil count, serum CCL17/18/26 and IgE levels in atopic dermatitis: upadacitinib phase 2 study analysis. *Allergy: european journal of allergy and clinical immunology* 2019; **74**: 81-2.
167. Beck LA, Blauvelt A, Sher L, Hussain I, Rossi AB, Chen Z, et al. 408 Long-term treatment with dupilumab minimizes use of systemic immunosuppressants as rescue medications in adults with moderate-to-severe atopic dermatitis. *Journal of Investigative Dermatology* 2020; **140**: S53.
168. Beck LA, Thaçi D, Deleuran M, Blauvelt A, Bissonnette R, de Bruin-Weller M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *American Journal of Clinical Dermatology* 2020; **21**: 567-77.
169. Beck LA, Boguniewicz M, Hatta T, Chiesa Fuxench Z, Simpson E, De Benedetto A, et al. 666 Effect of dupilumab on the host-microbe interface in atopic dermatitis. *Journal of Investigative Dermatology* 2021; **141**: S116.
170. Beck LA, Thaçi D, Deleuran M, de Bruin-Weller M, Chen Z, Khokhar FA, et al. Laboratory safety of dupilumab for up to 3 years in adults with moderate-to-severe atopic dermatitis: results from an open-label extension study. *Journal of Dermatological Treatment* 2021.
171. Bhutani T, Deleuran M, Fonacier L, Shi V, Shumack S, Biswas P, et al. EFFECTIVE MAINTENANCE OF RESPONSE IN ATOPIC DERMATITIS PATIENTS AFTER SWITCHING FROM DUPILUMAB TO ABROCITINIB (JADE-EXTEND). *Annals of Allergy, Asthma and Immunology* 2020; **125**: S50-S1.
172. Blake SC, Murrell DF. Monitoring trough levels in cyclosporine for atopic dermatitis: A systematic review. *Pediatric dermatology* 2019; **36**: 843-53.
173. Blauvelt A, Bieber T, Weisman J, Chen Z, Shumel B, Rossi AB. 15285 Dupilumab with concomitant topical corticosteroids promotes rapid and sustained improvement in clinical signs in patients with moderate to severe atopic dermatitis: LIBERTY AD CHRONOS trial. *Journal of the American Academy of Dermatology* 2020; **83**: AB146-.
174. Blauvelt A, Guttman E, Hussain I, Chen Z, Mina-Osorio P, Rossi AB, et al. 15108 Long-term efficacy and safety of dupilumab in adolescents with atopic dermatitis: Results from an open-label extension trial (LIBERTY AD PED-OLE). *Journal of the American Academy of Dermatology* 2020; **83**: AB141.
175. Blauvelt A, Guttman-Yassky E, Hussain I, Chen Z, Mina-Osorio P, Rossi AB, et al. Long-term efficacy and safety of dupilumab in adolescents with atopic dermatitis: Results from an open-label extension trial (LIBERTY AD PED-OLE). *British Journal of Dermatology* 2020; **183**: e96.
176. Blauvelt A, Hussain I, Beazley BA, Patel N, Genzyme S, Ruddy M, et al. 16292 Dupilumab treatment for up to 3 years demonstrates sustained efficacy in adult patients with moderate to severe atopic dermatitis: Results from LIBERTY AD Adult OLE. *Journal of the American Academy of Dermatology* 2020; **83**: AB175.
177. Blauvelt A, Guttman-Yassky E, Hussain I, Chen Z, Rossi AB, Bansal A. Long-term efficacy and safety of dupilumab in adolescents with atopic dermatitis: results from an open-label extension trial (LIBERTY AD PED-OLE). *Allergy, Asthma and Clinical Immunology* 2021; **17**.

178. Blauvelt A, Guttman-Yassky E, Hussain I, Worrell R, Chen Z, Mina-Osorio P, et al. Long-term efficacy and safety of dupilumab in adolescents with atopic dermatitis: Results from an open-label extension trial (LIBERTY AD PED-OLE). *Australasian Journal of Dermatology* 2021; **62**: 29-31.
179. Blauvelt A, Hussain I, Zhu X, Beazley B, Patel N, Worrell R, et al. Dupilumab treatment for up to 3 years demonstrates sustained efficacy and favorable safety in adult patients with moderate-to-severe atopic dermatitis: Results From LIBERTY AD Adult OLE. *Australasian Journal of Dermatology* 2021; **62**: 28-9.
180. Callewaert C, Knight R, Nakatsuji T, Hamilton JD, Guttman-Yassky E, Bissonnette R, et al. 102 Dupilumab Decreases Staphylococcus aureus Colonization and Increases Microbial Diversity in Patients With Atopic Dermatitis. *Journal of investigative dermatology* 2019; **139**: S231-.
181. Cork MJ, Eichenfield LF, Blauvelt A, Rosmarin D, Hussain I, Davis JD, et al. 605 Efficacy and safety of dupilumab in adolescent patients with moderate-to-severe atopic dermatitis. *Journal of Investigative Dermatology* 2019; **139**: S104.
182. Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L, et al. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. *Journal of Dermatological Treatment* 2020; **31**: 606-14.
183. Cork MJ, Lockshin B, Blauvelt A, Chen Z, Prescilla R, Bansal A. Laboratory safety of dupilumab in adolescent patients with atopic dermatitis: 52-week laboratory safety findings from an open-label study (LIBERTY AD PED-OLE). *Journal of Clinical and Aesthetic Dermatology* 2021; **14**: S13.
184. Cork MJ, Thaçi D, Eichenfield L, Arkwright PD, Chen Z, Delevry D, et al. Long-term efficacy and safety of dupilumab in a phase 3, open-label extension trial in children with uncontrolled, moderate-to-severe atopic dermatitis. *Pediatric Dermatology* 2021; **38**: 14.
185. Cork MJ, Thaci D, Eichenfield LF, Arkwright PD, Sun X, Chen Z, et al. Dupilumab provides favourable long-term safety and efficacy in children aged >= 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *The British journal of dermatology* 2021; **184**: 857-70.
186. De Bruin-weller M, Griffiths C, Prens E, Szepietowski JC, Etoh T, Rossi AB, et al. Signs, symptoms, and quality of life in atopic dermatitis: early and sustained clinically meaningful responses with dupilumab and concomitant topical corticosteroids: a phase 3 trial post hoc analysis. *Journal of the dermatology nurses' association* 2020; **12**.
187. De Bruin-Weller M, Griffiths CEM, Prens E, Szepietowski JC, Etoh T, Rossi AB, et al. Signs, symptoms, and quality of life in atopic dermatitis: early and sustained clinically meaningful responses with dupilumab and concomitant topical corticosteroids: a phase 3 trial post hoc analysis. *Allergy, asthma and clinical immunology* 2020; **16**.
188. Deng C, Xie R, Banfield C, Gupta P, Feeney C, Rojo R, et al. 170 Forecasting Phase 3 Dose-Response for Abrocitinib, an Oral Janus Kinase 1 Selective Inhibitor, Using Investigator's Global Assessment and Eczema Area and Severity Index. *Journal of investigative dermatology* 2019; **139**: S243-.
189. Drucker AM, Bercovitch L. Generating new evidence for old medications: the TREAT trial in paediatric atopic dermatitis. *British Journal of Dermatology* 2018; **179**: 813-4.
190. Elewski BE, St, er S, Zirwas M, Silvestre JF, Kalia S, et al. Early and sustained improvements in patientreported outcomes with tralokinumab in combination with topical corticosteroids as needed in moderate-to-severe atopic dermatitis. *British journal of dermatology* 2021; **184**: e83-e4.
191. Gooderham MJ, Girolomoni G, Moore JO, Silverberg JI, Curto M, Zhang W, et al. Predictors of maintenance of response in patients with moderate-to-severe atopic dermatitis after interruption of the oral Janus kinase 1-selective inhibitor abrocitinib. *British journal of dermatology* 2020; **183**: e106-.

192. Gooderham MJ, Girolomoni G, O'Neil Moore J, Silverberg JI, Curto M, Zhang W, et al. 16466 Predictors of maintenance of response in patients with moderate to severe atopic dermatitis after oral Janus kinase 1 selective inhibitor abrocitinib interruption. *Journal of the American Academy of Dermatology* 2020; **83**: AB64-.
193. Gooderham M, Boguniewicz M, Sher L, Weisman J, Bansal A, Staudinger HW, et al. Dupilumab in children aged ≥6 to <12 years significantly improves severe atopic dermatitis: results from phase 3 trial (LIBERTY AD PEDS). *Australasian journal of dermatology* 2021; **62**: 59-60.
194. Gooderham MJ, Bissonnette R, Chen Z, Rossi AB, Khokhar FA. Laboratory safety of long-term dupilumab treatment for up to 3 years in adults with moderate-to-severe atopic dermatitis (LIBERTY AD OLE). *Allergy, Asthma and Clinical Immunology* 2021; **17**.
195. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *The Journal of allergy and clinical immunology* 2019; **143**: 155-72.
196. Guttman-Yassky E, Pangan AL, Silverberg JI, Thaci D, Hong CH, Mohamed MEF, et al. Primary results from a Phase IIb, randomized, placebo-controlled trial of upadacitinib for patients with atopic dermatitis. *Journal of clinical and aesthetic dermatology* 2019; **12**: S16-S7.
197. Guttman-Yassky E, Silverberg JI, Papp KA, Hu X, Gu Y, Pangan A, et al. Efficacy and safety of upadacitinib treatment over 32 weeks for patients with atopic dermatitis from a Phase IIb, randomized, placebo-controlled trial. *Journal of clinical and aesthetic dermatology* 2019; **12**: S15-.
198. Guttman-Yassky E, Pavel AB, Silverberg J, Weidinger S, Parmentier J, Teixeira HD, et al. Eosinophil count, serum CCL17/18/26 and immunoglobulin E levels in atopic dermatitis: upadacitinib phase 2 study analysis. *World Allergy Organization journal* 2020; **13**.
199. Guttman-Yassky E, Pavel AB, Silverberg JI, Weidinger S, Parmentier J, Teixeira HD, et al. Eosinophil count, serum CCL17/18/26 and immunoglobulin e levels in atopic dermatitis: upadacitinib phase II study analysis. *British journal of dermatology* 2020; **183**: e97-e8.
200. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Safety and efficacy of upadacitinib monotherapy in adolescents and adults with moderate-to-severe atopic dermatitis: results from two pivotal, phase III, randomized, double-blinded, monotherapy, placebo-controlled studies (Measure Up 1 and Measure Up 2). *British journal of dermatology* 2021; **184**: e62-.
201. Lacour J-P. Effect of Dupilumab on health-related quality of life (HRQoL) in patients with moderate-to-severe atopic dermatitis (AD): results from two identical randomized phase 3 trials (LIBERTY AD SOLO 1 and 2). *Allergy, asthma and clinical immunology* 2020; **16**.
202. Lacour J-P. Effect of dupilumab on health-related quality of life (HRQOL) in patients with moderate-to-severe atopic dermatitis (AD): results from two identical randomized phase 3 trials (Liberty ad solo 1 and 2). *Journal of the dermatology nurses' association* 2020; **12**.
203. Lake E. JAAD Game Changers: Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *Journal of the American Academy of Dermatology* 2019; **80**: 882.
204. Lebwohl MG, Worm M, Stein Gold LF, Bangert C, Schmid-Grendelmeier P, Khan T, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: results from the open-label run-in period of JADE REGIMEN. *British journal of dermatology* 2021; **184**: e73-e4.
205. Lio P, Boguniewicz M, Alexis A, Lebwohl M, Reich K, Pink A, et al. Depth and Rapidity of Response With Abrocitinib and Dupilumab in Patients With Moderate-to-Severe Atopic Dermatitis (AD) in JADE COMPARE. *Journal of allergy and clinical immunology* 2021; **147**: AB34-.
206. Marcoux D, Wu JJ, Shumel B, Ohya Y, Zhang A, Chen Z. Dupilumab was well tolerated and significantly improved atopicdermatitis in children aged ≥ 6 to < 12 years: results from the liberty ad peds phase 3 trial. *Pediatrics* 2021; **147**: 300-.

207. McMichael A, Cork M, Teng J, Rojo R, Valdez H, Zhang F, et al. Patient-Reported Outcomes (PROs) With Abrocitinib Treatment in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): results From the Phase 3 JADE TEEN Study. *Journal of allergy and clinical immunology* 2021; **147**: AB156-.
208. Merola JF, Sidbury R, Wollenberg A, Chen Z, Zhang A, Shumel B, et al. 409 Dupilumab prevents flares in adults with moderate-to-severe atopic dermatitis in a 52-week, randomized, controlled, phase 3 trial. *Journal of investigative dermatology* 2020; **140**: S53-.
209. Merola JF, Sidbury R, Wollenberg A, Chen Z, Zhang A, Shumel B, et al. Dupilumab prevents flares in adults with moderate-to-severe atopic dermatitis in a 52-week randomized controlled phase 3 trial. *Journal of the American Academy of Dermatology* 2020.
210. Paller AS, Bansal A, Simpson EL, Boguniewicz M, Blauvelt A, Siegfried EC, et al. Dupilumab provides clinically meaningful responses versus placebo: a post hoc analysis of a phase 3 trial in adolescents with moderate-to-severe ad among patients not achieving iga score of 0/1. *Journal of the dermatology nurses' association* 2020; **12**.
211. Paller AS, Bansal A, Simpson EL, Boguniewicz M, Blauvelt A, Siegfried EC, et al. Clinically Meaningful Responses to Dupilumab in Adolescents with Uncontrolled Moderate-to-Severe Atopic Dermatitis: post-hoc Analyses from a Randomized Clinical Trial. *American journal of clinical dermatology* 2020; **21**: 119-31.
212. Paller AS, Siegfried EC, Gooderham M, Beck LA, Boguniewicz M, Sher L, et al. Dupilumab significantly improves atopic dermatitis in children aged 6-11 years: results from a phase III trial (LIBERTY AD PEDS). *British journal of dermatology* 2020; **183**: e121-.
213. Paller AS, Siegfried EC, Thaci D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. *Journal of the American Academy of Dermatology* 2020; **83**: 1282-93.
214. Paller A. Dupilumab induces rapid and sustained improvement in clinical signs in children with severe atopic dermatitis. *British journal of dermatology* 2021; **184**: e68-.
215. Paller A, Cork MJ, Marcoux D, Zhang H, Chuang C, Zhang A, et al. 484 Dupilumab provides clinically meaningful improvement in atopic dermatitis (AD) signs and symptoms and quality of life (QoL) in children with severe AD: results from the LIBERTY AD PEDS phase 3 clinical trial. *Journal of investigative dermatology* 2021; **141**: S84-.
216. Papp KA. Sustained effect of dupilumab with concomitant topical corticosteroids (TCS) on health-related quality of life (HRQOL) in patients with moderate-tosevere atopic dermatitis (AD): liberty ad chronos. *Journal of the dermatology nurses' association* 2020; **12**.
217. Peng G, Li L, Han X. 140 The clinical efficacy and safety of biologic agents for moderate to severe atopic dermatitis: a meta- analysis. *Journal of Investigative Dermatology* 2019; **139**: S238.
218. Raniga J, Norman JF, Simpson EL, Thyssen JP, Bissonnette R, Jia B, et al. Rapid and concurrent improvements in signs and symptoms of atopic dermatitis with baricitinib in phase 3 studies. *Australasian journal of dermatology* 2021; **62**: 99-100.
219. Reich K. Safety of baricitinib in patients with atopic dermatitis: results of pooled data from two phase III monotherapy randomized, double-blind, placebo-controlled 16-week trials (BREEZE-AD1 and BREEZE-AD2). *British journal of dermatology* 2020; **183**: e112-.
220. Reich K. 15057 Safety of baricitinib in patients with atopic dermatitis: results of pooled data from two phase 3 monotherapy randomized, double-blind, placebo-controlled 16-week trials (BREEZE-AD1 and BREEZE-AD2). *Journal of the American Academy of Dermatology* 2020; **83**: AB28-.
221. Reich K, Thaci D, Papp K, Anderson J, Hu X, Gu Y, et al. Treatment withdrawal and retreatment with upadacitinib in patients with moderate-to-severe atopic dermatitis from a phase IIb, randomized, controlled trial. *British journal of dermatology* 2020; **183**: e98-e9.

222. Reich K, Thaci D, Papp K, Anderson J, Hu X, Gu Y, et al. Treatment withdrawal and retreatment with upadacitinib in patients with moderate-to-severe atopic dermatitis from a phase 2b, randomized, controlled trial. *Journal of the dermatology nurses' association* 2020; **12**.
223. Siegfried EC, Simpson EL, Paller AS, Beck LA, Boguniewicz M, Khokhar FA, et al. Laboratory safety findings for dupilumab in adolescent patients with moderate-to-severe atopic dermatitis inadequately controlled with or ineligible for topical therapy. *Journal of the dermatology nurses' association* 2020; **12**.
224. Silverberg J. Sensitivity of Investigator's Global Assessment in discerning treatment-related clinical benefits in atopic dermatitis: a post hoc analysis of the LIBERTY AD SOLO studies. *Journal of the American Academy of Dermatology* 2018; **79**: AB259-.
225. Silverberg J. Dupilumab treatment induces rapid clinical improvement of itch in patients with moderate-to-severe atopic dermatitis. *Journal of the American Academy of Dermatology* 2018; **79**: AB113-.
226. Silverberg JI, Simpson EL, Guttman-Yassky E, Cork MJ, de Bruin-Weller M, Yosipovitch G, et al. Dupilumab Significantly Modulates Pain and Discomfort in Patients With Atopic Dermatitis: a Post Hoc Analysis of 5 Randomized Clinical Trials. *Dermatitis : contact, atopic, occupational, drug* 2020.
227. Silverberg JI, Barbarot S, Welzel J, Ameen M, Thyssen JP, Lomaga M, et al. Tralokinumab prevents flares in moderate-to-severe atopic dermatitis: post hoc analyses of a randomized phase III clinical trial (ECZTRA 3). *British journal of dermatology* 2021; **184**: e79-.
228. Silverberg JI, Boguniewicz M, Waibel J, Weisman J, Strowd L, Sun L, et al. Clinical tailoring of baricitinib 2 mg in atopic dermatitis: baseline body surface area and rapid onset of action identifies response at week 16. *British journal of dermatology* 2021; **184**: e69-e70.
229. Silverberg JI, Guttman-Yassky E, Gooderham M, Worm M, Rippon S, O'Quinn S, et al. Health-related quality of life with tralokinumab in moderate-to-severe atopic dermatitis: A phase 2b randomized study. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2021; **126**: 576-83.e4.
230. Silverberg JI, Simpson EL, Wollenberg A, Bissonnette R, Kabashima K, Delozier AM, et al. Long-term Efficacy of Baricitinib in Adults with Moderate to Severe Atopic Dermatitis Who Were Treatment Responders or Partial Responders: an Extension Study of 2 Randomized Clinical Trials. *JAMA dermatology* 2021.
231. Silverberg JI, Thyssen JP, Simpson EL, Yosipovitch G, Ständer S, Valdez H, et al. Impact of Oral Abrocitinib Monotherapy on Patient-Reported Symptoms and Quality of Life in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Patient-Reported Outcomes. *American Journal of Clinical Dermatology* 2021.
232. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Pariser DM, Blauvelt A, et al. Dupilumab efficacy and safety in adolescents with moderate-tosevere atopic dermatitis: results from a multicenter, randomized, placebo-controlled, double-blind, parallel-group, Phase III study. *Journal of clinical and aesthetic dermatology* 2019; **12**: S14-S5.
233. Simpson E, Forman S, Silverberg J, Zirwas M, Maverakis E, Han G, et al. Efficacy and safety of baricitinib in moderate-tosevere atopic dermatitis: results from a randomized, double-blinded, placebo-controlled phase 3 clinical trial (BREEZE-AD5). *British journal of dermatology* 2020; **183**: e96-e7.
234. Simpson EL, Gooderham M, King B, Taylor SC, Rosmarin D, Tatulych S, et al. 16405 Abrocitinib treatment in patients with moderate to severe atopic dermatitis: consistency of efficacy responses from randomized, controlled phase 3 and phase 2b clinical trials. *Journal of the American Academy of Dermatology* 2020; **83**: AB62-.
235. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield L, Bissonnette R, et al. Efficacy and safety of baricitinib in moderate to severe atopic dermatitis: results of two phase 3 monotherapy

randomized, double-blind, placebocontrolled 16-week trials (Breeze-AD1 and BREEZE-AD2). *Journal of the dermatology nurses' association* 2020; **12**.
236. Simpson EL, Thyssen JP, Bissonnette R, Jia B, Nunes FP, Casillas M, et al. Rapid and concurrent improvements in signs and symptoms of atopic dermatitis with baricitinib in phase III studies. *British journal of dermatology* 2020; **183**: e112-e3.
237. Simpson E. Safety of specifically targeting interleukin-13 with tralokinumab in adult patients with moderate-tosevere atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled phase III and phase II trials. *British journal of dermatology* 2021; **184**: e66-.
238. Simpson EL, Gooderham MJ, Thyssen JP, Chan G, Tatulych S, Biswas P, et al. Consistent efficacy responses of abrocitinib monotherapy across randomized controlled phase II/III clinical trials: results from JADE MONO-1, JADE MONO-2 and the phase IIb proof-of-concept trial. *British journal of dermatology* 2021; **184**: e76-.
239. Simpson EL, Thyssen JP, Flohr C, Katoh N, Papp K, Steffensen LA, et al. Tralokinumab provides progressive improvements beyond Week 16 in patients with atopic dermatitis with an initial partial response. *Journal of Clinical and Aesthetic Dermatology* 2021; **14**: S16.
240. Thaci D, Deleuran M, Bissonnette R, Bouaziz JD, Sun X, Patel N, et al. Safety efficacy of open-label dupilumab in adult patients with moderate-to-severe atopic dermatitis: An analysis up to 3 years (LIBERTY AD OLE). *British Journal of Dermatology* 2020; **183**: e94.
241. Thací D, Deleuran M, De Bruin-Weller M, Chen Z, Tomondy P, Ardeleanu M, et al. Dupilumab treatment for up to 100 weeks demonstrates sustained improvement in quality of life in adult patients with moderate-to-severe atopic dermatitis (LIBERTY AD OLE). *British Journal of Dermatology* 2020; **183**: 12-3.
242. Tofte SJ. Efficacy and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults: a pooled analysis of two phase 2 clinical trials. *J Am Assoc Nurse Pract* 2018; **30**: 529-41.
243. Wu JJ, Spelman L, Tan JL, Etoh T, Zhang H, Shumel B, et al. Dupilumab Maintains Long-Term Disease Control in Adults with Moderate-to-Severe Atopic Dermatitis as Measured by Well-Controlled Weeks: results From the LIBERTY AD CHRONOS Clinical Trial. *Dermatology and therapy* 2021; **11**: 327-30.
244. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; **64**: 1074-84.
245. Jin SY, Lim WS, Sung NH, Cheong KA, Lee AY. Combination of glucosamine and low-dose cyclosporine for atopic dermatitis treatment: a randomized, placebo-controlled, double-blind, parallel clinical trial. *Dermatol Ther* 2015; **28**: 44-51.
246. Dias S, Sutton, A.J., Welton, N.J., Ades, A.E. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011.

10 Appendices

10.1 Literature search strategies

10.1.1 RCTs to inform clinical effectiveness

10.1.1.1 MEDLINE (via OVID)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) (search date 1 August 2019 to 8 July 2021)

1. exp Eczema/ or eczema*.tw.

2. exp Dermatitis, Atopic/

3. exp Dermatitis/ or dermatitis.tw.

4. or/1-3

5. exp Cyclosporine/

6. (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw.

7. (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw.

8. (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw.

9. (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw.

10. (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw.

11. (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw.

12. exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/

13. ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw.

14. (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.

15. ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw.

16. (biologic* response modifier* or BRM*).tw.

17. targeted therap*.tw.

18. (systemic adj immunosuppressive treatment$).tw.

19. immuno-modulatory treatment$.tw.

20. anti inflammatory treatment$.tw.

21. exp Immunosuppressive Agents/

22. exp Anti-Inflammatory Agents/

23. exp Janus Kinase Inhibitors/

24. exp Interleukins/ or exp interleukin-4/ or exp interleukin-13/

25. or/5-24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. randomized.ab.

29. placebo.ab.

30. clinical trials as topic.sh.

31. randomly.ab.

32. trial.ti.

33. or/26-32

34. exp animals/ not humans.sh.

35. 33 not 34

36. 4 and 25 and 35

37. limit 36 to ed=20190801-20210708

10.1.1.2 EMBASE (via EMBASE)

Search date from 1 August 2019 to 8 July 2021

1. 'atopic dermatitis'/exp OR 'atopic dermatitis'

2. 'dermatitis'/exp

3. #1 OR #2

4. 'cyclosporine'/exp

5. c?closporin*:ab,ti OR 'Cy A':ab,ti,tt OR CyA:ab,ti,tt OR Cy-A:ab,ti,tt OR 'Cs A':ab,ti,tt or CsA:ab,ti,tt or Cs-A:ab,ti,tt or csaneoral:ab,ti,tt or neoral:ab,ti,tt or sandimmun*:ab,ti,tt

6. dupilumab:ab,ti,tt OR dupixent:ab,ti,tt OR 'regn 668':ab,ti,tt OR REGN-668:ab,ti,tt OR regn668:ab,ti,tt OR 'sar 231893':ab,ti,tt OR sar-231893:ab,ti,tt OR sar231893:ab,ti,tt OR 420K487FSG:ab,ti,tt OR 1190264-60-8:ab,ti,tt

7. baricitinib:ab,ti,tt OR olumiant:ab,ti,tt OR 'ly 3009104':ab,ti,tt OR ly3009104:ab,ti,tt OR ly-3009104:ab,ti,tt OR 'incb 028050':ab,ti,tt OR incb-028050:ab,ti,tt OR incb028050:ab,ti,tt OR 'incb 28050':ab,ti,tt OR incb-28050:ab,ti,tt OR incb28050:ab,ti,tt OR ISP4442I3Y:ab,ti,tt OR 1187594-09-7:ab,ti,tt

8. abrocitinib:ab,ti,tt OR 'pf 04965842':ab,ti,tt OR pf04965842:ab,ti,tt OR pf-04965842:ab,ti,tt OR 'pf 4965842':ab,ti,tt OR pf-4965842:ab,ti,tt OR pf4965842:ab,ti,tt OR 73SM5SF3OR:ab,ti,tt OR 1622902-68-4:ab,ti,tt

9. tralokinumab:ab,ti,tt OR 'cat 354':ab,ti,tt OR cat354:ab,ti,tt OR cat-354:ab,ti,tt OR GK1LYB375A:ab,ti,tt OR 1044515-88-9:ab,ti,tt

10. upadacitinib*:ab,ti,tt OR rinvoq*:ab,ti,tt OR 'ABT 494':ab,ti,tt OR ABT-494:ab,ti,tt OR ABT494:ab,ti,tt OR 4RA0KN46E0:ab,ti,tt OR 1310726-60-3:ab,ti,tt OR 1607431-21-9:ab,ti,tt

11. 'monoclonal antibody'/exp OR 'monoclonal antibody'

12. ((humani?ed) NEAR/5 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs OR fab*1)):ab,ti,tt OR rhuMAb*:ab,ti,tt

13. ((chim?eric) NEAR/3 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs)):ab,ti,tt

14. ((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* or agent* or product*)):ab,ti,tt

15. biologic* response modifier* OR BRM:ab,ti,tt

16. targeted therap*:ab,ti,tt

17. systemic NEAR/2 immunosuppressive treatment*:ab,ti,tt

18. immuno-modulatory treatment*:ab,ti,tt

19. anti inflammatory treatment*:ab,ti,tt

20. 'immunosuppressive agent'/exp OR 'immunosuppressive agent'

21. 'antiinflammatory agent'/exp OR 'antiinflammatory agent'

22. 'janus kinase inhibitor'/exp OR 'janus kinase inhibitor'

23. 'cytokine'/exp or 'cytokine'

24. interleukin 4:ab,ti,tt or interleukin 13:ab,ti,tt

25. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26. 'randomized controlled trial'/de

27. ‘controlled clinical trial’/de

28. #26 OR #27

29. random*:ti,ab,tt

30. ‘randomization’/de

31. ‘intermethod comparison’/de

32. placebo:ti,ab,tt

33. (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)

34. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))

35. (open NEXT/1 label):ti,ab,tt

36. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt

37. ‘double blind procedure’/de

38. (parallel NEXT/1 group*):ti,ab,tt

39. (crossover:ti,ab,tt OR ‘cross over’:ti,ab,tt)

40. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt

41. (assigned:ti,ab,tt OR allocated:ti,ab,tt)

42. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt

43. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)

44. ‘human experiment’/de

45. Trial:ti,tt

46. #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45

47. #46 NOT #28

48. (((random* NEXT/1 sampl* NEAR/8 (‘cross section*’ OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT (‘comparativestudy’/de OR ‘controlled study’/de OR ‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘randomly assigned’:ti,ab,tt))

49. (‘cross-sectional study’/de NOT (‘randomized controlled trial’/de OR ‘controlled clinical study’/de OR ‘controlled study’/de OR ‘randomisedcontrolled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘control group’:ti,ab,tt OR ‘control groups’:ti,ab,tt))

50. (‘case control*’:ti,ab,tt AND random*:ti,ab,tt NOT (‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt))

51. (‘systematic review’:ti,tt NOT (trial:ti,tt OR study:ti,tt))

52. (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)

53. ‘random field*’:ti,ab,tt

54. (‘random cluster’ NEAR/4 sampl*):ti,ab,tt

55. (review:ab AND review:it NOT trial:ti,tt)

56. (‘we searched’:ab AND (review:ti,tt OR review:it))

57. ‘update review’:ab

58. (databases NEAR/5 searched):ab

59. ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND ‘animal experiment’/de)

60. (‘animal experiment’/de NOT (‘human experiment’/de OR ‘human’/de))

61. #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR#57 OR #58 OR #59 OR #60

62. #47 NOT #61

63. #3 AND #25 AND #62

64. #63 AND [08/01/2019]/sd

10.1.1.3 CENTRAL (via CENTRAL)

Search date from 1 August 2019 to 8 July 2021

1. MeSH descriptor: [Dermatitis, Atopic] explode all trees

2. (atopic eczem*):ab,ti OR (atopic dermatit*):ab,ti

3. #1 OR #2

4. MeSH descriptor: [Cyclosporine] explode all trees

5. c?closporin*:ab,ti OR ‘Cy A’:ab,ti OR CyA:ab,ti OR Cy-A:ab,ti OR ‘Cs A’:ab,ti or CsA:ab,ti or Cs-A:ab,ti or csaneoral:ab,ti or neoral:ab,ti or sandimmun*:ab,ti

6. dupilumab:ab,ti OR dupixent:ab,ti OR ‘regn 668’:ab,ti OR REGN-668:ab,ti OR regn668:ab,ti OR ‘sar 231893’:ab,ti OR sar-231893:ab,ti OR sar231893:ab,ti OR 420K487FSG:ab,ti

7. baricitinib:ab,ti OR olumiant:ab,ti OR 'ly 3009104':ab,ti OR ly3009104:ab,ti OR ly-3009104:ab,ti OR 'incb 028050':ab,ti OR incb-028050:ab,ti OR incb028050:ab,ti OR 'incb 28050':ab,ti OR incb-28050:ab,ti OR incb28050:ab,ti OR ISP4442I3Y:ab,ti

8. abrocitinib:ab,ti OR 'pf 04965842':ab,ti OR pf04965842:ab,ti OR pf-04965842:ab,ti OR 'pf 4965842':ab,ti OR pf-4965842:ab,ti OR pf4965842:ab,ti OR 73SM5SF3OR:ab,ti

9. tralokinumab:ab,ti OR 'cat 354':ab,ti OR cat354:ab,ti OR cat-354:ab,ti OR GK1LYB375A:ab,ti

10. upadacitinib*:ab,ti OR rinvoq*:ab,ti OR 'ABT 494':ab,ti OR ABT-494:ab,ti OR ABT494:ab,ti OR 4RA0KN46E0:ab,ti

11. MeSH descriptor: [Antibodies, Monoclonal] explode all trees

12. ((humani?ed) NEAR/5 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs OR fab*1)):ab,ti OR rhuMAb*:ab,ti

13. ((chim?eric) NEAR/3 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs)):ab,ti

14. ((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* or agent* or product*)):ab,ti

15. biologic* response modifier* OR BRM:ab,ti

16. targeted therap*:ab,ti

17. systemic NEAR/2 immunosuppressive treatment*:ab,ti

18. immuno-modulatory treatment*:ab,ti

19. anti inflammatory treatment*:ab,ti

20. MeSH descriptor: [Immunosuppressive Agents] explode all trees

21. MeSH descriptor: [Anti-Inflammatory Agents] explode all trees

22. MeSH descriptor: [Janus Kinase Inhibitors] explode all trees

23. MeSH descriptor: [Cytokines] explode all trees

24. interleukin-4:ab,ti or interleukin-13:ab,ti

25. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26. #3 AND #25

Line 26 limited to "Trials" and Cochrane Publication Date from Aug 2019 to Jul 2021.

10.1.2 Observational studies to inform clinical effectiveness

10.1.2.1 MEDLINE (via OVID)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) (search date 1 January 2019 to 30 July 2021)

1. exp Eczema/ or eczema*.tw. (23947)

2 exp Dermatitis, Atopic/ (21311)

3 exp Dermatitis/ or dermatitis.tw. (127608)

4 1 or 2 or 3 (132745)

5 exp Cyclosporine/ (29766)

6 (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw. (66284)

7 5 or 6 (71828)

8 Epidemiologic studies/ (8749)

9 exp case control studies/ (1205579)

10 exp cohort studies/ (2182735)

11 Case control.tw. (135536)

12 (cohort adj (study or studies)).tw. (242326)

13 Cohort analy$.tw. (9285)

14 (Follow up adj (study or studies)).tw. (51599)

15 (observational adj (study or studies)).tw. (125356)

16 Longitudinal.tw. (270907)

17 Retrospective.tw. (604313)

18 Cross sectional.tw. (406301)

19 Cross-sectional studies/ (379528)

20 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3295061)

21 4 and 7 and 20 (182)

22 limit 21 to ed=20190101-20210730 (39)

10.1.2.2 EMBASE (via EMBASE)

Search date from 1 January 2019 to 30 July 2021

1. 'atopic dermatitis'/exp OR 'atopic dermatitis'

2. 'dermatitis'/exp

3. #1 OR #2

4. 'cyclosporine'/exp

5. c?closporin*:ab,ti OR 'Cy A':ab,ti,tt OR CyA:ab,ti,tt OR Cy-A:ab,ti,tt OR 'Cs A':ab,ti,tt or CsA:ab,ti,tt or Cs-A:ab,ti,tt or csaneoral:ab,ti,tt or neoral:ab,ti,tt or sandimmun*:ab,ti,tt

6. #4 OR #5

7. 'Clinical study'/exp

8. 'Case control study'/exp

9. 'Family study'/exp

10. 'Longitudinal study'/exp

11. 'Retrospective study'/exp

12. 'Prospective study'/exp

13. 'Randomized controlled trial (topic)'/exp

14. 12 not 13

15. 'Cohort analysis'/exp

16. (Cohort adj (study or studies)):ab,ti,tt

17. (Case control adj (study or studies)):ab,ti,tt

18. (follow up adj (study or studies)):ab,ti,tt

19. (observational adj (study or studies)):ab,ti,tt

20. (epidemiologic* adj (study or studies)):ab,ti,tt

21. (cross sectional adj (study or studies)):ab,ti,tt

22. #7 OR #8 OR #9 OR #10 OR #11 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

23. 3 AND 6 AND 23

24. #23 AND [01/01/2019]/sd

10.1.3 Economic evaluations

Medline

Table 79. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 07, 2021>

1 exp Eczema/ or eczema*.tw. (23877)
2 exp Dermatitis, Atopic/ (21241)
3 exp Dermatitis/ or dermatitis.tw. (127289)
4 or/1-3 (132406)
5 exp Cyclosporine/ (29732)
6 (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw. (66176)
7 (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw. (1031)
8 (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw. (481)
9 (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw. (32)
10 (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw. (79)
11 (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw. (165)
12 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (249671)
13 ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw. (7692)
14 (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw. (3898)
15 ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw. (27994)
16 (biologic* response modifier* or BRM*).tw. (3933)
17 targeted therap*.tw. (50825)
18 (systemic adj immunosuppressive treatment$).tw. (103)
19 immuno-modulatory treatment$.tw. (15)
20 anti inflammatory treatment$.tw. (2490)
21 exp Immunosuppressive Agents/ (325642)
22 exp Anti-Inflammatory Agents/ (528635)
23 exp Janus Kinase Inhibitors/ (635)
24 exp Interleukins/ or exp interleukin-4/ or exp interleukin-13/ (249951)
25 or/5-24 (1329133)
26 Economics/ (27346)
27 exp "Costs and Cost Analysis"/ (247076)
28 Economics, Nursing/ (4005)
29 Economics, Medical/ (9138)
30 Economics, Pharmaceutical/ (2998)
31 exp Economics, Hospital/ (25197)
32 Economics, Dental/ (1918)
33 exp "Fees and Charges"/ (30792)
34 exp Budgets/ (13849)

35 budget*.ti,ab,kf. (31686)
36 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (245409)
37 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (318761)
38 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (177361)
39 (value adj2 (money or monetary)).ti,ab,kf. (2613)
40 exp models, economic/ (15703)
41 economic model*.ab,kf. (3592)
42 markov chains/ (15088)
43 markov.ti,ab,kf. (24570)
44 monte carlo method/ (29848)
45 monte carlo.ti,ab,kf. (52739)
46 exp Decision Theory/ (12508)
47 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (27667)
48 or/26-47 (782831)
49 4 and 25 and 48 (146)
50 limit 49 to yr="2014 -Current" (59)
51 exp animals/ not humans.sh. (4857607)
52 50 not 51 (57)

Embase

Table 80. Elsevier Embase <1974 to July 09, 2021>

#37 #36 AND [2014-2021]/py 642
#36 #34 NOT #35 1771
#35 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de) AND [embase]/lim 2321323
#34 #3 AND #25 AND #33 1779
#33 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 3247837
#32 ('econometrics'/exp OR 'econometric':ti,ab) AND [embase]/lim 1368
#31 ('budget impact analysis'/exp OR 'budget impact':ti,ab) AND [embase]/lim 4338
#30 ('economic evaluation'/exp OR 'economic evaluation':ti,ab) AND [embase]/lim 266443
#29 ('economic model'/exp OR 'statistical model'/exp OR 'decision analysis'/exp OR 'discrete event simulation'/exp) AND [embase]/lim 147630
#28 ('economic model*':ti,ab OR 'decision tree':ti,ab OR 'markov':ti,ab OR 'decision analysis':ti,ab OR 'discrete event simulation':ti,ab) AND [embase]/lim 42539
#27 ('cost analysis':ti,ab OR 'cost-analysis':ti,ab OR 'cost effective*':ti,ab OR 'cost-effective*':ti,ab OR 'cost utility':ti,ab OR 'cost-utility':ti,ab OR 'costminimization':ti,ab OR 'costminimisation':ti,ab OR 'cost-minimisation':ti,ab OR 'cost-minimization':ti,ab OR 'cost minimization':ti,ab OR 'cost minimisation':ti,ab) AND [embase]/lim 175010
#26 ('health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'cost utility analysis'/exp OR 'cost minimization analysis'/exp) AND [embase]/lim 708212
#25 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 4061307

#24	('interleukin 4':ab,ti,tt OR 'interleukin 13':ab,ti,tt) AND [embase]/lim	13841
#23	('cytokine'/exp OR 'cytokine') AND [embase]/lim	1631402
#22	('janus kinase inhibitor'/exp OR 'janus kinase inhibitor') AND [embase]/lim	18353
#21	('antiinflammatory agent'/exp OR 'antiinflammatory agent') AND [embase]/lim	1991759
#20	('immunosuppressive agent'/exp OR 'immunosuppressive agent') AND [embase]/lim	1079320
#19	anti AND inflammatory AND treatment*:ab,ti,tt AND [embase]/lim	132898
#18	'immuno modulatory' AND treatment*:ab,ti,tt AND [embase]/lim 519	
#17	(systemic NEAR/2 immunosuppressive) AND treatment*:ab,ti,tt AND [embase]/lim	754
#16	targeted AND therap*:ab,ti,tt AND [embase]/lim	213262
#15	(biologic* AND response AND modifier* OR brm:ab,ti,tt) AND [embase]/lim	6359
#14	(((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)):ab,ti,tt) AND [embase]/lim	56354
#13	((chim?eric NEAR/3 (monoclonal* OR antibod* OR moab* OR mab OR mabs)):ab,ti,tt) AND [embase]/lim	105
#12	(((humani?ed NEAR/5 (monoclonal* OR antibod* OR moab* OR mab OR mabs OR fab*1)):ab,ti,tt) OR rhumab*:ab,ti,tt) AND [embase]/lim	14200
#11	('monoclonal antibody'/exp OR 'monoclonal antibody') AND [embase]/lim	625485
#10	(upadacitinib*:ab,ti,tt OR rinvoq*:ab,ti,tt OR 'abt 494':ab,ti,tt OR abt494:ab,ti,tt OR 4ra0kn46e0:ab,ti,tt OR '1310726 60 3':ab,ti,tt OR '1607431 21 9':ab,ti,tt) AND [embase]/lim	485
#9	(tralokinumab:ab,ti,tt OR cat354:ab,ti,tt OR 'cat 354':ab,ti,tt OR gk1lyb375a:ab,ti,tt OR '1044515 88 9':ab,ti,tt) AND [embase]/lim	137
#8	(abrocitinib:ab,ti,tt OR pf04965842:ab,ti,tt OR 'pf 04965842':ab,ti,tt OR 'pf 4965842':ab,ti,tt OR pf4965842:ab,ti,tt OR 73sm5sf3or:ab,ti,tt OR '1622902 68 4':ab,ti,tt) AND [embase]/lim	68
#7	(baricitinib:ab,ti,tt OR olumiant:ab,ti,tt OR ly3009104:ab,ti,tt OR 'ly 3009104':ab,ti,tt OR 'incb 028050':ab,ti,tt OR incb028050:ab,ti,tt OR 'incb 28050':ab,ti,tt OR incb28050:ab,ti,tt OR isp4442i3y:ab,ti,tt OR '1187594 09 7':ab,ti,tt) AND [embase]/lim	1041
#6	(dupilumab:ab,ti,tt OR dupixent:ab,ti,tt OR 'regn 668':ab,ti,tt OR regn668:ab,ti,tt OR 'sar 231893':ab,ti,tt OR sar231893:ab,ti,tt OR 420k487fsg:ab,ti,tt OR '1190264 60 8':ab,ti,tt) AND [embase]/lim	1771
#5	(c?closporin*:ab,ti OR cya:ab,ti,tt OR 'cy a':ab,ti,tt OR csa:ab,ti,tt OR 'cs a':ab,ti,tt OR csaneoral:ab,ti,tt OR neoral:ab,ti,tt OR sandimmun*:ab,ti,tt) AND [embase]/lim	84287
#4	'cyclosporine'/exp AND [embase]/lim	152680
#3	#1 OR #2	157924
#2	'dermatitis'/exp AND [embase]/lim	155248
#1	('atopic dermatitis'/exp OR 'atopic dermatitis') AND [embase]/lim	47130

Cost-Effectiveness Analysis (CEA) Registry

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term: “dermatitis”. Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved:

- Methods: 9

- Ratios: 3

International Network of Agencies for Health Technology Assessment (INAHTA) database

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term: "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved: 4.

10.1.4 HRQoL

Medline

Table 81. Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 07, 2021>

1	exp Eczema/ or eczema*.tw. (23877)
2	exp Dermatitis, Atopic/ (21241)
3	exp Dermatitis/ or dermatitis.tw. (127289)
4	or/1-3 (132406)
5	Quality-Adjusted Life Years/ (13489)
6	Value of Life/ (5752)
7	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (12037)
8	(quality adjusted or adjusted life year$).ti,ab,kf. (18927)
9	disability adjusted life.ti,ab,kf. (3933)
10	daly$1.ti,ab,kf. (3457)
11	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf. (867)
12	(multiattribute$ or multi attribute$).ti,ab,kf. (1013)
13	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf. (37025)
14	utility.ab. /freq=2 (19443)
15	utilities.ti,ab,kf. (7855)
16	disutili$.ti,ab,kf. (514)
17	(HSUV or HSUVs).ti,ab,kf. (84)
18	health$1 year$1 equivalent$1.ti,ab,kf. (40)
19	(hye or hyes).ti,ab,kf. (75)
20	(hui or hui1 or hui2 or hui3).ti,ab,kf. (1679)
21	(illness state$1 or health state$1).ti,ab,kf. (7132)
22	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf. (12804)
23	(eq-sdq or eqsdq).ti,ab,kf. (1)
24	(short form$ or shortform$).ti,ab,kf. (37081)

25	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (23691)
26	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf. (3511)
27	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (5288)
28	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf. (30)
29	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf. (344)
30	(15D or 15-D or 15 dimension).ti,ab,kf. (5600)
31	(standard gamble$ or sg).ti,ab,kf. (11899)
32	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2041)
33	or/5-32 (159787)
34	4 and 33 (387)
35	limit 34 to yr="2014 -Current" (215)
36	exp animals/ not humans.sh. (4857607)
37	35 not 36 (206)

Embase

Table 82. Elsevier Embase <1974 to July 09, 2021>

#16	#15 AND [2014-2021]/py 1527
#15	#13 NOT #14 2029
#14	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de) AND [embase]/lim 2321323
#13	#3 AND #12 2045
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 181954
#11	('health years equivalent':ti,ab OR 'health-years equivalent':ti,ab OR 'hye':ti,ab OR 'hui':ti,ab OR 'hui1':ti,ab OR 'hui2':ti,ab OR 'hui3':ti,ab OR 'sf36':ti,ab OR 'sf 36':ti,ab OR 'thirtysix':ti,ab OR 'thirty six':ti,ab OR 'sf6':ti,ab OR 'sf 6':ti,ab OR 'sf6d':ti,ab OR 'sf 6d':ti,ab OR 'sf six':ti,ab OR 'sfsix':ti,ab OR 'sf8':ti,ab OR 'sf 8':ti,ab OR 'sf eight':ti,ab OR 'sfeight':ti,ab OR 'sf12':ti,ab OR 'sf 12':ti,ab OR 'sf twelve':ti,ab OR 'sftwelve':ti,ab OR 'sf16':ti,ab OR 'sf 16':ti,ab OR 'sf sixteen':ti,ab OR 'sfsixteen':ti,ab OR 'sf20':ti,ab OR 'sf 20':ti,ab OR 'sf twenty':ti,ab OR 'sftwenty':ti,ab OR '15d':ti,ab OR '15-d':ti,ab OR '15 dimension':ti,ab) AND [embase]/lim 82935
#10	('qaly*':ti,ab OR 'quality adjusted':ti,ab OR 'quality-adjusted':ti,ab OR 'adjusted life year*':ti,ab OR 'disability adjusted':ti,ab OR 'disability-adjusted':ti,ab OR 'daly':ti,ab OR 'dalys':ti,ab) AND [embase]/lim 30513
#9	('euroqol':ti,ab OR 'euro qol':ti,ab OR 'eq5d*':ti,ab OR 'eq 5d*':ti,ab OR 'eq-5d*':ti,ab) AND [embase]/lim 21463
#8	('standard gamble':ti,ab OR 'time trade off':ti,ab OR 'time trade-off':ti,ab OR 'tto':ti,ab) AND [embase]/lim 3104
#7	('utility value*':ti,ab OR 'health utility':ti,ab OR 'health utilities':ti,ab OR 'hsuv':ti,ab OR 'hsuvs':ti,ab OR 'disutilit*':ti,ab) AND [embase]/lim 6666
#6	'quality of life assessment'/exp AND [embase]/lim 77916
#5	'utility value'/exp AND [embase]/lim 178
#4	'quality adjusted life year'/exp AND [embase]/lim 26535
#3	#1 OR #2 157951
#2	'dermatitis'/exp AND [embase]/lim 155275
#1	('atopic dermatitis'/exp OR 'atopic dermatitis') AND [embase]/lim 47139

Cost-Effectiveness Analysis (CEA) Registry

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved:

- Utility weights: 4

International Network of Agencies for Health Technology Assessment (INAHTA) database

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved: 4.

10.2 Quality assessment

10.2.1 RCTs informing on clinical effectiveness

10.2.1.1 Abrocitinib

Table 83. Quality assessment of studies evaluating abrocitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb (Study B7451006)				
Random sequence generation	✓			Randomisation by interactive response technology system.
Allocation concealment	✓			Blinded study drugs and matching placebo delivered to the study sites in blister packs.
Blinding (who [participants, personnel], and method)	✓			Double blind. Patients, investigators and sponsors were blinded to study treatment.
Blinding of outcome assessment	✓			Investigators and sponsors blinded to study treatment
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)			✓	High rate of discontinuation from randomised set. Higher rate of discontinuation in placebo, 10mg and 30mg abrocitinib groups (~50% attrition) compared to 100 and

				200mg abrocitinib groups (33% attrition).
Selective reporting	✓			Outcomes for which data are available were pre-specified.
JADE MONO-1 and JADE MONO-2				
Random sequence generation	✓			Randomisation administered by interactive response technology system.
Allocation concealment	✓			Randomised using computer generated randomisation schedule using interactive response technology.
Blinding (who [participants, personnel], and method)	✓			Patients, investigators and sponsors were blinded to treatment.
Blinding of outcome assessment	✓			Investigators and sponsors were blinded to treatment.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the abrocitinib groups. Discontinuations were mainly due to adverse events, lack of efficacy and withdrawal of consent
Selective reporting	✓			Outcomes for which data are available were pre-specified.
JADE TEEN				
Random sequence generation		✓		Random allocation. Randomization stratified by baseline disease severity.
Allocation concealment		✓		Method of concealment not reported
Blinding (who [participants, personnel], and method)	✓			Double blind study design
Blinding of outcome assessment	✓			Assessments will be conducted at the investigator site by a clinical assessor blinded to treatment assignment.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms.
Selective reporting		✓		NA (conference abstract).
JADE COMPARE				
Random sequence generation		✓		Described as “Randomised”

Allocation concealment	✓			Patients, investigators, and representatives of the sponsor were unaware of the trial-group assignment.
Blinding (who [participants, personnel], and method)	✓			Double-blind, double dummy study
Blinding of outcome assessment	✓			Most outcome measures were subjective but investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation. Thus, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and adverse events, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.

10.2.1.2 Tralokinumab

Table 84. Quality assessment of studies evaluating tralokinumab

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb dose ranging study				
Random sequence generation		✓		Method of randomisation not reported
Allocation concealment		✓		Method to maintain concealment of allocation not reported
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessor were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation, and there was low occurrence of treatment-related side effects that could

				suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low
Selective reporting	✓			Based on outcomes reported for the study on ClinicalTrials.gov, outcomes for which data are available were pre-specified
ECZTRA 1 and ECZTRA 2				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by region ((ECZTRA 1: North America, Japan and Europe; ECZTRA 2: North America, Europe, Australia and Korea) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias However, tralokinumab and placebo are visually distinct and not matched for viscosity. To minimise risk of revealing allocation, investigational medicinal products were handled and administered by a qualified, unblinded health-care professional at the site who was not involved in the management of trial participants and who did not perform any of the assessments
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation. There was low occurrence of treatment-

				related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent
Selective reporting	✓			Based on outcomes reported in the publication for ECZTRA 1 and 2, outcomes for which data are available were pre-specified
ECZTRA 5				
Random sequence generation		✓		Method of randomisation not reported
Allocation concealment	✓			Method to maintain concealment of allocation not reported
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			The study was designed to evaluate whether tralokinumab affects the body's immune response to vaccines. Most outcomes were based on results from laboratory assessments. For the outcomes of interest to the MTA, investigators and participants were masked to treatment allocation and, for this reason, risk of compromising masking of outcome assessment has been categorised as low risk
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low
Selective reporting	✓			Based on outcomes reported in the publication for ECZTRA 5, outcomes for which data are available were pre-specified

ECZTRA 3				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by region (North America and Europe) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias However, tralokinumab and placebo are visually distinct and not matched for viscosity. To minimise risk of revealing allocation, investigational medicinal products were handled and administered by a qualified, unblinded health-care professional at the site who was not involved in the management of trial participants and who did not perform any of the assessments
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation. There was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent
Selective reporting	✓			Based on outcomes reported in the publication for ECZTRA 3, outcomes for

				which data are available were pre-specified
ECZTRA 7				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by prior cyclosporin A use, country (Germany, yes or no) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation, and there was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent
Selective reporting	✓			Based on outcomes reported on the record for ECZTRA 7 on ClinicalTrials.gov, outcomes for which data are available were pre-specified

10.2.1.3 Upadacitinib

Table 85. Quality assessment of studies evaluating upadacitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb study				

Random sequence generation	✓			An interactive response system referring to a schedule previously generated via computer by statisticians from the study sponsor was used to randomize qualifying patients 1:1:1:1
Allocation concealment	✓			Each study drug kit was labelled with a unique code that was linked to the randomization schedule.
Blinding (who [participants, personnel], and method)	✓			Patients, investigators, and the sponsor were blinded to allocation. The placebo and upadacitinib tablets were identical in appearance to maintain blinding of treatment assignment.
Blinding of outcome assessment	✓			Most outcome measures were subjective but investigators and patients were blinded to treatment allocation and there were few-treatment related side effects that could give an indication of treatment allocation. Thus, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation seems to be dose dependent with higher discontinuation in the placebo and the low dose (7.5mg) upadacitinib groups.
Selective reporting	✓			Results for all specified outcomes were reported
HEADS UP				
Random sequence generation	✓			Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.

Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)		✓		Patient flow diagram not available
Selective reporting		✓		N/A (no publication)
MEASURE UP1 and MEASURE UP2				
Random sequence generation	✓	✓		Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo group than in either upadacitinib group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent.
Selective reporting				N/A (no publication available at the time of writing)
AD UP				
Random sequence generation	✓			Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with

				use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo group than in either upadacitinib group.
Selective reporting				N/A (no publication)
RISING UP				
Random sequence generation		✓		Study described as RCT but no details reported about random sequence generation
Allocation concealment		✓		Study described as RCT but no details reported about allocation concealment
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, Outcomes Assessor were all blinded to treatment assignment
Blinding of outcome assessment	✓			Participant, Care Provider, Investigator, Outcomes Assessor were all blinded to treatment assignment
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)		✓		Details not available
Selective reporting		✓		N/A (no publication and no CSR provided)

10.2.1.4 Baricitinib

Table 86. Quality assessment of studies evaluating baricitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
BREEZE-AD1 and BREEZE AD2				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of

				placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and lack of efficacy, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
Phase II (Guttman-Yassky 2019)				
Random sequence generation	✓			Randomised by an interactive response system.
Allocation concealment	✓			Blocked randomisation generated and maintained centrally with interactive response technology.
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)			✓	Loss to follow up was relatively high across all study arms, highest in the placebo group (41%). The main reasons for discontinuation were withdrawal by subject and lack of efficacy and adverse events.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
BREEZE-AD4				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets

Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. Treatment discontinuation was higher in the placebo group than the baricitinib groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
BREEZE-AD7				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and adverse events, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.

10.2.1.5 Dupilumab

Table 87 Quality assessment of studies evaluating dupilumab

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity and region.
Allocation concealment	✓			Blinded study drug kits coded providing masking to treatment assignment.

Blinding (who [participants, personnel], and method)	✓			The study remained blinded to all individuals (including patients, investigators, sponsors and study personnel) until the time of prespecified unblinding.
Blinding of outcome assessment	✓			The study remained blinded to principal investigators and study centre personnel until the time of prespecified unblinding.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
AD ADOL				
Random sequence generation		✓		"Randomised"
Allocation concealment	✓			Blinded study drug kits coded with a medication numbering system were used. To maintain blinding, lists linking codes with product lot numbers were not accessible to individuals involved in study conduct.
Blinding (who [participants, personnel], and method)	✓			The study remained blinded to all individuals (including patients, investigators, and study personnel) until the time of prespecified unblinding.
Blinding of outcome assessment	✓			The study remained blinded to study personnel until the time of prespecified unblinding, except for independent data monitoring committee members.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
SOLO-1 and SOLO-2				
Random sequence generation	✓			Randomization was conducted by means of a central interactive voice-response system, and stratified by disease severity and by region

Allocation concealment	✓			Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo groups than in dupilumab groups for both studies.
Selective reporting	✓			Results for all specified outcomes were reported
CAFE				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity, region, prior CSA exposure and candidate for CSA treatment.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment

				allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
CHRONOS				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity and by region
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo groups than in dupilumab groups.
Selective reporting	✓			Results for all specified outcomes were reported

10.2.2 Observational study informing clinical effectiveness

Table 88. Assessment of the quality of Ariens *et al.*[88] using the Newcastle Ottawa tool for Case–Control studies[116]

Component	Response
Selection	
Is the Case Definition Adequate?	* Yes, population for analysis is defined
Representativeness of the Cases	* Yes, population derived from trial registry and receiving CsA is comparable, in terms of baseline characteristics, to the population enrolled in the RCT informing the comparator group. No evidence of election bias.
Selection of Controls	* Comparator group is derived from an RCT.
Definition of Controls	N/A. Both groups have moderate-severe AD, which is appropriate for the primary objective of the study.
Comparability	
Comparability of Cases and Controls on the Basis of the Design or Analysis	* Comparator group is derived from an RCT and has similar baseline characteristics to those of the group receiving CsA. The authors used logistic regression analysis to assess outcomes and included sex, baseline EASI, and baseline TARC level as regressors.
Exposure	
Ascertainment of Exposure	* Data on group receiving CsA were selected based on information in secure records collated in a clinical database
Same method of ascertainment for cases and controls	* Yes.
Non-Response Rate	Not applicable to the objective of the study. The study compares active interventions and does not include a placebo group.

Abbreviations: EASI, Eczema Area and Severity Index; TARC, thymus and activation-regulated chemokine.

10.2.3 Economic evaluations – Drummond checklist

Paper	Canadian Agency for Drugs and Technologies in Health. 2020. Canada	Kuznik, A. et al, 2017. USA	Fanelli, F. et al, 2020. Italy (abstract)	Zimmermann, M. et al, 2018. USA	National Institute for Health and Care Excellence - TA534	National Institute for Health and Care Excellence - TA681	Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2011 & SMC2232)	Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2337)	Institute for Clinical and Economic Review
Study design									
1. The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. The rationale for choosing alternative programmes or interventions compared is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

5. The alternatives being compared are clearly described.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Data collection									
8. The source(s) of effectiveness estimates used are stated.	Yes	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	Not appropriate	Not appropriate	Not clear	Not appropriate	Not appropriate	Not appropriate	Yes	Yes	Not appropriate
10. Details of the methods of	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear

synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).									
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
12. Methods to value benefits are stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
13. Details of the subjects from whom valuations were obtained were given.	Yes	Yes	No	Not clear	Yes	Yes	No	No	No
14. Productivity changes (if included) are reported separately.	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
15. The relevance of productivity	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate

changes to the study question is discussed.									
16. Quantities of resource use are reported separately from their unit costs.	No	No	No	Not clear	Yes	Yes	No	No	Not clear
17. Methods for the estimation of quantities and unit costs are described.	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
18. Currency and price data are recorded.	Yes	Yes	No	Yes	Yes	Yes	Not clear	Not clear	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	No	Yes	No	Yes	Yes	Yes	No	No	Yes
20. Details of any model used are given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21. The choice of model used and the key	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

parameters on which it is based are justified.									
Analysis and interpretation of results									
22. Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. The discount rate(s) is stated.	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
24. The choice of discount rate(s) is justified.	No	Yes	No	No	Yes	Yes	No	No	No
25. An explanation is given if costs and benefits are not discounted.	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	No	No	Not appropriate
26. Details of statistical tests and confidence intervals are given for stochastic data.	Yes	Yes	No	No	Yes	Yes	No	No	No
27. The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
28. The choice of variables for	Yes	Yes	No	No	Yes	Yes	No	No	No

sensitivity analysis is justified.									
29. The ranges over which the variables are varied are justified.	Yes	Yes	No	No	Yes	Yes	No	No	No
30. Relevant alternatives are compared.	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
31. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
33. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

appropriate caveats.									

10.3 Data abstraction tables

10.3.1 RCTs informing on clinical effectiveness

10.3.1.1 Abrocitinib

10.3.1.1.1 Interventions assessed in the included studies

Table 89. Summary of interventions assessed in studies evaluating abrocitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
Phase IIb	Abrocitinib 200 mg QD	55	Placebo	56	12 weeks	–
	Abrocitinib 100 mg QD	56				
	Abrocitinib 30 mg QD	51				
	Abrocitinib 10 mg QD	49				
JADE MONO-1	Abrocitinib 200 mg QD	154	Placebo	77	12 weeks	–
	Abrocitinib 100 mg QD	156				
JADE MONO-2	Abrocitinib 200 mg QD	155	Placebo	78	12 weeks	–
	Abrocitinib 100 mg QD	158				
JADE TEEN	Abrocitinib 200 mg QD plus TCS	94	Placebo plus TCS	96	12 weeks	Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy.
	Abrocitinib 100 mg QD plus TCS	95				

JADE COMPARE	Abrocitinib 200 mg QD plus TCS	226	Dupilumab 300 mg Q2W plus TCS	242	20 weeks for abrocitinib regimens and placebo versus 16 weeks for dupilumab	Those allocated to abrocitinib and placebo received a placebo injection and those in the dupilumab group received a placebo tablet. Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy.
	Abrocitinib 100 mg QD plus TCS	238	Placebo QD plus TCS	131		

Abbreviations: QD, once daily; Q2W, every 2 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.1.2 Study characteristics

Table 90. Characteristics of studies evaluating abrocitinib

Characteristic	Phase II study	JADE MONO-1	JADE MONO-2	JADE TEEN	JADE COMPARE
Study references	Gooderham 2019[27]	Simpson 2020[28]	Silverberg 2020[29]	Eichenfield 2021[30]	Bieber 2021[156]
Country(ies) where the clinical trial was conducted	5 countries – USA, Australia, Canada, Germany, Hungary.	8 countries – UK, USA, Australia, Canada, Czechia, Germany, Hungary, Poland.	13 countries – UK, USA, Australia, Bulgaria, Canada, China, Czechia, Germany, Hungary, Japan, South Korea, Latavia, Poland.	14 countries – UK, USA, Australia, China, Czechia, Germany, Hungary, Italy, Japan, Latvia, Mexico, Poland, Spain, Taiwan.	18 countries – UK, USA, Australia, Bulgaria, Canada, Chile, Czechia, Germany, Hungary, Italy, Japan, Republic of Korea, Latvia, Mexico, Poland, Slovakia, Spain, Taiwan.
Multicentre trial (number, location)	58 locations	69 sites (UK 5 sites: London, 2x South Yorkshire, Devon, Birmingham	106 sites (UK 6 sites)	99 sites (UK two sites:)	194 sites (UK 11 sites: London x5, Devon, Peterborough, Warwickshire, Yorkshire, Corby, Glasgow)
Trial sponsors	Pfizer	Pfizer		Pfizer	Pfizer

Date the clinical trial was conducted	April 2016 to April 2017	December 2017 to March 2019	June 2018 to August 2019	February 2019 to April 2020	October 2018 to December 2019
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb parallel assignment RCT, double-blind	Phase III, multicentre, randomised, double-blind, placebo-controlled studies			Phase III parallel assignment RCT, double-blind
Trial duration (treatment duration and follow-up)	35-day screening period, 12-week intervention with additional 4-week follow-up	28-day screening period 12-week intervention and follow-up		12-week intervention and follow-up	28-day screening period 20-week intervention phase 16-week follow-up (primary endpoint measured at 12 weeks
Inclusion criteria	Subjects aged 18 years or older with diagnosis of AD with: • clinical diagnosis of chronic AD for at least 1 year; • inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable within 12 months; • Moderate to severe AD.	• ≥12 years of age with body weight of ≥40 kg • Diagnosis of AD for ≥1 year and current status of moderate to severe disease • Recent history of inadequate response or inability to tolerate topical AD treatments or require systemic treatments for AD control		• Aged between 12 and to 17 with a minimum body weight of 40 kg • Diagnosis of AD for at least 1 year and current status of moderate to severe disease	• Subjects aged 18 years or older with diagnosis of moderate to severe AD for at least 1 year. • Documented recent history of inadequate response to treatment with medicated topical therapy for AD or required systemic therapies.

Exclusion criteria	• History of HIV or positive HIV serology at screening • Infected with hepatitis B or hepatitis C viruses • Have evidence of active or latent or inadequately treated infection with TB	• Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study • Prior treatment with JAK inhibitors • Other active non-AD inflammatory skin diseases or conditions affecting skin • Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders and other medical conditions at the discretion of the investigator • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception	• Acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation • Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study • Prior treatment with JAK inhibitors • Other active non-AD inflammatory skin diseases or conditions affecting skin • Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, malignancies, current or history of certain infections, lymphoproliferative disorders and other medical conditions at the discretion of the investigator	• Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders and other medical conditions at the discretion of the investigator. • Other active non-AD inflammatory skin diseases or conditions affecting skin • Prior treatment with JAK inhibitors • Previous treatment with dupilumab • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception

			• Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception	
Concomitant medications	Not reported	Background medicated topical therapy was not permitted in the MONO trials.	Background therapy (medicated and non-medicated topical therapy) must have been applied BD for the duration of the treatment period.	Emollient BD. Topical therapies that were allowed during the trial included low or medium potency glucocorticoids, topical calcineurin inhibitors and topical phosphodiesterase 4-inhibitors.
Rescue therapy	Patients were allowed to use oral antihistamines and nonmedicated emollient; or Aquaphor and sunscreen.	Additional rescue therapy was prohibited	Additional rescue therapy was prohibited	Additional rescue therapy was prohibited
Outcomes	Primary endpoint: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12. Secondary endpoints: • Change in EASI score from baseline at week 12; • % achieving IGA response of 0 or 1 and	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12; • % achieving EASI response ≥75% improvement at week 12. Secondary endpoints: • Response based on a ≥50% and ≥90% improvement in EASI (EASI-50, EASI-90) from baseline at all scheduled time points;	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12; • % achieving EASI response ≥75% improvement at week 12. Secondary endpoints:	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12 • % achieving EASI response ≥75% improvement at week 12 Secondary endpoints:

	a reduction of ≥2 points at other time points; • % EASI score change from baseline; • Patients achieving ≥3 and ≥4 point improvement on PP-NRS; • Change from baseline of PP-NRS; • Change from baseline of SCORAD; • % change in BSA; • Adverse events; • POEM score; • HADS score. More secondary endpoints listed on clinicaltrials.gov	• Response based on ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points; • SCORAD subjective assessments of itch and sleep loss; • Change in DLQI or CDLQI at Week 12 or all other scheduled time points; • Change in HADS score at Week 12 and all other scheduled time points; • Change in POEM at Week 12 and all other scheduled time points; • Change of PtGA at Week 12 and all other scheduled time points; • Change of EQ-5D-5L or EQ-5D-Y at Week 12 and all other scheduled time points; • CHANGE in SF-36v2, acute, at Week 12 and all other scheduled time points; • Response based on PP-NRS; • Time from baseline to achieve PP-NRS; • Adverse events. More secondary endpoints listed on clinicaltrials.gov	• % with ≥4 improvement in the PP-NRS; • Change in PSAAD at week 12; • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at other time points; • % achieving EASI response ≥75% improvement at other timepoints; • Improvement of ≥50%, ≥90% and 100% of EASI; • % change in EASI from baseline; • PSAAD score; • DLQI score; • HADS score; • EQ-5D; • Adverse events. More secondary endpoints listed on clinicaltrials.gov	• % with ≥4 improvement in the PP-NRS • IGA and EASI-75 response at week 16 • Improvement of ≥50%, ≥90% and 100% of EASI • Time to itch response • % change in BSA • POEM score • PSAAD score • DLQI score • HADS score • % with SCORAD response ≥50% and ≥75% improvement • EQ-5D More secondary endpoints listed on clinicaltrials.gov
Subgroups	None	None	None	None
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥12	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10%	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10%	• IGA ≥3 • EASI ≥16

	• BSA involvement ≥10%	• PP-NRS ≥4	• PP-NRS ≥4	• BSA involvement ≥10% • PP-NRS ≥4

Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis.

10.3.1.1.3 Baseline characteristics

Table 91. Baseline characteristics of trial populations in studies evaluating abrocitinib

Characteristic	Phase IIb (study B7451006) Full trial population				
	Abrocitinib 200 mg QD (N=55)	Abrocitinib 100 mg QD (N=56)	Abrocitinib 30 mg QD (N=51)	Abrocitinib 10 mg QD (N=49)	Placebo (N=56)
Mean age (SD), years	38.7 (17.6)	41.1 (15.6)	37.6 (15.9)	44.3 (15.9)	42.6 (15.1)
Gender, n (%)	Female: 27 (49.1)	Female: 25 (44.6)	Female: 29 (56.9)	Female: 28 (57.1)	Female: 35 (62.5)
Duration of AD, years Median (range)	19.6 (1.9–68.8)	23.8 (1.1–66.7)	20.5 (1.2–66.6)	30.2 (1.8–60.6)	25.6 (1.1–67.1)
Race					
• White, n (%)	37 (67.3)	40 (71.4)	39 (76.5)	38 (77.6)	40 (71.4)
• Black or African American, n (%)	13 (23.6)	7 (12.5)	4 (7.8)	5 (10.2)	10 (17.9)
• Asian, n (%)	5 (9.1)	8 (14.3)	5 (9.8)	5 (10.2)	4 (7.1)
Mean EASI score (SD)	24.6 (13.5)	26.7 (11.8)	22.1 (10.7)	28.1 (13.1)	25.4 (12.9)
Mean IGA score	NR	NR	NR	NR	NR
Mean DLQI score	NR	NR	NR	NR	NR

Mean SCORAD score (SD)	62.7 (13.7)	65.4 (13.7)	62.4 (13)	65.3 (13.2)	65 (12.1)
Mean peak pruritus NRS score	6.9 (2.7)	7.4 (2.2)	7.6 (1.9)	7.6 (1.7)	7.6 (1.8)
Mean % BSA affected (SD)	38 (23.3)	41.9 (22.3)	34.1 (22.3)	44.2 (22.7)	40.1 (22.3)
Prior treatment					
OCS	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR
TCI	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE MONO-1 Full trial population			JADE MONO-1 Adult Generalisable population			JADE MONO-1 Adult Restricted population		
	Abrocitinib 200 mg QD (N=154)	Abrocitinib 100 mg QD (N=156)	Placebo (N=77)	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]
Mean age (SD), years	33.0 (17.4)	32.6 (15.4)	31.5 (14.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	Female: 73 (47.4)	Female: 66 (42.3)	Female: 28 (36.4)	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]
Mean duration of AD (SD), years	22.7 (14.5)	24.9 (16.1)	22.5 (14.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race									

• White, n (%)	104 (67.5)	113 (72.4)	62 (80.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	11 (7.1)	15 (9.6)	6 (7.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	26 (16.9)	26 (16.7)	6 (7.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	30.6 (14.1)	31.3 (13.6)	28.7 (12.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA, % moderate/severe	59.1/40.9	59.0/41.0	59.7/40.3	–	–	–	–	–	–
Baseline IGA score of 4, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	14.6 (6.8)	14.6 (6.5)	13.9 (7.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	64.3 (13.1)	67.1 (13.7)	64.5 (13.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	7.1 (1.9)	6.9 (2.0)	7.0 (1.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	49.9 (24.4)	50.8 (23.4)	47.4 (22.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment, n (%)									
Any	154 (100)	155 (99)	77 (100)	–	–	–	–	–	–

Topical (TCS or TCI)	82 (53)	69 (44)	34 (44)	–	–	–	–	–	–
Systemic with or without topical treatment	68 (44)	78 (50)	41 (53)	–	–	–	–	–	–
Dupilumab	9 (6)	13 (8)	8 (10)	–	–	–	–	–	–
Oral/injectable corticosteroids, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE MONO-2 Full trial population			JADE MONO-2 Adult Generalisable population			JADE MONO-2 Adult Restricted population		
	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo (N=78)	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo [redacted]	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo [redacted]

	(N=155)	(N=158)		[redacted]	[redacted]		[redacted]	[redacted]	
Mean age (SD), years	33.5 (14.7)	37.4 (15.8)	33.4 (13.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	Male: 88 (56.8)	Male: 94 (59.5)	Male: 47 (60.3)	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]	Male: [redacted]
Mean duration of AD (SD), years	20.5 (14.8)	21.1 (14.8)	21.7 (14.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race									
• White, n (%)	91 (58.7)	101 (63.9)	40 (51.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	6 (3.9)	9 (5.7)	6 (7.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	54 (34.8)	46 (29.1)	29 (37.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	29.0 (12.4)	28.4 (11.2)	28.0 (10.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	49 (31.6)	51 (32.3)	26 (33.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	14.8 (6.0)	15.4 (7.3)	15.0 (7.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	64.1 (13.1)	63.8 (11.4)	64.3 (12.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	7.0 (1.6)	7.1 (1.6)	6.7 (1.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean % BSA affected (SD)	47.7 (22.3)	48.7 (21.4)	48.2 (20.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment, n (%)									
Any	153 (99)	157 (99)	78 (100)	–	–	–	–	–	–
Topical (TCS or TCI)	93 (60)	87 (55)	46 (59)	–	–	–	–	–	–
Systemic with or without topical treatment	60 (39)	70 (44)	32 (41)	–	–	–	–	–	–
Dupilumab	5 (3)	7 (4)	2 (3)	–	–	–	–	–	–
Oral/injectable corticosteroids, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE TEEN Full trial population			JADE MONO-1 Adolescent population			JADE MONO-2 Adolescent population		
	Abrocitinib 200 mg QD plus TCS (N=94)	Abrocitinib 100 mg QD plus TCS (N=95)	Placebo plus TCS (N=96)	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]
Mean age (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	Female: 38 (40.4)	Female: 50 (52.6)	Female: 52 (54.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD (SD), years	9.7 (5.3)	9.8 (5.4)	10.5 (4.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race									
• White, n (%)	52 (55.3)	52 (54.7)	56 (58.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	5 (5.3)	9 (9.5)	3 (3.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	31 (33)	31 (32.6)	32 (33.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median EASI score (Q1, Q3)	[redacted]	[redacted]	[redacted]	–	–	–	[redacted]	[redacted]	[redacted]

Mean EASI score (SD)	29.5 (12.2)	31.0 (12.8)	29.2 (12.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA, % moderate/severe	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Baseline IGA score of 4, n (%)				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median DLQI score (Q1, Q3)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Median SCORAD score (Q1, Q3)	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Mean SCORAD score (SD)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median peak pruritus NRS score (Q1, Q3)	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Mean peak pruritus NRS score (SD)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median % BSA affected (Q1, Q3)	[redacted]	[redacted]	[redacted]	–	–	–	–	–	–
Mean % BSA affected (SD)	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EQ-5D score (SD)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment									
Oral/injectable corticosteroids, n (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other non-biologics systemic (i.e., ciclosporin or other)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic (i.e. dupilumab or other)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE COMPARE Full trial population				JADE COMPARE Adult Generalisable population				JADE COMPARE Adult Restricted population			
	Abrocitinib 200 mg QD plus TCS (N=226)	Abrocitinib 100 mg QD plus TCS (N=238)	Dupilumab 300 mg Q2W plus TCS (N=242)	Placebo plus TCS (N=131)	Abrocitinib 200 mg QD plus TCS [redacted]	Abrocitinib 100 mg QD plus TCS [redacted]	Dupilumab 300 mg Q2W plus TCS [redacted]	Placebo plus TCS [redacted]	Abrocitinib 200 mg QD plus TCS [redacted]	Abrocitinib 100 mg QD plus TCS [redacted]	Dupilumab 300 mg Q2W plus TCS [redacted]	Placebo plus TCS [redacted]
Mean age (SD), years	38.8 (14.5)	37.3 (14.8)	37.1 (14.6)	37.4 (15.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	Female: 122 (54)	Female: 118 (49.6)	Female: 134 (55.4)	Female: 54 (41.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD (SD), years	23.4 (15.6)	22.7 (16.3)	22.8 (14.8)	21.4 (14.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race												
• White, n (%)	161 (71.2)	182 (76.5)	176 (72.7)	87 (66.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

• Black or African American, n (%)	9 (4.0)	6 (2.5)	14 (5.8)	6 (4.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	53 (23.5)	48 (20.2)	46 (19)	31 (23.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	32.1 (13.1)	30.3 (13.5)	30.4 (12)	31 (12.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA, % moderate/severe	61.1/38.9	64.3/35.7	66.9/33.1	67.2/32.8	–	–	–	–	–	–	–	–
Baseline IGA score of 4, n (%)	–	–	–	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	16.3 (6.6)	15.5 (6.4)	15.6 (6.7)	15.2 (6.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	69.3 (12.7)	66.8 (13.8)	67.9 (11.4)	67.9 (12.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	7.6 (1.5)	7.1 (1.7)	7.3 (1.7)	7.1 (1.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	50.8 (23)	48.1 (23.1)	46.5 (22.1)	48.9 (24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment, n (%)												
Oral/injectable corticosteroids, n (%)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Other non-biologic systemics (i.e., ciclosporin or other)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.1.4 Data extracted on outcomes of interest

Table 92. Data on clinical effectiveness from studies evaluating abrocitinib and for populations of interest to the MTA

Outcome at 12 weeks	Phase II study					
	Generalisable			Restricted		
	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinued treatment at week 12, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily.

Outcome	JADE MONO-1								
	Adults (aged ≥18 years) Second-line adults – monotherapy						Adolescents		
	Generalisable			Restricted					
	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in EQ-5D score from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome at 12 weeks	JADE MONO-2								
	Adults (aged ≥18 years) Second-line adults – monotherapy						Adolescents		
	Generalisable			Restricted					
	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]	Abrocitinib 200 mg QD [redacted]	Abrocitinib 100 mg QD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in EQ-5D score from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome	JADE TEEN		
	Abrocitinib 200 mg QD plus TCS (N=94)	Abrocitinib 100 mg QD plus TCS (N=95)	Placebo plus TCS (N=96)

Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	67/93 (72.0)	61/89 (68.5)	39/94 (41.5)
Mean change in EQ-5D score from baseline	[redacted]	[redacted]	[redacted]
Proportion of patients who discontinue treatment at week 16 (additional request from clarification meeting), n/N (%)	3/94 (3.2)	3/95 (3.2)	6/96 (6.3)
Mean number of days free from TCS during treatment	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome (at 16 weeks)	**JADE COMPARE**							
	Generalisable Second-line adults – combination therapy				**Restricted Second-line adults – combination therapy**			
	Abrocitinib 200 mg QD plus TCS (N=42)	Abrocitinib 100 mg QD plus TCS (N=42)	Dupilumab 300 mg Q2W plus TCS (N=55)	Placebo plus TCS (N=24)	Abrocitinib 200 mg QD plus TCS (N=20)	Abrocitinib 100 mg QD plus TCS (N=21)	Dupilumab 300 mg Q2W plus TCS (N=32)	Placebo plus TCS (N=12)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline, LSM, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of patients who discontinue treatment at week 16 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment, LSM, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Table 93. Data on adverse effects and adverse effects of special interest informing the model for abrocitinib

Outcome	JADE MONO 1			JADE MONO 2			JADE COMPARE				Study B7451006		
	Placebo (N=77)	Abrocitinib 100 mg QD (N=156)	Abrocitinib 200 mg QD (N=154)	Placebo (N=78)	Abrocitinib 100 mg QD (N=158)	Abrocitinib 200 mg QD (N=155)	Abrocitinib 200 mg QD plus TCS (N=226)	Abrocitinib 100 mg QD (N=238)	Dupilumab 300 mg Q2W plus TCS (N=242)	Placebo plus TCS (N=131)	Placebo (N=56)	Abrocitinib 100 mg QD (N=56)	Abrocitinib 200 mg QD (N=55)
SAEs n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; QD, once daily; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, upper respiratory tract infection.

Outcome	JADE TEEN		
	Placebo plus TCS (N=96)	Abrocitinib 100 mg QD plus TCS (N=95)	Abrocitinib 200 mg QD plus TCS (N=94)
SAEs n (%)	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; QD, once daily; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary respiratory tract infection.

10.3.1.2 Tralokinumab

10.3.1.2.1 Interventions assessed in the included studies

Table 94. Summary of interventions assessed in studies evaluating tralokinumab

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose[a]	N	Name	N		
ECZTRA 1	Tralokinumab 300 mg Q2W	603	Placebo	199	16 weeks	Initial treatment given for 16 weeks, after which people entered a maintenance phase[b]
ECZTRA 2	Tralokinumab 300 mg Q2W	593	Placebo	201	16 weeks	Initial treatment given for 16 weeks, after which people entered a maintenance phase[b]
ECZTRA 5	Tralokinumab 300 mg Q2W	107	Placebo	108	16 weeks	Treatment phase followed by 14-week off-treatment follow-up period for the assessment of safety.

						Dependent on eligibility, people could transfer to an open-label, long-term trial at week 16 or later.
Phase IIb	Tralokinumab 300 mg Q2W plus TCS	52	Placebo	51	12 weeks	Leo Pharma confirmed that people did not receive a loading dose of tralokinumab.
	Tralokinumab 150 mg Q2W plus TCS	51				
	Tralokinumab 45 mg Q2W plus TCS	50				
ECZTRA 3	Tralokinumab 300 mg Q2W plus TCS	252	Placebo plus TCS	126	16 weeks	TCS was mometasone furoate 0.1% cream daily until control was achieved.
ECZTRA 7	Tralokinumab 300 mg Q2W plus TCS	140	Placebo plus TCS	137	26 weeks	TCS was mometasone furoate 0.1% cream daily until control was achieved.

[a] First dose of tralokinumab given at a dose of 600 mg, which is the loading dose.

[b] Those allocated to tralokinumab and achieving EASI 75 or IGA 0/1 were re-randomised 2:2:1 to tralokinumab 300 mg Q2W, tralokinumab 300 mg Q4W or placebo. People allocated to placebo arm and achieving EASI 75 or IGA 0/1 continued to receive placebo. People not reaching EASI 75 or IGA 0/1 in either the tralokinumab or placebo groups received tralokinumab 300 mg Q2W.

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroid.

10.3.1.2.2 Study characteristics

Table 95. Characteristics of studies evaluating tralokinumab

Characteristic	Phase IIb	ECZTRA 1	ECZTRA 2	ECZTRA 5	ECZTRA 3	ECZTRA 7
Study references	Wollenberg 2019[92]	Wollenberg 2021[35]	Wollenberg 2021[35]	ClinicalTrials.gov[36]	Silverberg 2021[37]	ClinicalTrials.gov[39]
Country(ies) where the clinical trial was conducted	6 countries – Australia, Canada, Germany, Japan, Poland, USA	5 countries – France, Germany, Japan, Spain, USA	9 countries – Australia, Canada, Denmark, Italy, Republic of Korea, Poland, Russian Federation, UK, USA	2 countries – Canada, USA	8 countries – Belgium, Canada, Germany, Netherlands, Poland, Spain, UK, USA	7 countries – Belgium, Czechia, France, Germany, Poland, Spain, UK
Multicentre trial (number, location)	57 sites	124 sites	108 sites	51 sites	64 sites	68 sites
Trial sponsors	MedImmune LLC	LEO Pharma	LEO Pharma	LEO Pharma	LEO Pharma	LEO Pharma

Date the clinical trial was conducted	23 January 2015 to 27 November 2015	30 May 2017 to 7 August 2018	12 June 2017 to 4 September 2018	13 July 2018 to 17 September 2019	22 February 2018 to 8 March 2019	28 December 2018 to 28 September 2020
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb parallel assignment RCT, double blind Four arms: 3 arms evaluating different doses of tralokinumab (45 mg, 150 mg or 300 mg QW) and a placebo arm Patients randomised 1:1	Phase III parallel assignment RCT, double blind Patients randomised 3:1		Phase III parallel assignment RCT, double blind Patients randomised 1:1	Phase III parallel assignment RCT, double blind Patients randomised 2:1	Phase III parallel assignment RCT, double blind Patients randomised 1:1
Trial duration (treatment duration and follow-up)	Post randomisation: initial treatment period of 12 weeks	Post randomisation: initial treatment period of 16 weeks. Those achieving a clinical response at week 16 (defined as IGA of 0 or 1 or at least 75% reduction EASI score from baseline) moved onto maintenance treatment that continued until week 52		Screening period of 2 to 6 weeks, followed by a treatment period of 16 weeks and a 14-week off-treatment follow-up period for the assessment of safety. Dependent on eligibility, people could transfer to an open-label, long-term trial at week 16 or later.	Post randomisation: Initial 16-week treatment period followed by re-randomisation of responders and a 16-week treatment period	Pre-randomisation: 6-week washout period of AD medication, with the exception of TCS and TCI Post-randomisation: 26-week treatment period
Inclusion criteria	• Age 18 to 75 years • Physician diagnosis of AD for greater than 1 year • AD involvement of ≥10% BSA	• Age 18 and above • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD • EASI ≥12 at screening and ≥16 at baseline • IGA 3 or 4, and worst daily pruritis NRS score ≥4		• Age 18 to 54 years • Diagnosis of AD as defined by Hanifin and Rajka (1980) criteria for AD	• Age 18 and above • Diagnosis of AD as defined by the Hanifin and Rajka	• Age 18 and above • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD

	• EASI score of ≥12 • SCORAD of ≥25 • IGA score of ≥3 • Effective birth control in line with protocol details	• AD involvement of ≥10% body surface area at screening and baseline • Diagnosis of AD for ≥1 year • Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation	• History of AD for ≥1 year • Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable • AD involvement of ≥10% BSA at screening and baseline • EASI score of ≥12 at screening and 16 at baseline • An IGA score of ≥3 at screening and at baseline • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation	(1980) criteria for AD • EASI ≥12 at screening and ≥16 at baseline • IGA 3 or 4, and worst daily pruritis NRS score ≥4 • AD involvement of ≥10% body surface area at screening and baseline • History of AD for ≥1 year • Recent history of inadequate response to treatment with topical medications • Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation	• EASI score at screening and baseline of ≥20 • IGA 3 or 4, and worst daily pruritis NRS score ≥4 • AD involvement of 10% (or more) BSA at screening and baseline (visit 3) according to component A of SCORAD • History of AD for 1 year or more • Subjects with a history within 1 year prior to screening of inadequate response to treatment with topical medications or subjects for whom topical treatments are otherwise medically inadvisable • Documented history of either no previous CsA

					exposure and not currently a candidate for CsA treatment OR previous exposure to CsA in which case CsA treatment should not be continued or restarted • Subjects must have applied a stable dose of emollient I twice daily (or more, as needed) for at least 14 days before randomisation
Exclusion criteria	• History of anaphylaxis following any biologic therapy • Hepatitis B, C or human immunodeficiency virus • Pregnant or breastfeeding • History of cancer	• Active dermatologic conditions that may confound the diagnosis of AD • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation • Treatment with TCS and/or TCI within 2 weeks prior to randomisation • Active skin infection within 1 week prior to randomisation	• Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Subjects for whom administration of the tetanus,	• Subjects for whom TCS are medically inadvisable e.g., due to important side effects or safety risks in the opinion of the investigator • Active dermatologic conditions that	• Subjects for whom TCSs are medically inadvisable in the opinion of the investigator • Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 6 weeks

	• Previous receipt of tralokinumab	• Clinically significant infection within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior to the date informed consent is obtained • History of anaphylaxis following any biologic therapy • Tuberculosis requiring treatment within the 12 months prior to screening • Known primary immunodeficiency disorder • Alanine aminotransferase or aspartate aminotransferase level ≥2.0 times the upper limit of normal at screening • Positive hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody or hepatitis C virus antibody serology at screening	diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immunomodulating medications and/or systemic corticosteroids within 4 weeks prior to randomisation • Treatment with the topical medications TCS, TCI or	may confound the diagnosis of AD • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation • Treatment with TCS, topical calcineurin inhibitors (TCI), or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation • Receipt of any marketed biological therapy (i.e.	prior to randomisation • Treatment with immunomodulatory medications or bleach baths within 4 weeks prior to randomisation • Treatment with topical phosphodiesterase-4 (PDE-4) inhibitor within 2 weeks prior to randomisation • Receipt of any marketed or investigational biologic agent (e.g. cell-depleting agents or dupilumab) within 6 months prior to randomisation or until cell counts return to normal, whichever is longer • History of any active skin infection within 1

			phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation • Receipt of any vaccine (except influenza virus vaccines) within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening> • Receipt of any marketed (i.e. immunoglobulin, anti-IgE) or investigational biologic agent, including dupilumab> • History of any active skin infection within 1 week prior to randomisation>	immunoglobulin, anti-immunoglobulin E) including dupilumab or investigational biologic agents within 3 months or 5 half-lives, whichever is longer prior to randomisation • Active skin infection within 1 week prior to randomisation • Clinically significant infection within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior to the date informed consent is obtained • Tuberculosis requiring treatment within the 12 months prior to screening	week prior to randomisation • History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy • Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per

			• History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation	• Known primary immunodeficiency disorder	local standard of care • History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
Concomitant medications	TCS	None	• Tdap vaccine: tetanus (lockjaw), diphtheria (infection of the nose and throat), and pertussis (whooping cough) vaccines • Meningococcal vaccine	None reported, other than combination TCS	None reported, other than combination TCS
Rescue therapy	Unclear	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last dose of systemic rescue treatment	Unclear	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last

				dose of systemic rescue treatment	dose of systemic rescue treatment
Outcomes	Primary outcomes: • Absolute change from baseline in EASI score at week 12; • Percentage of participants achieving IGA of 0 (Clear) or 1 (Almost Clear) and at least a 2-grade reduction from baseline at week 12. Secondary outcomes of interest to MTA: EASI 75 at week 12 are reported	Primary outcomes: • Proportion of patients with EASI 75 at week 16; • Proportion of patients with IGA 0/1 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment; • EASI 75 during maintenance treatment; • Combined endpoint: EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment; • EQ-5D-5L at week 16; • Reduction in Worst Daily Pruritis NRS at week 16.	Primary outcomes: • Positive anti-tetanus response at week 16; • Positive anti-meningococcal response at week 16. Secondary outcomes of interest to MTA: • Proportion of patients with EASI 75 at week 16; • Adverse effects.	Primary outcomes: • Proportion of patients with EASI 75 at week 16; • Proportion of patients with IGA 0/1 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment • EASI 75 during maintenance treatment • Combined endpoint: EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment • EQ-5D-5L at week 16 • Reduction in Worst Daily	Primary outcome: • Proportion of patients with EASI 75 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment; • EASI 75 during maintenance treatment; • Combined endpoint: EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment ; • EQ-5D-5L at week 16 • Reduction in Worst Daily Pruritis NRS at week 16

				Pruritis NRS at week 16	
Subgroups	None	None planned	None	None planned	None planned
Criteria for determination of moderate to severe AD	EASI score at baseline of ≥12 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at screening and baseline of ≥20 and IGA score of 3 or 4

Abbreviations: AD, atopic dermatitis; BSA, body surface area; CsA, cyclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol 5 dimensions; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PUVA, psoralen and ultraviolet A radiation; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.2.3 Baseline characteristics

Table 96. Baseline characteristics of trial populations in studies evaluating tralokinumab

Characteristic	Phase IIb dose ranging study[a] Full trial population		ECZTRA 5 Full trial population	
	Tralokinumab Q2W (N=52)	Placebo (N=51)	Tralokinumab Q2W (N=107)	Placebo (N=108)
Median age, years (IQR)	Mean age: 35.7 (SD 14.6)	Mean age: 39.4 (SD 14.5)	Mean age: 34.0 (SD 11.2)	Mean age: 34.4 (SD 10.8)
Gender, Male, n (%)	33 (63.5)	22 (43.1)	54 (50.5)	35 (32.4)
Median duration of AD, years (IQR)	N/A	N/A	N/A	N/A
Race				
• White, n (%)	28 (53.8)	31 (60.8)	62 (57.9)	56 (51.9)
• Black or African American, n (%)	7 (13.5)	8 (15.7)	25 (23.4)	27 (25.0)
• Asian, n (%)	16 (30.8)	10 (19.6)	16 (15.0)	18 (16.7)

Median EASI score (IQR)	N/A	N/A	Mean EASI: 26.26 (SD 10.79)	Mean EASI: 26.75 (SD 11.23)
Baseline IGA score of 4	N/A	N/A	34 (31.8)	36 (33.3)
Median DLQI score (IQR)	N/A	N/A	N/A	N/A
Median SCORAD score (IQR)	N/A	N/A	N/A	N/A
Median weekly average worst peak pruritus NRS score (IQR)	N/A	N/A	N/A	N/A
Median % BSA affected (IQR)	N/A	N/A	N/A	N/A
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A	N/A	N/A
Prior treatment				
OCS, n (%)	N/A	N/A	N/A	N/A
Immunosuppressant	N/A	N/A	N/A	N/A
•CsA	N/A	N/A	N/A	N/A
•Methotrexate	N/A	N/A	N/A	N/A
•Azathioprine	N/A	N/A	N/A	N/A
•Mycophenolate	N/A	N/A	N/A	N/A
•Other immunosuppressant	N/A	N/A	N/A	N/A
TCS, n (%)	N/A	N/A	N/A	N/A
TCI, n (%)	N/A	N/A	N/A	N/A

[a] Baseline characteristics are not available in Wollenberg 2019. Baseline characteristics are reported on ClinicalTrails.gov. However, tralokinumab groups are not labelled by dose given and so it unclear which baseline characteristics apply to the group receiving the 300 mg dose. Based on reporting in Wollenberg 2019, the EAG has assumed that group 3 in the record available on ClinicalTrials.gov has received the 300 mg dose of tralokinumab.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	ECZTRA 1 Full trial population		ECZTRA 1 ECZTRA 7-like population		ECZTRA 2 Full trial population		ECZTRA 2 ECZTRA 7-like population	
	Tralokinumab Q2W (N=603)	Placebo (N=199)	Tralokinumab Q2W (N=224)	Placebo (N=62)	Tralokinumab Q2W (N=593)	Placebo (N=201)	Tralokinumab Q2W (N=193)	Placebo (N=58)
Median age, years (IQR)	37·0 (27·0–48·0)	37·0 (26·0–49·0)	[redacted]	[redacted]	34·0 (25·0–48·0)	30·0 (23·0–46·0)	[redacted]	[redacted]
Gender, Male, n (%)	351 (58.2)	123 (61.8)	[redacted]	[redacted]	359 (60.5)	114 (56.7%)	[redacted]	[redacted]
Median duration of AD, years (IQR)	27.0 (19.0–38.0)	28.0 (18.0–41.0)	[redacted]	[redacted]	25.5 (17.0–39.0)	25.0 (18.0–36.0)	[redacted]	[redacted]
Race								
• White, n (%)	426 (70.6)	138 (69.3)	[redacted]	[redacted]	374 (63.1)	123 (61.2)	[redacted]	[redacted]
• Black or African American, n (%)	41 (6.8)	18 (9.0)	[redacted]	[redacted]	43 (7.3)	17 (8.5)	[redacted]	[redacted]
• Asian, n (%)	120 (19.9)	40 (20.1)	[redacted]	[redacted]	154 (26.0)	52 (25.9)	[redacted]	[redacted]
Median EASI score (IQR)	28.2 (21.3–40.0)	30.3 (22.0–41.5)	[redacted]	[redacted]	28.2 (19.8–40.8)	29.6 (20.6–41.4)	[redacted]	[redacted]
Baseline IGA score of 4	305 (50.6)	102 (51.3)	[redacted]	[redacted]	286 (48.2)	101 (50.2)	NR	NR

Median DLQI score (IQR)	17.0 (12.0–22.0)	16.0 (13.0–22.0)	[redacted]	[redacted]	18.0 (13.0–23.0)	18.0 (12.5–24.0)	[redacted]	[redacted]
Median SCORAD score (IQR)	69.2 (61.5–79.1)	70.8 (63.8–81.0)	[redacted]	[redacted]	69.5 (60.5–79.1)	69.9 (61.9–79.1)	[redacted]	[redacted]
Median weekly average worst peak pruritus NRS score (IQR)	7.9 (6.7–8.9)	7.9 (6.9–8.7)	Median peak pruritus NRS score (IQR)		8.0 (7.0–9.0)	8.1 (7.1–9.0)	Median peak pruritus NRS score (IQR)	
			[redacted]	[redacted]			[redacted]	[redacted]
Median % BSA affected (IQR)	50.0 (33.0–70.0)	52.5 (31.0–77.0)	[redacted]	[redacted]	50.0 (31.0–74.0)	50.0 (31.0–74.0)	[redacted]	[redacted]
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]
Prior treatment								
OCS, n (%)	357 (59.2)	119 (59.8)	[redacted]	[redacted]	410 (69.1)	125 (62.2)	[redacted]	[redacted]
Immunosuppressant								
•CsA	227 (37.6)	65 (32.7)	[redacted]	[redacted]	204 (34.4)	65 (32.3)	[redacted]	[redacted]
•Methotrexate	77 (12.8)	26 (13.1)	[redacted]	[redacted]	127 (21.4)	38 (18.9)	[redacted]	[redacted]
•Azathioprine	39 (6.5)	7 (3.5)	[redacted]	[redacted]	72 (12.1)	25 (12.4)	[redacted]	[redacted]
•Mycophenolate	27 (4.5)	9 (4.5)	[redacted]	[redacted]	37 (6.2)	14 (7.0)	[redacted]	[redacted]

•Other immunosuppressant	29 (4.8)	11 (5.5)	[redacted]	[redacted]	31 (5.2)	10 (5.0)	[redacted]	[redacted]
TCS, n (%)	591 (98.0)	195 (98.0)	[redacted]	[redacted]	584 (98.5)	200 (99.5)	[redacted]	[redacted]
TCI, n (%)	298 (49.4)	103 (51.8)	[redacted]	[redacted]	271 (45.7)	98 (48.8)	[redacted]	[redacted]

[a] Baseline characteristics are not available in Wollenberg 2019. Baseline characteristics are reported on ClinicalTrails.gov. However, tralokinumab groups are not labelled by dose given and so it unclear which baseline characteristics apply to the group receiving the 300 mg dose. Based on reporting in Wollenberg 2019, the EAG has assumed that group 3 in the record available on ClinicalTrials.gov has received the 300 mg dose of tralokinumab.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	ECZTRA 3 Full trial population		ECZTRA 3 ECZTRA 7-like population		ECZTRA 7	
	Tralokinumab Q2W plus TCS (N=253)	Placebo plus TCS (N=127)	Tralokinumab Q2W plus TCS (N=119)	Placebo plus TCS (N=62)	Tralokinumab Q2W plus TCS (N=140)	Placebo plus TCS (N=137)
Median age, years (IQR)	37.0 (28.0–52.0)	34.0 (24.0–50.0)	[redacted]	[redacted]	[redacted]	[redacted]
Gender, Male, n (%)	125 (49.4)	84 (66.1)	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of AD, years (IQR)	27.0 (17.0–39.0)	26.0 (18.0–39.0)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
• White, n (%)	203 (80.2)	85 (66.9)	[redacted]	[redacted]	[redacted]	[redacted]

• Black or African American, n (%)	23 (9.1)	12 (9.4)	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	17 (6.7)	24 (18.9)	[redacted]	[redacted]	[redacted]	[redacted]
Median EASI score (IQR)	24.7 (18.4–35.9)[c]	26.5 (19.9–39.3)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4	116 (45.8)	60 (47.2)	[redacted]	[redacted]	[redacted]	[redacted]
Median DLQI score (IQR)	18.0 (12.0–23.0)[b]	18.0 (12.0–23.0)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Median SCORAD score (IQR)	66.2 (57.6–76.3)[c]	67.9 (59.4–79.0)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Median weekly average worst peak pruritus NRS score (IQR)	8.0 (6.6–8.7)[a]	8.0 (7.0–9.0)[c]	Median peak pruritus NRS score (IQR)		[redacted]	[redacted]
			[redacted]	[redacted]		
Median % BSA affected (IQR)	41.0 (30.0–63.0)	40.0 (26.0–74.0)	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment						
OCS, n (%)	148 (58.5)	86 (67.7)	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressant						
•CsA	75 (29.6)	43 (33.9)	[redacted]	[redacted]	[redacted]	[redacted]
•Methotrexate	29 (11.5)	30 (23.6)	[redacted]	[redacted]	[redacted]	[redacted]
•Azathioprine	13 (5.1)	12 (9.4)	[redacted]	[redacted]	[redacted]	[redacted]
•Mycophenolate	7 (2.8)	5 (3.9)	[redacted]	[redacted]	[redacted]	[redacted]

•Other immunosuppressant	6 (2.4)	0	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	251 (99.2)	122 (96.1)	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	127 (50.2)	69 (54.3)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Data missing for two patients.

[b] Data missing for three patients.

[c] Data missing for one patient.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.2.4 Data extracted on outcomes of interest

Table 97. Data on clinical effectiveness from studies evaluating tralokinumab and for populations of interest to the MTA

Outcome at 16 weeks	**ECZTRA 1** **ECZTRA 7-like population** Second-line adults – monotherapy				**ECZTRA 2** **ECZTRA 7-like population** Second-line adults – monotherapy			
	Censoring for receipt of rescue medication		**No censoring for receipt of rescue medication**		**Censoring for receipt of rescue medication**		**No censoring for receipt of rescue medication**	
	Tralokinumab Q2W (N=224)	Placebo (N=62)	Tralokinumab Q2W (N=224)	Placebo (N=62)	Tralokinumab Q2W (N=193)	Placebo (N=58)	Tralokinumab Q2W (N=193)	Placebo (N=58)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

those who discontinue treatment after a response at a set time point as defined in the study)								
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• TCS (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Other topical (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Systemic steroid (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Immunosuppressant (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol-5 dimensions; IGA, Investigator Global Assessment; NA, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroid.

Outcome	**ECZTRA 3** **ECZTRA 7-like population** Second-line adults – combination therapy				**ECZTRA 7** Second-line adults – combination therapy			
	Censoring for receipt of rescue medication		**No censoring for receipt of rescue medication**		**Censoring for receipt of rescue medication**		**No censoring for receipt of rescue medication**	
	Tralokinumab Q2W plus TCS (N=119)	Placebo plus TCS (N=62)	Tralokinumab Q2W plus TCS (N=119)	Placebo plus TCS (N=62)	Tralokinumab Q2W plus TCS (N=138)	Placebo plus TCS (N=137)	Tralokinumab Q2W plus TCS (N=138)	Placebo plus TCS (N=137)

Proportion of people achieving EASI 50 + ΔDLQI ≥4. n (%)								
Proportion of people achieving EASI 75, n (%)								
Mean change in EQ-5D score from baseline (SD)								
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study)								
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)								
• TCS (%)								
• Other topical (%)								
• Systemic steroid (%)								
• Immunosuppressant (%)								
• Other systemic								
Mean number of days free from TCS during treatment (SD)								

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol-5 dimensions; IGA, Investigator Global Assessment; NA, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroid.

Table 98. Data on adverse effects and adverse effects of special interest informing the model for tralokinumab

Outcome	ECZTRA 1		ECZTRA 2		ECZTRA 1 & 2 pooled -ECZTRA 7 like subgroup		ECZTRA 3	
	Placebo (N=196)	Tralokinumab 300 mg Q2W (N=602)	Placebo (N=202)	Tralokinumab 300 mg Q2W (N=592)	Placebo	Tralokinumab 300 mg Q2W	Tralokinumab 300 mg Q2W plus TCS (N=252)	Placebo Q2W plus TCS (N=126)
SAEs n (%)	8	23	5	10	NR	NR	2	4
Injection site reaction								
Allergic conjunctivitis								
Conjunctivitis								
URTI								
Acne								
Oral herpes								

Abbreviations: AE, adverse event; NR, not reported; Q2W, every 2 weeks; SAE, serious adverse event; TCS, topical corticosteroid; URTI, upper respiratory tract infection.

10.3.1.3 Upadacitinib

10.3.1.3.1 Interventions assessed in the included studies

Table 99. Summary of interventions assessed in studies evaluating upadacitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		

Phase IIb	Upadacitinb 30 mg QD	42	Placebo	41	16 weeks	16-week double-blind, randomised treatment period followed by 72-week double-blind, randomised withdrawal period
	Upadacitinb 15 mg QD	42				
	Upadacitinb 7.5 mg QD	42				
HEADS UP	Upadacitinb 30 mg QD	325	Dupilumab 300 mg Q2W	325	24 weeks	Treatment period followed by 12-week follow-up
MEASURE UP1	Upadacitinb 30 mg QD	285	Placebo	281	16 weeks	Treatment phase followed by blinded extension period for up to 120 weeks of treatment
	Upadacitinb 15 mg QD	281				
MEASURE UP2	Upadacitinb 30 mg QD	282	Placebo	278	16 weeks	Treatment phase followed by blinded extension period for up to 120 weeks of treatment
	Upadacitinb 15 mg QD	276				
AD UP	Upadacitinb 30 mg QD plus TCS	297	Placebo plus TCS	304	16 weeks	Initial concomitant TCS was of medium potency (clinician choice), moving to low potency for 7 days once lesions became “clear” or “almost clear” or after 3 weeks, whichever occurred sooner. 16-week double-blind, randomised treatment period followed by 120-week blinded extension period
	Upadacitinb 15 mg QD plus TCS	300				
RISING UP	Upadacitinb 30 mg QD plus TCS	?	Placebo plus TCS	?	16 weeks	Study carried out in Japan and enrolled 272 people. Additional information not available.
	Upadacitinb 15 mg QD plus TCS	?				

Abbreviations: QD, once daily; Q2W, every 2 weeks; TCS, topical corticosteroid.

10.3.1.3.2 Study characteristics

Table 100. Characteristics of studies evaluating upadacitinib

Characteristic	Phase IIb	HEADS UP	MEASURE UP1	MEASURE UP2	AD UP	Rising UP
Study references	Guttman-Yassky 2020[93]	CS, clinicaltrials.gov (NCT03738397)[41]	Guttman-Yassky 2021,[40] CS, clinicaltrials.gov (NCT03569293)	Guttman-Yassky 2021,[40] CS, clinicaltrials.gov (NCT03607422)	Reich 2021,[42] CS, clinicaltrials.gov (NCT03568318)	CS, clinicaltrials.gov (NCT03661138)[94]
Country(ies) where the clinical trial was conducted	8 countries – Australia, Canada, Finland, Germany, Japan, the Netherlands, Spain, USA	23 countries – UK, Croatia, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Spain, Sweden, Ukraine, Canada, USA, Australia, New Zealand, Malaysia, Singapore, Taiwan	24 countries – UK, Bosnia & Herzegovina, Bulgaria, Croatia, Denmark, Finland, France, Germany, Italy, Romania, Turkey, Switzerland, Canada, USA (including Puerto Rico), Argentina, Columbia, Australia, New Zealand, Ukraine, Russia, Estonia, China, Japan, Malaysia	23 countries – UK, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Spain, Canada, USA, Australia, New Zealand, Singapore, South Korea, Taiwan	22 countries – UK, Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Slovakia, Spain, Sweden, Canada, USA (including Puerto Rico), Australia, New Zealand, China, Japan	Japan
Multicentre trial (number, location)	Not reported	142 locations UK (6 sites: Brighton, Cardiff, Glasgow, 2 x London, Fife)	151 locations UK (4 sites: 3 x London, Manchester,)	154 locations UK (4 sites: London, Newcastle, Plymouth, Southampton)	171 locations UK (5 sites: Dundee, Leeds, 2 x London, Oxford)	43 sites in Japan
Trial sponsors	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie

Date the clinical trial was conducted	Unknown	February 2019 to December 2020	August 2018 to October 2025	July 2018 to December 2025	August 2018 to November 2025	October 2018 to August 2022
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb, double-blind, parallel-group, dose-ranging RCT	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase 3 parallel assignment RCT, double-blind
Trial duration (treatment duration and follow-up)	16-week double-blind, randomised treatment period followed by 72-week double-blind, randomised withdrawal period	24-week double-blind, double-dummy treatment period followed by 12-week follow-up	16-week double-blind, randomised treatment period followed by 120-week blinded extension period			16-week double blind period followed by a long-term extension
Inclusion criteria	Adults aged 18-75 years, Moderate to severe AD, inadequate response to TCS or TCI within a year of screening, or patients for whom topical treatment were medically inadvisable	• Adults aged 18-75 years • Moderate to severe AD who are candidates for systemic therapy or have recently required systemic therapy	• Adolescents and adults aged 12–75 years • Moderate to severe AD who are candidates for systemic therapy or have recently required systemic therapy			• Adolescents and adults aged 12-75 years • Moderate to severe AD who are candidates for systemic therapy or have recently required systemic therapy and are able to tolerate TCS
Exclusion criteria	Not reported	• Prior exposure to any JAK inhibitor • Prior exposure to dupilumab. • Unable or unwilling to discontinue	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to the study • Requirement of prohibited medications during the study			• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to the study.

		current AD treatments prior to the study. • Requirement of prohibited medications during the study. • Other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions. • Female participant who is pregnant, breastfeeding, or considering pregnancy during the study	• Other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions • Female subject who is pregnant, breastfeeding, or considering pregnancy during the study			• Requirement of prohibited medications during the study. • Female participant who is pregnant, breastfeeding, or considering pregnancy during the study.
Concomitant medications	Emollient BD	Emollient BD	Emollient BD	Emollient BD	• Emollient BD • TCS	TCS
Rescue therapy	Not reported	Rescue therapy could be provided from week 4 at the discretion of the investigator if participants had EASI response of <50% at any two consecutive study visits. The first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. Study drug was discontinued if a systemic treatment or phototherapy was required.				Not reported

Outcomes	Primary endpoint: • % improvement from baseline at week 16 in EASI. Secondary outcomes: • EASI 50/75/90 at weeks 8 and 16; • IGA 0/1 (%) at week 16; • % improvement from baseline at week 8 in EASI; • % improvement from baseline in pruritus NRS by week; • % of patients achieving pruritus NRS improvement from baseline of ≥4 at each visit (among patients with baseline NRS >4 points); • % improvement from baseline in SCORAD at weeks 8 and 16; • SCORAD 50/75/90) at	Primary endpoint: • EASI 75 (%) at week 16 Secondary endpoints: • % change from baseline in WP-NRS at week 16; • EASI 100 (%) at week 16; • EASI 90 (%) at week 16; • % change from baseline in WP-NRS at week 4; • EASI 75 (%) at week 2; • % change from baseline in WP-NRS at week 1. Additional outcomes used in model: • % of participants achieving EASI 50 at week 16; • % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from	Primary endpoints: • IGA 0/1 (%) with at least two grades of reduction from baseline at week 16; • EASI 75 (%) at week 16. Secondary endpoints: • % of participants with WP-NRS ≥4 at Baseline with a change of ≥4 in WP-NRS at week 16; • EASI 100 (%) at week 16; • EASI 90 (%) at week 16; • EASI 75 (%) at week 2; • % of participants with WP-NRS ≥4 at Baseline and Randomized to Dose A with a change of ≥4 in WP-NRS at Day 2; • % of participants with WP-NRS ≥4 at Baseline and Randomized to Dose B with a change of ≥4 in WP-NRS at Day 3; • % experiencing a flare at week 16; • % with a change of ≥12 in ADerm-SS Sleep Domain Score at week 16; • % with a change of ≥4 in ADerm-SS Skin Pain Score at week 16; • % with a change of ≥28 in ADerm-SS Total Symptom Score at week 16; • % with a change of ≥11 in ADerm-IS Emotional State Domain Score at week 16; • % with a change of ≥14 in ADerm-IS Daily Activities Score at week 16; Additional outcomes used in model:	Primary endpoints: • IGA 0/1 (%) with at least two grades of reduction from baseline at week 16; • EASI 75 (%) at week 16 Secondary endpoints: • % of participants with WP-NRS ≥4 at Baseline with a change of ≥4 in WP-NRS at week 16; • EASI 100 (%) at week 16 for participants in Arm A and Arm C ; • EASI 90 (%) at week 16; • EASI 75 (%) at week 2. Additional outcomes used in model: • % of participants achieving EASI 50 at week 16;	Primary endpoint: • number of patients experiencing AE

	weeks 8 and 16; and change from baseline in BSA at week 16.	baseline at week 16 for participant with DLQI ≥4 at baseline.	• % of participants achieving EASI 50 at week 16; • % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from baseline at week 16 for participant with DLQI ≥4 at baseline.	• % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from baseline at week 16 for participant with DLQI ≥4 at baseline.	
Subgroups	Baseline IGA of 3 or 4	• Age: <40 years, ≥40 to <65 years, ≥65 years • Gender: male, female • BMI: normal (<25), overweight (≥25 to <30), obese (≥30) • Race: White, Asian, Black, other • Weight: <median, ≥median • Geographic region: US/Puerto Rico/Canada and other • Baseline IGA-AD: <4, ≥4	• Age: adolescents vs adults <18 years, ≥18 years • Age: <18 years, ≥18 to <40 years, ≥40 to <65 years, ≥65 years • Gender: male, female • BMI: normal (<25), overweight (≥25 to <30), obese (≥30) • Race: White, Asian, Black, other • Weight: <median, ≥median • Geographic region: US/Puerto Rico/Canada and other • Baseline IGA-AD: <4, ≥4 • Baseline EASI: <median, ≥median • High-sensitivity C-reactive protein: <median, ≥median • Previous systemic therapy: with, without • Participants who reported an intolerance to at least one prior TCS or TCI therapy • Participants who reported an inadequate response to at least one prior topical treatment		Not reported

		• Baseline EASI: <median, ≥median • High-sensitivity C-reactive protein: <median, ≥median • Previous systemic therapy: with, without		
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10%	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10% • WP-NRS ≥4		Unclear

Abbreviations AD, atopic dermatitis; BSA, body surface area; CsA, cyclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol 5 dimensions; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PUVA, psoralen and ultraviolet A radiation; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; WP-NRS, Worst Pruritus-Numerical Rating Scale.

10.3.1.3.3 Baseline characteristics

Table 101. Baseline characteristics of trial populations in studies evaluating upadacitinib

Characteristic	Phase IIb Full trial population				HEADS UP Full trial population		HEADS UP First-line population		HEADS UP Second-line population	
	Upadacitinib 30 mg QD (N=42)	Upadacitinib 15 mg QD (N=42)	Upadacitinib 7.5 mg QD (N=42)	Placebo (N=41)	Upadacitinib 30 mg QD (N=348)	Dupilumab 300 mg Q2W (N=344)	Upadacitinib 30 mg QD (N=298)	Dupilumab 300 mg Q2W (N=288)	Upadacitinib 30 mg QD (N=50)	Dupilumab 300 mg Q2W (N=56)
Mean age (SD), years	39.9 (15.3)	38.5 (15.2)	41.5 (15.4)	39.9 (17.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gender, female, n (%)	20 (48)	12 (29)	14 (33)	17 (41)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD since diagnosis (SD), years	24.2 (13.6)	22.6 (15.8)	30.4 (18.1)	26.8 (18.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race										
• White, n (%)	23 (55)	21 (50)	24 (57)	28 (68)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	6 (14)	10 (24)	7 (17)	6 (15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	13 (31)	9 (21)	9 (21)	7 (17)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	28.2 (11.6)	31.4 (12.3)	31.4 (15.8)	32.6 (14.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	11 (26)	23 (55)	13 (31)	23 (56)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean or median DLQI score	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Mean or median SCORAD score	NR	NR	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Mean pruritus NRS score (SD)	6.3 (2.1)	6.4 (1.7)	6.8 (1.8)	6.5 (1.9)	Worst Pruritus Numerical Rating Scale		[redacted]	[redacted]	[redacted]	[redacted]
					[redacted]	[redacted]				
Mean % BSA affected (SD)	42.1 (20.4)	50.6 (21.5)	46.9 (24.9)	45.7 (22.8)	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment										
OCS	NR	NR	NR	NR	Received previous systemic therapy, n (%)		[redacted]	[redacted]	[redacted]	[redacted]

Immunosuppressant	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS	NR	NR	NR	NR			[redacted]	[redacted]	[redacted]	[redacted]
TCI	NR	NR	NR	NR			[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	MEASURE UP1 Full trial population			MEASURE UP1 Adults first-line			MEASURE UP1 Adults second-line			MEASURE UP1 Adolescents		
	Upa 30 mg QD (N=285)	Upa 15 mg QD (N=281)	Placebo (N=281)	Up 30 mg QD (N=211)	Upa 15 mg QD (N=200)	Placebo (N=201)	Upa 30 mg QD (N=32)	Upa 15 mg QD (N=39)	Placebo (N=40)	Upa 30 mg QD (N=42)	Upa 15 mg QD (N=42)	Placebo (N=40)
Mean age (SD), years	33.6 (15.8)	34.1 (15.7)	34.4 (15.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, male, n (%)	155 (54.4)	157 (55.9)	144 (51.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD since diagnosis (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race												
• White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

• Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	28.98 (11.1)	30.57 (12.8)	28.84 (12.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	131 (46.0)	127 (45.2)	125 (44.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	16.4 (7.0)	16.2 (7.0)	17.0 (6.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Weekly worst pruritus NRS score (SD)	7.28 (1.5)	7.23 (1.6)	7.27 (1.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment												
With prior systemic therapy, n (%)	[redacted]	[redacted]	[redacted]									
OCS	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressant	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	MEASURE UP2 Full trial population			MEASURE UP2 Adults first-line			MEASURE UP2 Adults second-line			MEASURE UP2 Adolescents		
	Upa 30 mg QD (N=282)	Upa 15 mg QD (N=276)	Placebo (N=278)	Up 30 mg QD (N=178)	Upa 15 mg QD (N=164)	Placebo (N=169)	Upa 30 mg QD (N=56)	Upa 15 mg QD (N=73)	Placebo (N=60)	Upa 30 mg QD (N=35)	Upa 15 mg QD (N=33)	Placebo (N=36)
Mean age (SD), years	34.1 (16.0)	33.3 (15.7)	33.4 (14.8)									
Gender, male, n (%)	162 (57.4)	155 (56.2)	154 (55.4)									
Mean duration of AD since diagnosis (SD), years												
Race												
• White, n (%)												
• Black or African American, n (%)												
• Asian, n (%)												
Mean EASI score (SD)	29.65 (12.2)	28.60 (11.7)	29.08 (12.1)									

Baseline IGA score of 4, n (%)	156 (55.3)	150 (54.3)	153 (55.0)									
Mean DLQI score (SD)	16.7 (6.93)	16.9 (7.04)	17.1 (7.17)									
Mean SCORAD score (SD)												
Mean Weekly worst pruritus NRS score (SD)	7.26 (1.6)	7.15 (1.6)	7.34 (1.6)									
Mean % BSA affected (SD)	47.02 (23.2)	45.12 (22.4)	47.61 (22.7)									
Mean baseline EQ-5D Score (SD)	NR	NR	NR									
Prior treatment												
With prior systemic therapy, n (%)												
OCS	NR	NR	NR									
Immunosuppressant	NR	NR	NR									
TCS	NR	NR	NR									
TCI	NR	NR	NR									

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	AD UP Full trial population			AD UP Adults first-line			AD UP Adults second-line			AD UP Adolescents		
	Upa 30 mg QD plus TCS (N=297)	Upa 15 mg QD plus TCS (N=300)	Placebo plus TCS (N=304)	Up 30 mg QD plus TCS (N=203)	Upa 15 mg QD plus TCS (N=203)	Placebo plus TCS (N=209)	Upa 30 mg QD plus TCS (N=57)	Upa 15 mg QD plus TCS (N=58)	Placebo plus TCS (N=55)	Upa 30 mg QD plus TCS (N=37)	Upa 15 mg QD plus TCS (N=39)	Placebo plus TCS (N=40)
Mean age (SD), years	35.5 (15.8)	32.5 (14.0)	34.3 (15.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, male, n (%)	190 (64.0)	179 (59.7)	178 (58.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD since diagnosis (SD), years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race												
• White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	29.72 (11.8)	29.16 (11.8)	30.26 (13.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	157 (52.9)	157 (52.3)	163 (53.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean DLQI score (SD)	17.1 (7.0)	16.4 (7.2)	16.3 (7.0									
Mean SCORAD score (SD)												
Mean Weekly worst pruritus NRS score (SD)	7.36 (1.7)	7.06 (1.8)	7.14 (1.6)									
Mean % BSA affected (SD)	48.53 (23.1)	46.68 (21.7)	48.57 (23.1)									
Mean baseline EQ-5D Score (SD)	NR	NR	NR									
Prior treatment												
With prior systemic therapy, n (%)				NR	NR	NR	NR	NR	NR	NR	NR	NR
OCS	NR	NR	NR									
Immunosuppressant	NR	NR	NR									
TCS	NR	NR	NR									
TCI	NR	NR	NR									

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.3.4 Data extracted on outcomes of interest

Table 102. Data on clinical effectiveness from studies evaluating upadacitinib and for populations of interest to the MTA

Outcome at 16 weeks	HEADS UP Second-line adults – monotherapy			
	Censoring for receipt of rescue medication		No censoring for receipt of rescue medication	
	Upa 30 mg QD (N=50)	DUPI 300 mg Q2W (N=56)	Upa 30 mg QD (N=50)	DUPI 300 mg Q2W (N=56)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	NR	NR	NR	NR
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline	NR	NR	NR	NR
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study)	NR	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	NR	NR	NR	NR
Number of days free from TCS during treatment	NR	NR	NR	NR
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	NR	NR	NR	NR
Serious adverse effects of treatment	NR	NR	NR	NR

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome at 16 weeks	MEASURE UP1											
	Adults second-line – monotherapy						Adolescents					
	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication			Censoring for receipt of rescue medication			No censoring for receipt of rescue medication		
	Upa 30 mg QD (N=31)	Upa 15 mg QD (N=39)	Placebo (N=40)	Upa 30 mg QD (N=32)	Upa 15 mg QD (N=39)	Placebo (N=40)	Upa 30 mg QD (N=42)	Upa 15 mg QD (N=42)	Placebo (N=40)	Upa 30 mg QD (N=42)	Upa 15 mg QD (N=42)	Placebo (N=40)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted] (N=31)	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA

• TCS High Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCS Medium Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCS Low Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCI	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Other Topical Therapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Biologic systemic	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Non-biologic Systemics	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Other Systemic therapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Phototherapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
Number of days free from TCS during treatment	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome at 16 weeks	MEASURE UP2											
	Adults second-line – monotherapy						Adolescents					
	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication			Censoring for receipt of rescue medication			No censoring for receipt of rescue medication		
	Upa 30 mg QD (N=56)	Upa 15 mg QD (N=73)	Placebo (N=60)	Upa 30 mg QD (N=58)	Upa 15 mg QD (N=75)	Placebo (N=64)	Upa 30 mg QD (N=35)	Upa 15 mg QD (N=33)	Placebo (N=36)	Upa 30 mg QD (N=35)	Upa 15 mg QD (N=33)	Placebo (N=36)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	NR	NR
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCS High Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCS Medium Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA

• TCS Low Potency	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• TCI	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Other Topical Therapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Biologic systemic	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Non-biologic Systemics	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Other Systemic therapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
• Phototherapy	[redacted]	[redacted]	[redacted]	NA	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA	NA
Number of days free from TCS during treatment	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Outcome at 16 weeks	AD UP	
	First-line adults – combination therapy	Second-line adults – combination therapy

	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication			Censoring for receipt of rescue medica			No censoring for receipt of rescue medication		
	Upa 30 mg QD plus TCS (N=203)	Upa 15 mg QD plus TCS (N=203)	Placebo plus TCS (N=209)	Upa 30 mg QD plus TCS (N=203)	Upa 15 mg QD plus TCS (N=203)	Placebo plus TCS (N=209)	Upa 30 mg QD plus TCS (N=57)	Upa 15 mg QD plus TCS (N=58)	Placebo plus TCS (N=55)	Upa 30 mg QD plus TCS (N=57)	Upa 15 mg QD plus TCS (N=58)	Placebo plus TCS (N=55)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• TCS High Potency	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			

• TCS Medium Potency	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• TCS Low Potency	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• TCI	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• Other Topical Therapy	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• Biologic systemic	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• Non-biologic Systemics	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• Other Systemic therapy	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
• Phototherapy	[redacted]	[redacted]	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]			
Number of days free from TCS during treatment	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Proportion of people maintaining for a set period of time the level of response (as	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

defined in the study) initially achieved												

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid.

Table 103. Data on adverse effects and adverse effects of special interest informing the model for upadacitinib

Adolescents	MEASURE UP1			MEASURE UP2			AD UP		
Outcome	Placebo (N=40)	Upadacitinib 15 mg (N=42)	Upadacitinib 30 mg (N=42)	Placebo (N=36)	Upadacitinib 15 mg (N=33)	Upadacitinib 30 mg (N=35)	Placebo plus TCS (N=39)	Upadacitinib 15 mg plus TCS (N=39)	Upadacitinib 30 mg plusTCS (N=37)
SAEs n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; NR, not reported; SAE, serious adverse event; TCS, topical corticosteroid; URTI, upper respiratory tract infection.

Adults	MEASURE UP1 0verall population[a]			MEASURE UP2 0verall population[a]			AD UP 0verall population[a]			HEADS UP		Guttman-Yassky 2020			
	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	Placebo +TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg +TCS	Dupilumab 300 mg	Upadacitinib 30 mg	Placebo	Upadacitinib 7.5mg QD	Upadacitinib 15mg QD	Upadacitinib 30mg QD
N	281	281	285	278	276	282	303	300	297	344	348	40	42	42	42
SAEs n (%)															
Injection site reaction															
Allergic conjunctivitis															
Conjunctivitis															
URTI															
Acne															
Oral herpes															

[a] AEs for Measure UP1, Measure UP2 and AD UP are for the overall population with data for adults presented where available.

Abbreviations: AE, adverse event; NR, not reported; QD, once daily; SAE, serious adverse event; TCS, topical corticosteroid; URTI, upper respiratory tract infection.

10.3.1.4 Baricitinib

10.3.1.4.1 Interventions assessed in the included studies

Table 104. Summary of interventions assessed in studies evaluating baricitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
BREEZE-AD1	Baricitinib 4 mg QD	125	Placebo	249	16 weeks	–
	Baricitinib 2 mg QD	123				
	Baricitinib 1 mg QD	127				
BREEZE-AD2	Baricitinib 4 mg QD	123	Placebo	244	16 weeks	–
	Baricitinib 2 mg QD	123				
	Baricitinib 1 mg QD	125				
Phase II	Baricitinib 4 mg QD plus TCS	38	Placebo plus TCS	49	16 weeks	Concomitant TCS was triamcinolone 0.1%.
	Baricitinib 2 mg QD plus TCS	37				
BREEZE-AD4	Baricitinib 4 mg QD plus TCS	92	Placebo plus TCS	93	52 weeks	Background TCS therapy with moderate-potency and/or low-potency TCS.
	Baricitinib 2 mg QD plus TCS	185				
	Baricitinib 1 mg QD plus TCS	93				
BREEZE-AD7	Baricitinib 4 mg QD plus TCS	111	Placebo plus TCS	109	16 weeks	Patients were allowed to use concomitant TCS that were of moderate or low potency.
	Baricitinib 2 mg QD plus TCS	109				

Abbreviations: QD, once daily; TCS, topical corticosteroid.

10.3.1.4.2 Study characteristics

Table 105. Characteristics of studies evaluating baricitinib

Characteristic	BREEZE-AD1 (JAHL)	BREEZE-AD2 (JAHM)	Phase II	BREEZE-AD4 (JAIN)	BREEZE-AD7 (JAIY)
Study references	Committee papers for NICE recommendation for Baricitinib in AD	Committee papers for NICE recommendation for Baricitinib in AD	Guttman-Yassky 2019	Committee papers for NICE recommendation for Baricitinib in AD	Committee papers for NICE recommendation for Baricitinib in AD
Country(ies) where the clinical trial was conducted	10 countries – Czechia, Denmark, France, Germany, India, Italy, Japan, Mexico, Russian Federation, Taiwan	10 countries – Argentina, Australia, Austria, Hungary, Israel, Japan, Republic of Korea, Poland, Spain, Switzerland	2 countries – Japan, USA	14 countries –Austria, Belgium, Brazil, Finland, France, Germany, Italy, Japan, The Netherlands, Poland, Russian Federation, Spain, Switzerland, UK	10 countries –Argentina, Australia, Austria, Germany, Italy, Japan, Republic of Korea, Poland, Spain, Taiwan
Multicentre trial (number, location)	93 locations (9 sites in).	80 locations	13 locations	103 locations (6 sites in UK)	68 locations
Trial sponsors	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company
Date the clinical trial was conducted	November 2017 to January 2019	November 2017 to December 2018	February 2016 to March 2017	May 2018 to November 2019	November 2018 to August 2019
Trial design (e.g. parallel, crossover, or cluster trial)	BREEZE-AD1 (JAHL) and BREEZE-AD2 (JAHM) were concurrent multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase III studies.		Multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase IIb study.	An international Phase III, multicentre, long-term extension study.	Multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase III study.
Trial duration (treatment duration and follow-up)	4-week wash-out for systemic treatments and 2 weeks for topical treatments 16-week intervention 4-week post-treatment follow-up		16-week intervention and follow-up	5-week wash-out 52-week treatment period (followed by a 52-week double-blind long-term extension which included a down-titration sub-study for responders and	5-week wash-out 16-week intervention 4-week post-treatment follow-up

			re-randomisation for non-responders) 4-week post-treatment follow-up	
Inclusion criteria	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition with a history of clinically significant adverse reactions to topical therapy or a history of inadequate response to topical or systemic therapies.	• Adults with moderate-to-severe AD. • Diagnosed with AD at least 2 years prior • Have a history of inadequate clinical response to other eczema treatments	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition, a history of inadequate response to topical therapy and a history of intolerance to, contraindication to, or inadequate response to ciclosporin.	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition and a history of inadequate response to topical or systemic therapy.
Exclusion criteria	• Currently experiencing, or have a history of, other concomitant skin conditions, including psoriasis or lupus erythematosus, which would interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation and/or intravenous treatment for skin infections. • Eczema herpeticum within 12 months prior to screening or more than twice in the past. • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active frequent monitoring	• Females who are pregnant or nursing • Participants who do not agree to use adequate contraception • Are currently experiencing or have a history of: • Skin conditions such as psoriasis or lupus erythematosus	• Currently experiencing, or have a history of, other concomitant skin conditions which would interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation and/or intravenous	• Currently experiencing, or have a history of, other concomitant skin conditions, including psoriasis or lupus erythematosus, which would interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation

		• Skin disease that requires frequent hospitalizations or intravenous treatment • Serious illness that could interfere with study participation, • Active or latent tuberculosis • Have received certain types of vaccination	treatment for skin infections. • Have an important side effect to TCS which would prevent further use. • Eczema herpeticum within 12 months prior to screening or more than twice in the past • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active frequent monitoring.	• and/or intravenous treatment for skin infections. • Eczema herpeticum within 12 months prior to screening or more than twice in the past • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active frequent monitoring • Have an important side effect to TCS (e.g. intolerance to treatment or hypersensitivity reactions) which would prevent further use
Concomitant medications	Systemic and topical treatments were allowed as rescue therapy at the investigator's discretion if patients experienced worsening or unacceptable AD symptoms.	• Triamcinolone cream was provided to patients to use throughout the study according to the labelling or as recommended by the investigator	All concomitant therapies for AD were prohibited throughout the trial except for: • Daily use of emollients • Background TCS therapy with moderate-potency	• Background TCS therapy with moderate-potency and/or low-potency TCS. • High- or ultra-high potency TCS permitted only as rescue therapy.

			and/or low-potency TCS • TCIs, or topical PDE-4 inhibitor in place of TCS on areas where application of TCS is considered inappropriate • Intranasal or inhaled steroids • Topical anaesthetics and topical and systemic anti-infective medications • Non-live seasonal vaccines and/or emergency vaccinations • Antihistamine ophthalmic preparations	• TCIs or topical PDE-4 inhibitor were permitted in place of TCS on areas where application of TCS was considered inappropriate by the investigator • Ophthalmic drugs containing antihistamines, corticosteroids or other immunosuppressants
Rescue therapy	Emollient	As above	Emollient	Emollient
Outcomes	Primary endpoint: • % of patients achieving IGA ≤1 with a ≥2-point improvement at week 16 Secondary endpoints: • Signs and symptoms of AD at Week 16; • EASI scores; • SCORAD scores; • Atopic Dermatitis Sleep Scale Item 2 score;	Primary endpoint: • Percentage of participants with a ≥50% reduction in the EASI 50 Secondary endpoints: • Change in EASI • Change in SCORAD	Primary endpoints • Proportion of patients in the ITT population achieving EASI 75 at Week 16 of treatment. Secondary endpoints:	Primary endpoint: • % of patients achieving IGA ≤1 with a ≥2-point improvement at week 16. Secondary endpoints:

	• Itch NRS; • Skin Pain NRS; • DLQI; • EQ-5D-5L; • Adverse events, serious adverse events and treatment-emergent adverse events by Week 16	• Change in IGA • Change in DLQI • Change in itch NRS • Adverse events	Improvement in signs and symptoms at Week 16: • EASI75; • EASI90; • Percent change in EASI score; • SCORAD75. Improvement in signs and symptoms at Week 24: • IGA of 0 or 1 with a ≥2-point; improvement • EASI75. Patient-reported outcome measures at Week 16: • 4-point improvement in Itch NRS at Week 1, 2, 4 and 16 of treatment; • Mean change in Item 2 of ADSS score at Week 1 or 16 of treatment; • Mean change from baseline in Skin Pain NRS at Week 16 of treatment. HRQoL outcomes at Week 16:	• Patients achieving EASI75 and EASI90 at week 16; • Itch NRS; • ADSS score; • Skin pain NRS. Additional outcomes listed in supplement 2 of study paper and on clinicaltrials.gov

			• DLQI; • EQ-5D-5L. Other outcomes listed on clinicaltrials.gov	
Subgroups	• Gender • Age group (<65, ≥65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Baseline weight (<60, ≥60 to <100, ≥100 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m2) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Baseline renal function status: impaired (eGFR <60 mL/min/1.73m2) or not impaired (eGFR ≥60 mL/min/1.73m2) • Region (Europe, Japan, rest of world) • Specific regions (Europe, other) • Specific country (Japan, other) • Prior systemic therapy use (Yes/No) • Baseline disease severity (IGA 3 or 4)	None reported	• Gender • Age group (<65, ≥65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Baseline weight (<60, ≥60 to <100, ≥100 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m2) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Ethnicity (Hispanic, non-Hispanic) • Baseline renal function status: impaired (eGFR <60 mL/min/1.73m2) or not impaired (eGFR ≥60 mL/min/1.73m2)	As for BREEZE AD1 and BREEZE AD2

			• Region (Europe, Japan, rest of world) • Specific regions (Europe, other) • Specific country (Japan, other) • Prior TCI use • Prior systemic therapy use • Baseline disease severity (IGA 3 or 4)	
Criteria for determination of moderate to severe AD	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%	• EASI score ≥12 • BSA involvement ≥10%	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%

Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; eGFR, Estimated Glomerular Filtration Rate; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis; TCI, Topical calcineurin inhibitors.

10.3.1.4.3 Baseline characteristics

Table 106. Baseline characteristics of trial populations in studies evaluating baricitinib

Characteristic	BREEZE-AD1 (JAHL) Full trial population[b]				BREEZE-AD2 (JAHM) Full trial population[b]			
	Baricitinib 4 mg QD (N=125)	Baricitinib 2 mg QD (N=123)	Baricitinib 1 mg QD (N=127)	Placebo (N=249)	Baricitinib 4 mg QD (N=123)	Baricitinib 2 mg QD (N=123)	Baricitinib 1 mg QD (N=125)	Placebo (N=244)
Mean, years (SD)	37 (12.9)	35 (13.7)	36 (12.4)	35 (12.6)	34 (14.1)	36 (13.2)	33 (10.0)	35 (13.0)

Gender, n (%)	Female: 42 (33.6)	Female: 41 (33.3)	Female: 49 (38.6)	Female: 101 (40.6)	Female: 41 (33.3)	Female: 58 (47.2)	Female: 45 (36.0)	Female: 90 (36.9)
Duration of AD	25 (14.9)	25 (14.6)	27 (14.9)	26 (15.5)	23 (15)	24 (14)	24 (13)	25 (14)
Race								
• White, n (%)	70 (56.5)	75 (61.0)	74 (58.3)	147 (59.5)	82 (66.7)	85 (69.1)	85 (68.0)	169 (69.3)
• Asian, n (%)	41 (33.1)	35 (28.5)	40 (31.5)	73 (29.6)	38 (30.9)	37 (30.1)	36 (28.8)	72 (29.5)
• Other, n (%)	14 (11.2)	13 (10.6)	13 (10.2)	27 (10.9)	2 (2.4)	1 (0.8)	4 (3.2)	3 (1.2)
Mean EASI score (SD)	32 (12.7)	31 (11.7)	29 (11.8)	32 (13.0)	33 (12.7)	35 (16.0)	33 (12.7)	33 (12.8)
IGA of 4 at baseline, n (%)	51 (40.8)	52 (42.3)	53 (41.7)	105 (42.2)	63 (51.2)	62 (50.4)	63 (50.8)	121 (49.6)
Mean DLQI score (SD)	14 (7.1)	13 (7.7)	13 (6.9)	14 (7.4)	14 (8.4)	14 (7.7)	15 (8.1)	15 (8.1)
Mean SCORAD score (SD)	68 (13.0)	68 (13.0)	66 (14.3)	68 (14.0)	68 (13.6)	69 (13.3)	67 (12.9)	68 (12.7)
Mean peak pruritus NRS score (SD)	NR	NR	NR	NR	NR	NR	NR	NR
Mean % BSA affected (SD)	52 (21.8)	50 (22.1)	47 (21.2)	53 (23.1)	54 (21.5)	55 (26.1)	55 (21.9)	52 (21.7)
Prior treatment								
OCS	Unavailable[a]	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
Immunosuppressant	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
TCS	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
TCI	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable

[a] Data were redacted from the Committee papers available for baricitinib.

[b] Data on subgroups of interest from relevant trials were redacted from the Committee papers available for baricitinib.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	Phase II (Guttman-Yassky 2019) Full trial population[a]			BREEZE-AD4 (JAIN) Full trial population[a]				BREEZE-AD7 (JAIY) Full trial population[a]		
	Baricitinib 4 mg QD plus TCS (N=38)	Baricitinib 2 mg QD plus TCS (N=37)	Placebo plus TCS (N=49)	Baricitinib 4 mg QD plus TCS (N=92)	Baricitinib 2 mg QD plus TCS (N=185)	Baricitinib 1 mg QD plus TCS (N=93)	Placebo plus TCS (N=93)	Baricitinib 4 mg QD plus TCS (N=111)	Baricitinib 2 mg QD plus TCS (N=109)	Placebo plus TCS (N=109)
Median, years (IQR)	32.5 (26–48)	42 (26–52)	35 (28–48)	Mean age (SD)				Mean age (SD)		
				39 (13)	37 (14)	39 (14)	39 (14)	33.9 (11.4)	33.8 (12.8)	33.7 (13.2)
Gender, n (%)	Male: 22 (58)	Male: 22 (59)	Male: 24 (49)	Female: 35 (38)	Female: 52 (28)	Female: 35 (38)	Female: 44 (47)	Female: 36 (32)	Female: 39 (36)	Female: 38 (35)
Median duration of AD (IQR)	22 (6.4–30.7)	26.4 (18.3–40.5)	17.7 (7.3–29.5)	NR	NR	NR	NR	Mean duration of AD (SD)		
								25.5 (13.2)	24.6 (14.8)	22 (12.2)
Race										
• White, n (%)	18 (47)	20 (54)	23 (47)	71 (77)	144 (78)	70 (75)	74 (80)	54 (49)	50 (46)	46 (42)
• Asian, n (%)	9 (24)	9 (24)	7 (14)	NR	NR	NR	NR	54 (49)	57 (52)	57 (52)
• Black, n (%)	9 (24)	8 (22)	16 (33)	NR	NR	NR	NR	3 (3)	2 (2)	6 (6)
• Other, n (%)	2 (5)	0	3 (6)							
Median (IQR) EASI score	19.5 (13.7–25.9)	22.1 (16.8–32.3)	22.1 (15.3–28)	Mean EASI score (SD)				Mean EASI score (SD)		
				33 (13.7)	31 (12.4)	34 (13.5)	31 (11.6)	30.9 (12.6)	29.3 (11.9)	28.5 (12.3)
Median IGA score (IQR)	3 (3–4)	3 (3–4)	3 (3–4)	IGA of 4 at baseline, %				IGA of 4 at baseline, n (%)		
				51	51	51	54	50 (45)	50 (46)	48 (44)
Median DLQI score (IQR)	11 (8–17)	10 (7–17)	15 (10–19)	Mean DLQI score (SD)				Mean DLQI score (SD)		
				14.0 (8.1)	13.6 (7.4)	14.3 (8.3)	14.5 (6.9)	14.7 (7.9)	15 (7.7)	15 (7.9)

Median SCORAD score (IQR)	57.6 (49.5–64.9)	53.3 (49.9–61.1)	55 (44.9–63.8)	Mean SCORAD score (SD)				Mean SCORAD score (SD)		
				69 (13.4)	68 (13.4)	71 (14.1)	69 (13.0)	68.3 (13.2)	66.8 (14)	66.6 (13.8)
Median peak pruritus NRS score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mean % BSA affected (SD)	NR	NR	NR	NR	NR	NR	NR	52.1 (23.3)	50.6 (21.6)	48.1 (24.4)
Prior treatment				NR	NR	NR	NR	NR	NR	NR
OCS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[a] Data on subgroups of interest from relevant trials were redacted from the Committee papers available for baricitinib.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.4.4 Data extracted on outcomes of interest

Table 107. Data on clinical effectiveness from studies evaluating baricitinib and for populations of interest to the MTA

Outcome	BREEZE AD4 Second-line adults – combination therapy			
	Bar 4 mg QD plus TCS (N=92)	Bar 2 mg QD plus TCS (N=185)	Bar 1 mg QD plus TCS (N=93)	Placebo plus TCS (N=93)
Proportion of people achieving EASI 75	29	51	21	16

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; QD, once daily; TCS, topical corticosteroid.

Table 108. Data on adverse effects and adverse effects of special interest informing the model for bariticinib

Outcome	BREEZE AD 4				BREEZE AD 7		
	Placebo plus TCS (N=93)	Bar 1 mg QD plus TCS (N=NR)	Bar 2 mg QD plus TCS (N=NR)	Bar 4 mg QD plus TCS (N=92)	Placebo +TCS (N=108)	Bar 2 mg QD plus TCS (N=109)	Bar 4 mg QD plus TCS (N=111)
SAEs n (%)	2	NR	NR	6 (1 allergic conjunctivitis)	4	2	4
Injection site reaction	NA	NA	NA	NA	NA	NA	NA
Allergic conjunctivitis	NR	NR	NR	NR	NR	NR	NR
Conjunctivitis	NR	NR	NR	NR	2	3	0
URTI	NR	NR	NR	NR	2	8	3
Acne	NR	NR	NR	NR	1	1	4
Oral herpes	3	NR	NR	5	0	4	4

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; QD, once daily; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

10.3.1.5 Dupilumab

10.3.1.5.1 Interventions assessed in the included studies

Table 109. Summary of interventions assessed in studies evaluating dupilumab

Study name	Intervention[a]		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
Phase IIb	Dupilumab 300 mg Q4W	65	Placebo	61	16 weeks	–
	Dupilumab 300 mg Q2W	64				

	Dupilumab 300 mg QW	63				
	Dupilumab 200 mg Q2W	61				
	Dupilumab 100 mg Q4W	65				
AD ADOL	Dupilumab 300 mg Q4W	84	Placebo	82	16 weeks	In the dupilumab Q2W group, dose was weight-based, with those weighing <60 kg receiving 200 mg Q2W after a loading dose of 400 mg. Those weighing ≥60 kg received 300 mg Q2W after a loading dose of 600 mg.
	Dupilumab 200 mg or 300 mg Q2W	82				
SOLO-1	Dupilumab 300 mg Q2W	224	Placebo	224	16 weeks	–
	Dupilumab 300 mg QW	223				
SOLO-2	Dupilumab 300 mg Q2W	233	Placebo	236	16 weeks	–
	Dupilumab 300 mg QW	239				
CAFE	Dupilumab 300 mg Q2W plus TCS	107	Placebo plus TCS	108	16 weeks	Initial concomitant TCS was of medium potency applied once daily to active lesions. Low-potency TCS could be applied to areas of thin skin.
	Dupilumab 300 mg QW plus TCS	110				
CHRONOS	Dupilumab 300 mg Q2W plus TCS	106	Placebo plus TCS	315	52 weeks	Topical therapies allowed during the trial included low or medium potency TCS and TCI. People were allowed to use more than one topical therapy. Initial concomitant TCS was of medium potency, moving to low potency for 7 days once lesions became “clear” or “almost clear”.
	Dupilumab 300 mg QW plus TCS	319				

[a] Initial dose of dupilumab was 600 mg, which was a loading dose

Abbreviations: QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid.

10.3.1.5.2 Study characteristics

Table 110. Characteristics of studies evaluating dupilumab

Characteristic	Phase IIb	AD ADOL	SOLO-1	SOLO-2	CAFE	CHRONOS
Study references	Simpson 2016b/Thaci 2016	Simpson 2020[99]	Simpson 2016[75] TA534[12]	Simpson 2016[75] TA534[12]	de Bruin-Weller 2018[100] TA534[12]	Blauvelt 2017[157] TA534[12]
Country(ies) where the clinical trial was conducted	7 countries – USA, Canada, Czechia, Germany, Hungary, Japan, Poland	2 countries – USA, Canada	10 countries – USA, Bulgaria, Canada, Denmark, Estonia, Finland, Germany Japan, Singapore, Spain	11 countries – USA Canada, France, Germany, Hong Kong, Italy, Korea, Lithuania, Poland, Sweden, UK	Countries where systemic CsA was approved for the treatment of AD including Austria, Belgium, Germany, Ireland, The Netherlands, Poland, Russian Federation, Slovakia, Spain, UK.	14 countries – USA, Australia, Canada, Czech Republic, Hungary, Italy, Japan, Republic of Korea, The Netherlands, New Zealand, Poland, Romania, Spain, UK
Multicentre trial (number, location)	84 locations	45 locations	101 locations	93 locations	Approximately 115 study sites	149 locations
Trial sponsors	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi
Date the clinical trial was conducted	May 2015 and Jan 2014	March 2017 to June 2018	October 2014 to February 2016	November 2014 to January 2016	January 2016 to March 2017	September 2014 to October 2016
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb, double-blind, randomised, placebo-controlled, parallel-group	Phase III, double-blind, randomised, placebo-controlled, parallel-group	Identical Phase III studies, 16-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies.		Phase III, double-blind, randomised, placebo-controlled, parallel-group	Phase III, multicentre, randomised, double-blind, placebo-controlled study

Trial duration (treatment duration and follow-up)	16-week intervention phase plus 16-week follow-up	16-week intervention phase plus 12-week follow-up	16-week intervention phase plus 12-week follow-up	16-week intervention phase plus 16 week follow-up	64 weeks 52 weeks of treatment plus 12 weeks of follow-up
Inclusion criteria	Adults (age >18 years) with moderate to severe AD, defined by IGA score 3 or higher, with disease not adequately controlled by topical medications or for whom topical treatment was inadvisable. Patients were required to have chronic AD, defined by consensus criteria, present for 3 or more years before screening; an EASI score of 12 or higher at screening and 16 or higher at baseline; an IGA score of 3 or higher; and AD involvement 10% or more of BSA.	Eligible patients were 12 years or older to younger than 18 years with moderate to severe AD inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable. Patients had chronic AD, as per American Academy of Dermatology criteria for 1 year or more before screening.	Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable.	Adult patients with moderate-to-severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable	Adult patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS
			Additionally, eligible patients presented with chronic AD (present for at least 3 years and meeting the American Academy of Dermatology Consensus Criteria and with a documented recent history (within 6 months before the screening visit) of an inadequate response to topical prescription medications, or in whom those therapies were not advisable. In addition, an average maximum itch intensity of ≥3 on the pruritus NRS was required at baseline. The studies therefore represent a patient population with AD lesions affecting a large portion of their BSA and experienced high levels of AD symptoms, including pruritus, which are not adequately controlled by topical prescription therapies alone, and were candidates for systemic AD therapies.			
Exclusion criteria	• Active acute or chronic infections; use of topical medications for AD (other than bland emollients) within 1 week of baseline;	• Participation in a prior dupilumab clinical study • Treatment with a systemic investigational drug	• Participation in a prior Dupilumab clinical study • Treatment with an investigational drug within 8 weeks or within 5 half-lives • Having used immunosuppressive/ immunomodulating drugs or	• Participation in a prior dupilumab clinical study • Treatment with an investigational drug within 8 weeks or within 5 half-lives (if	• Participation in a prior Dupilumab clinical trial; • Important side effects of topical medication • Having used immunosuppressive/

	• Systemic immunosuppressive/ immunomodulating drugs within 4 weeks of baseline; or significant comorbidities or laboratory abnormalities	before the baseline visit • Treatment with a topical investigational agent within 4 weeks or within 5 half-lives • Treatment with TCS or TCI within 2 weeks before the baseline visit • Having used immunosuppressive/ immunomodulating drugs or phototherapy within 4 weeks before the baseline visit • Treatment with live vaccine within 4 weeks • Body weight <30kg • Regular use of tanning booths • Known history of HIV • Pregnant or breastfeeding women • Women unwilling to use adequate birth	phototherapy within 4 weeks before the baseline visit • Regular use of a tanning booth/ parlour within 4 weeks of the screening visit • Treatment with a live vaccine within 12 weeks before the baseline visit • Known or suspected history of immunosuppression • Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active	known), whichever is longer, before the screening visit • Hypersensitivity and/or intolerance to corticosteroids or to any other ingredients contained in the TCS product used in the study • Systemic CSA, systemic corticosteroids, or phototherapy within 4 weeks prior to screening, and azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or Janus kinase (JAK) inhibitors within 8 weeks prior to screening • Treatment with TCI within 1 week before the screening visit • Regular use of a tanning booth/	immunomodulating drugs or phototherapy within 4 weeks before the baseline visit • Treatment with a live vaccine within 12 weeks before the baseline visit; • Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit; • Active or acute infection requiring systemic treatment within 2 weeks before baseline visit; • Known or suspected history of immunosuppression; • Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active

		control, if of reproductive potential and sexually active		parlour within 4 weeks of the screening visit • Known or suspected history of immunosuppression • Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active	
Concomitant medications	–	–	• Basic skin care emollients, topical anaesthetics, topical and systemic antihistamines, and topical and systemic anti-infective medications for any duration. • Medications used to treat chronic disease such as diabetes, hypertension, and asthma were permitted.	Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. Low to medium dose TCS.	• Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. Use of TCS restricted to locally approved products and according local country guidelines. • Use of TCI was reserved for problem areas.
Rescue therapy	Rescue treatment (medication and/ or	Systemic nonsteroidal immunosuppressants,	Rescue treatment for AD if medically necessary (i.e., to control intolerable AD symptoms), was provided to study patients at the discretion of the investigator after week 2. Patients who received		

	phototherapy) was allowed at the investigator's discretion; patients who received such therapy were discontinued from study treatment, but were asked to continue with assessments.	systemic or topical corticosteroids, topical calcineurin inhibitors, and topical crisaborole could be used only as rescue treatment by patients with intolerable AD symptoms at the discretion of the investigator.	rescue treatment prior to week 2 were to permanently discontinue study treatment. Patients who received rescue treatment continued study treatment if rescue consisted of topical medications. TCI could be used for rescue, but were reserved for problem areas only. Patients could be rescued directly with higher potency topical medications or with systemic treatments. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/ immunomodulating drugs study treatment was immediately, temporarily discontinued. After the treatment with these medications was completed, study treatment could be resumed but not sooner than 5 half-lives after the last dose of systemic rescue medication. Dose modification for an individual patient was not allowed. Patients who were discontinued from study drug were to remain in the study and complete all study visits and assessments.		
Outcomes	Primary endpoint: • % improvement in EASI score from baselines to Week 16. Secondary endpoints: • Participants who achieved IGA response; • Percent change in weekly average of peak; • daily pruritus NRS from baseline; • Percent change in EASI score from baseline; • percentage change in SCORAD; • >50%, >75% and >90% improvement	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percentage changes from baseline in EASI and Peak Pruritus NRS • Proportion of patients with a 3-point or more or 4-point or more	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of peak daily pruritus NRS from baseline; • Proportion of patients achieving a reduction of ≥4 points in weekly average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI;	Primary endpoint: • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of peak daily pruritus NRS from baseline; • Proportion of patients achieving a reduction of ≥4 points in weekly	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of

	from baseline in EASI (EASI-50/EASI-75/EASI-90); • Change from baseline in POEM.	improvement from baseline in Peak Pruritus NRS • 50% or more or 90% or more improvement from baseline in EASI • (EASI-50/EASI-90) • percentage change in SCORAD • Changes in Children's Dermatology Life • Quality Index • POEM scores • HADS scores	• Change from baseline in POEM; • Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.	average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI; • Change from baseline in POEM; • Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.	peak daily pruritus NRS from baseline; • Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI; • Change from baseline in POEM; • Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.
Subgroups	None reported	Bodyweight (<60 kg vs ≥60 kg)	SOLO CAFÉ-like: patients from SOLO-1 and SOLO-2 who showed an inadequate efficacy response to oral ciclosporin, inadequate efficacy response or were intolerant to oral ciclosporin or patients who did not receive prior oral ciclosporin treatment because ciclosporin was	CSA prior exposure vs CSA naïve • Age (≥18 to <40 years, ≥40 to <65 years, ≥65 years)	CHRONOS CAFÉ-like: patients who showed an inadequate efficacy response to oral ciclosporin, patients who showed an inadequate efficacy response or were

			contraindicated or otherwise medically inadvisable. • Age (≥18 to <40 years, ≥40 to <65 years, ≥65 years) • Sex (male, female) • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years) • Baseline weight (<70 kg, ≥70 kg to <100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) • Region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe) • Region for Japan submission (Japan, rest of world).	• Sex (male, female), • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years) • Baseline weight (<70 kg, ≥70 kg to <100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) • Region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe) • Region for Japan submission (Japan, rest of world).	intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or because treatment with oral ciclosporin was otherwise medically inadvisable. • Age (≥18 to <40 years, ≥40 to <65 years, ≥65 years) • Sex (male, female), • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years) • Baseline weight (<70 kg, ≥70 kg to <100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2)

						• Region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe) • Region for Japan submission (Japan, rest of world).
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement	• IGA ≥3 • ≥10% BSA involvement	• IGA ≥3 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥ 20 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement

Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis.

10.3.1.5.3 Baseline characteristics

Table 111. Baseline characteristics of trial populations in studies evaluating dupilumab

Characteristic	Phase IIb Full trial population					
	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Dupilumab 200 mg Q2W	Dupilumab 300 mg Q4W	Dupilumab 100 mg Q4W	Placebo QW
N patients	63	64	61	65	65	61
Mean age, years (SD)	36.2 (10.7)	39.4 (12.1)	35.8 (14.9)	36.8 (10.8)	36.6 (11.6)	37.2 (13.1)
Gender male, n (%)	43 (68.3)	41 (64.1)	36 (59.0)	40 (61.5)	34 (52.3)	40 (65.6)
Duration of AD (years), mean (SD)	25.8 (12.2)	28.6 (16.5)	25.6 (13.2)	27.1 (11.6)	28.0 (14.7)	31.2 (14.2)

Race						
• White, n (%)	NR	NR	NR	NR	NR	NR
• Black or African American, n (%)	NR	NR	NR	NR	NR	NR
• Asian, n (%)	NR	NR	NR	NR	NR	NR
• Other, n (%)	NR	NR	NR	NR	NR	NR
Mean EASI score (SD)	30.1 (11.2)	33.8 (14.5)	32.9 (15.5)	29.4 (11.5)	32.2 (13.5)	32.9 (13.8)
IGA score, n (%)						
• 3	32 (50.8)	34 (53.1)	31 (50.8)	37 (56.9)	34 (52.3)	32 (52.5)
• 4	31 (49.2)	30 (46.9)	30 (49.2)	28 (43.1)	31 (47.7)	29 (47.5)
Mean DLQI score (SD)	NR	NR	NR	NR	NR	NR
Mean SCORAD score (SD)	65 (12.2)	68.5 (12.6)	68.3 (14)	67.2 (12.3)	68.2 (15)	67.1 (13.6)
Weekly average peak daily pruritus NRS score, Mean (SD)	NR	NR	NR	NR	NR	NR
% BSA affected, mean (SD)	48.4 (20.9)	53.2 (24.8)	50.8 (25.4)	50.8 (22.6)	48.7 (23.9)	51.1 (23.5)
Prior treatment						
Corticosteroids	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	AD ADOL Full trial population			SOLO-1 Full trial population			SOLO-2 Full trial population			SOLO-1 and SOLO-2 Pooled CAFÉ-like population		
	Dup 200/300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)	Dup 300 mg Q2W (N=224)	Dup 300 mg QW (N=223)	Placebo (N=224)	Dup 300 mg Q2W (N=233)	Dup 300 mg QW (N=239)	Placebo (N=236)	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=96)	Placebo (N=88)
Mean age, years (SD)	14.5 (1.7)	14.4 (1.6)	14.5 (1.8)	39.8 (14.7)	39.3 (14.4)	39.5 (13.9)	36.9 (14.0)	37.1 (14.5)	37.4 (14.1)	38.0 (13.5)	37.6 (12.5)	38.8 (12.9)
Gender male, n (%)	43 (52.4)	52 (61.9)	53 (62.4)	130 (58.0)	142 (63.7)	118 (52.7)	137 (58.8)	139 (58.2)	132 (55.9)	75 (72.1)	56 (58.3)	55 (62.5)
Duration of AD (years), mean (SD)	12.5 (3.0)	11.9 (3.2)	12.3 (3.4)	28.5 (16.1)	27.9 (15.8)	29.5 (14.5)	27.2 (14.2)	27.4 (15.0)	28.2 (14.4)	29.0 (14.4)	28.3 (15.3)	29.9 (14.7)
Race												
• White, n (%)	54 (65.9)	55 (65.5)	48 (56.5)	155 (69.2)	149 (66.8)	146 (65.2)	165 (70.8)	168 (70.3)	156 (66.1)	75 (72.1)	69 (71.9)	52 (59.1)
• Black or African American, n (%)	7 (8.5)	8 (9.5)	15 (17.6)	10 (4.5%)	20 (9.0%)	16 (7.1%)	13 (5.6%)	15 (6.3%)	20 (8.5%)	1 (1.0%)	2 (2.1)	0
• Asian, n (%)	12 (14.6)	13 (15.5)	13 (15.3)	54 (24.1)	51 (22.9)	56 (25.0)	44 (18.9)	45 (18.8)	50 (21.2)	23 (22.1)	23 (24.0)	30 (34.1)
• Other, n (%)	NR	NR	NR	5 (2.2)	3 (1.3)	6 (2.7)	6 (2.6)	4 (1.7)	7 (3.0)	5 (4.8)	2 (2.0)	6 (6.8)
Mean EASI score (SD)	35.3 (13.8)	35.8 (14.8)	35.5 (14.0)	33.0 (13.6)	33.2 (14.0)	34.5 (14.5)	31.8 (13.1)	31.9 (12.7)	33.6 (14.31	36.9 (14.6)	35.7 (14.7)	35.6 (14.3)
Mean IGA score (SD)	NR	NR	NR	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.7 (0.5)	3.6 (0.5)	3.6 (0.5)
Proportion with IGA score of 3/4 at baseline, n (%)	39 (47.6)/43 (52.4)	38 (45.2)/46 (54.8)	39 (45.9)/46 (54.1)	Score of 4: 108 (48.2)	Score of 4: 106 (47.5)	Score of 4: 110 (49.1)	Score of 4: 115 (49.4)	Score of 4: 112 (46.9)	Score of 4: 115 (48.7)	NR	NR	NR

Mean DLQI score (SD)	13.0 (6.2)	14.8 (7.4)	13.1 (6.7)	13.9 (7.4)	14.1 (7.5)	14.8 (7.2)	15.4 (7.1)	16.0 (7.3)	15.4 (7.7)	15.7 (6.8)	16.8 (7.8)	16.6 (7.9)
Mean SCORAD score (SD)	70.6 (13.9)	69.8 (14.1)	70.4 (13.3)	66.9 (14.0)	67.5 (13.6)	68.3 (14.0)	67.2 (13.5)	67.5 (13.1)	69.2 (14.9)	72.2 (13.9)	70.9 (13.4)	72.8 (13.4)
Peak pruritus NRS score, Mean (SD)	7.5 (1.5)	7.5 (1.8)	7.7 (1.6)	Weekly average Peak daily pruritus NRS score, Mean (SD)								
				7.2 (1.9)	7.2 (2.1)	7.4 (1.8)	7.6 (1.6)	7.5 (1.8)	7.5 (1.9)	7.6 (1.6)	7.4 (1.8)	7.8 (1.5)
% BSA affected, mean (SD)	56.0 (21.4)	56.9 (23.5)	56.4 (24.1)	54.7 (23.2)	56.1 (23.0)	57.5 (23.4)	52.7 (21.2)	52.2 (21.5)	54.3 (23.1)	58.8 (21.9)	59.0 (22.7)	59.9 (23.7)
Prior treatment												
Corticosteroids	21 (25.6)	27 (32.5)	21 (24.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	20 (24.4)	15 (18.1)	17 (20.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	CAFÉ			CHRONOS Full trial population			Pooled data for CAFÉ & CHRONOS-CAFÉ-like		
	Dupilumab 300 mg Q2W plus TCS (N=107)	Dupilumab 300 mg QW plus TCS (N=110)	Placebo plus TCS (N=108)	Dupilumab 300 mg Q2W plus TCS (N=106)	Dupilumab 300 mg QW plus TCS (N=319)	Placebo plus TCS (N=315)	Dupilumab 300 mg Q2W plus TCS (N=130)	Dupilumab 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)
Mean age, years (SD)	37.5 (12.9)	38.7 (13.2)	38.9 (13.4)	39.6 (14.0)	36.9 (13.7)	36.6 (13.0)	37.8 (12.9)	38.4 (12.9)	38.1 (13.0)
Gender male, n (%)	65 (60.7)	66 (60.0%	68 (63.0)	62 (58.5)	191 (59.9)	193 (61.3)	77 (59.2)	98 (60.1)	102 (60.4)
Duration of AD (years), mean (SD)	29.6 (15.6)	32.3 (14.0)	29.2 (14.7)	30.1 (15.5)	27.9 (14.5)	27.5 (14.3)	29.9 (15.4)	31.6 (14.5)	28.9 (15.1)

Race									
• White, n (%)	104 (97.2)	105 (95.5)	104 (96.3)	74 (69.8)	208 (65.2)	208 (66.0)	121 (93.1)	145 (89.0)	152 (89.9)
• Black or African American, n (%)	0	2 (1.8)	0	2 (1.9)	13 (4.1)	19 (6.0)	1 (0.8)	2 (1.2)	3 (1.8)
• Asian, n (%)	2 (1.9)	2 (1.8)	2 (1.9)	29 (27.4)	89 (27.9)	83 (26.3)	7 (5.4)	14 (8.6)	12 (7.1)
• Other, n (%)	1 (0.9)	1 (0.9)	2 (1.9)	1 (0.9)	9 (2.8)	5 (1.6)	0	2 (1.2)	2(1.2)
Mean EASI score (SD)	33.3 (9.9)	33.1 (11.0)	32.9 (10.8)	33.6 (13.3)	32.1 (12.8)	32.6 (12.9)	33.6 (10.5)	34.2 (11.7)	34.8 (12.0)
Mean IGA score (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
Mean DLQI score (SD)	14.5 (7.6)	13.8 (8.0)	13.2 (7.6)	14.5 (7.3)	14.4 (7.2)	14.7 (7.4)	14.6 (7.5)	15.0 (8.0)	14.8 (7.7)
Mean SCORAD score (SD)	68.6 (11.9)	66.0 (12.7)	67.0 (12.2)	69.3 (15.2)	65.9 (13.6)	66.0 (13.5)	69.3 (12.9)	67.6 (13.4)	68.7 (12.8)
Weekly average peak daily pruritus NRS score, Mean (SD)	6.6 (2.1)	6.2 (2.0)	6.4 (2.2)	7.4 (1.7)	7.1 (1.9)	7.3 (1.8)	6.9 (2.1)	6.6 (2.0)	6.9 (2.1)
% BSA affected, mean (SD)	56.1 (17.8)	56.0 (19.3)	55.0 (20.5)	59.5 (20.8)	54.1 (21.8)	56.9 (21.7)	57.3 (18.5)	57.3 (20.5)	58.9 (21.7)
Prior treatment									
OCS	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCI	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

10.3.1.5.4 Data extracted on outcomes of interest

Table 112. Data on clinical effectiveness from studies evaluating dupilumab and for populations of interest to the MTA

Outcome at 16 weeks	**Ariens et al** First-line adults – combination therapy		**CHRONOS** Full trial population		
	CsA with or without TCS (N=39)	Dup 300 mg Q2W plus TCS (N=106)	Dup 300 mg Q2W plus TCS (N=106)	Dup 300 mg QW plus TCS (N=319)	Placebo plus TCS (N=315)
Proportion of people achieving EASI 75, n (%)	20	80	78	226	102

Abbreviations: CsA, ciclosporin A; EASI, Eczema Area and Severity Index; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroid.

Outcome at 16 weeks	**Pooled analysis of SOLO-1 and SOLO-2** Second-line adults - monotherapy						**Pooled analysis of CAFÉ and CHRONOS CAFÉ-LIKE** Second-line adults – combination therapy					
	Censoring for receipt of rescue medication			**No censoring for receipt of rescue medication**			**Censoring for receipt of rescue medication**			**No censoring for receipt of rescue medication**		
	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=95)	Placebo (N=88)	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=95)	Placebo (N=88)	Dup 300 mg Q2W plus TCS (N=130)	Dup 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)	Dup 300 mg Q2W plus TCS (N=130)	Dup 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	54	–	10	61	58	21	89	–	35	95	117	47

Proportion of people achieving EASI 75, n (%)	42	–	10	47	49	15	83	–	43	87	103	51

Abbreviations: Dup, dupilumab; EASI, Eczema Area and Severity Index; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroid.

Outcome at 16 weeks	AD ADOL Adolescents					
	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication		
	Dup 200 mg or 300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)	Dup 200 mg or 300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)
Proportion of people achieving EASI 75, n (%)	34	32	7	34	32	7

Abbreviations: EASI, Eczema Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 113. Data on adverse effects and adverse effects of special interest informing the model for dupilumab

Outcome	SOLO 1			SOLO 2			CAFE			CHRONOS		
	Placebo (N=222)	Dup 300 mg Q2W (N=229)	Dup 300 mg QW (N=218)	Placebo (N=234)	Dup 300mg Q2W (N=236)	Dup 300mg QW (N=237)	Placebo plus TCS (N=108)	Dup 300 mg Q2W plus TCS (N=107)	Dup 300 mg QW plus TCS (N=110)	Placebo plus TCS (N=315)	Dup 300 mg Q2W plus TCS (N=110)	Dup 300 mg QW plus TCS (N=315)
Treatment discontinuations n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SAEs n (%)	11	7	2	13	4	8	2	2	2	6	3	4
AEs of special interest												

Injection site reaction	13	19	41	15	32	31	0	1	4	18	11	51
Allergic conjunctivitis	2	12	7	2	2	3	7	16	10	9	7	19
Conjunctivitis	2	11	7	1	9	9	3	12	8	2	0	3
URTI	5	6	11	5	7	9	1	1	3	20	7	21
Acne										6	0	6
Oral herpes	4	9	4	4	8	9	0	3	5	5	3	8

Abbreviations: AE adverse effect; Dup, dupilumab; NA, not applicable; NR, not reported; QD, once daily; QW, every week; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

Outcome	AD ADOL		
	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200/300 mg Q2W (N=82)
SAEs n (%)	1	0	0
Injection site reaction	3	5	7
Allergic conjunctivitis	3	4	3
Conjunctivitis	1	3	4
URTI	15	6	10
Acne	NR	NR	NR
Oral herpes	NR	NR	NR

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

10.3.2 Economic evaluations

Author, year, country	Perspective, discounting & cost year	Model type	Patient population	Intervention/ comparator	Outcomes	Results ICER (per QALY gained) incl. uncertainty
Canadian Agency for Drugs and Technologies in Health. 2020. Canada	Perspective: Canadian public healthcare payer Discounting: annual discount rate of 1.5% for costs and QALYS Cost year: 2019	Short-term 1-year decision tree followed by a long-term maintenance Markov model. Short-term model included 16- and 52-week assessments points for response based on data from the AD-1526, SOLO 1, SOLO 2, LIBERTY AD CHRONOS AND LIBERTY AD CAFE trials. Non-responders in the short-term model transitioned to best supportive care (BSC) in the long-term model. In the long-term model, BSC was split by response status. Responders at 16 and 52 weeks transitioned to the response state in the long-term model and could discontinue to BSC during any cycle. The Markov-model included	Patients aged 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable. Analysis includes a subgroup of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies (reimbursement population)	Intervention: dupilumab plus standard of care (SOC). In adolescents aged 12 to 17 years old who weigh <60kg, two subcutaneous injections of 200 mg in the first week (loading dose), then one 200 mg subcutaneous injection Q2W. For adolescents who weigh >60 kg, two 300 mg subcutaneous injections, followed by 300 mg subcutaneous injections Q2W. Comparator: SOC, assumed to be topical therapy (type of topical treatments not listed in study). However, the cost of topical treatment was not included in the model.	Response to treatment was based on 50% or more improvement in EASI score compared with baseline (EASI 50). Response at 16 weeks was based on AD-1526 for dupilumab + SOC (61.0%) and SOC (12.9%). Conditional response at 52-weeks for those who achieved a response at 16 weeks was taken from the CHRONOS study, but data are redacted. CADTH implemented alternative response data for their base case, which was based on pooled data from the SOLO trials that estimated 67% of dupilumab+SOC patients and 23.3% of SOC patients achieved EASI 50 as week 16. CADTH also explored the use of EASI 75 for response. CADTH were	In the sponsor base case, dupilumab+SOC versus SOC resulted in incremental costs and QALYs of $127,607 and 2.55 QALYs, respectively. The ICER was estimated to be $50,133 per QALY gained. The CADTH ICER was $136,025 per QALY gained. For a subgroup of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies the sponsor ICER was $52,168 per QALY gained.

		annual cycles with half-cycle correction.			unable to verify the sponsor's 52-week conditional probability response and instead implemented the following based on data from the CHRONOS study: 97.2% for dupilumab + SOC and 81.4% for SOC. Long-term response was informed from clinical expert feedback that suggested the probability for sustaining a response to dupilumab was 98% in year 2, reducing to 92% in year 5 and beyond. For SOC, the probability of long-term response was estimated to be 37% in year 2, reducing to 0% in year 4 and beyond. CADTH disagreed with the sponsor's treatment waning assumptions for SOC and instead preferred to assume the following: year 2 = 43%; year 3 = 18%; year 4 = 8%; and year 5+ = 3%. A treatment discontinuation	

					rate of 6.3% per model cycle was applied for patients on dupilumab and was based on data from the SOLO trials. The impact of adverse events was only modelled to affect costs. Adverse events in the model included allergic conjunctivitis, infectious conjunctivitis, oral herpes, and skin infections. The source of adverse event rates was not reported.	
Kuznik *et al*. 2017. USA	Perspective: US payer Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2016	16-week decision tree, followed by a lifetime horizon Markov model. Patients enter the model on either dupilumab 300 mg or standard care (SC). At 16 weeks, patients are assessed for treatment response. Responders to dupilumab treatment enter the long-term Markov model in the maintenance health state and dupilumab non-responders move to the SC health state. Patients	Adult patients with moderate-to-severe AD	Intervention: dupilumab (administered as a 300-mg subcutaneous injection Q2W) plus emollients Comparator: standard care, assumed to be emollients as required.	Therapeutic response was used as the main outcome in the model and was defined as a 75% improvement in EASI score (EASI 75). Based on pooled data from the SOLO trials, 48% and 13% of dupilumab q2w and SC patients, respectively, achieved the EASI 75 response. Dupilumab treatment discontinuation was included in the model and was based on data from the	For the base case, dupilumab was estimated to produce 1.12 more QALYs over the lifetime horizon compared with SC (15.95 vs. 14.83) and result in cost savings of approximately $32,000 for other medical costs. The annual maintenance price for dupilumab therapy to be considered cost-effective at a threshold of $100,000 per QALY gained would be $28,769 and $39,941 when the threshold increases to $150,000 per QALY gained.

		on SC in the short-term model remain in the SC health state in the long-term model. A 4-month cycle length was used for the Markov model.			open label extension studies for SOLO 1 and SOLO 2, where 6.3% of previously responding patients discontinued by 52 weeks. This annual value was converted to a constant 4-month probability for use in the model. Adverse events associated with dupilumab treatment were included in the model and were based on data from the SOLO trials. The primary adverse events modelled were injection site reaction, included once in the first cycle of the model and infectious conjunctivitis, which was included in every model cycle.	
Fanelli *et al*. 2020. Italy (abstract)	Perspective: Italian National Healthcare Service Discounting: Not reported Cost year: Not reported	1-year decision tree, followed by a lifetime horizon Markov model.	Adolescents (aged 12-17) with uncontrolled moderate-to-severe AD	Intervention: Dupilumab Comparator: Current supportive care	In the base-case, dupilumab generated 1.53 additional QALYs compared with current supportive care. However, dupilumab was associated with an increase in treatment costs (+ €61,121.17), but a	The ICER was €33,918.29 per QALY gained

					decrease in the costs of disease management and the management of complications of the disease (respectively -€8,349.80 and - €907.84). The abstract does not report what measure of treatment effectiveness was used to estimate costs and QALYs for the cost-effectiveness analysis.	
Zimmermann . 2018. USA	Perspective: US health system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2017	Lifetime Markov model with 4-month cycles. Model health states were based on treatment response using the EASI score (EASI 50, EASI 75 or EASI 90). All patients enter the model in the no response (usual care) health state and can transition to any of the responder health states based on their response to treatment defined by EASI score. Patients could not transition between the different EASI category health states. Over time, patients can discontinue	Adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable.	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) Comparator: Usual care (emollients)	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data for response came from the dupilumab trials and were provided by Sanofi. For moderate AD patients, the percentage achieving EASI 75 scores were 17.6% and 8.3% for dupilumab and usual care, respectively. For severe AD patients, the percentage achieving EASI 75 scores were 14.2% and 3.9% for dupilumab and usual care, respectively. EASI 50 and	For the base case, dupilumab was estimated to produce an incremental QALY gain of 1.91 and incremental costs of $238,132 (list price) over the lifetime horizon compared with usual care. The ICER was estimated to be $124,541 per QALY gained (list price). The cost-effectiveness results for the 95% credible interval range are as follows: Incremental QALYs = 1.24-1.91 Incremental cost (list price) = $135,800 - $219,200 ICER (list price) = $66,400 - $116,400 per QALY gained

		treatment or experience treatment waning and thus transition to the no response (usual care) health state.			EASI 90 data are also reported in Table 1 of the publication. Dupilumab treatment discontinuation was assumed to be 6.3% annually (data provided by Sanofi). For responders on usual care, the probability of transitioning to the non-response health state was assumed to be 65.8% every model cycle. Adverse events were modelled with rates obtained from the literature. Adverse events included injection site reaction (DUP=11%), allergic conjunctivitis (DUP=3%; usual care=0.9%) and infectious conjunctivitis (DUP=4.3%; usual care=0.7%).	
National Institute for Health and Care Excellence -	Perspective: UK NHS Discounting: annual discount rate of 3.5% for	Short-term 1-year decision tree followed by a long-term three-state Markov model. Short-term model included 16- and 52- week	Adult patients with moderate-to-severe AD who are contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose). However, the appraisal committee only considered evidence for	The appraisal committee's preferred definition of treatment response for the economic model was EASI-50 (reduction in of at least 50% in the EASI score from	The ICER range considered plausible by the appraisal committee was £27,410 to 28,495 per QALY gained.

TA534. 2018. UK	costs and QALYS Cost year: 2016	assessment points for response to treatment. Responders to dupilumab at 16 weeks continued treatment up to 52 weeks and non-responders discontinued to BSC. Patients on BSC remain on BSC irrespective of response status. At the 52-week assessment point, if response to dupilumab is maintained, patients enter the Markov maintenance treatment health state. If response to dupilumab treatment is lost at 52 weeks, patients enter the Markov BSC health state. All BSC patients and dupilumab patients who discontinued to BSC at the 16-week assessment point continue to the Markov BSC health state. The cycle length in the Markov model is annual, with half-cycle correction. At the end of each cycle, patients in the maintenance treatment health state can	medically inadvisable to receive treatment with a systemic immunosuppressant.	dupilumab in combination with topical corticosteroids. Comparator: BSC, which includes emollients, low-to-mid potency topical corticosteroids, and rescue therapy which may include higher potency topical corticosteroids, oral corticosteroids or topical calcineurin inhibitors. After the first appraisal committee meeting, the company revised BSC to also include phototherapy and psychological support.	baseline) plus an improvement in the DLQI of at least 4. Data on response was obtained from the CAFE study and the CAFE-like population from the CHRONOS study, which compared dupilumab+TCS with BSC. From the trials, the all-observed dataset was used, which does not exclude patients who received rescue treatment. At week 16 the proportion of patients on dupilumab+TCS and BSC responding to treatment was 73.1% and 27.8%, respectively. Response to treatment at 52 weeks was conditional on response to treatment at 16 weeks. The 52-week conditional response probability for dupilumab+TCS and BSC was 0.939 and 0.767, respectively. In the long-term model, an annual treatment	

		discontinue treatment and transition to the BSC health state or die.			discontinuation rate of 3.7% for patients on dupilumab+TCS was accepted by the appraisal committee. The annual rate of treatment discontinuation was based on data from the CHRONOS study and reflected the proportion of patients who responded to treatment at week 16 but who withdrew from the trial by 52 weeks. In addition to treatment discontinuation, loss of response was considered in the model. The appraisal committee accepted that patients on dupilumab+TCS have a sustained response and that by year 5 onwards, 8% of patients would lose response. For patients on BSC, the committee considered that by year 5 onwards, up to 97% of patients would lose response to treatment. Adverse events included in the model were injection site reaction, allergic	

					conjunctivitis, infectious conjunctivitis and oral herpes.	
National Institute for Health and Care Excellence - TA681. 2021. UK.	Perspective: UK NHS Discounting: annual discount rate of 3.5% for costs and QALYS Cost year: 2019	A four-state, lifetime (62-year) Markov model. Health states included 'induction', representing a series of tunnel states for the short-term initial treatment phase, 'maintenance' which reflects long-term treatment, 'non-response' and 'death'. The model cycle length was 4 weeks and no half cycle correction was applied. All patients enter the model in the induction health state and remain there for 16 weeks. At week 16, patients can transition to the maintenance health state and remain on treatment or transition to the non-response health state and receive BSC. Transitions at week 16 are determined by patients' response to their allocated treatment.	Adult patients with moderate-to-severe AD who have previously failed one or more systemic therapies.	Intervention: Baricitinib 4 mg once daily in combination with topical corticosteroids Comparators: BSC, which includes emollients, low-to-mid potency topical corticosteroids, phototherapy, psychological support and rescue therapy. Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) in combination with topical corticosteroids	The appraisal committee's preferred definition of treatment response for the economic model was EASI-50 (reduction in of at least 50% in the EASI score from baseline) plus an improvement in the DLQI of at least 4, in line with the recommendations in TA534. Data on response was based on an indirect treatment comparison and included data for baricitinib from the BREEZE-AD4 (JAIN) study and a subgroup of patients from the BREEZE-AD7 (JAIY) study who had previously failed on, or were intolerant or contraindicated to ciclosporin (JAIN-like JAIY). Equivalent data for dupilumab was obtained from the CAFE study and a subpopulation from the CHRONOS study (CAFE-like CHRONOS population). Response rates at week 16	The cost-effectiveness results demonstrated that baricitinib + TCS was associated with cost savings and QALY loss compared with dupilumab + TCS, but the committee's preferred ICER was not presented in the final appraisal document. For the comparison of baricitinib + TCS with BSC, the appraisal committee considered that assumptions around quality of life waning made the ICERs uncertain and as such did not state a preferred ICER but concluded baricitinib is likely to be cost-effective.

		Between week 16 and 52, patients in the maintenance health state receive continuous treatment until they lose response and from year 2 onwards can discontinue treatment for other reasons such as adverse events (based on all cause discontinuation) and move to the non-response health state, where they start 1st line BSC and start a second set of induction tunnel states, with response to treatment measured at 16 weeks post induction.			for baricitinib, dupilumab and BSC were 49.0%, 79.3% and 31.3% respectively. The ERG produced alternative estimates of response, but these data are redacted. For response at week 52, the appraisal committee preferred the use of all-cause discontinuation being applied post week 16, as per the ERG's recommendation instead of conditional response probabilities applied at week 52 based on response at week 16. The ERG preferred discontinuation data for baricitinib from the JAHN extension study, but data are redacted. The ERG preferred per cycle rate of discontinuation for dupilumab was obtained from the CHRONOS study and estimated to be 0.29% discontinuation per model cycle. For BSC, an annual discontinuation rate of 57% was assumed for BSC.	

Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2011 & SMC2232). UK. 2019	Perspective: Scottish National Health Service health system Discounting: Not reported Cost year: Not reported	Short-term (1 year) decision tree, followed by a long-term (lifetime) Markov model with annual cycles. In the decision tree, response to treatment was evaluated at 16 weeks. Patients on dupilumab who did not respond to treatment at week 16 discontinued to BSC. However, it is not reported what happens to responders between week 16 and 52. The Markov model was based on three health states: maintenance treatment with dupilumab, BSC treatment and death. Costs and benefits for dupilumab patients in the maintenance health state were differentiated by response status. However, for the BSC arm, costs were differentiated based on response status, but benefits were based on an average of responder	Patients who have had an inadequate response to existing systemic immunosuppressants such as ciclosporin, or in whom such treatment is considered unsuitable. The adult population was assessed in SMC2011 and the adolescent population was assessed in SMC2232	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) Comparator: BSC (not defined)	A composite response outcome of EASI 50 plus DLQI >4 at week 16 was used in the short-term model. Response data was based on pooled data from CAFE study and the CAFE-life population from the CHRONOS study for dupilumab in combination with TCS. For dupilumab monotherapy, data were taken from the CAFE-like population from the SOLO trials. From all trials, the "all observed dataset" was used instead of the primary analysis dataset, where patients were considered non-responders after rescue medication. Dupilumab treatment discontinuation was assumed to be 3.7% annually, but the source of the data was not reported. Adverse events were included in the model but only in terms of costs. Types and rates of adverse events were not reported.	The base case results including PAS discount (not reported) for dupilumab+TCS and dupilumab monotherapy compared with BSC were £63,911 and £41,532, respectively. The SMC considered alternative assumptions (reported in Table 6 of the publication) and produced what it considered was a more plausible cost-effectiveness base case. The SMC results (including PAS) for dupilumab+TCS and dupilumab monotherapy compared with BSC were £40,089 and £31,560, respectively. It should be noted that the above results only correspond to the adult population. In SMC2232, ICERs for the adolescent population are not provided.

		and non-responder utility values.			It should be noted that the above results only correspond to the adult population. In SMC2232, data for the adolescent population are not provided.	
Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2337). UK. 2021.	Perspective: Scottish National Health Service health system Discounting: Not reported Cost year: Not reported	Lifetime Markov model consisting of four health states, including induction, maintenance, non-response and death. All patients enter the model in the induction health state and remain there for the first 16 weeks of the model, after which they can transition to the maintenance phase if they achieve an EASI 75 response. For patients who do not achieve a response, they can transition to the next line of treatment and enter the second induction phase or move to no response at the third line of treatment. Over time, patients can discontinue maintenance treatment and move to	Adult patients with moderate-to-severe AD who are candidates for systemic therapy who have failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.	Intervention: Baricitinib 4 mg once daily (with or without topical corticosteroids) Comparators: Dupilumab, BSC (not defined)	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of ≥75% (EASI 75) at week 16. Response data were derived from a pooled analysis of BREEZE-AD4 and the BREEZE-AD4-like population from the BREEZE-AD7 study. An indirect comparison was used to derive treatment response data for dupilumab. At week 16, the percentage of patients achieving EASI 75 was 42%, 57% and 22% for baricitinib, dupilumab and BSC, respectively. Between week 16 and 52, a conditional probability of EASI 75 response in patients achieving a week	The base case results for baricitinib compared with BSC and dupilumab were £65,466 and £113,459 (SW quadrant), respectively.

		the next line of treatment. In the BSC maintenance state, no discontinuation was assumed to reflect the waxing and waning nature of response to BSC.			16 response was applied for the baricitinib and dupilumab arms of the model. After year 1, all cause discontinuation rate at week 52 was used to calculate a constant rate of discontinuation (data not reported).	
Institute for Clinical and Economic Review. USA. 2017	Perspective: US health system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2017	Lifetime Markov model with 4-month cycles. Model health states were based on treatment response using the EASI categories (EASI 50, EASI 75 or EASI 90). All patients enter the model in the non-responder health state. After the first cycle, patients can transition to any of the responder health states based on their response to treatment defined by EASI score. In subsequent cycles, patients could transition to the non-responder health state due to treatment discontinuation or treatment waning. Patients could not	Adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable.	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) Comparator: Usual care (emollients)	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data for response was supplied by Sanofi. For moderate AD patients, the percentage achieving EASI 75 scores were 17.6% and 8.3% for dupilumab and usual care, respectively. For severe AD patients, the percentage achieving EASI 75 scores were 14.2% and 3.9% for dupilumab and usual care, respectively. EASI 50 and EASI 90 data are also reported in Table 5 and Table 6 of the publication.	For the base case, dupilumab was estimated to produce an incremental QALY gain of 1.91 and incremental costs of $238,132 (list price) over the lifetime horizon compared with usual care. The ICER was estimated to be $124,541 per QALY gained (list price). The cost-effectiveness results for the 95% credible interval range are as follows: Incremental QALYs = 1.23-2.64 Incremental cost (list price) = $101,073 - $436,399 ICER (list price) = $49,805 - $247,604 per QALY gained

		transition between the different EASI category health states.			Dupilumab treatment discontinuation was assumed to be 6.3% annually (data from Sanofi). For responders on usual care, the probability of transitioning to the non-response health state was assumed to be 65.8% every model cycle. Adverse events were modelled and included injection site reaction (DUP=11%), allergic conjunctivitis (DUP=3%; usual care=0.9%) and infectious conjunctivitis (DUP=4.3%; usual care=0.7%). Data were provided by Sanofi.	
Institute for Clinical and Economic Review. USA. 2021.	Perspective: US health system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2021	5-year Markov model with 4-month cycles. Model health states were based on treatment response using the EASI categories (EASI 50, EASI 75 or EASI 90). All patients enter the model in the non-responder health state. After the first cycle, patients can	Patients with moderate-to-severe atopic dermatitis.	Interventions: - Abrocitinib 200 mg once daily - Tralokinumab 300 mg Q2W - Upadacitinib 30 mg once daily - Baricitinib 2 mg once daily	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data on response by EASI score is redacted. Treatment specific per-cycle treatment	ICERs - intervention vs SoC Abrocitinib - $148,300 Tralokinumab - $129,400 Upadacitinib - $248,400 Baricitinib - $71,600 Dupilumab - $110,300 ICERs - intervention vs dupilumab

		transition to any of the responder health states based on their response to treatment defined by EASI score. In subsequent cycles, patients could transition to the non-responder health state due to treatment discontinuation or treatment waning. Patients could not transition between the different EASI category health states.		Comparator: Standard of care (emollients), dupilumab 300 mg Q2W	discontinuation rates (all cause) for the first year after initial treatment and then for all subsequent years over the model time horizon where data was available was used in the model. Per cycle discontinuation rates were derived from long-term follow-up data for patients who achieved a minimum of EASI 50 at their initial 16-week assessment. Long-term discontinuation data for AD patients were not available for upadacitinib and such rate equal to the highest rate within the class was assumed. Dupilumab treatment discontinuation was assumed to be 3.77% in the first year and then 4.87% thereafter. For tralokinumab, treatment discontinuation was 5.04% annually. Discontinuation data for all other treatments are redacted. For responders on usual care, the probability of	Abrocitinib - $303,400 Tralokinumab - dominated Upadacitinib - $1,912,200 Baricitinib - dominated

					transitioning to the non-response health state was assumed to be 25.4% annually. Adverse events were not included in the model as the authors did not identify evidence of any serious adverse events occurring in >5% of subjects among any of the clinical trials.	

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CS, company submission; DLQI, Dermatology Life Quality Index; DUP, dupilumab; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; kg, kilogram; mg, milligram; NHS, National Health Service; PAS, patient access scheme; QALY, quality-adjusted life year; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SC, standard care; SD, standard deviation; SE, standard error; SMC, Scottish Medicines Consortium; SoC, standard of care; SW, south-west; TCS, topical corticosteroids; TE, technical engagement; UK, United Kingdom; US, United States

HRQOL – articles

#	Author, year, country	Sample size	Patient population	Instrument (Valuation)	Utility results
1	Andersen, 2020, Europe (France, Germany, the UK) and the USA	Of the 1,098 respondents with moderate-to-severe AD, 118 were from the UK. Sample size according to severity (PO-SCORAD score), all	People with AD, recruited from the 2016 NHWS (US also the 2015 NHWS). Mean age (SD) according to severity (PO-SCORAD score), years: Mild (<25): 47.4 (17.2) Moderate (25-30): 48.5 (15.3) Severe 1 (51-60): 49.3 (13.1)	HRQoL measured using the EQ-5D-5L. Valuation method unclear (all EQ-5D index scores were calculated using their respective 5L value sets).	The unadjusted mean (SD) utility in the UK across all severity categories was 0.62 (0.30). The unadjusted mean (SD) utility across all countries in respondents with moderate-to-severe AD was 0.70 (0.26) and with mild AD 0.88 (0.16) Utility according to severity

		countries (UK): Mild (<25): 134 (23) Moderate (25-30): 825 (77) Severe 1 (51-60): 141 (19) Severe 2 (61-70): 83 (12) Severe 3 (71+): 49 (10)	Severe 2 (61-70): 46.7 (12.7) Severe 3 (71+): 45.5 (12.4)		(PO-SCORAD score): Europe adjusted mean; USA adjusted mean Mild: NR Moderate (25-30): 0.77; 0.74 Severe 1 (51-60): 0.69; 0.67 Severe 2 (61-70): 0.64; 0.66 Severe 3 (71+): 0.42; 0.56 The mean was adjusted for country, age, sex, alcohol use, smoking, body mass index category, household income, CCI and years since atopic dermatitis diagnosis.
2	Girolomoni, 2021, EU5 (France, Germany, Italy, Spain, and the UK).	Of the 1,014 respondents with moderate-to-severe AD, 283 were from the UK. Sample size according to severity (DLQI score), all countries (UK): Moderate (6-10): 597 (177) Severe 1 (11-20): 348 (83) Severe 2 (21-30): 69 (23)	People with moderate-to-severe AD, recruited from the 2017 EU5 NHWS. Mean age (SD) according to severity (DLQI score), years: Moderate (6-10): 42.3 (16.3) Severe 1 (11-20): 40.3 (14.2) Severe 2 (21-30): 39.7 (13.5)	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Adjusted utility means by comorbidity category across EU5 countries Sleep difficulties: none, 0.66; mild, 0.63; moderate, 0.52; severe, 0.46 Anxiety: no, 0.76; yes, 0.66 Depression (PHQ-9): none-minimal, 0.76; mild, 0.70; moderate, 0.65; moderately severe, 0.56; severe, 0.42 Adjusted for age, sex, country, income, employment status, BMI, CCI score, and presence of other atopic conditions.
3	Hsieh, 2021, Taiwan	Sample size according to severity (SCORAD score): Mild (<25): 70	People with AD recruited from two regional hospital clinics in Taiwan from April 2018 to April 2019. Mean age (SD) according to severity (SCORAD score), years:	HRQoL measured using the EQ-5D-5L. Valued using the	Mean (SD) utility according to severity (SCORAD score): Severe (<25): 0.70 (0.22)

		Moderate (25-50): 72 Severe (>50): 58	Mild (<25): 35.3 (13.7) Moderate (25-50): 35.0 (12.2) Severe (>50): 32.3 (10.9)	value set for Taiwan (Lin 2018).	Moderate (25-50): 0.82 (0.19) Mild (>50): 0.91 (0.12)
4	Kwatra, 2021, US	1,017 respondents with moderate-to-severe AD.	People with moderate-to-severe AD, recruited from the 2017 US NHWS. Mean age 37.4 years (SD 14.5 years).	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Adjusted utility means by comorbidity category Sleep difficulties: none, 0.67; mild, 0.63; moderate, 0.60; severe, 0.51 Anxiety: no, 0.76; yes, 0.68 Depression (PHQ-9): none-minimal, 0.75; mild, 0.68; moderate, 0.64; moderately5severe, 0.59; severe, 0.49 Adjusted means were calculated based on the results of generalised linear models that controlled for age, sex, race/ethnicity, education, income, employment status, body mass index, smoking status, alcohol use, CCI, and the presence of other atopic conditions.
5	Misery, 2018, France	Sample size according to severity (PO-SCORAD score): Mild (<25): 283 Moderate (25-50): 414 Severe (>50): 327	People with AD were members of the French Association of Eczema or outpatients recruited in 4 dermatology centres in France. Known as the ECLA study. Mean age 42.7 years (SD 15.2 years).	HRQoL measured using the EQ-5D (3L assumed based on reference to Essink-Bot 1993). Valuation method unclear.	Mean (SD) utility according to severity (PO-SCORAD score): Mild (<25): 0.79 (0.24) Moderate (25-50): 0.68 (0.28) Severe (>50): 0.60 (0.32)
6	Nyberg, 2018, Europe (France, Germany, the UK) and the USA (abstract)	Of the 1,098 respondents with moderate-to-severe AD, 548 were from Europe and 550 were from the US. Sample size according	People with moderate-to-severe AD, recruited from the NHWS. Mean (SD) age, years: Europe, 45.3 (13.5); US, 51.3 (15.3).	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Unadjusted mean (SD) utility according to severity (PO-SCORAD score), Europe; US: Moderate (25-50): 0.788 (0.204); 0.786 (0.128) Severe (>50): 0.606 (0.293); 0.684 (0.190) Severe 1 (51-60): 0.680 (0.244); 0.713 (0.151) Severe 2 (61-70): 0.612 (0.262); 0.697 (0.164) Severe 3 (71-80): 0.535 (0.305); 0.596 0.263) Severe 4 (81+): 0.204 (0.404); 0.385 (0.376)

		to severity (PO-SCORAD score), Europe; US: Moderate (25-50): 413; 412 Severe (>50): 135; 138 Severe 1 (51-60): 62; 79 Severe 2 (61-70): 46; 37 Severe 3 (71-80): 18; 18 Severe 4 (81+): 9; 4			Adjusted mean utility according to severity (PO-SCORAD score), Europe; US: Moderate (25-50): 0.77; 0.74 Severe (>50): NR Severe 1 (51-60): 0.69; 0.67 Severe 2 (61-70): 0.64; 0.66 Severe 3 (71-80): 0.42; 0.56 Severe 4 (81+): NR Adjusted for age, gender, country, smoking behaviour, alcohol use, BMI category, CCI, household income, and years since AD diagnosis.
7	Retzler, 2018, NR (abstract)	484 respondents from the general population	Seven vignettes described different skincare regimens for people with moderate-to-severe AD. These were developed with input from healthcare professionals. No further details reported.	HRQoL was valued using the TTO.	As skincare regimens increased in intensity (0.7968 for the most intense; 0.9999 for the least), utility values decreased. There were no significant differences between skincare regimens followed by patients with good disease control (0.9862 to 0.9999), however, when compared with those involving corticosteroid and emollient combinations (0.7968 to 0.8835), significant differences were observed ($p<0.001$). The largest disutilities (0.1521 to 0.1705) were between skincare regimens describing the use of corticosteroid plus emollient and those followed by patients with good disease control.

8	Retzler, 2019, UK	484 respondents from the general population	Seven vignettes described different skincare regimens for people with moderate-to-severe AD. These were developed with input from healthcare professionals. 44% of respondents reported having used TCS to treat skin conditions. 89.9% of respondents White or White British. Age of respondents, years, n(%): 18–24: 55 (11.4%) 25–34: 85 (17.6%) 35–44 : 80 (16.5%) 45–54 : 90 (18.6%) 55–64 : 70 (14.5%) 65 and over: 104 (21.5%)	HRQoL was valued using the TTO (with 10 years to live).	Skincare regimen: N; mean (SD) 1 Steroid twice daily and emollient four times daily: 473; 0.7968 (0.2159) 2 Steroid twice daily and emollient twice daily: 466; 0.8471 (0.1744) 3 Steroid once daily and emollient twice daily: 446; 0.8835 (0.1469) 4 Light emollient twice daily: 404; 0.9862 (0.0340) 5 Light emollient once daily: 396; 0.9906 (0.0267) 6 Light emollient once every other day: 370; 0.9997 (0.0021) 7 Light emollient on occasion, as needed: 371; 0.9999 (0.0012)
9	Silverberg, 2019, USA	602 participants with AD and 2,291 participants without AD. Sample size according to self-reported AD severity: Mild 289 Moderate 172 Severe 34	Adults from the GfK knowledge panel were invited to participate. Participants with AD; without AD: Mean age, years (SD): 51.0 (15.7); 52.2 (16.4) Caucasian/White, n (%): 396 (65.8%); 1,684 (73.5%)	HRQoL measured using the SF-6D. Valued using the Brazier scoring method and US population-based weights (Brazier 2002).	Mean SF-6D scores (95% CI) according to self-reported global AD severity: Severe 0.59 (0.54-0.64) Moderate 0.64 (0.62-0.66) Mild 0.73 (0.72-0.75) Overall mean SF-6D score in adults with AD and without AD: 0.69 (0.68-0.70) and 0.79 (0.77-0.79), respectively.
10	Silverberg, 2019, USA (abstract)	602 participants	Adults with AD. No further details reported.	HRQoL measured using the SF-6D. Valuation method unclear.	Overall mean SF-6D score in adults with AD and without AD: 0.69 (0.68-0.70) and 0.79 (0.77-0.79), respectively. Moderate-to-severe AD was associated with a mean SF-6D score of 0.53 to 0.66.

11	Simpson, 2017, Multiple study locations	1,379 patients with moderate-to-severe AD. Number of patients according to treatment arm: Placebo, n = 460 Dupilumab 300 mg qw, n = 462 Dupilumab 300 mg q2w, n = 457	Patients enrolled in two phase 3 clinical trials which included adults with moderate-to-severe AD whose disease was inadequately controlled by topical treatment (SOLO 1 NCT02277743 and SOLO 2 NCT02277769, Simpson 2016). These trials compared placebo, subcutaneous dupilumab 300 mg qw or q2w. Both trials are included in a pooled analysis. Mean age 38.3 years (SD 14.3 years).	HRQoL measured using the EQ-5D-3L. Valuation method unclear.	Mean utility according to treatment arm with censoring after rescue treatment and last-observation-carried-forward for imputation of missing data (full analysis set). All patients: baseline (SD); LS mean change at week 16 (SE): Placebo: 0.611 (0.340); 0.031 (0.012) Dupilumab 300 mg qw: 0.607 (0.338); 0.207 (0.012) Dupilumab 300 mg q2w: 0.629 (0.319); 0.210 (0.012) Responders (EASI =>50): N; baseline (SD); LS mean change at week 16 (SE): Placebo: 107; 0.693 (0.34); 0.189 (0.016) Dupilumab 300 mg qw: 282; 0.636 (0.314); 0.255 (0.010) Dupilumab 300 mg q2w: 306; 0.627 (0.325); 0.253 (0.010) Responders (EASI =>75): N; baseline (SD); LS mean change at week 16 (SE): Placebo: 61; 0.712 (0.347); 0.251 (0.020) Dupilumab 300 mg qw: 232; 0.629 (0.314); 0.262 (0.010) Dupilumab 300 mg q2w: 218; 0.631 (0.327); 0.257 (0.011)
12	Simpson, 2016, Multiple study locations	380 patients with moderate-to-severe were randomized and 379 received 1 or	Patients enrolled in a phase 2b, dose-ranging study of dupilumab (NCT01859988, Thaci 2015). This study included adults with moderate-to-severe AD that was inadequately controlled by topical treatment.	HRQoL measured using the EQ-5D-3L. Valued using UK-	Mean utility according to treatment arm (full analysis set, defined as all randomized patients who received 1 or more doses of study drug, with last observation carried forward for imputation of

		more doses of study treatment. Number of patients according to treatment arm: Placebo qw, n = 61 Dupilumab 100 mg q4w, n = 65 Dupilumab 300 mg q4w, n = 65 Dupilumab 200 mg q2w, n = 61 Dupilumab 300 mg q2w, n = 64 Dupilumab 300 mg qw, n = 63	Mean (SD) age, years: Placebo qw: 37.2 (12.1) Dupilumab 100 mg q4w: 36.6 (11.6) Dupilumab 300 mg q4w: 36.8 (10.8) Dupilumab 200 mg q2w: 35.8 (14.9) Dupilumab 300 mg q2w: 39.4 (12.1) Dupilumab 300 mg qw: 36.2 (10.7) Rescue treatment (medication and/ or phototherapy) was allowed at the investigator's discretion; patients who received such therapy were discontinued from study treatment, but were asked to continue with assessments.	based preferences (Dolan 1997).	missing continuous variables). All patients: baseline (SD); LS mean change at week 16 (SE): Placebo qw: 0.654 (0.310); 0.028 (0.034) Dupilumab 100 mg q4w: 0.578 (0.336); 0.106 (0.034) Dupilumab 300 mg q4w: 0.590 (0.327); 0.176 (0.031) Dupilumab 200 mg q2w: 0.608 (0.339); 0.166 (0.034) Dupilumab 300 mg q2w: 0.587 (0.351); 0.230 (0.032) Dupilumab 300 mg qw: 0.658 (0.288); 0.240 (0.031)
13	Simpson, 2016, Multiple study locations	380 patients with moderate-to-severe AD (number randomized at screening)	Patients enrolled in a phase 2b, dose-ranging study of dupilumab (NCT01859988, Thaci 2015). This study included adults with moderate-to-severe AD that was inadequately controlled by topical treatment. Mean age: 37.0 years (SD 12.2 years). White race: n = 257 (67.6%)	HRQoL measured using the EQ-5D-3L. Valued using UK-based preferences (Dolan 1997).	The overall mean utility was 0.659 (SD 0.305).
14	Song, 2019, Korea	155 participants from the general public	Recruited people aged 20-60 years from the general population in Korea. 19 participants had AD. Mean age was 39.7 years.	HRQoL measured using the TTO and EQ-5D-5L. EQ-5D-5L valued using the Korean value set (Kim 2016).	Two health states were described in detail: response and no response. These were developed from in-depth interviews with 20 dermatologists and 10 patients with AD. Mean (SD) utility values, all participants: response; no response TTO based on 10 years: 0.847 (0.120); 0.380 (0.218)

					TTO based on life expectancy: 0.865 (0.119); 0.476 (0.271) EQ-5D-5L: 0.814 (0.074); 0.279 (0.128) Mean utiltiy values, participants with AD: response; no response TTO based on 10 years: 0.898; 0.440 TTO based on life expectancy: 0.902; 0.552 EQ-5D-5L: 0.826; 0.276
15	Vietri, 2017, France, Germany, the UK (abstract)	Of the 548 respondents with moderate-to-severe AD, 118 were from the UK. Sample size according to severity (PO-SCORAD score): Moderate (25-50): 413 Severe (>50): 135	People with moderate-to-severe AD. Respondents had a mean age of 45 years.	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Mean utility according to severity (PO-SCORAD score): Moderate (25-50): 0.79 Severe (>50): 0.61
16	Zimmerman, 2018, USA	NR (population described in Sanofi-Regeneron data on file)	The target population for the economic model was adults in the US with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. Utility values were collected in three dupilumab clinical trials. Population described in Sanofi-Regeneron data on file. The modelled population had a mean age of 38 years.	HRQoL measured using the EQ-5D (levels unclear). Valuation method unclear.	Utilities were collected at baseline and 16 weeks for three clinical trials, and were consistent across the three trials. Mean utility, moderate patients; severe patients: Baseline / no response: 0.684; 0.535 EASI 50: 0.892; 0.882 EASI 75: 0.893; 0.890 EASI 90: 0.907; 0.911

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSC, best supportive care; CCI, Charlson Comorbidity Index; CI, confidence interval; CS, company submission; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; EU, European Union; HRQoL, health-related quality of life; LS, least squares; mg, milligram; MMRM,

mixed model repeated measurement; NHWS, National Health and Wellness Survey; PHQ, patient health questionnaire; PO-SCORAD, Patient-Oriented SCORing Atopic Dermatitis; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids; TE, technical engagement; TTO, time trade-off

HRQOL – HTA submissions

#	Author, year	Sample size	Patient population	Instrument (Valuation)	Utility results
1	SMC2011, 2018	HRQoL data was obtained from the 'all observed' dataset and regressions were conducted at the trial level using CAFÉ, CHRONOS and SOLO and not at the base case population level (CHRONOS- CAFÉ like or SOLO CAFÉ like subgroups). Trial sample sizes CHRONOS: Dupilumab + TCS, n = 106; Placebo + TCS, n = 315 SOLO 1: Dupilumab, n = 204; Placebo, n = 224 SOLO 2: Dupilumab, n = 233; Placebo, n = 236 CAFÉ: Dupilumab + TCS, n = 107; Placebo + TCS, n = 108	Adults with moderate-to-severe AD included in the CHRONOS, CAFÉ and SOLO studies: CHRONOS: patients had an inadequate response to medium or higher potency TCS CAFE: patients who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable SOLO 1 and SOLO 2: patients whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable.	HRQoL measured using the EQ-5D (levels unclear). Valuation method unclear.	Regression analyses were used to estimate utilities in the various states of the model. The baseline utility was 0.66 for patients in the CAFÉ and CHRONOS- CAFÉ like group, rising to 0.898 for a dupilumab responder or 0.797 for both a non-responder to dupilumab or a patient treated with BSC (regardless of whether a responder to BSC or not).
2	SMC2237, 2021	It is unclear which dataset was used to analyse HRQoL data	Adults with moderate-to-severe AD included in the BREEZE-AD4 and BREEZE-AD7 studies:	HRQoL measured using the EQ-5D-5L	Patient-level utilities were included in a mixed-model repeated measures analysis to estimate the

		and how the data from the trials was pooled. Trial sample sizes BREEZE-AD4: Baricitinib 4 mg + TCS, n = 92; Placebo + TCS, n = 93 BREEZE-AD7: Baricitinib 4 mg + TCS, n = 111; Placebo + TCS, n = 109	In BREEZE-AD7, patients had an inadequate response to topical therapies or failure to respond to systemic immunosuppressant therapies. In BREEZE-AD4, patients had an inadequate response to topical therapies and a documented history of an inadequate response, intolerance, or contraindication to ciclosporin.	and mapped to the EQ-5D-3L using a cross walk algorithm (van Hout 2021). Valued using the UK value set (Dolan 1997).	change in utility score at week 16 for an EASI response and non-response. This resulted in mean health state utility values of: Induction: 0.62 Maintenance: 0.84 Non-response: 0.76
3	NICE TA534, 2018	HRQoL data was obtained from the 'all observed' dataset and regressions were conducted at the trial level using CAFÉ, CHRONOS and SOLO and not at the base case population level (CHRONOS- CAFÉ like or SOLO CAFÉ like subgroups). Trial sample sizes CHRONOS: Dupilumab + TCS, n = 106; Placebo + TCS, n = 315 SOLO 1: Dupilumab, n = 204; Placebo, n = 224 SOLO 2: Dupilumab, n = 233; Placebo, n = 236 CAFÉ: Dupilumab + TCS, n = 107; Placebo + TCS, n = 108	Patients included in the LIBERTY trial programme: CHRONOS: adults patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS CAFE: adult patients with moderate-to-severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable SOLO 1 and SOLO 2: adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable Mean (SD) years of age, % Caucasian: CHRONOS: Dupilumab + TCS, 40 (14), 70%; Placebo + TCS, 37 (13), 66% SOLO 1: Dupilumab, 40 (15), 69%; Placebo, 40 (14), 65% SOLO 2: Dupilumab, 37 (14), 71%; Placebo, 37 (14), 66% CAFÉ:	HRQoL measured using the EQ-5D-3L. Valued using UK-based preferences (Dolan 1997).	Mixed regression models were fitted for each trial using a forward selection process, controlling for baseline age, gender, baseline EQ-5D utility score, total EASI score, weekly average of peak daily pruritus, EASI-pruritus interaction and treatment. Results included in the CS, base case (included in the model according to the ERG): All observed dataset, CHRONOS-CAFÉ-like (combination therapy with TCS) Baseline: 0.66 Week 16, dupilumab: 0.898 (0.891) Week 16, BSC: 0.811 (0.797) EASI-50 + DLQI=>4 responder, dupilumab: 0.904 (0.898) All observed dataset, SOLO-CAFÉ-like (monotherapy) Baseline: 0.55 Week 16, dupilumab: 0.830 (0.817) Week 16, BSC: 0.718 (0.6986) EASI-50 + DLQI=>4 responder, dupilumab: 0.855

			Dupilumab + TCS, 38 (13), 97%; Placebo + TCS, 39 (13), 96%		(0.845) Beyond week 16 in the BSC arm of the model, and beyond week 16 for non-responders to dupilumab, all patients share the same overall utility value; i.e. that estimated for all patients in the BSC arm at week 16. In the original economic model, dupilumab non-responders accrued the generalised BSC utility value. The committee suggested that it was more appropriate to use the utility value specific to people whose condition had not responded to dupilumab at 16 weeks than the utility value from everyone having BSC. In response, the company revised their base case: Week 16 - dupilumab non-responders accrue the average of the dupilumab and the BSC non-responder utility value (0.8205) From Week 52 onwards - dupilumab non-responders accrue the BSC non-responder utility value (0.7732)
4	NICE TA681, 2021	HRQoL data was obtained from the pooled population of JAIN + JAIN-like JAIY patients. All observed values across patients receiving all baricitinib dose groups and placebo were included in the analysis. Trial sample sizes BREEZE-AD4 (JAIN) Placebo, n = 93 Baricitinib 1 mg + TCS, n = 93	Patients included in the BREEZE-AD4 (JAIN) and BREEZE-AD7 (JAIY) trials: BREEZE-AD4 (JAIN) is an ongoing multicentre, double-blind, randomised, placebo-controlled Phase III study in adult patients with moderate-to-severe AD. Patients were required to have a documented history of inadequate response to topical treatment and a documented history of failed ciclosporin treatment, defined as an inadequate response following its administration, or a documented contraindication, intolerance or	HRQoL measured using the EQ-5D-5L and mapped to the EQ-5D-3L using a cross walk algorithm (van Hout 2021). Valued using the UK value set (Dolan 1997).	A MMRM approach was used to generate health state utility values. Model parameters included: response variable, gender, visit, age, EQ-5D baseline score, visit-EQ-5D baseline score interaction. Results included in the CS, base case: Induction/baseline: 0.5979 Maintenance (EASI-50 + DLQI=>4 responder): 0.7800 Non-response: 0.5979

		Baricitinib 2 mg + TCS, n = 185 Baricitinib 4 mg + TCS, n = 92 Number of patients in BREEZE-AD7 (JAIY) redacted.	unacceptable toxicity to its use. BREEZE-AD7 (JAIY) was a multicentre, randomised, double-blind, placebo-controlled Phase III trial in adult patients with moderate-to-severe AD. Patients were required to have a documented history of an inadequate response to, or intolerance to, topical medication. BREEZE-AD4 (JAIN): Placebo; 1 mg; 2 mg; 4 mg Mean age, years (SD): 39 (14;) 39 (14); 37 (14); 39 (13) Caucasian: 80%; 75%; 78%; 77% Baseline characteristics in BREEZE-AD7 (JAIY) redacted.		The ERG conducted two scenario analysis a) HRQoL data from the JAIN and JAIN-like JAIY patients and modelled considering a more appropriate comparative analysis. This scenario intends to illustrate the issues with the values provided and how they serve to undermine the model structure used by the company Induction/baseline: 0.5979 Maintenance/response: 0.7800 Non-response: 0.8021 b) values based on those reported in TA534. In this scenario, treatment specific utilities are applied such that patients on maintenance baricitinib and dupilumab are assigned the reported utility of responders to dupilumab. Patients on BSC, including patients classified as non-responders are assigned a single utility value based on the average of all placebo patients at week 16 Induction/baseline: 0.66 Maintenance/response, baricitinib/dupilumab: 0.898 Maintenance/response, BSC: 0.797 Non-response: 0.797 Results included in the company's TE response: Induction/baseline: 0.6182 Change from baseline at Week 16, mean LS: response (EASI-75) 0.2310 Change from baseline at Week 16, mean LS: non-response 0.1445 The committee concluded that, given the flaws with

					the company's utility values, the utility values from TA534 were preferable.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CS, company submission; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; HRQoL, health-related quality of life; LS, least squares; mg, milligram; MMRM, mixed model repeated measurement; SD, standard deviation; TCS, topical corticosteroids; TE, technical engagement

10.4 Tables of excluded studies with rationale

Table 114. Studies excluded from the systematic review of RCTs for clinical effectiveness with rationale

Study	Reason for exclusion
Correction[158]	Wrong population
Alexis 2020[159]	Wrong outcome
Andres 2020[160]	Wrong study type
Armstrong 2020[161]	Wrong study type
Armstrong 2021a[162]	Wrong study type
Armstrong 2021b[163]	Wrong study type
Beck 2014[69]	Wrong intervention
Beck 2019a[164]	Wrong outcome
Beck 2019b[165]	Wrong outcome
Beck 2019c[166]	Wrong outcome
Beck 2020a[167]	Wrong study type
Beck 2020b[168]	Wrong study type
Beck 2021a[169]	Wrong outcome
Beck 2021b[170]	Wrong study type
Bhutani 2020[171]	Wrong population
Bieber 2014[70]	Wrong intervention
Blake 2019[172]	Wrong outcome
Blauvelt 2019[72]	Wrong intervention
Blauvelt 2020a[173]	Wrong study type
Blauvelt 2020b[174]	Wrong study type
Blauvelt 2020c[175]	Wrong study type
Blauvelt 2020d[176]	Wrong study type
Blauvelt 2021a[177]	Wrong study type
Blauvelt 2021b[178]	Wrong study type
Blauvelt 2021c[179]	Wrong study type
Callewaert 2019[180]	Wrong outcome
Cork 2019[181]	Wrong study type
Cork 2020[182]	Wrong outcome
Cork 2021a[183]	Wrong outcome
Cork 2021b[184]	Wrong population
Cork 2021c[185]	Wrong study type
de Bruin-Weller 2020a[186]	Wrong outcome
de Bruin-Weller 2020b[187]	Wrong outcome
Deng 2019[188]	Wrong study type

Drucker 2018[189]	Wrong study type
Elewski 2021[190]	Wrong outcome
Gooderham 2020a[191]	Wrong population
Gooderham 2020b[192]	Wrong population
Gooderham 2021a[193]	Wrong population
Gooderham 2021b[194]	Wrong study type
Guttman-Yassky 2019a[195]	Wrong intervention
Guttman-Yassky 2019b[196]	Wrong outcome
Guttman-Yassky 2019c[197]	Wrong study type
Guttman-Yassky 2019d[73]	Wrong intervention
Guttman-Yassky 2020a[198]	Wrong outcome
Guttman-Yassky 2020b[199]	Wrong outcome
Guttman-Yassky 2021[200]	Wrong outcome
Hamilton 2014[74]	Wrong intervention
Lacour 2020a[201]	Wrong study type
Lacour 2020b[202]	Wrong study type
Lake 2019[203]	Wrong study type
Lebwohl 2021[204]	Wrong study type
Lio 2021[205]	Wrong outcome
Marcoux 2021[206]	Wrong population
McMichael 2021[207]	Wrong outcome
Merola 2020a[208]	Wrong outcome
Merola 2020b[209]	Wrong outcome
Paller 2020a[210]	Wrong population
Paller 2020b[211]	Wrong population
Paller 2020c[212]	Wrong population
Paller 2020d[213]	Wrong population
Paller 2021a[214]	Wrong population
Paller 2021b[215]	Wrong population
Papp 2020[216]	Wrong outcome
Peng 2019[217]	Wrong intervention
Raniga 2021[218]	Wrong outcome
Reich 2020a[219]	Wrong outcome
Reich 2020b[220]	Wrong outcome
Reich 2020d[221]	Wrong study type
Reich 2020e[222]	Wrong study type
Seigfried 2020[223]	Wrong outcome
Silverberg 2018a[224]	Wrong outcome
Silverberg 2018b[225]	Wrong outcome

Silverberg 2020[226]	Wrong outcome
Silverberg 2021a[227]	Wrong outcome
Silverberg 2021b[228]	Wrong outcome
Silverberg 2021c[229]	Wrong outcome
Silverberg 2021d[230]	Wrong population
Silverberg 2021e[231]	Wrong outcome
Simpson 2019[232]	Wrong outcome
Simpson 2020a[233]	Wrong outcome
Simpson 2020b[234]	Wrong outcome
Simpson 2020c[235]	Wrong outcome
Simpson 2020d[236]	Wrong outcome
Simpson 2021a[237]	Wrong study type
Simpson 2021b[238]	Wrong outcome
Simpson 2021c[239]	Wrong population
Thaci 2020a[240]	Wrong study type
Thaci 2020b[241]	Wrong study type
Tofte 2018[242]	Wrong study type
Tsianakas 2018[77]	Wrong intervention
Wu 2021[243]	Wrong outcome
Zheng 2020[60]	Wrong study type

Economic evaluations

Table 115. Excluded studies list: economic evaluations

#	Bibliographic reference	Reason for exclusion
1	Ariëns LFM, van Nimwegen KJM, Shams M, de Bruin DT, van der Schaft J, van Os-Medendorp H, De Bruin-Weller M. Economic Burden of Adult Patients with Moderate-to-severe Atopic Dermatitis Indicated for Systemic Treatment. Acta Derm Venereol. 2019 Jul; 99(9): 762-768.	Irrelevant study design
2	Ariëns LFM, van der Schaft J, van Os-Medendorp H, De Bruin-Weller M. The economic impact of patients with moderate-to-severe atopic dermatitis eligible for systemic treatment. Br. J. Dermatol. 2018; 179(1): e38.	Irrelevant study design
3	Cabout E, Eymere S, Launois R, Aslanian F, Taïeb C, Seité S. Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis. Clin Cosmet Investig Dermatol. 2020; 13: 987-996	Irrelevant comparison
4	Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy: Analisi costo-utilità di dupilumab per il trattamento della dermatite atopica grave negli adulti in Italia. Glob Reg Health Technol Assess. 2020; 7(1): 57-65	Non-English publication

5	Edwards HA, McMeniman EK. 12-month cost comparison of dupilumab treatment versus alternatives for severe atopic dermatitis. The Australasian College of Dermatologists. 2021	Irrelevant study design
6	Edwards HA, McMeniman EK. The cost of dupilumab treatment for severe atopic dermatitis is largely offset by broader health-care savings and improvement in quality of life. Australas J Dermatol. 2020 May; 61(2): e273-e275	Irrelevant study design
7	Freund D, Choi J. Is ICER NICEr?. PharmacoEconomics. 2018; 36: 385–386	Irrelevant study design
8*	Gutknecht M, Reinert R, Augustin M. Review of Health Economic Analysis in Atopic Dermatitis. 2019	Irrelevant study design
9	Sach TH, McManus E, Levell NJ. Understanding economic evidence for the prevention and treatment of atopic eczema. Br J Dermatol. 2019; 181(4): 707-716	Irrelevant study design
10	Takenaka M, Matsumoto M, Murota H, Inoue S, Shibahara H, Yoshida K, Takigawa S, Ishimoto A. Cost-effectiveness analysis of delgocitinib in adult patients with atopic dermatitis in Japan. J Cutan Immunol Allergy. 2021; 00: 1-9	Irrelevant comparison
11	Wu AC, Fuhlbrigge AL, Robayo MA, Shaker M. Cost-Effectiveness of Biologics for Allergic Diseases. J Allergy Clin Immunol Pract. 2021 Mar; 9(3): 1107-1117	Irrelevant study design Irrelevant comparison

*Exported reference from the electronic databases could not be identified (J. Dermatol. Nurses' Assoc. 2020; 12(2):1945-760X). As such, the abstract at the 24th World Congress of Dermatology Milan 2019 which included the same authors and title was considered for inclusion.

HRQoL

Table 116. Excluded studies list: economic evaluations

#	Bibliographic reference	Reason for exclusion
1	Alegre-Sanchez A, de Perosanz-Lobo D, Pascual-SÃ¡nchez A, Pindado-Ortega C, Fonda-Pascual P, Moreno-Arrones ÃM, JaÃon-Olasolo P. Impact on Quality of Life in Dermatology Patients Attending an Emergency Department, Actas Dermo-Sifiliográficas (English Edition). 2017; 108(10): 918-923	Irrelevant population
2	Ali FM, Kay R, Finlay AY, Piguet V, Kupfer J, Dalgard F, Salek MS. Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression. Qual Life Res. 2017 Nov; 26(11): 3025-3034	Irrelevant population
3	Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Ständer S, Steinke S, Kirsten N, Silva N, Sommer R. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. J Eur Acad Dermatol Venereol. 2020 Jan; 34(1): 142-152	Irrelevant outcome
4	Blauvelt A, Szepietowski JC, Papp K, Simpson, E, Silverberg JI, Kim, BS, Kwatra SG, Kuligowski ME, Venturanza ME, Sun K, Kircik L. 325 Ruxolitinib cream rapidly decreases skin pain in atopic dermatitis. Journal of Investigative Dermatology. 2021 May; 141(5): S57	Abstract with insufficient detail

5	Cabout E, Trouiller JB, Launois R, Taieb C,SEITE, S. PSY1 COST-EFFECTIVENESS OF EMOLLIENTS IN PATIENTS WITH ATOPIC DERMATITIS. Value in Health. 2019; 22: S901.	Original HRQoL data not reported
6	Cabout E, Eymere S, Launois R, Aslanian F, Taïeb C, Seité S. Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis. Clin Cosmet Investig Dermatol. 2020 Dec 21; 13: 987-996	Original HRQoL data not reported Irrelevant population
7	Canadian Agency for Drugs and Technologies in Health (CADTH). Drug Reimbursement Review Dupilumab (Dupixent). 2018	Original HRQoL data not reported Utility data redacted
8	Carvalho D, Aguiar P, Mendes-Bastos P, Palma-Carlos A, Freitas J, Ferrinho P. Quality of Life and Characterization of Patients With Atopic Dermatitis in Portugal: The QUADEP Study. J Investig Allergol Clin Immunol. 2020; 30(6): 430-438	Irrelevant outcome Irrelevant population
9	Cheng B, Silverberg J. 599 Impact of atopic dermatitis on overall health-related quality of life and health utility scores in US adult patients. Journal of Investigative Dermatology. 2019 May; 139(5): S103	Abstract with insufficient detail
10	Cheng BT, Silverberg JI. Association between atopic dermatitis and lower health utility scores in US adults. Ann Allergy Asthma Immunol. 2020 Jan; 124(1): 88-89	Abstract with insufficient detail
11	Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L, Girolomoni G, de Bruin-Weller M, Wollenberg A, Kataoka Y, Remitz A, Beissert S, Mastey V, Ardeleanu M, Chen Z, Gadkari A, Chao J. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. J Dermatolog Treat. 2020 Sep; 31(6): 606-614	Irrelevant outcome
12	Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy: Analisi costo-utilità di dupilumab per il trattamento della dermatite atopica grave negli adulti in Italia. Glob Reg Health Technol Assess. 2020; 7(1): 57-65	Non-English publication
13	Bruin-Weller M, Pink AE, Patrizi A, Giménez-Arnau AM, Agner T, Roquet-Gravy P-P, Jayawardena S, Ardeleanu M, Kerkmann U, Rizova E. 161 EUROSTAD Prospective Observational Study: Baseline Characteristics, Atopic Dermatitis Severity, and Patient-Reported Outcomes. Journal of Investigative Dermatology. 2019; 139(9): S241	Irrelevant outcome
14	Bruin-Weller M, Pink AE, Patrizi A, Giménez-Arnau AM, Agner T, Roquet-Gravy P-P, Jayawardena S, Ardeleanu M, Kerkmann U, Rizova E. EUROSTAD prospective observational study: Baseline characteristics, atopic dermatitis severity, and patient-reported outcomes. Journal of Investigative Dermatology. 2019; 81(4): AB58	Irrelevant outcome
15	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan S. Impact of atopic dermatitis on patient self-reported quality of life, productivity loss, and activity impairment: An analysis using the National Health and Wellness survey. J. Am. Acad. Dermatol. 2016; 74(5): AB87	Abstract with insufficient detail
16	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan S. Comparison of atopic dermatitis with psoriasis on patient self-reported quality of life and productivity	Abstract with insufficient detail

	loss: Analysis of the National Health and Wellness Survey. J. Am. Acad. Dermatol. 2016; 74(5): AB85	
17	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. J Am Acad Dermatol. 2017 Aug; 77(2) :274-279	AD severity unclear. Authors contacted with no response
18	Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. J Am Acad Dermatol. 2019 Jul; 81(1): 187-195	Irrelevant outcome
19	Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in atopic dermatitis (AD) patients by self-reported severity: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Presented at European Academy of Allergy and Clinical Immunology (EAACI), June 17–21, 2017, Helsinki, Finland	Irrelevant outcome
20	Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Allergy Eur. J. Allergy Clin. Immunol. 2017; 72(0): 44	Abstract with insufficient detail
21	Fanelli F, Pedone MP, Serra A, Bitonti R, Furneri G. PBI11 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Atopic Dermatitis in Adolescent Patients in Italy. Value in Health. 2020; 23: S412	Abstract with insufficient detail
22	Huet F, Shourick J, Séité S, Taïeb C, Misery L. Pain in Atopic Dermatitis: An Online Population-based Survey. Acta Derm Venereol. 2020 Jul; 100(14): adv00198.	Irrelevant outcome
23	Ikeda M, Uehara H, Tsuge M. Efficacy and safety of long-term treatment with dupilumab for moderate-to-severe atopic dermatitis. 2019	Unavailable
24	Kamei K, Horise T, Yoshii N, Tanaka A. Burden of illness, medication adherence, and unmet medical needs in Japanese patients with atopic dermatitis: A retrospective analysis of a cross-sectional questionnaire survey. J Dermatol. 2021; 00: 1–8	Irrelevant population (authors confirmed patients with mild AD included, proportion unknown)
25	Kornmehl H, Singh S, Johnson M, Armstrong A. Direct-access online care for the management of atopic dermatitis: A randomized controlled clinical trial examining patient quality of life. J. Invest. Dermatol. 2017; 137(5): S58	Irrelevant outcome
26	Kornmehl H, Singh S, Johnson MA, Armstrong AW. Direct-Access Online Care for the Management of Atopic Dermatitis: A Randomized Clinical Trial Examining Patient Quality of Life. Telemed J E Health. 2017 Sep; 23(9): 726-732	Irrelevant population
27	Kupfer J, Schut C, Gieler U, Tomas-aragones L, Lien L, Dalgard F. THE BURDEN OF ATOPIC DERMATITIS AND ACNE - A COMPARISON WITH A STRATIFIED CONTROL GROUP. Acta Dermato Venereologica. 2016; 96:123	Abstract with insufficient detail
28	Kuznik A, Bégo-Le-Bagousse G, Eckert L, Gadkari A, Simpson E, Graham CN, Miles L, Mastey V, Mahajan P, Sullivan SD. Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. Dermatol Ther (Heidelb). 2017 Dec; 7(4): 493-505	Original HRQoL data not reported
29	Kwatra SG, Huang AH, Jhaveri M, Gruben D, Fung S, DiBonaventura M. 16443 Prevalence and impact of psychosocial comorbidities on health status	Irrelevant outcome

	among patients with moderate-to-severe atopic dermatitis in the United States: Analysis of the 2017 US National Health and Wellness Survey. J. Am. Acad. Dermatol.2020; 83(6): AB179	
30	Kwatra SG, Huang AH, Jhaveri M, Gruben D, Fung S, DiBonaventura M. 16434 Health status, work productivity, and health care resource utilization in patients with moderate-to-severe atopic dermatitis: Analysis of the 2017 United States National Health and Wellness Survey. J. Am. Acad. Dermatol. 2020; 83(6): AB63	Irrelevant outcome
31	Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. J Eur Acad Dermatol Venereol. 2014 Jun; 28(6): 719-26	Irrelevant outcome
32	Le PH, Vo TQ, Nguyen NH. Quality of life measurement alteration among Vietnamese: Impact and treatment benefit related to eczema. J Pak Med Assoc. 2019 Jun;69(Suppl 2)(6):S49-S56	Abstract with insufficient detail
33	Lee SH, Lee SH, Lee SY, Lee B, Lee SH, Park YL. Psychological Health Status and Health-related Quality of Life in Adults with Atopic Dermatitis: A Nationwide Cross-sectional Study in South Korea. Acta Derm Venereol. 2018 Jan 12; 98(1): 89-97	AD severity unclear. Authors contacted with no response
34	Lio PA, Wollenberg A, Thyssen JP, Pierce EJ, Rueda MJ, DeLozier AM, Ross Terres JA, Anderson P, Milligan G, Piercy J, Silverberg JI, Paul C. Impact of Atopic Dermatitis Lesion Location on Quality of Life in Adult Patients in a Real-world Study. J Drugs Dermatol. 2020 Oct 1;19(10):943-948	Irrelevant population
35	Marron SE, Alcalde-Herrero VM, Garcia-Latasa FJ, Moncin-Torres Dpharm, CA, Fuentelsaz-del-Barrio MV, Alvarez-Salafranca M, Tomas-Aragones L. Dupilumab for the treatment of adult atopic dermatatis patients in routine clinical practice. J. Am. Acad. Dermatol. 2019; 81(4): AB48	Abstract with insufficient detail
36	Marron SE, Tomas-Aragones L, Moncin-Torres CA, Gomez-Barrera M, Aranibar FJG. Patient Reported Outcome Measure in Atopic Dermatitis Patients Treated with Dupilumab: 52-Weeks Results. Life (Basel). 2021 Jun 25; 11(7): 617	Irrelevant outcome
37	Mastey V, Simpson E, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham N, Pirozzi G, Sutherland E. The patient burden of atopic dermatitis: insights from a dupilumab phase 2 clinical trial in adults with moderate-to-severe disease. Experimental Dermatology. 2014; 23: 4	Abstract with insufficient detail
38	Misery L, Seneschal J, Reguiai Z, Merhand S, Héas S, Huet F, Taieb C, Ezzedine K. The impact of atopic dermatitis on sexual health. J Eur Acad Dermatol Venereol. 2019 Feb;33(2):428-432	Irrelevant outcome
39	Misery L, Seneschal J, Ezzedine K, Heas S, Merhand S, Reguiai Z, Taieb C. PSS40 Atopic dermatitis is associated with poor quality of life in adult patients. Value in Health. 2017: A399-A811	Abstract with insufficient detail
40	Misery L, Reguiai Z, Seneschal J, Heas S, Merhand S, Taieb C, Ezzedine K. Atopic dermatitis is associated with poor quality of life in adult patients. J. Am. Acad. Dermatol. 2018; 79(3): AB50	Abstract with insufficient detail
41	Nguyen SH, Nguyen LH, Vu GT, Nguyen CT, Le THT, Tran BX, Latkin CA, Ho CSH, Ho RCM. Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. Int J Environ Res Public Health. 2019 Jan 23; 16(3): 305	AD severity unclear. Authors contacted with no response.

42	Ock M, Han JW, Lee JY, Kim SH, Jo MW. Estimating quality-adjusted life-year loss due to noncommunicable diseases in Korean adults through to the year 2040. Value Health. 2015 Jan; 18(1): 61-6	Irrelevant outcome
43	Park YL, Lee SH, Kim HJ, Hong KR, Young Park A, Lee JS. Psychologic health status and health-related quality of life in adults with atopic dermatitis. J. Am. Acad. Dermatol. 2018; 79(3): AB234	Abstract with insufficient detail
44	Rencz F, Baji P, Gulácsi L, Kárpáti S, Péntek M, Poór AK, Brodszky V. Discrepancies between the Dermatology Life Quality Index and utility scores. Qual Life Res. 2016 Jul; 25(7): 1687-96	Irrelevant population
45	Schwartzman G, Lei D, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R, Chavda R, Gabriel S, Patel KR, Singam V, Kantor R, Hsu DY, Silverberg JI. Validity and reliability of Patient-Reported Outcomes Measurement Information System Global Health scale in adults with atopic dermatitis. J Am Acad Dermatol. 2021 Jan 20: S0190-9622(21)00180-8.	Irrelevant outcome
46	Seneschal J, Ezzedine K, Reguiai Z, Heas S, Merhand S, Misery L, Taieb C. PSS41 Atopic dermatitis in adults: Impact on sexuality. Value in Health. 2017: A399-A811	Irrelevant outcome
47	Seneschal J, Misery L, Reguiai Z, Heas S, Merhand S, Taieb C, Ezzedine K. Atopic dermatitis in adults: Impact on sexuality. J. Am. Acad. Dermatol. 2018; 79(3): AB50	Irrelevant outcome
48	Silverberg J, Gelfand JM, Margolis D, Boguniewicz M, Fonacier L, Grayson M, Ong P, Fuxench ZC, Simpson EL. 245 Validation and interpretation of short form 12 and comparison with dermatology life quality index in adult atopic dermatitis. Journal of Investigative Dermatology. 2019; 139(5): S42	Irrelevant outcome
49	Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Chiesa Fuxench ZC, Simpson EL. Validation and Interpretation of Short Form 12 and Comparison with Dermatology Life Quality Index in Atopic Dermatitis in Adults. J Invest Dermatol. 2019 Oct; 139(10): 2090-2097	Irrelevant outcome
50	Silverberg JI, Kragh N, Guttman-Yassky E, Wollenberg A. Tralokinumab with topical corticosteroids (TCS) improves health-related quality of life (HRQoL) in adults with moderate-to-severe atopic dermatitis (AD): A Phase 2b, randomized, double-blind, placebo-controlled study. Experimental dermatology. 2018; 27: 41-42	Irrelevant outcome
51	Silverberg JI, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Fuxench ZC, Simpson EL. Validation of five patient-reported outcomes for atopic dermatitis severity in adults. Br J Dermatol. 2020 Jan; 182(1): 104-111	Irrelevant outcome
52	Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Simpson EL, Ong PY, Chiesa Fuxench ZC. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018 Sep; 121(3): 340-347	Irrelevant outcome
53	Silverberg JI, Guttman-Yassky E, Gooderham M, Worm M, Rippon S, O'Quinn S, van der Merwe R, Kragh N, Kurbasic A, Wollenberg A. Health-related quality of life with tralokinumab in moderate-to-severe atopic dermatitis: A phase 2b randomized study. Ann Allergy Asthma Immunol. 2021 May; 126(5): 576-583	Irrelevant outcome
54	Silverberg JI, Simpson EL, Guttman-Yassky E, Cork MJ, de Bruin-Weller M, Yosipovitch G, Eckert L, Chen Z, Ardeleanu M, Shumel B, Hultsch T, Rossi AB, Hamilton JD, Orengo JM, Ruddy M, Graham NMH, Pirozzi G, Gadkari A.	Irrelevant outcome

	Dupilumab Significantly Modulates Pain and Discomfort in Patients With Atopic Dermatitis: A Post Hoc Analysis of 5 Randomized Clinical Trials. Dermatitis. 2020 Nov 5.	
55	Silverberg JI, Chiesa-Fuxench Z, Margolis D, Boguniewicz M, Fonacier L, Grayson M, Simpson E, Ong P. Sleep Disturbances in Atopic Dermatitis in US Adults, Dermatitis: March 5, 2021	Irrelevant population Irrelevant outcome
56	Simpson E, Worm M, Soong W, Blauvelt A, Eckert L, Wu R, Ardeleanu M, Graham N, Pirozzi G, Sutherland ER, Mastey V. 544 Dupilumab improves patient-reported outcomes (PROS) in a phase 2 study in adults with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2015; 135(2): AB617	Abstract with insufficient detail
57	Steinke S, Langenbruch A, Ständer S, Franzke N, Augustin M. Therapeutic benefits in atopic dermatitis care from the patients' perspective: results of the German national health care study 'Atopic Health'. Dermatology. 2014; 228(4): 350-9	Irrelevant outcome
58	Takenaka M, Matsumoto M, Murota H, Inoue S, Shibahara H, Yoshida K, Takigawa S, Ishimoto A. Cost- effectiveness analysis of delgocitinib in adult patients with atopic dermatitis in Japan. J Cutan Immunol Allergy. 2021; 00: 1–9.	Irrelevant outcome
59	Thaci D, Deleuran M, De Bruin-Weller M, Chen Z, Tomondy P, Ardeleanu M, Boklage S, Shumel B, Surendranathan T. 009 Dupilumab treatment for up to 100 weeks demonstrates sustained improvement in quality of life in adult patients with moderate-to-severe atopic dermatitis (LIBERTY AD OLE). British Association of Dermatologists. 2020; 183(Suppl. 1): 9–25	Abstract with insufficient detail
60	Thaçi D, L Simpson E, Deleuran M, Kataoka Y, Chen Z, Gadkari A, Eckert L, Akinlade B, Graham NMH, Pirozzi G, Ardeleanu M. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). J Dermatol Sci. 2019 May; 94(2): 266-275	Irrelevant outcome
61	Vilsbøll A, Kragh N, Hahn-Pedersen J, Jensen CE. An algorithm to generate EQ-5D-5L utility scores from the dermatology life quality index: A direct mapping study in a population with atopic dermatitis. Qual. Life Res. 2018; 27(0): S28-S29	Abstract with insufficient detail
62	Vilsbøll AW, Kragh N, Hahn-Pedersen J, Jensen CE. Mapping Dermatology Life Quality Index (DLQI) scores to EQ-5D utility scores using data of patients with atopic dermatitis from the National Health and Wellness Study. Qual Life Res. 2020 Sep; 29(9): 2529-2539	Irrelevant population
63	Whiteley J, Emir B, Seitzman R, Makinson G. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. Curr Med Res Opin. 2016 Oct; 32(10): 1645-1651	Abstract with insufficient detail

10.5 Clinical effectiveness sensitivity analysis

Table 117. Results of sensitivity analysis adjusting for differences in placebo response, generated by NMA

	NMA OR (95% CrI)		
Population	**Adult 2L monotherapy**	**Adult 2L monotherapy**	**Adolescents**
Outcome	**EASI 50 + ΔDLQI ≥4**	**EASI 75**	**EASI 75**
Treatments versus placebo			
Abro 200 mg QD	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W	[redacted]	[redacted]	[redacted]
Dup 300 mg QW	[redacted]	[redacted]	NA
Tralokinumab	[redacted]	[redacted]	NA
Upa 30 mg QD	[redacted]	[redacted]	NA
Upa 15 mg QD	[redacted]	[redacted]	[redacted]
Treatments versus Dup 200 mg or 300 mg every 2 weeks			
Abro 200 mg QD	[redacted]	[redacted]	[redacted]
Abro 100 mg QD	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	NA
Upa 30 mg QD	[redacted]	[redacted]	NA
Upa 15 mg QD	[redacted]	[redacted]	[redacted]
Treatment doses versus each other			
Abro 200 mg QD vs abro 100 mg QD	[redacted]	[redacted]	[redacted]
Upa 30 mg QD vs upa 15 mg QD	[redacted]	[redacted]	NA

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

10.6 Summary of TA534, TA681 and the company submission and EAG approach

Table 118 presents a detailed overview of TA534, TA681 and the company submission and EAG approach.

Table 118. Summary of TA534, TA681 and the company submission and EAG approach

	Committee decisions (TA534 &TA681)	Abrocitinib (Pfizer)	Tralokinumab (Leo Pharma)	Upadacitinib (AbbVie)	EAG approach
Population	TA534 - dupilumab in combination with TCS is recommended for treating moderate-to-severe AD in adults if the disease has not responded to at least 1 other systemic therapy, such as CsA, methotrexate, azathioprine and mycophenolate, or these are contraindicated or not tolerated. The data informing the assessment were based on the subgroup of patients who had an inadequate response to CsA, or where CsA was not tolerated or was contraindicated. Patients who had failed on other systemic therapies such as methotrexate, azathioprine and mycophenolate, were excluded.	Patients with moderate-to-severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. The company submission includes both adults and adolescents (aged 12 and older). However, the clinical data informing the company's base case is for patients who were previously treated with at least one systemic treatment for AD (referred to as the "generalisable population"). The company's sensitivity analyses were conducted using the "restricted"	Adult patients with moderate-to-severe AD that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated. The clinical data informing the company's base case are for patients who had inadequate control with, or intolerance or contraindications to CsA.	The population considered by the company is adults and adolescents (12 years and older) with moderate-to-severe AD who are candidates for systemic therapy. The company split the population by line of therapy, as follows: - In people who are candidates for conventional systemic treatment (referred to as 'systemic eligible'). - In people in whom the disease has not responded to at least one other conventional systemic therapy (CsA, methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic	The populations considered of relevance to the MTA are adolescents aged 12 to 18 years and adults aged 18 years and older. The definition of the populations in the MTA are as follows: - First-line systemic therapy denotes those who are eligible for systemic treatment on inadequate response to topical treatments, and; - Second-line systemic therapy captures those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (often CsA azathioprine or

	TA681 - Baricitinib is recommended for treating moderate-to-severe AD in adults if the disease has not responded to at least 1 other systemic immunosuppressant, such as CsA, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable. The data informing the NMA were based on the subgroup of patients who had an inadequate response to CsA, or where CsA was not tolerated or was contraindicated. Patients who had failed on other systemic therapies such as methotrexate, azathioprine and mycophenolate, were excluded.	population for abrocitinib based on the subgroup of patients who have failed or were intolerant to CsA. However, contraindication to CsA was not captured in trials evaluating abrocitinib and, therefore, the restricted population is limited to those who did not achieve an adequate response to CsA.		therapy is not suitable (referred to as 'systemic exposed'). The clinical data informing the adult systemic eligible population includes patients who have been treated with conventional systemic therapies and thus overlaps with the adult exposed population. With regards to the adolescent systemic-eligible population, clinical data include patients who have had systemic therapy and may not be generalisable to the adolescent exposed population that received dupilumab in clinical practice. The adult systemic-exposed is limited to those who had received CsA or were intolerant of or experienced a medical complication of CsA as contraindication to CsA was not captured in trials evaluating upadacitinib.	methotrexate). Abrocitinib, tralokinumab and upadacitinib will be assessed in the population position proposed by the company of each drug. Dupilumab and baricitinib will be included as comparators as per the population position in the NICE recommendations in TA534 and TA681. The clinical data informing the different populations includes: • adults with moderate-to-severe AD and inadequate response to topical treatments receiving first-line systemic treatment, • adults with moderate-to-severe AD receiving second-line systemic treatment after inadequate response to CsA, or where CsA was not tolerated or was contraindicated; • adolescents, irrespective of prior therapy.

Interventions	Dupilumab 600mg loading dose followed by 300mg Q2W. Baricitinib 4mg once daily. Dupilumab and baricitinib, both as monotherapy and in combination with TCS. However, combination therapy was considered more clinically relevant for both TA534 and TA681.	Abrocitinib 200mg once daily (tablet). 100mg dose available for patients aged >65 years. Separate analyses were performed to model abrocitinib as a 100 mg or 200 mg dose. The company assessed abrocitinib as both monotherapy and in combination with medicated topical therapy. The company's primary analysis is for the combination therapy as that is how they anticipate abrocitinib will be used in clinical practice	Tralokinumab 600mg loading dose followed by 300mg Q2W. Option for tralokinumab maintenance therapy to be given as 300mg Q4W for patients who achieve clear or almost clear skin. The company assess tralokinumab as both monotherapy and in combination with TCS. Furthermore, the company includes a base case assumption that [redacted] of patients switched to Q4W dosing at week 52.	Upadacitinib 15mg or 30 mg once daily (tablet). 2 doses (15/30mg) either given as a monotherapy or in combination with TCS. The company present results for both doses of upadacitinib and the licensed dose for adolescents expected to be 15mg. However, the company did not explore dose escalation to upadacitinib 30mg for adult patients on upadacitinib 15mg in the presence of treatment effect waning.	Abrocitinib 200mg or 100mg once daily (tablet). Tralokinumab 600mg loading dose followed by 300mg Q2W. Upadacitinib 15mg or 30 mg once daily (tablet) Each treatment will be considered as monotherapy and in combination with TCS. Where appropriate, dose reductions will be considered.
Comparators	BSC was the accepted comparator for both TA534 and TA681. In TA681, dupilumab was also considered as a comparator. TA534 - CsA modelled as 5 mg/kg daily week 1 to 6 and 3 mg/kg daily week 6 to 52.	Dupilumab 300mg Q2W with an initial loading dose based on weight of 600mg (>60kg) or 400mg (<60kg) Baricitinib 4mg once daily. Both comparators assessed as monotherapy and in combination with TCS.	Dupilumab 600mg loading dose followed by 300mg Q2W, assessed as both monotherapy and in combination with TCS. BSC, defined as a combination of emollients, low-to-mid potency TCS in the case of combination therapy, and rescue therapy (such as higher potency topical or oral corticosteroids and TCIs).	CsA (systemic eligible only) 3 mg/kg daily for weeks 1-16 followed by 5 mg/kg daily for the remainder of the year. Company's dosing of CsA based on clinical expert opinion. Dupilumab 600mg loading dose followed by 300mg Q2W, assessed as both monotherapy and in combination with TCS. BSC, defined as a combination of emollients, low-to-mid potency TCS	For adult patients with moderate-to-severe AD that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated, dupilumab and baricitinib are both recommended and will be considered as comparators in this position. Each treatment will be considered as both monotherapy and in combination with TCS.

				and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs) phototherapy and psychological support.	Dupilumab is also provided for adolescents under the NHS England Medicines for Children Policy and will be considered as a comparator in the adolescent analyses. For patients eligible for systemic treatment, CsA (using the licensed dose regimen) will be considered as the comparator as it is the only licensed treatment for this position.
Model structure	TA534 - One year decision tree with outcomes based on response, followed by a 3-state Markov Model with annual cycles. Health states in the Markov model included maintenance, BSC and death. TA681 - 4-state Markov model with 4-week cycles. Health states in the model include induction, maintenance, non-response and death. For both TA534 and TA681, the committee accepted the model structures as suitable	1 year decision tree followed by a 3-state Markov model, with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include, maintenance, BSC and death. The BSC health state in the Markov model is a weighted average of responders and non-responders.	1 year decision tree followed by a 3-state Markov chain with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include maintenance, BSC and death. In the tralokinumab, baricitinib and dupilumab model engines, there is a single health state for BSC non-responders. Patients who switch from maintenance therapy to BSC are assumed to remain BSC non responders for the remainder of the modelled time horizon. In the BSC	1 year decision tree followed by a 4-state Markov chain with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include maintenance, BSC non-responders, BSC responders and death. Patients who switch from maintenance therapy to BSC can only transition to the BSC non responder health state.	As per TA534, the model structure will be based on a one-year decision tree with outcomes based on response, followed by a 3-state Markov Model with annual cycles. Health states in the Markov model included maintenance, BSC and death. The BSC health state will be one overall BSC health state composed of responders and non-responders and these proportions will be informed by week 16 data.

	for decision making. However, for TA681, the committee considered the model structure was similar to the structure accepted in TA534.		model engine, the BSC health state is subdivided into BSC responders and BSC non-responders.		
Time horizon	TA534 - Lifetime (up to a maximum age of 100 years) TA681 - Lifetime (model time horizon was 62 years)	Lifetime (up to a maximum age of 100 years).	Lifetime (100 years)	Lifetime (up to a maximum age of 100 years)	Lifetime (up to a maximum age of 100 years)
Efficacy (outcomes)	Treatment response at 16 weeks based on EASI 50 and DLQI>4. TA534 - response to treatment at 52 weeks was conditional on response to treatment at 16 weeks (week 16 responders who lose response by week 52). TA681 - sustained response at 52 weeks should be based on all cause stopping rate for people whose condition responded to treatment at week 16 but withdrew from treatment at week 52.	Treatment response at 16 weeks based on EASI-50 and DLQI>4. The company assumed that the average time to response for "responders" is 8 weeks. The company use data for the generalisable population, defined as people who have failed systemic treatment (not restricted to CsA) for the base case. However, scenario analyses are conducted for the restricted populated, defined as people who have failed CsA. Furthermore, rescue medication was prohibited in the abrocitinib clinical trials and as such may not reflect the patient population seen in UK clinical practice.	Treatment response at week 16 based on EASI-50 and DLQI>4. Non-responder imputation used for the company base case, which means that any patient who used rescue therapy was treated as a non-responder. Scenario analysis conducted for all-observed population, where patients who used rescue therapy were still included in the analysis. Sustained response at week 52 conditional on response at week 16.	Treatment response at week 16 based on EASI-50 and DLQI>4 was used for the adult systemic-exposed population. To capture early response to treatment, efficacy was applied from week 8 in the model. For the adult and adolescent systemic-eligible population, the composite outcome could not be obtained from the key trials and as such treatment response at week 16 was based on EASI 75. For the company base case, clinical data for the all-observed population has been used. The all-observed population patients were classed as	Treatment response at 16 weeks based on EASI 50 and DLQI>4, using the all-observed populations (defined as patients classed as responders irrespective of rescue medication use) from the key clinical trials. The committee for TA681 preferred the use of conditional discontinuation rates instead of conditional response (accepted in TA534) for week 52 outcomes. As TA681 supersedes TA534, assumption of conditional discontinuation for week 52 outcomes will be used in the model. Conditional

		For the adolescent population combination treatment analyses, the company assumed that the adult combination treatment composite outcome holds for adolescents. Adolescent combination treatment data for abrocitinib are available, however equivalent data for dupilumab are unavailable and thus could not be included in the NMA. Sustained response at 52 weeks estimated using conditional discontinuation data (proportion of patients discontinuing treatment at week 52 from those who achieve response at week 16). Data taken from EXTEND for full trial population. Discontinuation defined as lack of efficacy, adverse event or withdrawal by patient. However data reflects week 44 (compare) and week 48 (mono 1 +2)		responding to treatment, regardless of whether they received rescue medication. Sustained response at week 52 was conditional on response at week 16, calculated as the ratio of the proportion of responders at week 52 by the proportion of responders at week 16. For CsA, the company used the efficacy of BSC at week 16 (32.3%) as a proxy to estimate the proportion of patients who respond to BSC when they discontinue CsA at week 52.	response will be explored in a scenario.
Network meta-analysis	TA534 - the key comparator was BSC which was captured in the dupilumab trials.	Abrocitinib 200 mg and 100 mg were compared with dupilumab 300 mg and	NMAs were conducted for data at 12 or 16 weeks follow up (induction phase) and at	Separate NMAs were performed for each subpopulation:	Separate NMAs were conducted for adolescents, 1L adults and 2L adults at

	Therefore no NMA was necessary. An indirect comparison with CsA was made through a MAIC. The data sources for CsA were Haeck 2011[244] and Jin 2015[245]. TA681 - NMAs were conducted to compare baricitinib 4 mg with dupilumab. Primary analysis based on censoring patients following initiation of rescue therapy. Used FE model as no between-study heterogeneity identified, outcomes analysed included EASI 50, EASI 75, EASI 90, NRS > 4 and EASI 50 + DLQI >4. Sensitivity analysis using 1) including patients who receive therapy with TCS, 2) European patients only for JAIN. Results reported as OR, RR and risk difference.	baricitinib 4 mg and 2 mg Separate NMAs were performed for adolescents and adult for data at 12 or 16 weeks follow up. Long-term comparisons with dupilumab were performed through unanchored STC. Separate NMAs were conducted using the restricted population (patients who had failed on CsA), generalisable population (patients who had failed on at least one systemic therapy) and the full trial population for abrocitinib. The comparator in the adolescent NMA was dupilumab, and for the adult population it was dupilumab and baricitinib. Primary analysis based on censoring patients who received rescue therapy in the dupilumab and baricitinib trials as rescue therapy was not allowed in the abrocitinib trials. Both FE and RE models were assessed, with either informative priors or non-informative prior used for between-trial heterogeneity for RE models. Meta-	26 weeks or later (maintenance phase). The comparators in the NMAs were dupilumab, baricitinib and BSC. Primary analyses reported for both censoring patients who received rescue therapy (non-responder imputation) and including patients who received rescue therapy (as observed). Both FE and RE models were assessed. A half-normal prior was used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 50, EASI 75, IGA 0/1 and EASI 50 + DLQI >4. Sensitivity analysis included baseline-risk adjustment. Results reported as median RR with 95% CrI.	adolescents, adult systemic-exposed and adult systemic-eligible populations. The comparators in the adolescent and adult systemic-exposed NMAs were dupilumab and BSC, and for the adult systemic-eligible it was CsA. Primary analysis based on including patients who received rescue therapy. Both FE and RE models were assessed. Vague prior used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 50, EASI 75, and EASI 50 + DLQI >4. Sensitivity analysis included 1) censoring patients who receive rescue therapy, 2) baseline-risk adjustment (DSU TSD3).[246] Results reported as OR with 95% CrI.	12- or 16-weeks follow-up. The comparator in the adolescent population was dupilumab, in the 1L adult population it was CsA, and in the 2L adult population it was dupilumab or baricitinib. The primary analysis was based on including patients who received rescue therapy (where possible). Both FE and RE models were assessed. Informative prior was used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 75 and EASI 50 + DLQI >4. Sensitivity analysis included 1) censoring patients who receive rescue therapy, 2) using the generalisable population for abrocitinib, 3) baseline-risk adjustment (DSU TSD3).[246] Results reported as OR with 95% CrI

		regression performed to identify evidence of covariate effects on any of the outcomes in the full trial populations. Outcomes analysed included EASI 50/75/90 alone, EASI 50/75/90 + DLQI >4, PP-NRS 4, PP-NRS CFB, and DLQI CFB. Sensitivity analysis included RE models with informative priors for the heterogeneity SD. Results reported as mean effect (OR or CFB difference) with 95% CrI			
Other outcomes	TA534 - From year 2 onwards, an annual treatment discontinuation probability of 3.7% for dupilumab was accepted by committee. The discontinuation rate was based on the observed probability of week 16 responders discontinuing treatment by week 52. With regards to treatment waning, the appraisal committee accepted that patients on dupilumab have a sustained response and that by year 5 onwards, 8% of patients would lose response.	Long-term treatment discontinuation modelled using conditional discontinuation data at week 52 from the EXTEND trial, modelled as a constant rate converted to annual probabilities. Treatment effect waning applied as loss of utility in the maintenance and BSC Markov model health states. Data on the probability of sustained response for abrocitinib was unavailable and so the company applied	Long-term treatment discontinuation for all biologics based on discontinuation data (due to adverse events or loss of efficacy) from the ECZTEND trial Treatment waning based on loss of response associated with biologics. The company assumed that 2-3% of patients would lose response annually up to year 4, with 1% losing response annually from year 5 onwards. Tralokinumab patients who	Long-term treatment discontinuation modelled as an annual rate at which patients discontinue active treatment due to lack of long-term efficacy, adverse events, patient preference of physician preference. Treatment discontinuation data for upadacitinib+TCS is taken from 52-week data from AD UP and for dupilumab+TCS data was from a dupilumab open label extension study (6.4%). For all monotherapy treatments,	The EAG's approach to long-term discontinuation will be consistent with the committee's preferences in TA534 and TA681. That is, treatment-specific all cause discontinuation rates at week 52 for responders at week 16 based will be applied from year 2 onwards. Treatment waning assumptions will be based on the committee's preferred approach in TA534, as no definitive

	Upon loss of response, dupilumab patients transition to the BSC health state. For patients on BSC, the committee considered that by year 5 onwards, up to 97% of patients would lose response to treatment and this was applied in the model as a return to baseline utility by year 5. TA681 - Consistent with TA534, all-cause discontinuation rates applied in the post-52-week period were accepted by committee. For treatment waning, proportions losing response to treatment and BSC were taken from TA534. Upon loss of response, patients returned to baseline utility. The ERG considered the company overestimated treatment waning for BSC patients and the approach separated utilities from costs in both arms of the model. However, the committee considered that the impact of treatment-waning for BSC on cost-effectiveness was likely to be	assumptions from TA534 and TA681 to the base case. In TA534, the appraisal committee accepted that patients on dupilumab have a sustained response and that by year 5 onwards, 8% of patients would lose response and this was used to estimate treatment waning for abrocitinib. For patients on BSC, the company assumed that by year 5 onwards, up to 96% of patients would lose response to treatment and this was used for the abrocitinib base case. Upon treatment waning, patients accrued a non-responder utility value for their respective treatment.	lose response discontinue to BSC. For all patients on BSC, loss of treatment benefit assumed to occur linearly with all benefit lost by 5 years and patients returning to baseline utility.	discontinuation data are from SOLO-CONTINUE (6.3%). Discontinuation data was based on all patients Treatment waning is assumed for both active treatment and BSC. For BSC responders and non-responders, all patients (regardless of response) return to baseline utility and incur non-responder costs over a 5-year period. For patients on CsA, BSC waning assumptions were applied, as treatment is given for a maximum of 1 year and then patients receive BSC thereafter. For patients on upadacitinib and dupilumab, treatment waning rates are taken from TA534 and are applied from years 1 to 5. From years 6 to 10, an annual treatment waning rate of 1% was assumed. After 10 years, no treatment waning is assumed. Upon treatment waning, upadacitinib and	recommendation was provided in TA681. However, treatment-waning assumptions will be explored in scenarios to account for the points made in the committee discussion for TA681.

	between the company and ERG's estimates. Furthermore, the committee considered that treatment waning assumptions for the active treatment arms had little impact on the cost-effectiveness results.			dupilumab patients move to the BSC non-responder health state and first incur the utility of BSC non-responders then gradually return to the baseline utility following BSC non-responders waning rates.	
Utility values and sources	TA534 - treatment specific utility values preferred. Key assumptions accepted by the committee included at week 16 after starting treatment, dupilumab non-responders accrued the average utility of a dupilumab non-responder and BSC non-responder (0.82) and after week 52 accrued the utility value of BSC non-responders (0.77). TA681 - treatment-specific utility values from TA534 were preferred by committee.	EQ-5D-5L (mapped to EQ-5D-3L) and EQ-5D-Y from the abrocitinib trials (COMPARE, TEEN and MONO-1/2). Utilities presented in the submission are based on the full trial populations. Treatment was included as a covariate in the utility regressions to allow for treatment specific utility values to be estimated. **Key utility assumptions:** - Baseline utility is applied between weeks 0 and 8, regardless of treatment or response. - Treatment specific utilities applied between week 8 and 16, using utility at week 16 assessment point, regardless of response. - For non-responders on	EQ-5D-5L data (mapped to EQ-5D-3L) collected in the ECZTRA trials. **Key utility assumptions:** - Treatment specific utilities included in the model. - Responders at week 16 accrue the mean of the biologic/ BSC responder utility and baseline utility between week 0 and 16. - Non-responders to biologic therapy accrue the mean of the biologic non-responder utility and BSC non-responder utility. - A proportion of BSC patients revert to baseline utility each year and by year 5, all BSC patients accrue baseline utility. - Disutility associated with AEs not included.	EQ-5D-5L data (mapped to EQ-5D-3L) collected in Measure UP 1 & 2 and AD UP trials (all-observed dataset). **Key utility assumptions:** - Utility values applied in the model are not treatment specific. - Upadacitinib-treated patients only incur the baseline utility for weeks 0-7. At week 8 they incur the initial response utility (regardless of response) until week 16. - Patients on the comparator treatments never incur the initial response utility as they move directly from the baseline utility to the responder or non-responder utility at week	The companies for abrocitinib, tralokinumab and upadacitinib have supplied treatment specific utility data from their respective key trials. However, due to missing data, uncertainty due to small numbers and relevance of the populations for utility values, the EAG has decided to implement utilities based on drug class using UK representative trial data. For JAK inhibitors, utilities based on upadacitinib data from Measure UP 1 & 2 (mono) and AD UP (combo) will be used for the first- and second-line population. This is because mono and combo upadacitinib utility data are available for adults

		abrocitinib/ comparator, between week 16 and 52, average utility of non-responder and BSC applied regardless of response at week 16, and beyond week 52 average utility of BSC at week 16 regardless of response. - For patients on BSC between after week 16 and for the remainder of the model time horizon, weighted average utility of BSC responders and non-responders. - Disutility associated with AEs not included.		16. - BSC non-responder" health state is sub-divided into "recent" non-responders and non-responders in their baseline state. The "recent" non-responders incur a non-responder utility which is in-between the utility of responders and baseline while non-responders in their baseline state incur the baseline utility - Disutility associated with AEs not included.	and mono data are available for the adolescent population for both the composite outcome and EASI 75. For monoclonal antibody drugs, utilities based on tralokinumab data will be used for the adult second line population and adolescents. The key reason tralokinumab utility data was selected over dupilumab data for monoclonal antibodies is because the dupilumab CS does not consistently report utility data for treatment as a monotherapy or using the EASI 75 response outcome whereas the data are available from the tralokinumab trials Scenario analyses will be conducted using accepted utility values from TA534.
Costs and sources	TA534 - Costs sourced from the BNF (2017), eMIT, PSSRU and the National Reference Costs (2015) and the National Schedule of Reference Costs (2015-2016), and NHS Reference	Costs sourced from NHS reference costs (2018-19), PSSRU 2020, BNF and eMIT. Resource use assumptions taken from TA534 and TA681. Concomitant medications	Costs sourced from NHS reference costs (2018-19), PSSRU 2019, MIMS and the published literature. Resource use assumptions taken from TA534. BSC concomitant medication	Costs sourced from the National schedule of reference costs, PSSRU 2019, HES 2018/19, the Drug Tariff, BNF and eMIT. Resource use assumptions taken from TA534.	Costs and resource use assumptions accepted for TA534 were used in TA681 and as such will be implemented in the model. Cost sources will reflect the most up to date cost data

	Costs (2014). Resource use for AEs were based on dupilumab clinical trials TA681 - Costs sourced from the BNF (2019), MIMS, PSSRU and National Reference Costs (2019) and the National Schedule of NHS Costs (2018- 2019). Resource use was based on TA534. The committee preferred to omit the cost of bathing products from the model.	consisted of TCS, emollients and TCI but excluded bathing products.	costs include TCS, emollients and TCI but excluded bathing products.	Concomitant medications include TCS, emollients, TCI and bathing products.	from standard sources such as NHS reference costs, PSSRU and the BNF. Furthermore, cost assumptions preferred by the committee for TA534 and TA681 will be taken into consideration.
Adverse events	TA534 - Key AEs reported in the dupilumab clinical trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes TA681 - Most frequent and serious AEs reported in the baricitinib AD trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes	Treatment emergent AEs occurring in >5% of patients in either arm in the full trial populations for abrocitinib. AEs include injection site reaction, allergic conjunctivitis, infectious conjunctivitis, headache, nasopharyngitis, nausea, upper respiratory tract infection, folliculitis, pharyngitis, oral herpes. Adverse events in submission are based on full trial population.	AEs based on an NMA and include injection site reactions, oral herpes, allergic conjunctivitis and infectious conjunctivitis	Treatment emergent AEs occurring in >5% of the study population in the upadacitinib and dupilumab clinical trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis, skin infections, upper respiratory tract infection, acne	Serious treatment emergent adverse events specific to treatment will be included in the model.

Company base case ICERs	**TA534 dupilumab + TCS - adults** vs. BSC - plausible ICER range of £27,410 to £28,495. Committee concluded that dupilumab + TCS is a cost-effective use of NHS resources. **TA681 baricitinib - adults** vs. dupilumab - ICER was in the SW quadrant (less costly, less effective) and were within what NICE would consider an acceptable use of NHS resources. vs. BSC - £27,037 (scenario 1) and £28,396 (scenario 2). Committee considered that there was uncertainty related to the ICERs related to quality of life waning assumptions associated with BSC, but considered it was likely to be at the upper end of what NICE considers an acceptable use of NHS resources. As such, the committee concluded baricitinib is likely to be cost-effective compared with BSC.	List price ICERs were provided in the company submission and are presented below. **Abrocitinib 100 mg - adult combination** vs. dupilumab = £142,241 (SW quadrant) vs. baricitinib = £69,593 **Abrocitinib 200 mg - adult combination** vs. dupilumab = £218,356 (SW quadrant) vs. baricitinib = £60,757 **Abrocitinib 100 mg - adolescent combination** vs. dupilumab = £102,345 (SW quadrant) **Abrocitinib 200 mg - adolescent combination** vs. dupilumab = £168,861 (SW quadrant) **Abrocitinib 100 mg - adult monotherapy** vs. dupilumab = £125,278 (SW quadrant) vs. baricitinib = £88,344	List price ICERs were not provided in the company submission. Results presented include the PAS discount for tralokinumab **Tralokinumab - adult combination** vs. BSC = £26,969 vs. dupilumab = £115,545 (SW quadrant) **Tralokinumab - adult monotherapy** vs. BSC = £24,666 vs. dupilumab = £125,178	List price ICERs were not provided in the company submission. Results presented below include the PAS discount for upadacitinib. **Upadacitinib 15 mg + TCS - adult systemic eligible** vs. CsA + TCS = £13,173 **Upadacitinib 30 mg + TCS - adult systemic eligible** vs. CsA + TCS = £29,934 **Upadacitinib 15 mg + TCS - adult systemic exposed** vs. BSC = £10,583 vs. dupilumab + TCS = £128,057 (SW quadrant) **Upadacitinib 30 mg + TCS - adult systemic exposed** vs. BSC = £25,163 vs. dupilumab + TCS = Dominant **Upadacitinib 15 mg + TCS - adolescent**	N/A

		Abrocitinib 200 mg - adult monotherapy vs. dupilumab = £167,991 (SW quadrant) vs. baricitinib = £53,040 **Abrocitinib 100 mg - adolescent monotherapy** vs. dupilumab = £96,811 (SW quadrant) **Abrocitinib 200 mg - adolescent monotherapy** vs. dupilumab = £160,010 (SW quadrant)		**systemic eligible** vs. dupilumab + TCS = £10,287 **Upadacitinib 30 mg + TCS - adolescent systemic eligible** vs. dupilumab + TCS = Dominant	

Abbreviations: AD, atopic dermatitis; AE, adverse events; BNF, British National Formulary; BSC, best supportive care; CFB, change from baseline; combo, combination; CsA, ciclosporin; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQoL five dimension; FE, fixed effects; HES, Hospital Episodes Statistics; IGA, Investigator's Global Assessment; mg, milligram; MIMS, Monthly Index of Medical Specialities; mono, monotherapy; NHS, National Health Service; NMA, network meta-analysis; OR, odds ratio; PP-NRS, Peak Pruritus Numerical Rating Scale; PSSRU, Personal Social Services Research Unit; Q2W, once every two weeks; Q4W, once every four weeks; RE, random effects; RR, relative risk; SD, standard deviation; SW, south-west; TA, technology assessment; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

10.7 Additional Treatment effectiveness data

Table 119. Week 16 response probabilities based on EASI 75 - Adults Second-line systemic treatment

Intervention	Monotherapy	Combination therapy
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]
Baricitinib	N/A	[redacted]
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; N/A, not available.

Table 120. Week 16 response NMA mean (95% CrI) log odds ratios versus placebo – Adults

Intervention	Monotherapy	Combination therapy
Adult first-line systemic treatment - EASI 75		
CsA	N/A	[redacted]
Upadacitinib - 15 mg	N/A	[redacted]
Upadacitinib - 30 mg	N/A	[redacted]
Adult second-line systemic treatment - EASI 50 +DLQI ≥4		
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]
Baricitinib	N/A	N/A
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]
Adult second-line systemic treatment - EASI 75		
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]
Baricitinib	N/A	[redacted]
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]
Adolescents - EASI 75		
Abrocitinib - 100 mg	[redacted]	N/A
Abrocitinib - 200 mg	[redacted]	N/A
Dupilumab	[redacted]	N/A

Upadacitinib - 15 mg	[redacted]	N/A

Abbreviations: CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; N/A, not available; NMA, network meta-analysis.

Table 121. Rescue therapy censoring scenario data - monotherapy

Treatment	Adult second-line systemic treatment - EASI 50 +DLQI ≥4		Adolescents - EASI 75	
	Mean log odds ratios (95% CrI)	Response at week 16	Mean log odds ratios (95% CrI)	Response at week 16
Abrocitinib - 100 mg	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram;

For the scenario assessing placebo response adjustment for the treatment effectiveness estimates, the baseline probability (log odds) was taken from the mean log odds for placebo included in the adjusted NMA. The baseline log odds for the adult second-line systemic treatment analyses was - [redacted] and for the adolescent analyses was [redacted].

Table 122. Placebo response adjusted scenario data - monotherapy

Treatment	Adult second-line systemic treatment - EASI 50 +DLQI ≥4		Adolescents - EASI 75	
	Mean log odds ratios (95% CrI)	Response at week 16	Mean log odds ratios (95% CrI)	Response at week 16
Abrocitinib - 100 mg	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram;

10.7.1 Conditional discontinuation – EASI 75

Table 123. Conditional discontinuation data

Treatment	Conditional discontinuation at Week 52	Source/ assumptions
Monotherapy – Adults, EASI 75		
Abrocitinib 100 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Abrocitinib 200 mg	[redacted]	Assumed to be the same as upadacitinib 30 mg.
Dupilumab	5.1%	Assumed to be the same as dupilumab combination therapy
Tralokinumab Q2W	[redacted]	ECZTRA 2. Conditional discontinuation data based on those achieving EASI 75 for the ECZTRA 7-like population (n/N = [redacted])
Tralokinumab Q4W	[redacted]	Pooled data based on those achieving EASI 75 for the ECZTRA 7-like population from ECZTRA 1 (n/N = [redacted]) and ECZTRA 2 (n/N = [redacted]).
Upadacitinib 15 mg	[redacted]	Pooled data from Measure UP 1 (n/N = [redacted]) and Measure UP 2 (n/N = [redacted]). Only second-line systemic treatment reported.
Upadacitinib 30 mg	[redacted]	Pooled data from Measure UP 1 (n/N = [redacted]) and Measure UP 2 (n/N = [redacted]). Only second-line systemic treatment reported.
Combination therapy - Adults, EASI 75		
Abrocitinib 100 mg	[redacted]	Assumed to be the same as upadacitinib 15 mg.
Abrocitinib 200 mg	[redacted]	Assumed to be the same as upadacitinib 30 mg.
Baricitinib	[redacted]	NICE TA681 ACM slide 47 (provided by Pfizer).
Dupilumab	5.1%	TA534. Data based on annual discontinuation in CHRONOS, defined as non-completers in the 52-week treatment period among EASI 75 responders at week 16 (n/N = 4/78).
Tralokinumab Q2W	[redacted]	Assumed to be the same as tralokinumab Q2W monotherapy.
Upadacitinib 15 mg	[redacted]	AD UP. Data are based on second-line systemic treatment subgroup only (n/N = [redacted]).
Upadacitinib 30 mg	[redacted]	AD UP. Data are based on second-line systemic treatment subgroup only (n/N = [redacted]).

Abbreviations: EASI, Eczema Area and Severity Index; mg, milligram; Q2W, once every two weeks; Q4W, once every four weeks.

10.8 BSC treatment waning – TA534, TA681 and company assumptions

In TA534 and explored in TA681, the two sensitivity analyses were presented around the proportion of BSC patients that lost treatment benefit over 5 years which were deemed plausible by the committee (see Table 124). However, the ERG for TA681 did not agree that treatment waning should

be applied to BSC patients, but preferred to model BSC response and non-response in one health state to capture the waxing and waning nature of AD for patients on BSC. In the abrocitinib model, BSC treatment waning in the base case was informed by sensitivity analysis 1 in TA534. The assumptions in the tralokinumab and upadacitinib models deviated from the committee preferred assumptions in TA534 and TA681 as 100% of BSC patients were assumed to lose response by year 5.

All of the company models, including TA534 and TA681, implemented BSC treatment waning as a loss of utility benefit. With the exception of the abrocitinib model, BSC patients who experience a loss of response return to baseline utility. In the abrocitinib model, BSC patients who lose response accrue the BSC non-responder utility value. The upadacitinib model goes one step further to also assume that BSC patients who lose response also incur non-responder BSC costs. Furthermore, in the upadacitinib model, treatment waning for CsA was assumed to be the same as BSC.

Table 124. Treatment waning proportions scenario analyses

Year	Active treatment	BSC – TA534 sensitivity analysis 1	BSC – TA534 sensitivity analysis 2
2	2%	82%	57%
3	5%	90%	82%
4	7%	94%	92%
5+	8%	96%	97%

Abbreviations: BSC, best supportive care

10.9 Adverse events in TA534, TA681 and the company models

Table 125 presents a comparison of AEs included in TA534, TA681 and the company models as well as those included in the EAG's analysis.

Table 125. Comparison of AEs included in models

Adverse events	TA534	TA681	Abrocitinib	Tralokinumab	Upadacitinib	EAG approach
Injection site reaction	✓	✓	✓	✓	✓	✓
Allergic conjunctivitis	✓	✓	✓	✓	✓	✓
Infectious conjunctivitis	✓	✓	✓	✓	✓	✓
Oral herpes	✓	✓	✓	✓	-	✓
Upper respiratory tract infection	-	✓	✓	-	✓	✓

Acne	-	-	-	-	✓	✓
Skin infection	-	-	-	-	✓	-
Folliculitis	-	-	✓	-	-	-
Headache	-	-	✓	-	-	-
Nausea	-	-	✓	-	-	-
Pharyngitis	-	-	✓	-	-	-
Nasopharyngitis	-	-	✓	-	-	-

Abbreviations: AE, adverse events; EAG, evidence assessment group.

10.10 Additional health related quality of life information

10.10.1 Utility regressions

As discussed in Section 5.2.1.10, the EAG has used a drug class approach for the utility data. For the Janus Kinase (JAK) inhibitors, utility data provided by the company for upadacitinib was used. Company utility data for tralokinumab was used for the monoclonal antibodies. The following subsections describe the companies utility data and regression analysis.

Upadacitinib utility data

The EQ-5D-5L was used to capture HRQoL data in the Measure UP 1, Measure UP 2 and AD-UP trials at baseline, week four, week 16, week 32, week 52 and every 24 weeks post the week 52 visit. In line with NICE guidance, the company mapped the EQ-5D-5L responses onto the EQ-5D-3L value set using the van Hout *et al.* 2012 algorithm.[144] Measure UP 1 and Measure UP 2 assessed upadacitinib monotherapy 15 mg and 30 mg in both adults and adolescents. Upadacitinib 15 mg and 30 mg in combination with TCS 15 in both adults and adolescents was assessed in AD UP.

The EAG requested the company to run utility regression models according to the subgroups assessed in the MTA model (adult first-line systemic treatment, adult second-line systemic treatment and adolescents). All-observed baseline and week-16 data from the upadacitinib trials informed the regressions. Utility data from Measure UP 1 and Measure UP 2 were used for the upadacitinib monotherapy analyses and for the combination therapy analyses, data from AD UP were used. Additionally the company provided separate analyses for EASI 50 + DLQI ≥4 and EASI 75 for the adult second-line systemic treatment population. Only EASI 75 data were available for adult first-line systemic treatment and adolescent populations, but this is aligned with the MTA model outcomes for these populations.

Model selection was performed using backward selection and covariates included age, baseline Investigator Global Assessment (IGA), baseline EASI, sex, TCI/TCS intolerance and treatment (at the request of the EAG). Baseline utility was included for the week 16 regressions. Covariates were included in the model if they met the statistical significance threshold of $p<0.1$. However, for the results by treatment and/or response status, respective covariates were retained in the model irrespective of statistical significance. Mean utility values and standard errors were estimated using the least squared means approach using equal weights for covariates across groups.

Table 126. Covariates included in regression models

Population and outcome	Monotherapy	Combination therapy
Adult first-line systemic treatment - EASI 75	N/A	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline
Adult second-line systemic treatment - EASI 50 + DLQI ≥4	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 50 + DLQI ≥4 response at week 16, crosswalk UK baseline	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 50 + DLQI ≥4 response at week 16, crosswalk UK baseline
Adult second-line systemic treatment - EASI 75	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline
Adolescents - EASI 75	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline, age	N/A

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; N/A, not applicable; UK, United Kingdome.

Tralokinumab utility data

The EQ-5D-5L was used to capture HRQoL data in the ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7 trials at baseline and every two weeks up to the week 16 assessment point and week 16 in ECZTRA 7. In line with NICE guidance, the company mapped the EQ-5D-5L responses onto the EQ-5D-3L value set using the van Hout *et al.* 2012 algorithm.[144] ECZTRA 1 and ECZTRA 2 assessed tralokinumab monotherapy in adults who are candidates for systemic therapy. ECZTRA 3 assessed tralokinumab in

combination with TCS also in adults who are candidates for systemic therapy. ECZTRA 7 assessed tralokinumab in combination with TCS in adults who do not have adequate control with, or have intolerance or contraindications to, CSA.

The EAG requested the company to run utility regression models for the adult second-line systemic treatment population (known as the ECZTRA-7 like subgroup). The company used a mixed model with repeated measures (MMRM) on mapped EQ-5D-3L data. To make full use of the utility data available, all-observed data (all patient population) from ECZTRA 1 and 2 (monotherapy analyses) and ECZTRA 3 and 7 (combination therapy analyses) using ECZTRA 7-like inputs informed the regressions. The company provided separate analyses for EASI 50 + DLQI ≥4 and EASI 75 for the adult second-line systemic treatment population. Only statistically significant covariates were included in the final model.

Covariates assessed were based on those used in TA534 and included baseline EQ-5D, age, sex, EASI score and treatment. In the company submission, worst pruritus and an interaction term with worst pruritus and EASI score was included, but as pruritus is not an outcome in the MTA model, the EAG requested the company to exclude these covariates from the regressions.

ECZTRA 7-like baseline inputs for the regressions (age, proportion male, baseline EASI and baseline EQ-5D) were based on the mean across all ECZTRA 7-like patients in ECZTRA 1 and 2 for the monotherapy analyses and ECZTRA 3 and 7 for the combination analyses.

The company provided utility data for week 0 to 16 (induction) and week 16 to 52 (maintenance). The company noted limitations with the maintenance period data as only tralokinumab responders could be included and only EASI 75 responders were eligible for inclusion and re-randomisation, thus maintenance data could not be generated for the composite outcome. To align with the upadacitinib data, the EAG focussed only on the induction period utility data.

10.10.2 Utility data for scenarios

Table 127 and Table 128 presents utility values used for the adults second-line systemic treatment EASI 75 scenario analysis.

Table 127. Drug class utility values for adults second-line systemic treatment - EASI 75

Health state	JAK inhibitor – low dose	JAK inhibitor – high dose	Monoclonal antibody	Source/ assumptions
Monotherapy				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – Measure UP 1 & 2 Monoclonal antibody – ECZTRA 7-like subgroup from ECZTRA 1 & 2
Responder	[redacted]	[redacted]	[redacted]	
Combination therapy				
Baseline	[redacted]	[redacted]	[redacted]	JAK inhibitors – AD UP Monoclonal antibody – ECZTRA 7 and ECZTRA 7-like subgroup from ECZTRA 3
Responder	[redacted]	[redacted]	[redacted]	

Abbreviations: EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

Table 128. BSC utility values - adults second-line systemic treatment - EASI 75

BSC	Utility value	Source/ assumptions
Monotherapy		
Responder	[redacted]	Measure UP 1 and 2. Combination data used as patients in the BSC likely to get TCS as a subsequent treatment.
Non-responder	[redacted]	
Weighted average	[redacted]	Responder to BSC = [redacted]
Combination therapy		
Responder	[redacted]	AD UP
Non-responder	[redacted]	
Weighted average	[redacted]	Responder to BSC = [redacted]

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

Table 129. TA534 utility values

BSC	Active treatment	Best supportive case	Assumptions
Baseline	0.663	-	-
Responder	0.898	0.797	Patients who are non-responders to systemic treatment transition to BSC. Patients on BSC are assigned a weighted utility value based on the proportion of patients who respond to BSC at Week 16
Non-responder	-		Patients on BSC are assigned a weighted utility value based on the proportion of patients who respond to BSC at Week 16

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

10.11 Additional cost and resource use information

Table 130. Concomitant medication costs included in the model

Drug	Pack cost	Pack size	Source[152, 153]
TCI			
Protopic 0.1% ointment, tacrolimus	£45.56	60	BNF drug tariff, Part VIIIA Category M, last updated August 2021
TCS			
Mometasone 0.1% ointment	£2.58	100	eMIT last updated March 2021
Emollient			
Aveeno cream (Johnson & Johnson Ltd)	£6.47	500	BNF NHS indicative price, last updated August 2021
Cetraben ointment (Thornton & Ross Ltd)	£5.39	450	BNF NHS indicative price, last updated August 2021
Dermol cream (Dermal Laboratories Ltd)	£6.63	500	BNF NHS indicative price, last updated August 2021
Diprobase ointment (Bayer Plc)	£5.99	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Epaderm ointment (Molnlycke Health Care Ltd)	£12.42	1000	BNF NHS indicative price, last updated August 2021
Hydromol ointment (Alliance Pharmaceuticals Ltd)	£8.31	1000	BNF NHS indicative price, last updated August 2021
White soft paraffin 50% / Liquid paraffin 50% ointment (A A H Pharmaceuticals Ltd)	£4.32	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Oilatum cream (Thornton & Ross Ltd)	£5.28	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021

Abbreviations: BNF, British National Formulary; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 131. Concomitant medication resource use included in the model (amount per week)

Drug	Systemic treatment (responders)	BSC (responders and non-responders)	Source
TCI			
Protopic 0.1% ointment, tacrolimus	NA	1.75g	CS for TA534 (Table 3.27) and CS for TA681 (Table 96)
TCS			
Mometasone 0.1% ointment	56.70g	112.04g	CS for TA534 (Table 3.26) and CS for TA681 (Table 96)

Emollient			
Aveeno cream (Johnson & Johnson Ltd)	0.50	1.00	CS for TA534 (Table 3.25) and CS for TA681 (Table 96)
Cetraben ointment (Thornton & Ross Ltd)	0.50	1.00	
Dermol cream (Dermal Laboratories Ltd)	0.50	1.00	
Diprobase ointment (Bayer Plc)	0.50	1.00	
Epaderm ointment (Molnlycke Health Care Ltd)	0.25	0.50	
Hydromol ointment (Alliance Pharmaceuticals Ltd)	0.25	0.50	
White soft paraffin 50% / Liquid paraffin 50% ointment (A A H Pharmaceuticals Ltd)	0.50	1.00	
Oilatum cream (Thornton & Ross Ltd)	0.25	0.50	

Abbreviations: BSC, best supportive care; CS, company submission; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 132. Monitoring unit costs included in the model

Visit/ test	Unit cost	Source[150, 155]
Dermatologist outpatient consultation	£124.83	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D
Dermatologist nurse visit	£31.25	Unit Costs of Health and Social Care 2020. 15 minutes of a band 6 hospital-based nurse (£50 per working hour). Note: each hour spent with a client requires 2.5 paid hours
GP consultation	£39.00	Unit Costs of Health and Social Care 2020. Per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications
A&E visit	£170.98	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Weighted average VB06Z-VB09Z
Hospitalisation	£1,611.14	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Skin Disorders: Non-elective short stay, weighted average JD07A-JD07K (134,484 at £587) Non-elective long stay, weighted average JD07A-JD07K (99,096 at £3,001)
Day case	£439.00	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Day case, Skin Disorders, weighted average JD07A-JD07K
FBC	£2.58	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. DAPS05 Haematology

Phototherapy	£107.24	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. JC47Z Total HRGs & Currencies Phototherapy or Photochemotherapy
Psychological support	£324.88	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 656, clinical psychology, consultant led, weighted average WF01A-WF01D, WF02A-WF02B

Abbreviations: A&E, accident and emergency; FBC, full blood count; GP, General Practitioner; NHS, National Health Service

Table 133. Monitoring resource use included in the model (number per year)

Visit/ test	Non-responders	Responders	Source
Dermatologist outpatient consultation	6.00	4.32	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Dermatologist nurse visit	0.46	0.35	ERG for TA534 (Table 38), CS for TA681 (Table 100)
GP consultation	12.81	6.15	ERG for TA534 (Table 38), CS for TA681 (Table 100)
A&E visit	0.082	0.021	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Hospitalisation	0.13	0.017	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Day case	0.20	0.00	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
FBC (biologic treatment)	4.00	NA	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
FBC (BSC)	4.00	4.00	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
Phototherapy	0.06	NA	Company ACD response for TA534, CS for TA681 (Table 101)
Psychological support	0.07	NA	Company ACD response for TA534, CS for TA681 (Table 101)

Abbreviations: ACD, Appraisal Committee document; CS, company submission; ERG, Evidence Review Group; NA, not applicable.

Table 134. Flare medication acquisition costs

Drug	Pack cost	Pack size	Source[152, 153]
TCS potent			
Betamethasone valerate cream	£2.71	100	eMIT last updated March 2021
Cutivate 0.005% ointment (GlaxoSmithKline UK Ltd)	£4.24	30	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
TCS very potent			
Eumovate 0.05% ointment	£5.44	100	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021

Dermovate 0.05% cream (GlaxoSmithKline UK Ltd)	£7.90	100	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Systemic steroid			
Prednisolone 5 mg	£0.40	28	eMIT last updated March 2021
TCI			
Protopic 0.1% ointment, tacrolimus	£45.56	60	BNF drug tariff, Part VIIIA Category M, last updated August 2021

Abbreviations: BNF, British National Formulary; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 135. Flare medication resource use

Drug	Number of packs per flare	Source
TCS potent		
Betamethasone valerate cream	1	CS for TA681 (Table 98)
Cutivate 0.005% ointment (GlaxoSmithKline UK Ltd)	3.33	CS for TA681 (Table 98)
TCS very potent		
Eumovate 0.05% ointment	1	CS for TA681 (Table 98)
Dermovate 0.05% cream (GlaxoSmithKline UK Ltd)	1	CS for TA681 (Table 98)
Systemic steroid		
Prednisolone 5 mg	1	CS for TA681 (Table 98)
TCI		
Protopic 0.1% ointment, tacrolimus	0.40	CS for TA681 (Table 98)

Abbreviations: BNF, British National Formulary; CS, company submission; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

10.13 Disaggregated cost-effectiveness results

10.13.1 Adult first-line systemic treatment population

Table 136. Disaggregated costs: adult first-line systemic treatment population, combination therapy – EASI 75 – (list prices)

Cost component	Upadacitinib 15mg + TCS (1)	Upadacitinib 30mg + TCS (2)	CsA + TCS (3)	Incremental	
				(1-3)	(2-3)
Intervention acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flare costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids

Table 137. Disaggregated QALYs for upadacitinib 15mg + TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list prices)

Utility component	Upadacitinib 15mg + TCS (1)	Upadacitinib 30mg + TCS (2)	CsA + TCS (3)	Incremental	
				(1-3)	(2-3)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response / maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response / BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids

10.13.2 Adult second-line systemic treatment population

Table 138. Disaggregated costs: adults second-line systemic treatment, monotherapy therapy – EASI 50 + DLQI ≥4 (list price)

Cost component	Abro 100 mg (1)	Abro 200 mg (2)	Upa 15 mg (3)	Upa 30 mg (4)	Tralo (5)	Dup (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Intervention acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flare costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; AE, adverse event; BSC, best supportive care; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; upa, upadacitinib.

Table 139. Disaggregated QALYs: adults second-line systemic treatment, monotherapy therapy – EASI 50 + DLQI ≥4 (list price)

Utility component	Abro 100 mg (1)	Abro 200 mg (2)	Upa 15 mg (3)	Upa 30 mg (4)	Tralo (5)	Dup (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response / maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response / BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; AE, adverse event; BSC, best supportive care; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; upa, upadacitinib.

Table 140. Disaggregated costs: adults second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list price)

Cost component	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Intervention acquisition costs	[redacted]										
Concomitant medication costs	[redacted]										
Monitoring costs	[redacted]										
Flare costs	[redacted]										
AE costs	[redacted]										
TOTAL costs	[redacted]										

Abbreviations: Abro, abrocitinib; AE, adverse event; BSC, best supportive care; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; upa, upadacitinib.

Table 141. Disaggregated QALYs: adults second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list price)

Utility component	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Baseline	[redacted]										
Response / maintenance	[redacted]										
No response / BSC	[redacted]										
AE disutility	[redacted]										
TOTAL QALYs	[redacted]										

Abbreviations: Abro, abrocitinib; AE, adverse event; BSC, best supportive care; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; upa, upadacitinib.

10.13.3 Adolescents

Table 142. Disaggregated costs: adolescents, monotherapy – EASI 75 – (list prices)

Cost component	Abro 100 mg (1)	Abro 200 mg (2)	Upa 15 mg (3)	Dup (4)	Incremental		
					(1-4)	(2-4)	(3-4)
Intervention acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Flare costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; AE, adverse event, Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; upa, upadacitinib.

Table 143. Disaggregated QALYs: adolescents, monotherapy – EASI 75 – (list prices)

Cost component	Abro 100 mg (1)	Abro 200 mg (2)	Upa 15 mg (3)	Dup (4)	Incremental		
					(1-4)	(2-4)	(3-4)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response / maintenance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response / BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; AE, adverse event, Dup, dupilumab; EASI, Eczema Area and Severity Index; mg, milligram; QALY, quality-adjusted life-year; Upa, upadacitinib.

10.14 Probabilistic sensitivity plots

10.14.1 Adult first-line systemic treatment population

Table 144. Location of PSA simulations on the CE plane: Adult first-line systemic treatment population, combination therapy – EASI 75

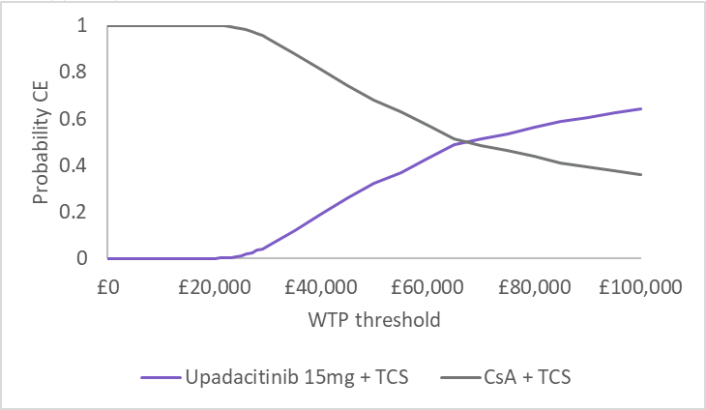
Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Upadacitinib 15 mg + TCS vs CsA + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs CsA + TCS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PAS, patient access scheme; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west; TCS, topical corticosteroids.

Figure 30. CE plane for upadacitinib 15 mg + TCS vs CsA + TCS, probabilistic vs deterministic: adults first-line - EASI 75 – combination therapy (list prices)

Abbreviations: CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life-year; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 31. CEAC for upadacitinib 15 mg+ TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)

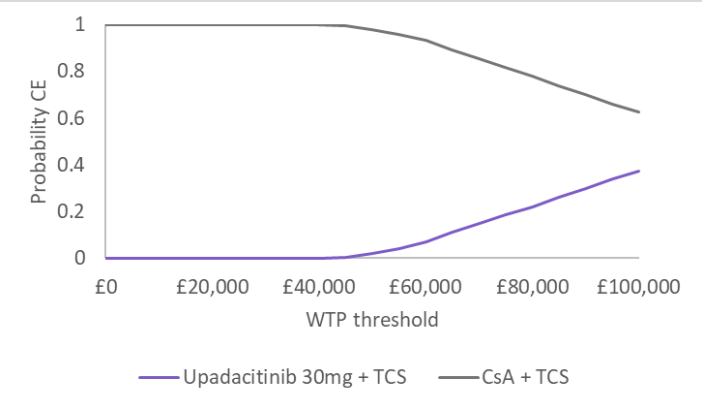


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 32. CE plane for upadacitinib 30 mg + TCS vs CsA + TCS, probabilistic vs deterministic: adults first-line - EASI 75 – combination therapy (list prices)

Abbreviations: CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life-year; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 33. CEAC for upadacitinib 30 mg+ TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)



Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

10.14.2 Adult second-line systemic treatment population – monotherapy

Table 145. Location of PSA simulations on the CE plane: Adult second-line systemic treatment population, monotherapy – EASI 50 + DLQI ≥4

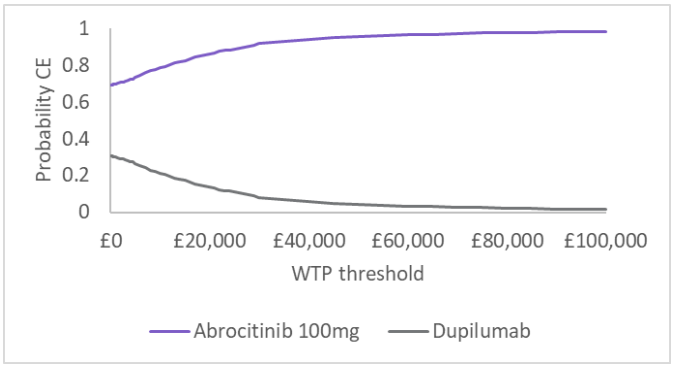
Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Abrocitinib 100 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PAS, patient access scheme; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west.

Figure 34. CE plane for abrocitinib 100mg vs dupilumab, probabilistic vs deterministic: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 35. CEAC for abrocitinib 100mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

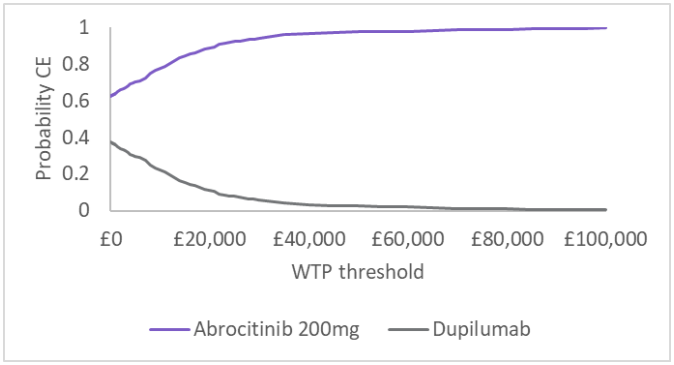


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 36. CE plane for abrocitinib 200mg vs dupilumab, probabilistic vs deterministic: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 37. CEAC for abrocitinib 200mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

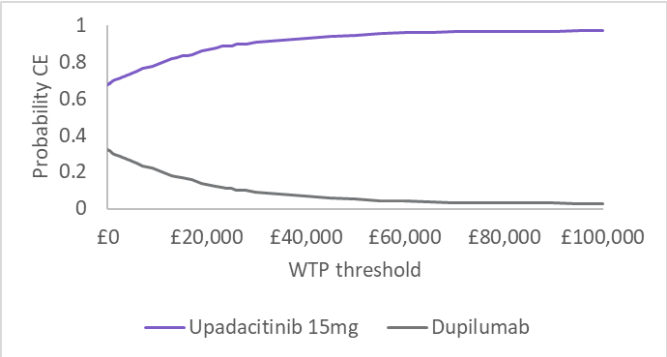


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 38. CE plane for upadacitinib 15mg vs dupilumab, probabilistic vs deterministic: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 39. CEAC for upadacitinib 15mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

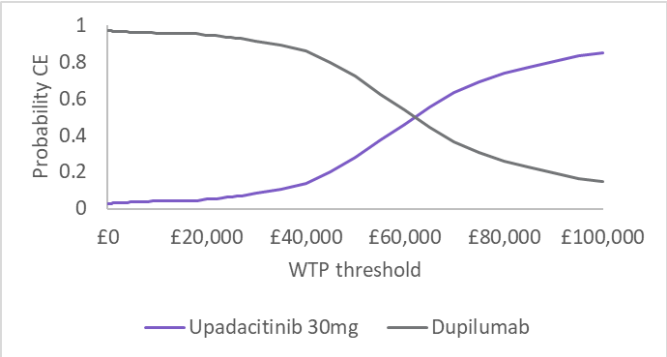


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 40. CE plane for upadacitinib 30mg vs dupilumab, probabilistic vs deterministic: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 41. CEAC for upadacitinib 30mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

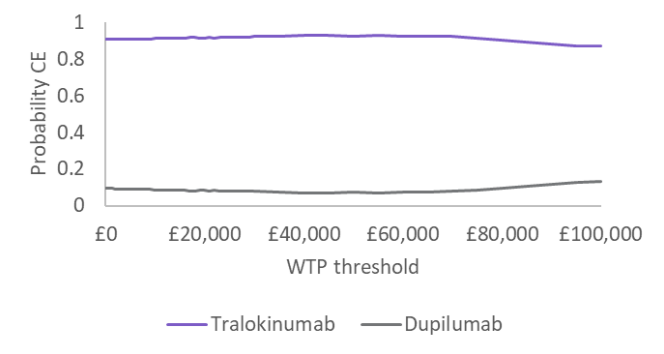


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 42. CE plane for tralokinumab vs dupilumab, probabilistic vs deterministic: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 43. CEAC for tralokinumab vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)



Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

10.14.3 Adult second-line systemic treatment population – combination therapy

Table 146. Location of PSA simulations on the CE plane: Adult second-line systemic treatment population, combination therapy – EASI 50 + DLQI ≥4

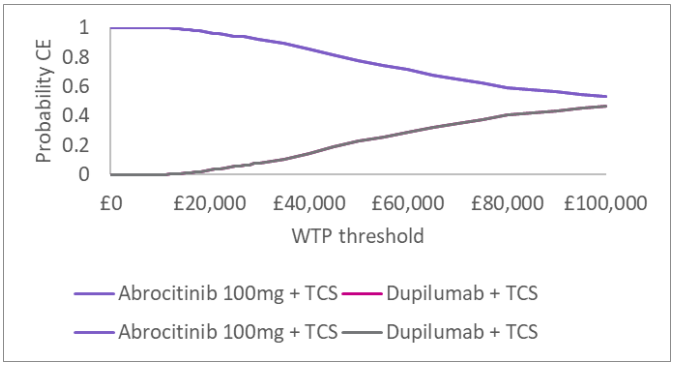
Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Abrocitinib 100 mg + TCS vs dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg + TCS vs dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + TCS vs dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS vs dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PAS, patient access scheme; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west; TCS, topical corticosteroids.

Figure 44. CE plane for abrocitinib 100 mg + TCS vs dupilumab + TCS, probabilistic vs deterministic: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 45. CEAC for abrocitinib 100 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

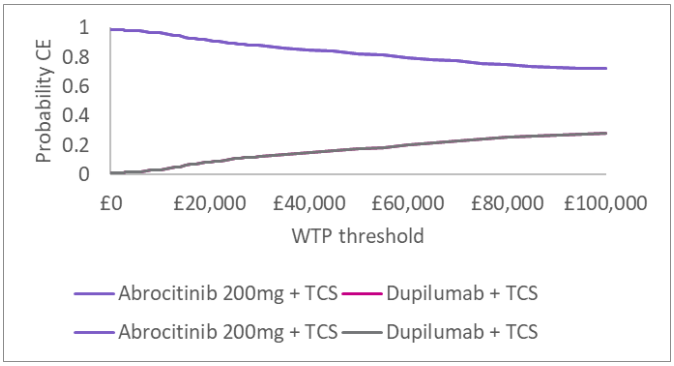


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 46. CE plane for abrocitinib 200 mg + TCS vs dupilumab + TCS, probabilistic vs deterministic: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 47. CEAC for abrocitinib 200 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

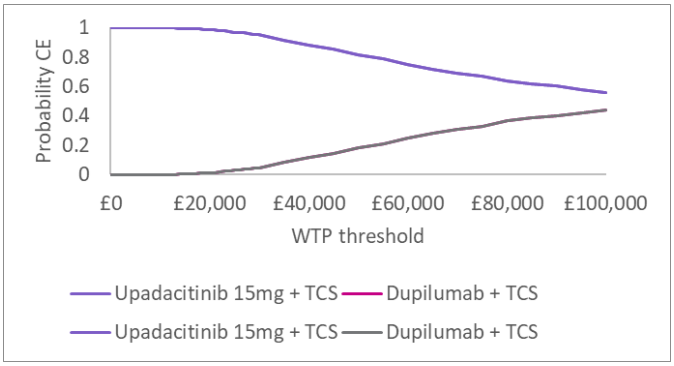


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 48. CE plane for upadacitinib 15 mg + TCS vs dupilumab + TCS, probabilistic vs deterministic: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 49. CEAC for upadacitinib 15 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

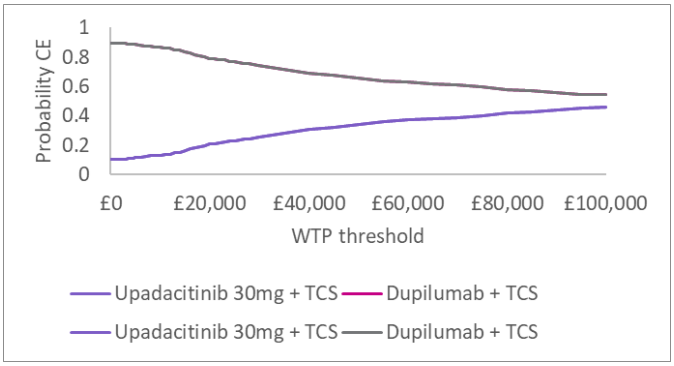


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 50. CE plane for upadacitinib 30 mg + TCS vs dupilumab + TCS, probabilistic vs deterministic: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 51. CEAC for upadacitinib 30 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

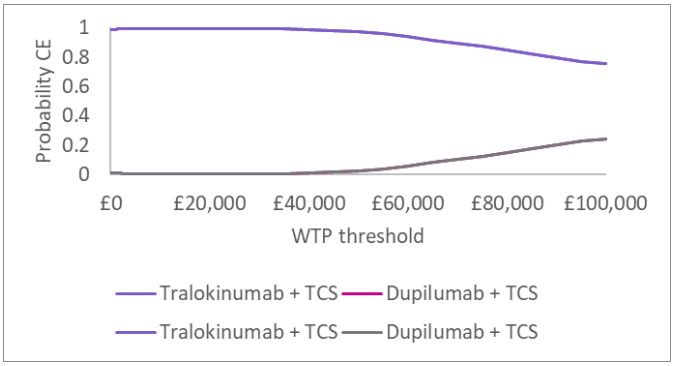


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 52. CE plane for tralokinumab + TCS vs dupilumab + TCS, probabilistic vs deterministic: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; QALY, quality-adjusted life year; WTP, willingness to pay.

Figure 53. CEAC for tralokinumab + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)



Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

10.14.4 Adolescents

Table 147. Location of PSA simulations on the CE plane: Adolescents, monotherapy – EASI 75

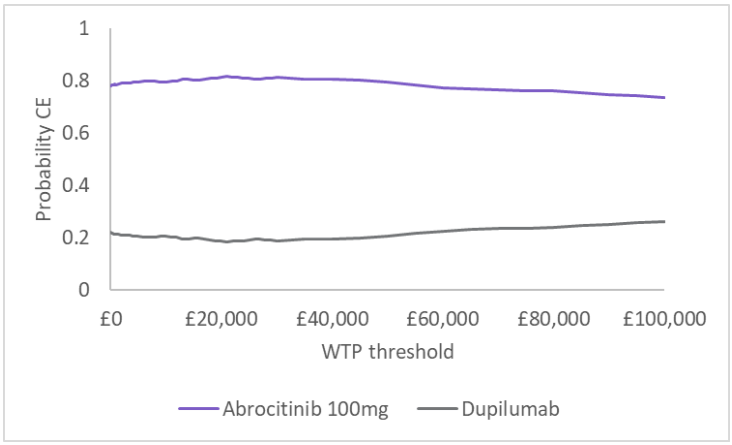
Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Abrocitinib 100 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg vs dupilumab	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CE, cost-effectiveness; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PAS, patient access scheme; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west.

Figure 54. CE plane for abrocitinib 100 mg vs dupilumab, probabilistic vs deterministic: adolescents - EASI 75 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life-year; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 55. CEAC for abrocitinib 100 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

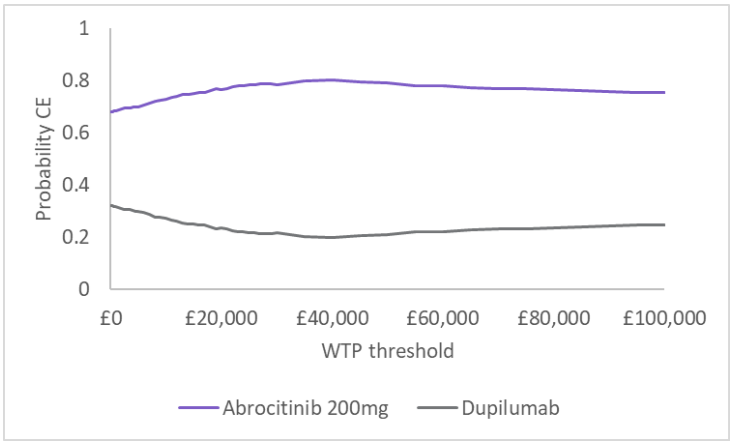


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 56. CE plane for abrocitinib 200 mg vs dupilumab, probabilistic vs deterministic: adolescents - EASI 75 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life-year; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 57. CEAC for abrocitinib 200 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

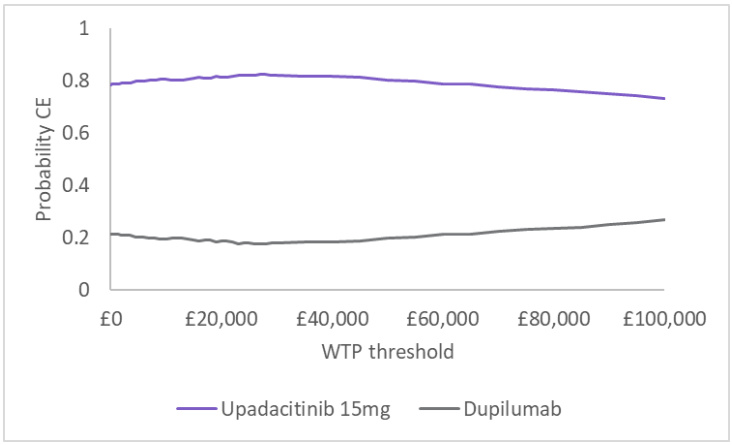


Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

Figure 58. CE plane for upadacitinib 15 mg vs dupilumab, probabilistic vs deterministic: adolescents - EASI 75 – monotherapy (list prices)

Abbreviations: CE, cost-effectiveness; EASI, Eczema Area and Severity Index; Inc., incremental; mg, milligram; QALY, quality-adjusted life-year; TCS, topical corticosteroids; WTP, willingness to pay.

Figure 59. CEAC for upadacitinib 15 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)



Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Issues for consultation

28 January 2022

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic dermatitis response_28Jan2022	V1.0	Yes	28-Jan-2022

Contents

Summary

This document outlines AbbVie's perspective on the key issues for consultation. AbbVie are broadly aligned to the clinical and cost-effectiveness cases presented by the External Assessment Group (EAG); however, we believe the following issues should be revised and implemented to base case results to allow for a more robust analysis.

- In the first-line adult population:
    - A fixed effect model is more appropriate (Issue 1).
    - Yearly flare rates should be increased for ciclosporin (CsA) compared to upadacitinib (Issue 2).

- In the second-line adult population:
    - "No active treatment waning" should form the base-case rather than a scenario to mitigate double counting of discontinuation effects (Issue 3).
    - Best supportive care (BSC) effect waning should be implemented (Issue 4).

- In the adolescent population:
    - The odds ratio (OR) of upadacitinib vs dupilumab requires correction (Issue 6).

First-line adult population

Issue 1: EAG NMA choice may not be the appropriate method

The network meta-analysis (NMA) results, which drives efficacy in the model, differ between the AbbVie analysis and the EAG analysis.

The key driver of differing results between the two analyses appears to be the use of a random effects model by the EAG, compared with the use of a fixed effects model by AbbVie.

The use of a random effects model is generally preferred in a Bayesian indirect comparison, as it allows for between-studies heterogeneity in the estimates of treatment effect. However, where there is a single data source for the treatment, as is the case for this analysis, this benefit is negated.

Furthermore, in the situation where single studies feed into the analysis, a random effects model will yield zero-estimates for type I error, probably reflecting unchanged non-informative priors[1,2].This effect results in the lack of face validity seen in the EAG model, which yielded an estimate of 95% confidence intervals (CI) that substantially exceeded the 95% CI seen in the source study. We consequently believe that, in this situation, the fixed effects model should be considered equally plausible for base case analysis due to the low number of trials used to estimate between study variability. Further minor differences in are discussed in Appendix A.

Adapting the EAG model to include the results of the fixed effects NMA, results in substantial differences in the ICERs in favour of upadacitinib at list price (~22% more favourable).

Detailed results of this analysis can be found in Table 3 of Appendix A, along with the fixed effects NMA results from the analysis carried out by AbbVie used as inputs in the model, which can be found in Table 4.

Table 1: Odds ratio from the NMA carried out by EAG and AbbVie

	EAG (EAG report, page 94)	AbbVie (Document B, Table 32)
Upadacitinib 15 mg vs CsA OR (95% CrI)	[redacted]	[redacted]
Upadacitinib 30 mg vs CsA OR (95% CrI)	[redacted]	[redacted]

Based on these results, we believe a base case deriving early response from the fixed effect model is the appropriate approach for base case analysis, considering that all other CsA data is assumed equal to upadacitinib.

Issue 2: Flare rates inconsistent with effectiveness estimates for upadacitinib and CsA

In their modelling, the EAG assumed that flare rates with CsA were equivalent to those with upadacitinib (Table 43, pages 177-179).

In contrast, in the original modelling submitted by AbbVie for the STA process a decrement of 15% was applied to the rate of flare observed with BSC (Document B, Table 72). This assumption was validated by clinicians at the time, whereby more effective treatments were deemed to reduce yearly flare rates.

Further clinical opinion sought to inform this response suggests that response to CsA is not as deep as that with upadacitinib, which means flares would be more frequent with CsA than with upadacitinib.

The flare rates at 52 weeks extracted from the AD UP[3] study and the Measure UP studies (Table 2) show that flares are consistently linked to the effectiveness of the treatment, i.e., flare rates are lower with upadacitinib 30 mg dose in most cases and validates the clinical input.

The assumption that CsA flare rates can be linked with the either upadacitinib 15 mg or 30 mg is therefore inconsistent with the EAGs effectiveness estimates. We believe that the EAG's assumption is incorrect and a new base case where flare rates with CsA are increased relative to upadacitinib is required.

Table 2: 16-week and 52-week data for flare (defined as use of rescue medication) adult population

	First line			Second line		
AD UP	**Upa 30 mg +TCS**	**Upa 15 mg +TCS**	**Placebo plus TCS**	**Upa 30 mg +TCS**	**Upa 15 mg +TCS**	**Placebo plus TCS**
	(N=203)	(N=203)	(N=209)	(N=57)	(N=58)	(N=55)
16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Measure UP 1	**Upa 30 mg**	**Upa 15 mg**	**Placebo**	**Upa 30 mg**	**Upa 15 mg**	**Placebo**
	(N=211)	(N=200)	(N=201)	(N=32)	(N=39)	(N=40)
16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Measure UP 2	**Upa 30 mg**	**Upa 15 mg**	**Placebo**	**Upa 30 mg**	**Upa 15 mg**	**Placebo**
	(N=189)	(N=168)	(N=178)	(N=58)	(N=75)	(N=64)
16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA

Other considerations: There is an unmet need for a new systemic treatment in first-line

Current first-line conventional systemic treatments, of which CsA is the only licensed treatment, are limited by adverse events (AE), restriction of their use to <1 year, monitoring that can be onerous, and some patients will be contra-indicated to their use[4] (Document B, Table 4).

Conventional systemic therapies are usually given for a limited period due to short-term clinical benefits and high rates of safety-related discontinuation. There is limited published clinical evidence to support use of these therapies in atopic dermatitis (AD), therefore efficacy and tolerability is difficult to predict and both clinicians and patients may face concerns when initiating a new treatment.

There is a clinical need for wider choice of treatment options and new systemic therapies to be made available for first-line use in some patients. In the Dupilumab Committee Meeting (TA 534) and Baricitinib Committee Meeting (TA 681) respective clinical experts (both Consultant Dermatologists) were asked whether there was an unmet need at first-line and both have stated that there is, indeed, an unmet need.

Clinical experts suggested specific patient groups who might benefit from upadacitinib first-line including those in whom a long-term option would be preferable and those who require a rapid onset of action.

Upadacitinib has demonstrated efficacy in both monotherapy and combination with topical corticosteroids (TCS) which is an important consideration, given that younger adults living with AD may find extensive use of TCS burdensome.

The response to treatment is modelled from Eczema Area and Severity Index (EASI) 75 given availability of data. Upadacitinib has demonstrated rapid and durable response on this end-point, which according to experts is clinically relevant to UK practice and valued by patients. However, EASI 75 may not entirely capture the benefits associated with a higher efficacy response rate such as a higher quality of life (QOL) and improvements in healthcare resource utilisation.

Therefore, these analyses may not reflect the full benefits associated with upadacitinib, which has demonstrated high response rates for EASI 90 and EASI 100 and improvement of worst pruritus numerical rating scale (NRS) score

Second-line adult population

Issue 3: Double counting of effects with discontinuation and treatment effect waning in EAG model

Discontinuation and waning are key drivers in the model and any increase in rates will have an impact on cost-effectiveness.

We agree with the EAG that there is double counting of negative effects by combining discontinuation, which includes discontinuation due to efficacy, and active treatment effect waning in the EAG model.

Therefore, we believe the EAG base case is pessimistic about long-term effectiveness of upadacitinib, and the scenario analysis “No active treatment waning” should be presented as the base case.

Issue 4: BSC effect waning not included

BSC effect waning was only included as a sensitivity analysis in the EAG model via variability around placebo response rates. While we recognise that modifications to BSC state was required from previous Technology Appraisals, it’s not clear that variance around a BSC response rate appropriately handles a long-term impact on waning of effect in the BSC state. The EAG model should include BSC waning informed by Committee preferences in previous Technology Appraisals.

Issue 5: Baricitinib comparison is based on inappropriate use of upadacitinib data

We have several concerns around the scenario analysis where a comparison to baricitinib is explored and the assumptions required.

We believe these concerns result in a scenario analysis that is a 16-week comparison of baricitinib to upadacitinib with the remainder of the lifetime horizon predominantly comparing upadacitinib to upadacitinib. With a lifetime perspective, this hugely underestimates the incremental quality adjusted life year (QALY) improvement of either dose of upadacitinib.

1. The EAG results are inconsistent in that the NMA showed that both doses of upadacitinib were more effective than baricitinib 4 mg (EASI 75 for adults in the second-line setting) (EAG report, Table 20). However, in the health economic analysis upadacitinib 15 mg + TCS is less effective (SW quadrant) than baricitinib (EAG report, Table 76).

2. Related to issue 1, the EAG suggest that conditional discontinuation data from upadacitinib 30 mg can be used to describe the efficacy of baricitinib. However, the EAG NMA supports that both doses of upadacitinib are more effective than baricitinib 4 mg. Conditional discontinuation was shown in the MTA report to be generally improved in more effective treatments, which means the assumption lacks face validity. We are also not aware of any analysis performed that supports this interpretation. Consequently, an updated analysis where conditional discontinuation for baricitinib is informed by the appropriate data source is required before the scenario can be presented for decision making.

3. The EAG suggest that of those eligible for second-line systemic treatment, annual uptake of baricitinib and dupilumab is expected to be around 25% and 60%, respectively (EAG report, page 51). We believe that the rate for baricitinib is an overestimate; market share data obtained by AbbVie suggests that the total share of AD market is reasonably stable around [redacted] for baricitinib with approximately [redacted] occupied by dupilumab.

Because of these issues, the scenario analysis is uninformative at best and misleading at worst and should be discarded.

Other considerations: Upadacitinib can reduce reliance on TCS

In the monotherapy NMA performed by the EAG, both doses of upadacitinib vs placebo are more effective than dupilumab vs placebo (EAG report, Table 14). However, in the combination therapy NMA performed by the EAG, upadacitinib 15 mg vs placebo is of similar efficacy to dupilumab vs placebo and upadacitinib 30 mg vs placebo is more effective than dupilumab vs placebo (EAG report, Table 18).

This impacts on the economic model: in the adult second-line systemic treatment population, upadacitinib 15 mg as monotherapy dominates dupilumab and in combination with TCS is less costly and less effective than dupilumab.

While combination treatment with TCS is clinical practice, upadacitinib is effective without the need for TCS which represents a significant change for patients allowing more choice in daily life of people living with AD.

Patients will not have the inconvenience of applying daily TCS, and the risk and concern over TCS AEs such as skin thinning will be removed. A TCS-free treatment regimen will be of great benefit to those patients with steroid phobia.

Adolescent population

Issue 6: Incorrect NMA results vs dupilumab

The NMA performed by the EAG found that upadacitinib 15 mg was less effective than dupilumab (OR vs dupilumab [redacted]XXX, 95% CrI: [redacted]) (EAG report, page 122). However, the economic modelling found that upadacitinib dominated dupilumab (EAG report, Table 63).

On investigation, we found that the OR was reported incorrectly in the EAG report. The OR for dupilumab vs placebo is [redacted] and the OR for upadacitinib 15 mg vs placebo is [redacted]. The EAG divided dupilumab by upadacitinib to get [redacted] ([redacted]/[redacted]), however, the calculation should have been made as [redacted]/[redacted], the OR for upadacitinib vs dupilumab is therefore actually [redacted].

The update results in less conflicting clinical interpretation as upadacitinib 15mg is more effective than dupilumab, aligning with the cost-effectiveness results. We welcome a correction to the EAG report.

Other considerations: There is an unmet need for a new oral systemic treatment for adolescents

The burden of AD and unmet need is particularly high in adolescents. AD has a significant impact on school attendance and achievement at school resulting in significant life course impairment in this age group[5].

Clinical experts confirmed that there is a very real unmet need in the adolescent population with moderate to severe AD.

'There is a high clinical need in adolescents. AD in adolescence impacts on pivotal steps, schooling, sleep and can lead to significant impairment. The impairment in life course and trajectory is concerning'.

Furthermore, the National Eczema Society survey revealed that of the parents surveyed, more than half said their child had to take time off school due to their eczema and one in seven children took more than 10 days off during the last year. One-fifth of parents in the survey said their child limited their activities at school and

regularly mentions difficulty concentrating in class because of their AD[5]. Additionally the psychological impact of living with AD can be overwhelming for this age group in coping with their AD, in addition to teasing, bullying and managing emollients at school[6].

Finally, needle phobia is relatively common (20%-50%) in adolescents and continues into adulthood for some people, which makes subcutaneous (SC) injection challenging for some[7]. Indeed, a survey carried out in the UK and US in 320 people with moderate to severe AD found that respondents preferred oral treatment over injectable treatment and that mode of administration was the second most important attribute in a treatment for AD[8]. The Consultant Dermatologist who specialises in managing AD in adolescents pointed out that AD manifests differently in adolescents than in adults and that there is a significant problem with *Staphylococcus aureus* skin infection.

There is an unmet need for a treatment which will quickly minimise the symptoms of AD.

The analysis for the adolescent population provides data using the EASI 75 endpoint with upadacitinib 15 mg as monotherapy, which represents a meaningful improvement in symptom control for people living with AD.

We expect that the results in the adult combination analyses could be extrapolated to the adolescent population. Indeed, clinical experts, consulted for our original Single Technology Appraisal submission, confirmed that proven clinical efficacy, safety and cost-effectiveness data for upadacitinib + TCS in adult patients would be considered relevant for adolescent patients.

Discrepancies in the economic modelling to EAG report

AbbVie notes a number of discrepancies in the version of the economic model shared for consultation compared to the MTA report results and would therefore welcome an EAG comment on which results should be considered accurate.

Monitoring costs (adolescent and adult models)

The unit costs of 'dermatologist outpatient consultation' and 'psychological support' in the model do not match those detailed in the report (EAG report, Table 50). This discrepancy drives a mismatch between EAG reported total monitoring costs and model total monitoring costs when run using list prices. The affected cells in the model can be found in the 'Costs - monitoring' tab: E10, E16, E29 and E37. This issue is applicable to both the adolescent and adult models.

Incorrect totalling of costs and QALYs in the first year for dupilumab (adolescent model)

In the adolescent model, week 0 costs and QALYs are not accounted for when the total first year costs and QALYs are calculated in the dupilumab decision tree. This can be seen in row 68 SUM calculations in the 'Engine Dup' tab of the adolescent model. The SUM calculation starts from row 14 rather than row 13, therefore not including week 0 costs and QALYs. This leads to small but noticeable differences between the incremental costs seen in the model results versus those presented in the AEG report results. QALYs are not affected as few were accrued in week 0.

Incorrect abrocitinib results in the adult model and report

The ICER result in the model is unresponsive to any changes made to the price of abrocitinib in the 'Costs - treatment' tab. This is because the model engine uses the acquisition cost of upadacitinib 30 mg.

This is seen in the 'Engine Int' tab in cells: K6, K7 and AM7 where the week 16 acquisition cost, weekly acquisition cost and annual acquisition cost of upadacitinib 30 mg is being pulled through instead of abrocitinib 100 mg/200 mg. The modeller has failed to finish the VLOOKUP formula with 'FALSE'. E.g., cell AM7 should read ‘=VLOOKUP(Intervention,'Costs - treatment'!C9:Q16,15,**FALSE**)’.

References

1. Song F, Clark A, Bachmann MO, Maas J. Simulation evaluation of statistical properties of methods for indirect and mixed treatment comparisons. *BMC Med Res Methodol* 2012; **12**: 138.
2. Pullenayegum EM. An informed reference prior for between-study heterogeneity in meta-analyses of binary outcomes. *Stat Med* 2011; **30**(26): 3082-94.
3. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**(10290): 2169-81.
4. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available at https://bnf.nice.org.uk/; 2021.
5. Leo Pharma and National Eczema Society. Eczema unmasked: revealing the true impact of life with eczema 2020.
6. National Eczema Society. Eczema: an information pack for schools 2016.
7. McLenon J, Rogers MAM. The fear of needles: A systematic review and meta-analysis. *J Adv Nurs* 2019; **75**(1): 30-42.
8. Boeri M, Sutphin J, Hauber B, Cappelleri JC, Romero W, Di Bonaventura M. Quantifying patient preferences for systemic atopic dermatitis treatments using a discrete-choice experiment. *J Dermatolog Treat* 2020: 1-10.
9. Ariëns LFM, Gadkari A, van Os-Medendorp H, et al. Dupilumab Versus Cyclosporine for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults: Indirect Comparison Using the Eczema Area and Severity Index. *Acta Derm Venereol* 2019; **99**(10): 851-7.

Appendix A – NMA results for first line (systemic eligible) population

The EAG used a similar approach as AbbVie for their NMA. A paper by Ariëns et al[9] used patient-level data from the phase III dupilumab study, CHRONOS and data from patients receiving CsA as their unit to perform a logistic regression analysis to assess an efficacy outcome EASI 75.

Coefficients from the adjusted regression models were then used to estimate the mean predicted rate of responders under each treatment scenario (dupilumab vs CsA) for dupilumab and CsA populations separately. This enabled the prediction of responder rates for dupilumab and CsA within each of the study populations, which were linked in an NMA using CHRONOS and AD UP.

In the EAG base case, data from Ariëns et al. (CsA vs dupilumab) and from CHRONOS (dupilumab vs placebo), were analysed as two separate studies. Whereas, in the AbbVie base case it was assumed that the CsA arm from Ariëns et al. was an additional arm of the CHRONOS study (Document B, Figure 29). The EAG carried this analysis out as a sensitivity analysis and found similar results to their base case, but with smaller credible intervals (CrI) (EAG report, Table 6).

Table 3: Difference in cost-effectiveness for EAG and AbbVie NMA specification

Upadacitinib 15 mg + TCS vs CsA + TCS			
	Incremental costs	**Incremental QALYs**	**ICER (quadrant)**
Original MTA random effects model results	[redacted]	[redacted]	[redacted]
Updated MTA fixed effects model results	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs CsA + TCS			
Original MTA random effects model results	[redacted]	[redacted]	[redacted]
Updated MTA fixed effects model results	[redacted]	[redacted]	[redacted]

Table 4: AbbVie NMA results (Document B, Table 32)

	Placebo + TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS	CsA + TCS	Dupilumab 300 mg Q2W + TCS
EASI 75					
Placebo +TCS		[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + TCS	[redacted]		[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]		[redacted]	[redacted]
CsA + TCS	[redacted]	[redacted]	[redacted]		[redacted]

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

LEO Pharma EAG report comments - TA10856

January, 2022

File name	Version	Contains confidential information	Date
[ID3960] EAG_Report_LEO_ Comments	**1**	**Y [Redacted]**	**28/01/2021**

1 The proportion of patients assumed to switch to the Q4W dose at week 52

- Tralokinumab is licensed for two treatment regimens, Q2W and Q4W. It's our understanding that the EAG has assumed no patients switch to Q4W in the base case. What is the rationale for this assumption? Are the EAG proposing that tralokinumab only be reimbursed for use with the Q2W dose and not the licenced Q2W and Q4W dosing? If the EAG would like patients to benefit fully from the licensed use of tralokinumab then this should be reflected within their modelling approach. There are a number of ways in which the EAG's approach could be modified:
    - We have presented evidence (in Appendix I.2 in the STA company submission) to demonstrate that clinicians would look to switch patients to the Q4W dose. The improved convenience of this dose for patients, and reduced risk of injection site reactions, are key advantages of tralokinumab Q4W and we believe this should be acknowledged in the base case analysis.
    - The scenario analysis undertaken by the EAG that includes the Q4W regimen, assumes [redacted] and [redacted] of patients switch for monotherapy and combination therapy, respectively. These figures seem to be informed by the proportion of patients entering each treatment arm within the ECZTRA trials during maintenance therapy. For example, in ECZTRA 3, patients treated with tralokinumab Q2W in the initial treatment period and who had a clinical response were re-randomised in a 1:1 ratio to receive either the Q2W dosing or the Q4W dose thereafter. Responders treated with placebo in the initial treatment period remained on placebo. This re-randomisation approach meant that out of patients who achieved an EASI 75 at Week 16 [redacted] patients were assigned to receive Q2W, Q4W and placebo respectively in the post-hoc ciclosporin-IR subgroup. The [redacted] used by the EAG in combination therapy is therefore [redacted] Q4W patients out of [redacted] EASI 75 responders. This indicates that the proportions used in the EAG model are arbitrary and an artefact of the re-randomisation scheme used within the specific clinical trials and may not be representative of their use within clinical practice. Appendix I.2 in the STA company submission includes a more appropriate set of estimates, informed by consultation within clinicians.

  There also exists an issue relating to the calculations within the EAG economic model. We believe we have identified a formula error in the EAG economic model that has an impact on tralokinumab cost-effectiveness results, especially in monotherapy. In cell Q18 within the "Utilities" tab, the Q4W utility estimate is applied to Q2W patients and vice versa.

2 Unexpected results within the network meta-analysis

There are a number of specific results within the NMA that are unexpected. We would like to check whether these results are correct:

- In the primary analysis in Table 14 in the EAG report, the OR of tralokinumab versus dupilumab for EASI 75 in monotherapy is reported as [redacted]. To which dose of dupilumab is tralokinumab being compared in this statistic? It more closely matches the dupilumab QW dosing result from the LEO Pharma submitted NMA than the dupilumab Q2W dose. For reference we have provided a comparison of EAG and LEO Pharma NMA result values (as odds ratios since the STA submission included risk ratios) in Table 1 below.

- Also, in Table 14 in the EAG report, for the rescue therapy sensitivity analysis (which uses the non-responder imputation [NRI] estimand where patients receiving rescue therapy are censored) for EASI 75 in monotherapy, the OR of tralokinumab versus dupilumab is reported as [redacted]. In the NMA submitted by LEO Pharma, the odds ratio for tralokinumab versus dupilumab Q2W was [redacted]. Since most results from the EAG's NMA and the LEO NMA are relatively aligned, and there is a substantial discrepancy in this case, we ask the EAG to check this result. For reference a comparison of EAG and LEO Pharma NMA result values is included in Table 1 below.

  Table 1 : Comparison of EAG NMA and LEO Pharma NMA result values.

Comparison	EAG NMA		LEO Submission NMA	
	NMA OR (95% CrI)		NMA OR (95% CrI)	
	Primary	Sensitivity Rescue therapy	Primary	Sensitivity Rescue therapy
Combination therapy				
EASI 50 & DLQI ≥ 4 (Table 18 in EAG report)				
Tralokinumab Q2W versus placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W versus dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 (Table 20 in EAG report)				
Tralokinumab Q2W versus placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W versus dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Monotherapy				
EASI 50 & DLQI ≥ 4 (Table 12 in EAG report)				
Tralokinumab Q2W versus placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W versus dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 (Table 14 in EAG report)				
Tralokinumab Q2W versus placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W versus dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]

- Could the EAG please advise what data from BREEZE-AD4 they used in the primary analysis of EASI 75 for second-line combination therapy? LEO Pharma could not find EASI 75 outcomes using the estimand with no censoring of patients who received rescue therapy from this study from published materials (i.e. CT.gov and the unredacted sections of the committee papers for TA681). Table 107 in the EAG report appendix presents only the NRI values from CT.gov. Data based on different estimands should not be combined in the same analysis as there is a risk it could introduce bias in favour of the drug for which patients are censored after receiving rescue therapy as rescue tends to occur more frequently in the placebo arm. In Table 47 of Document B and in Table 134 of the appendix to Document B in LEO Pharma's original STA submission the effect of tralokinumab versus baricitinib in monotherapy varies substantially between the NRI and all-observed regardless of rescue estimands. This highlights the potential impact of combining outcomes across methods of handling rescue and demonstrates that it is not appropriate. As such, any conclusions regarding the relationship between tralokinumab and baricitinib should be revised to account for a lack of comparability in the estimand and associated uncertainty. Examples include:
    - Page 14: "Tralokinumab therapy led to a lower EASI 75 response than baricitinib 2 mg and 4 mg ([redacted])"
    - Page 132: "The NMA results indicate that treatment of adults in the second line setting with tralokinumab leads to a better response treatment, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than placebo but an inferior response to dupilumab treatment and baricitinib 4 mg treatment (only available for EASI 75)".
- In Table 12, Table 14, Table 18 and Table 20 in the EAG report, it would be helpful to amend the label for the treatment effects of each drug versus dupilumab. It currently states "Treatments versus Dup 200 mg or 300 mg every 2 weeks". Since only the 300 mg every 2 weeks dose of dupilumab is relevant in the adult population, it would be clearer and more accurate to re-label as "Treatments versus Dup 300 mg every 2 weeks".

3 The baseline-risk adjusted NMA

- We are pleased to see that the EAG performed baseline-risk adjusted NMAs to explore the impact of heterogeneity in the evidence. We note that these analyses produced results for the second-line monotherapy networks, but not for the second-line combination therapy networks due to a lack of convergence. We ask the EAG to please provide further explanation of why the combination therapy model did not converge, especially given that they report on page 91 that all three companies performed and submitted a baseline-risk adjusted model.
- LEO speculate that it could be driven by the sparsity of data available for the restricted population. Although the patient numbers in the monotherapy networks are also small, there are more trials per treatment and per comparison to inform the synthesis, including the adjustment covariate. For most comparisons in the combination therapy network, there is only one study contributing to the synthesis. The exceptions to this are for comparisons between placebo and dupilumab and placebo and tralokinumab. It is therefore not unexpected that the model might not converge because there is insufficient data. Furthermore, it would be difficult to differentiate between the treatment effect and covariate effect using the evidence from the single studies of abrocitinib, upadacitinib and baricitinib. Indeed, that the model failed to converge is not unexpected and even if it did converge, it is unclear

how one would interpret the results. LEO argue that simply stopping due to a lack of convergence is insufficient because there are other ways to explore the issue in order to understand the significant implications of the underlying heterogeneity in the evidence.

- LEO acknowledge that the evidence for the restricted second-line population is most applicable to the position sought for reimbursement; however, this evidence alone is insufficient to explore the potential biases caused by between-trial heterogeneity, particularly in the combination therapy population. As the issue of variability in placebo arm response rates is common to both the restricted population and the overall randomised population, it is worth exploring the application of the baseline-risk adjusted model in the all randomised patient populations of the included trials. Looking again at Table 46, Table 47 and Table 134 from the original LEO submission, the differences between results of the ECZTRA 7-like subgroup analysis and the analysis including all randomised patients are relatively small. This suggests that although the subgroup data might be more directly applicable to the decision problem, data for the overall randomised population might still be informative, especially where its use could allow for the estimation of the size and direction of potential bias and the effect of controlling for it. To note, LEO accept that any analysis on the overall population should not inform the base case analysis of the cost-effectiveness model but could be used in a sensitivity analysis like the placebo-adjusted model results for second-line monotherapy.
- LEO seek clarification on the preference for the non-baseline-risk-adjusted model in the second-line monotherapy population. The EAG state: “The sensitivity analysis adjusting for heterogeneity in placebo response gave a lower DIC than the primary, unadjusted analysis, indicating a better model fit. However, the total residual deviance, for this analysis, was lower than the number of unconstrained data points, indicating that the model may be “overfitting” the data. That is, the model predicts the underlying trial data extremely well (and hence a lower DIC) but is likely to be less generalisable to the population of interest than the unadjusted analysis using observed data.” In general terms, LEO agree with the standards the EAG says they use to assess model fit and determine choice of model; however, LEO disagree slightly with the application in this case. The difference in DIC is slightly larger than 5, and although the total residual deviance is slightly lower than the number of unconstrained data points, the difference between these numbers (22.0-20.2=1.8) is smaller than the difference between the same numbers for the non-adjusted analysis (25.0-22.0=3). We are unaware of guidance to suggest that a total residual deviance that is slightly lower than the number of unconstrained data points is always less preferable than the reverse. We are also missing crucial information on the significance of the parameter associated with the baseline adjustment. Unless this parameter is highly non-significant and/or equal to a value very close to zero, then the dismissal of the baseline-risk adjusted model is not so clear cut given the >5-point difference in DIC, and the fact that the total residual deviance is actually closer to the number of unconstrained data points than with the non-adjusted model.

4 Inappropriate assumption of parity in monitoring burden between biologics and oral JAKs

- The current EAG model does not seem to account for the additional monitoring expected with oral JAKs. These treatments are associated with substantial safety concerns, relating to severe cardiovascular events and malignancies. Indeed,

abrocitinib, baricitinib and upadacitinib are associated with a black box warning in the US. When we have consulted with clinical experts, they repeatedly informed us that oral JAKs would be associated with additional monitoring to minimise the risk of these events. This was also discussed in TA681. LEO Pharma recommends that the monitoring costs associated with oral JAKs are acknowledged in the report and incorporated within the analysis in a manner that is comparable to the approach taken to model ciclosporin (see Table 53 in EAG report).

5 Lack of NMA for adverse events

- The approach taken by the EAG for determining adverse event probabilities was to use trial data (or pooled trial data) directly. This is not best practice as it will not account for variation between trials and therefore an NMA of adverse events would have been preferred (as performed in LEO's company submission for the STA). LEO acknowledge, however, that the impact of adverse events on the overall cost-effectiveness of each intervention seems to be limited.

6 Application of administration costs

- The EAG report mentions the following regarding administration costs: "LEO Pharma has indicated that training on how to self-administer tralokinumab will be provided to the NHS free of charge. As such, no administration costs are incurred by tralokinumab-treated patients in the base case analysis." This does not seem to be reflected in the programming in the EAG model, the formula in K4 in the "Engine Int" tab includes an administration cost when tralokinumab is selected as the intervention.

7 Suspected issues in EAG model engines

- The decision trees in the EAG model (for example in the "Engine Int" tab) appear to include 53 weeks' worth of costs and QALYs due to the inclusion of 0 weeks.
- There is a slight difference in the model horizon between interventions. For dupilumab, if the time horizon up to 100 years of age, then costs and QALYs stop accruing at 99 years old. For tralokinumab, costs and QALYs also accrue in the subsequent year. This is because the formula in column X in the "Engine Int" tab contains "<=" while the corresponding formula in the "Engine Dup" tab has "<" only.

8 Suspected issues in NMA results in EAG model

- In the EAG model in the "Second combo NMA – Week 16" tab, in the table that occupies X31:AC39 it seems as though median values have been used instead of lower 95% CrI values in some cases. Please see the cells with red text in Table 2 below. This issue also appears in Table 120 in the EAG report.

  Table 2 :Combination therapy NMA results from "Second combo NMA – Week 16" tab

Comparison	mean ln OR	median ln OR	SD	Lower 95% CrI	Upper 95% CrI
Abrocitinib 100 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dupilumab 300 mg Q2w + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS vs placebo + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9 Lack of face validity in annual flare costs

- The difference in the annual cost of flares for tralokinumab and dupilumab in monotherapy is not plausible (dupilumab annual flare cost is £0.03 and tralokinumab annual flare cost is [redacted]). A major cause of the difference is the distribution of treatments used for flares. For tralokinumab, the distribution of treatments uses pooled data from ECZTRA 7-like population of ECZTRA 1 & 2. For dupilumab, the values used are from Table 2.32 in TA534 (as shown in
- Figure ***1***). Table 2.32 states that 82 patients received rescue therapy in SOLO 1 & 2 but only provides the type of rescue therapy for 13 patients and therefore is incomplete. Based on these data, it appears that the EAG have assumed that 16% of dupilumab patients who experience a flare receive a systemic steroid and that the rest receive no treatment, which could be an underestimation. LEO Pharma recommend using the distribution of treatments from the ECZTRA 7-like population from ECZTRA 1 & ECZTRA 2 for both dupilumab and tralokinumab in this analysis.

Figure 1: Table 2.32 from TA534

	SOLO 1			SOLO 2		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Rescue therapy n (%)						
Any rescue therapy	115 (51.3%)	47 (21.0%)	52 (23.3%)	123 (52.1%)	35 (15.0%)	49 (20.5%)
Systemic corticosteroids	17 (7.6%)	2 (0.9%)	5 (2.2%)	30 (12.7%)	3 (1.3%)	6 (2.5%)
Immunosuppressants	5 (2.2%)	3 (1.3%)	2 (0.9%)	16 (6.8%)	1 (0.4%)	2 (0.8%)
Oral calcineurin inhibitors	4 (1.8%)	2 (0.9%)	1 (0.4%)	13 (5.5%)	1 (0.4%)	2 (0.8%)
Systemic immunosuppressants	0	1 (0.4%)	1 (0.4%)	0	0	0
Other immunosuppressants	1 (0.4%)	0	0	4 (1.7%)	0	0

QW, once a week; Q2W, every two weeks

10 Potential bias due to varying rescue therapy usage

- On Page 100 of the EAG report, it states: “The primary analysis for the monotherapy NMAs was based on using all observed data, regardless of rescue medication use to determine response, with a sensitivity analysis conducted where patients requiring rescue medication were considered non-responders. Patients were not allowed

rescue therapy in the abrocitinib trials." Was the bias that this could have introduced into the NMA considered?

11 Conditional response versus conditional discontinuation

- On page 166 of the report, the EAG state: "The tralokinumab model also based Week 52 outcomes on conditional response data, which was used to inform an NMA for response to treatment at Week 52 even though the recommendations for TA681 had been published prior to the company's submission to NICE. LEO Pharma did not present a justification for using conditional response over conditional discontinuation." Although these statements are factually correct, LEO wish to clarify that the publication of TA681 occurred less than 7 weeks before the deadline of LEO's submission for tralokinumab. As a practical point, this is an exceptionally short timeline on which to make substantial structural amendments to an economic model and revise a submission. LEO would also like to clarify that although no justification was provided for the use of conditional response, none was requested by the EAG at either of 2 rounds of clarification questions.
- LEO maintain that the conditional response approach is appropriate as any patients who discontinued the trial between week 16 and week 52 would have counted as not having sustained response given the approach to handling missing data. That said, LEO accept the conditional discontinuation approach preferred by the committee in TA681 and implemented by the EAG.

12 Minor textual comments

- Page 118 of the EAG report states the following: "The use of rescue medication was markedly reduced in patients receiving active treatment (dupilumab, tralokinumab or upadacitinib) compared with placebo (**Error! Reference source not found.**). The only exception was ECZTRA 1, in which a similar proportion of patients received rescue therapy in the tralokinumab and placebo arms of the trial." ECZTRA 1 should not appear in this section as it is referring to combination therapy trials.
- Page 132 of the EAG report states the following: "The NMA results indicate that treatment of adults in the second line setting with tralokinumab leads to a better response treatment, assessed as either EASI 50 + ΔDLQI ≥4 or EASI 75, than placebo but an inferior response to dupilumab treatment and baricitinib 4 mg treatment (only available for EASI 75)." Use of term "inferior" implies statistical significance, which was not always demonstrated.
- There seems to be a minor error in Table 12 in the EAG report. The primary NMA odds ratio for tralokinumab versus placebo is reported as [redacted] while in the model the median odds ratio, presented on the natural scale, in cell P35 in the "Second mono NMA – Week 16" tab is [redacted] (which equates to an odds ratio of [redacted]).
- In Figure 13, it appears as though an arrow is missing to allow for non-responders to dupilumab/baricitinib to discontinue and move to BSC.
- On line 3 of page 167, there appears to be a typo. Where it refers to Week 16, we think it should read Week 52.
- In Table 43, the n/N data listed as coming from the ECZTRA 7-like population from ECZTRA 2 is incorrect. The values that were submitted as part of LEO's response to clarification questions was [redacted]. Similarly, the n/N data listed as coming from the

ECZTRA 7-like population from ECZTRA 3 is incorrect. The values that were submitted as part of LEO's response to the clarification questions was [redacted].

- The headings of the final 2 columns of Table 52 are identical but provide different values. Is this a typo?

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Consultation response to assessment group report

Pfizer

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Introduction

Pfizer welcomes the opportunity to provide feedback on the Expert Assessment Group (EAG) report and model for the appraisal of upadacitinib, abrocitinib & tralokinumab [ID3768]. Please see below comments on the executable model in Section 1 and broader comments on the report in Section 2. Additional evidence to support the clinical and economic case for abrocitinib is provided in Sections 3 – Section 5 [redacted] and data on the systemic-naïve trial population to support the first-line systemic positioning for adults for abrocitinib.

Section 1: Executable model

A significant error has been identified in the EAG cost-effectiveness model for adults (*ID3960 MTA atopic dermatitis adults list price final_redacted*) which is having a substantial impact on the overall acquisition costs being pulled through into the ICERs for abrocitinib 200mg and 100mg. This issue has been flagged to the EAG and they have confirmed it will be corrected in the final version of their report shared with the committee.

This error is highlighted in the tables below alongside other issues related to the EAG models for adults and/or adolescents. Given that there are several inputs within the models that are commercial or academic in confidence, we have provided a description of the expected impact of the error on the ICERs rather than quantifying this.

Issue 1 Abrocitinib acquisition costs

Description of problem	Description of proposed amendment	Expected impact on the ICER
Drug costs incorporated into the ICERs for abrocitinib 100mg and 200mg in the adult model. In cells K6, K7 and AM7 of the 'Engine Int' sheet, VLOOKUP formulas are used to pull through the drug acquisition cost for the intervention. However, the formula does not specify a range lookup argument, meaning it is set to true by default. This in turn leads to an error in the calculation of drug costs when abrocitinib is selected as the comparator, as the cost of upadacitinib 30mg is used. For example, if you change the cost of upadacitinib 30mg in cell P13 within the 'Costs-treatment' tab then this is pulled through into the 'Engine Int' sheet in the model even when abrocitinib 200mg is selected.	Correct formulas to ensure abrocitinib costs are being pulled through into the model engine	Substantial impact on results is expected

Issue 2 Additional cycle in the intervention engine

Description of problem	Description of proposed amendment	Expected impact on the ICER
In the adult model, an additional cycle has been included in the Markov model for the intervention arm. The sheet 'Engine Int', column X, considers a cycle to be within the time horizon if patients age is less than or equal to the value on 'Model settings'!F25. In the sheets 'Engine Bar' and 'Engine Dup' a cycle is considered to be within the	The engines for baricitinib and dupilumab should be updated to match the intervention engine.	Minimal impact on results is expected.

time horizon if the patients age is less than, but not equal to, 'Model settings'!F25.		

Issue 3 Discounting

Description of problem	Description of proposed amendment	Expected impact on the ICER
In the Markov model for all comparators in both the adult and adolescent models, the discounting factor has been calculated using the time at the end of the cycle, rather than at the start of the cycle.	The discounting formulas should be updated to reflect time at the start of the cycle.	Minimal impact on results is expected.

Section 2: Comments from AG report

Issue 4 Assumption around a JAK class for inputs/assumptions within the model

In page 8 of the EAG report it is stated that "where there was a paucity of data, the EAG adopted a drug class approach to fill the gaps, where upadacitinib was used to inform Janus Kinase Inhibitors and tralokinumab used to inform monoclonal antibodies."

For illustrative purposes we have summarised in Table 1 several inputs incorporated within the EAG model across treatments considered within the MTA. The data are for adults being treated with a second-line systemic (i.e., achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy). Further, the data are based on using EASI75 as a measure of response given that only data for this endpoint has been sourced by the EAG.

The EAG have assumed that baricitinib 4mg discontinuation rates and utility data would be comparable to the higher doses of abrocitinib (200mg) and upadacitinib (30mg). It is also assumed that discontinuation rates and utility values for the lower doses of abrocitinib (100mg) and upadacitinib (15mg) would be comparable.

Table 1 EAG model inputs, EASI75, adults combination therapy

EASI75 Combo	Abro 200mg	Abro 100mg	Dupi	Bari 4mg	Upa 30mg	Upa 15mg	Tralo
% responders (week 16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual disc	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Baseline utility	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	NR
Responder utility	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]	NR
QALYs	[redacted]	[redacted]	-	[redacted]	-	-	-

High-dose JAK Low-dose JAK; NR, not reported

The EAG have not fully described the rationale provided by clinicians they consulted with as to why they thought these inputs would be appropriate. Our assumption would be that clinicians would expect utility and discontinuation rates amongst treatments to vary, and in relation to the JAKs have made a crude assumption that high-dose JAKs have better efficacy than low-dose JAKs.

However, whilst generally this trend holds based on the efficacy data for abrocitinib and upadacitinib, it does not for baricitinib. The baricitinib 4mg dose, whilst being the 'higher-dose,' in the arbitrary sense of being the highest marketed dose, has substantially lower efficacy compared with both doses of abrocitinib and upadacitinib as illustrated in Table 1. The percentage of EASI75 responders at week 16 is

[redacted] for baricitinib 4mg compared with [redacted] for the lower doses of abrocitinib and upadacitinib, and [redacted] for the higher doses. We would strongly argue that it is inappropriate to assume the same discontinuation and utility for baricitinib 4mg and the high doses of abrocitinib and upadacitinib. Based on the efficacy data, the profile for baricitinib 4mg would not be comparable to even the lower doses of abrocitinib and upadacitinib.

A clinical expert who we have discussed these assumptions with has confirmed that from a clinical perspective these assumptions are inappropriate, particularly in relation to the baricitinib 4 mg data.

Further, these assumptions around discontinuation and baseline/responder utility, which are not deemed by clinical experts to be plausible, have a significant impact on the overall cost-effectiveness conclusions and result in a substantial bias in favour of baricitinib. These assumptions also result in counterintuitive results. For example, although the response rate (EASI75) for abrocitinib 100mg is almost [redacted] higher than for baricitinib 4mg dose, it is associated with fewer QALYs in the EAG model ([redacted]).

We have explored further the utility and discontinuation assumptions below.

Utility data for responders

It is expected that the utility value associated with being a responder on a more efficacious treatment would be higher given that a greater proportion of patients achieve higher thresholds of response (e.g., EASI90). Table 2 presents the relative treatment effects (probit score differences) based on the original fixed effects NMA submitted for abrocitinib using a multinomial-probit EASI50/75/90 model, with 95% CrI that do not cross 0 indicating significant differences. [redacted]

Table 2 Cross tables on probit scales, adult combination therapy, fixed effect NMA using multinomial-probit EASI50/75/90 model. Significant differences for the comparisons of abrocitinib vs baricitinib are shown in bold and italics.

Full trial population	[redacted]					
	[redacted]					
	[redacted]					
	[redacted]					
	[redacted]					
	[redacted]					

Generalisable population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Restricted population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Utility data at baseline

There is no clinical rationale for the EAG's use of different baseline utility values across therapies. Although improvement in utility may differ, a common baseline should be applied in the EAG model.

Discontinuation

Notably, baricitinib discontinuation data (Table 2) was provided to Pfizer, with permission from Eli Lilly, for inclusion within our initial STA submission for abrocitinib. The data was shared within the first appraisal committee meeting within the baricitinib appraisal process [TA681] although it was marked as academic in confidence. We appreciate that permission may not have been obtained to use this data within the MTA process, but would argue it is highly relevant given that discontinuation is a significant driver of the ICER. As shown in Table 2, the annual discontinuation rate reported for baricitinib based on their trial data is considerably higher than the assumed value incorporated within the EAG model, which may not be clinically plausible (Table 3).

Table 3 Summary of baricitinib discontinuation rates, annual discontinuation week 52 +

NICE baricitinib appraisal TA681[a]		EAG model	
EASI 75	**EASI 50 + DLQI≥50**		**EASI 50 + DLQI≥50**
[redacted]	[redacted]	[redacted]	-

[a]Slide 47 appraisal committee slides; company and ERG alignment

Summary and recommendation: The rates of discontinuation and utility for baricitinib should not be assumed to be equivalent to the higher , or even the lower doses, of abrocitinib and upadacitinib. We request that the EAG revisit these assumptions with clinical experts to ensure their clinical plausibility, considering the outputs from the NMA and relative efficacy across treatments, as well as the data from the baricitinib appraisal [TA681].

Issue 5 Modelling of BSC

The EAG model assumes that there is a waning in the utility benefit associated with active treatment and that the response rates seen in clinical trials will not hold in the long-term. However, the model does not include any waning of BSC utility and instead models the BSC as a weighted average of responders and non-responders to BSC, with efficacy taken from the placebo arms of AD UP or MEASURE UP 1 and 2. This is in line with the ERG's preferred approach in TA681, however is at odds with clinical opinion, the approach taken in the company submissions and the committee's preferred assumptions in the baricitinib appraisal (TA681).

Clinical opinion provided to the company indicated that the response to BSC seen in clinical trials would be expected to drop off quickly, with one clinician stating that utility for BSC would be more comparable to that of non-responders. Company submissions have included a waning effect for BSC, with up to 97% of BSC patients losing their response over 5 years. Further, the preferred assumptions of the committee in TA681 fell between the ERG and company approaches. The conclusion from the committee in the baricitinib FAD was that "the ERG's approach …. overestimated the quality of life of patients having best supportive care, because it was implausible that there would be no loss of quality-of-life benefit over time on average."

While BSC is not a comparator in the EAG model, the utility values and resource use for patients ending up on BSC remains an important factor. The current approach produces counterintuitive results as in overestimating the utility values for patients receiving BSC in the long-term, the model overstates the QALY gains for treatments with lower response rates and higher rates of discontinuation.

We would ask the EAG to revisit the assumptions incorporated within the model related to the utility benefit and apply a waning over time. The assumptions in Table 4 are between the company and ERG base cases in the baricitinib appraisal (TA681) and were explored within scenario analysis in the original abrocitinib submission (Scenario 3, p183).

Table 4 Waning of utility benefit for BSC in the model

Year	
2	18%
3	10%
4	10%
5	10%

Abbreviations: BSC, best supportive care.

Summary and recommendation: Given that the assumptions included by the EAG around the modelling of BSC are at odds with the committee's preferred assumptions in the baricitinib appraisal (TA681), we would request that these assumptions are reconsidered. Table 4 represents assumptions related to the waning of utility benefit that are between the company and ERG base cases in the baricitinib appraisal.

[redacted]

[redacted]

[redacted]:

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Clinical outcomes

- In JADE COMPARE, EASI (±DLQI) response rates for abrocitinib 100mg and dupilumab are comparable. For several critical response measures (e.g., PP-NRS itch response at Week 2, [redacted]) abrocitinib 200mg is statistically significantly better than dupilumab; otherwise no significant differences between these treatments were observed (Abrocitinib submission Document B, Section B.2.6.1 [page 68]).
- [redacted] (Abrocitinib submission Document B, Section B.2.9.5 [page 113]).
- Results from the NMA (Abrocitinib submission Document B, Section B.2.9.5 [page 113]) also suggests that [redacted]

[redacted]

[redacted]

Section 5: Case for systemic naïve population

Adolescents

As per Section 5.2.1.1 in the EAG report, the EAG has evaluated abrocitinib 200mg and 100mg as a first-line and second-line systemic for adolescents with moderate to severe AD.

As per the EAG report we define first-line treatment to be for those patients who are eligible for systemic treatment based on inadequate response to topical treatments and who have not received prior systemic therapy. Second-line systemic therapies are for patients who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy.

As per email communication shared with NICE for EAG attention on 16 December 2021, we are requesting that abrocitinib 200mg and 100mg doses are considered as a first-line systemic treatment for adolescents in line with the EAG's modelling and consideration of dupilumab as an appropriate comparator.

We flagged in our fact check response that we had initially positioned both doses of abrocitinib as a second-line systemic treatment for adolescents but based on the evidence that has been compiled, there is a strong clinical and economic case for abrocitinib 200mg and 100mg to be positioned as a 1L systemic for adolescents with moderate to severe AD.

Adults

We are also requesting that abrocitinib be considered as a first-line systemic for adults based on a comparison with ciclosporin and the methodological approach employed by the EAG. To support an NMA including abrocitinib as a first-line systemic, efficacy data for the trial population who had not been previously exposed to systemic treatment (systemic naïve population) has been provided in an appendix.

Clinicians who have been engaged have confirmed that there would be appetite for using JAK inhibitors as a first-line systemic or as an alternative to systemic immunosuppressants.

Given that the efficacy profiles for abrocitinib 100mg and 200mg are comparable to upadacitinib 15mg and 30 mg, respectively, which are proposed to be positioned as first-line systemic treatment for moderate to severe AD, we would expect the QALY gain to be comparable. We would request that the EAG incorporate this data into the NMA and modelling in the first line setting for this MTA so this can be fully explored.

Timing

We appreciate that NICE had several reasons incorporating abrocitinib into an MTA alongside upadacitinib and tralokinumab, however this appraisal process is lengthier than an STA, given the onus on the EAG to build an NMA and model to assess clinical effectiveness and cost-effectiveness respectively. In order to avoid further delays to patient access we would propose to prioritise and conclude the second-line systemic positioning for abrocitinib in the first appraisal meeting and consider the first-line systemic positioning in a second appraisal meeting should more time be required by the NICE committee to fully evaluate abrocitinib (and other JAK inhibitors) in the first-line setting.

Appendix: Systemic naïve clinical effectiveness data for adults

The appendix included the relevant clinical effectiveness data and baseline characteristics of the systemic naïve population from JADE COMPARE, JADE DARE, MONO1 & MONO2 for **adults.**

As per Section 5 we are requesting that abrocitinib is considered within the NICE appraisal process as a first-line systemic treatment and that the provided data is incorporated within the NMA & modelling for the MTA based on this additional positioning.

Population: Systemic-naïve in adults, meaning patients who have not been previously treated with systemic therapies for atopic dermatitis prior to participation in the trials

Available timepoints: week 16 data have been provided for JADE COMPARE & JADE DARE as per the data presented within the EAG report. For MONO-1 & MONO-2 Week 12 data is presented as this was the length of treatment duration in the trials.

Available endpoints: The following endpoints have been provided for consideration of abrocitinib in the 1L setting given these are the primary outcome measures that have informed NICE's decision making for appraisal in atopic dermatitis.

- Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)
- Proportion of people achieving EASI 75, n/N (%)

JADE COMPARE

Table 4 Clinical effectiveness at week 16, systemic naïve population, JADE COMPARE

	Abrocitinib 200 mg OD plus TCS (■■■)	Abrocitinib 100 mg OD plus TCS (■■■)	Dupilumab 300 mg Q2W plus TCS (■■■)	Placebo plus TCS (■■■)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	■	■	■	■
Proportion of people achieving EASI 75, n/N (%)	■	■	■	■

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.

*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

Table 5 Baseline characteristics, systemic naïve population, JADE COMPARE

	Abrocitinib 200 mg OD plus TCS (■■■)	Abrocitinib 100 mg OD plus TCS (■■■)	Dupilumab 300 mg Q2W plus TCS (■■■)	Placebo plus TCS (■■)
Mean age, years (SD)	■	■	■	■
Gender, n (%)	■	■	■	■
Male	■	■	■	■
Mean duration of AD, years (SD)	■	■	■	■
Race	■	■	■	■
White, n (%)	■	■	■	■
Black or African American, n (%)	■	■	■	■
Asian, n (%)	■	■	■	■
Other, n (%)	■	■	■	■
Mean EASI score (SD)	■	■	■	■
Baseline IGA score of 4, n (%)	■	■	■	■
Mean DLQI score (SD)	■	■	■	■
Mean SCORAD score (SD)	■	■	■	■
Mean peak pruritus NRS score (SD)	■	■	■	■
Mean % BSA affected (SD)	■	■	■	■
Mean baseline EQ-5D Score (SD)	■	■	■	■
Prior treatment	■	■	■	■
Oral/injectable corticosteroids, n (%)	■	■	■	■
Other non-biologic systemics (i.e., ciclosporin or other)	■	■	■	■
Biologics (excluding dupilumab*)	■	■	■	■
Topical agents only	■	■	■	■
High potency corticosteroids	■	■	■	■
Medium-low potency corticosteroids	■	■	■	■
Unknown strength corticosteroids	■	■	■	■
TCI, n (%)	■	■	■	■

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Patients with prior use of dupilumab were excluded from the JADE COMPARE trial

Table 6 JADE DARE

	Abrocitinib 200 mg OD plus TCS (N)	**Dupilumab 300 mg Q2W plus TCS (N)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.
*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

Table 7 Baseline characteristics, systemic naïve population, JADE DARE

	Abrocitinib 200 mg OD plus TCS (N)	**Dupilumab 300 mg Q2W plus TCS (N)**
Mean age, years (SD)	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]
Male	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]
Race	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]
Other/missing, n (%)	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]
Prior treatment		

Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]
Biologics (excluding dupilumab*)	[redacted]	[redacted]
Topical agents only	[redacted]	[redacted]
High potency corticosteroids	[redacted]	[redacted]
Medium-low potency corticosteroids	[redacted]	[redacted]
Unknown strength corticosteroids	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid. *Patients with prior use of dupilumab were excluded from the JADE COMPARE trial		

Table 8 JADE MONO-1

Clinical effectiveness at week 12, systemic naïve population, adults, JADE MONO-1

	Abrocitinib 200 mg OD ([redacted])	**Abrocitinib 100 mg OD ([redacted])**	**Placebo ([redacted])**
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.			

Table 9 Baseline characteristics, systemic naïve population, adults, JADE MONO-1

Characteristic	**Abrocitinib 200 mg OD ([redacted])**	**Abrocitinib 100 mg OD ([redacted])**	**Placebo ([redacted])**
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]

Male	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Other/not reported, n (%)	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D VAS Score (SD)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Index Value (SD)	[redacted]	[redacted]	[redacted]
Prior treatment	[redacted]	[redacted]	[redacted]
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]
Topical agents only	[redacted]	[redacted]	[redacted]
High potency corticosteroids	[redacted]	[redacted]	[redacted]
Medium-low potency corticosteroids	[redacted]	[redacted]	[redacted]
Unknown strength corticosteroids	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Table 10 JADE MONO-2

Clinical effectiveness at week 12, systemic naïve population, adults, JADE MONO-2

	Generalisable		
	Abrocitinib 200 mg OD (■)	**Abrocitinib 100 mg OD (■)**	**Placebo (■)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	■	■	■
Proportion of people achieving EASI 75, n/N (%)	■	■	■
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.			

Table 11 Baseline characteristics, systemic naïve population, adults, JADE MONO-2

	Abrocitinib 200 mg OD (■)	**Abrocitinib 100 mg OD (■)**	**Placebo (■)**
Mean age, years (SD)	■	■	■
Gender, n (%)	■	■	■
Male	■	■	■
Mean duration of AD, years (SD)	■	■	■
Race	■	■	■
White, n (%)	■	■	■
Black or African American, n (%)	■	■	■
Asian, n (%)	■	■	■
Other, n (%)	■	■	■
Mean EASI score (SD)	■	■	■
Baseline IGA score of 4, n (%)	■	■	■
Mean DLQI score (SD)	■	■	■
Mean SCORAD score (SD)	■	■	■
Mean peak pruritus NRS score (SD)	■	■	■
Mean % BSA affected (SD)	■	■	■
Mean baseline EQ-5D VAS Score (SD)	■	■	■
Mean baseline EQ-5D Index Value (SD)	■	■	■
Prior treatment	■	■	■
Oral/injectable corticosteroids, n (%)	■	■	■
Other non-biologic systemics (i.e., ciclosporin or other)	■	■	■

Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]
Topical agents only	[redacted]	[redacted]	[redacted]
High potency corticosteroids	[redacted]	[redacted]	[redacted]
Medium-low potency corticosteroids	[redacted]	[redacted]	[redacted]
Unknown strength corticosteroids	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

December 2021

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Dr Jane Ravenscroft) Presentation of results in the abstract lacks clarity. The assessment abstract does not make clear that all the considered drugs show evidence of efficacy and represent a huge step forward for the management of atopic dermatitis. The relative merits and placement in the treatment pathway cannot be determined at this time, but this information will become clearer with time due, in part, to the BEACON study, which is a UK live research platform designed to compare different treatments. The treatment classes are very different in terms of administration, monitoring, immunosuppressive effect (narrow for biologics vs broad for JAK), and other adverse events, so their use will need to be tailored to the individual. The first statement 'Abrocitinib 200 mg and Upadacitinib 30 mg maybe more effective and tralokinumab less effective than dupilumab and baricitinib as second line' does not give meaningful information because there are too many variables, and it lumps dupilumab and baricitinib together which is not helpful. Throughout the abstract different drugs,	Start with the statement that all the considered drugs show evidence of efficacy and represent a huge step forward for the management of atopic dermatitis. Then make clear that it is not possible to draw any meaningful conclusions about the cost effectiveness or clinical placement for these drugs due to lack of critical information, absence of direct comparisons and individual patent factors. This is compounded by redaction and withholding of some data by drug companies, including true current costs to NHS. Then consider defining the situations more clearly.	Easier understanding and greater transparency.

doses, ages, situations and analyses (effectiveness/cost effectiveness) are mixed together leading to confusion about what is being stated.		

Issue 2

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Emphasis is given throughout the assessment regarding the difference between 'monotherapy' and 'combination therapy with TCS'. However, in clinical practice most clinicians would not consider use of topical steroids to be 'combination therapy'. It is difficult to understand how the results differ so greatly depending on whether TCS are used or not. For example, in adult second-line therapy, upadacitinib 15 mg monotherapy dominates dupilumab but upadacitinib plus TCS is less effective and more expensive than dupilumab plus TCS.	Consider changing terminology to 'with topical TCS' rather than 'combination' Sense-check the results.	May affect conclusions if monotherapy and combination therapy are considered together.

Issue 3

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There are conflicting statements in the assessment regarding effectiveness of upadacitinib 15 mg vs dupilumab in adolescents, with some sections stating it	Check and correct the inaccuracies.	May affect conclusions.

is more effective, and others stating less effective.		

Issue 4

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The most commonly used first-line systemic drug for AD in the UK is methotrexate. This has understandably not been included because it is not licensed. However, there is literature showing that ciclosporin and methotrexate are similarly effective. Methotrexate is much cheaper, and its inclusion may change the assessment.	State the importance of including methotrexate in any future recommendations on placement.	May affect future recommendations.

Issue 5

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The health economic data does not include blood tests and adverse blood parameters (neutropenia, hyperlipidaemia) which are recognised adverse effects of JAK inhibitors and have significant associated costs of monitoring. In contrast, dupilumab does not require regular blood monitoring.	Include costs for blood monitoring as per SmPC.	May affect health economic evaluation and pathway placement.

Issue 6

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
No attention is given to patient factors such as: 1. Choice between an injection every other week or tablets every day (twice a day for ciclosporin). 2. Blood monitoring required for JAK inhibitors and ciclosporin but not for dupilumab.	State that patient factors may need to be considered in any recommendations. This can particularly apply to adolescents.	May affect future recommendations.

Issue 7

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In the cost evaluations, the assumption is that patients on ciclosporin will return to BSC after 1 year, i.e. topical treatments only. This is not valid as most patients will need to move on to an alternative systemic therapy after stopping ciclosporin. Currently, this may be methotrexate, azathioprine, mycophenolate mofetil or, increasingly, dupilumab. If these costs are taken into account in the long-term model, then ciclosporin becomes much less favourable. There are also significant side effects of ciclosporin, which have not been mentioned including renal impairment. SmPC has not been followed for costs of monitoring. Ciclosporin is rarely used in	Factor transition to another long term drug into the ciclosporin calculations.	May affect health economic calculations and future recommendations.

adolescents due to high risk of adverse events such as hirsutism, gum hypertrophy and knowledge that it will need to be stopped after 1 year, with probable flares of eczema (very distressing for adolescents).		

Issue 8

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Dr Michael Ardern-Jones) Firstly, most of the phase III trials had a primary endpoint at 12 weeks. It is not clear how these data were used to compare decision-making at 16 weeks. This is especially a concern for ciclosporin – they state 'no RCT for ciclosporin was available to inform an NMA'.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 9

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The methods section implies that where data were missing a class affect was applied. This would suggest that baricitinib/ abrocitinib/upadacitinib data were assumed to be similar, which is clearly not the case, and the same is true for tralokinumab and dupilumab. This approach is flawed, but it is not clear what the impact of this was.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 10

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The reporting is very confusing, with some recommendations stating that certain drugs are not good value while others are, but only with or without topical steroids. Why in adults second line would it be better to use upadacitinib or tralokinumab at low dose without TCS but not good value using them with TCS? This seems inappropriate and likely to imply that the differences referred to are due to methodological problems.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 11

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
In the ICER analysis, in comparison to dupilumab, the higher doses of upadacitinib and abrocitinib in combination with TCS are not cost effective second- line option in adults, whereas the lower doses are cost effective. In view of the fact that the data suggests that the efficacy of lower doses of upadacitinib/abrocitinib are roughly equivalent to dupilumab, whereas the higher doses are better, this underscores that the problem here is that the work is dependent upon the use of published list prices which we know are not the actual cost. Therefore, the ICER analysis needs	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

to be heavily cautioned more than it is already and is essentially meaningless. Indeed, most of the new drugs referred to: upadacitinib, baricitinib, dupilumab, are actually fully licensed for use and approved by NICE (albeit upadacitinib in a rheumatology indication), so the real cost is known to the NHS and should be the actual cost that is used, even if redacted.		

Issue 12

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Overall, the main issues are that while we have good clinical data to compare, the clinical comparisons have not been used as the main readout of the NMA. Instead, the authors have gone on to base their conclusions largely on a cost-based approach derived from published list prices which we know are not what the NHS is actually paying for the drugs. Additionally, there are challenges in comparing different endpoints in the trials and this needs to be better acknowledged. This especially applies to the first-line treatment as clinical data on ciclosporin is very limited. We would suggest that either ciclosporin is exclude from the analysis and work on second-line treatments only at list cost, or remove the ICER comparisons to an appendix, or re-cost with actual prices for	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

the drugs (list price for abrocitinib, with comment on that).		

Issue 13

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Dr Alexa Shipman) Section 1.2.2: whilst topicals might be cheap they have to be prescribed in large quantities. Adults with moderate-to-severe eczema can get through a 30 g tube of TCS in one day, they will need multiple different strengths and regular prescriptions. Therefore, it should be noted that this treatment is expensive to the NHS as it is likely that the patient needs new prescriptions every week for numerous items. It is also very time consuming for GPs dealing with these requests and also most expensive for patients (who are not eligible for free prescriptions as are other patients).	Topical emollients and steroids for the control of moderate to severe eczema is costly to patient, and NHS regarding time and quantity of prescriptions required. An average adults might need 2 kg of emollient (£16-20), 500 ml of a soap substitute (£5-10), 200 g of potent steroid (£6-100 depending on brands), 100 g of moderate or weak steroid (£10) and perhaps a calcineurin inhibitor 60 g (£36-50) each week to control their eczema. This is £80-100 on average in drug costs per week, and at least five prescription charges for a patient and has to be repeated weekly if we wanted to provide the patient with enough topicals for excellent skin control.	Good topical management of eczema is expensive for the patient and the NHS in time and drug supplies with costs varying but easily approaching £5000 a year for topical treatments plus a large amount of time spent of doctor and pharmacist time doing repeat prescriptions, medicine reviews, etc.

Issue 14

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Professor Sara Brown)	Consider focusing assessment on treatment combined with	Conclusions with respect to efficacy and cost-

The focus on efficacy in 'monotherapy' is not helpful because it is so far removed from clinical practice; data showing efficacy when combined with TCS could/should be the primary analysis. The use of 'TCS-free-days' is not a treatment goal that my patients request so I am unsure why it has been selected as an important outcome here.	emollient and TCS use, to reflect standard care.	effectiveness will be more directly relevant for NHS practice

Issue 15

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
It would be helpful – though challenging – to have a clearer summary of study heterogeneity in important aspects such as wash-out period before treatment; use of concomitant emollients and/or TCS; availability of rescue therapy and what that is (as in clinical practice).	If feasible please summarise these important aspects of study heterogeneity and comment on possible impact on interpretation.	Conclusions with respect to efficacy and cost-effectiveness will be more relevant for NHS practice

Issue 16

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The primary outcome of "a combined response of EASI 50 + DLQI ≥4" does not state the time of assessment (most are at 16 weeks – but some therapies show improvements in efficacy over longer	Clarify time of assessment throughout and consider possible use of longer time to assessment to include delayed responses. Correct and standardise the annotation for the reduction in	Readers will be able to interpret the findings more fully for practical application.

timescales which could be useful clinically) and the terminology “DLQI ≥4” is ambiguous – presumably this means a *reduction* in DLQI by 4 or more points. Additionally, it is at times referred to as “DLQI ≥4” and others as “ΔDLQI ≥4” – neither would signify a *reduction* in DLQI scores by at least 4 points.	DLQI scores by at least 4 points throughout the document.	

Issue 17

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The manuscript reports “consistent trends” whilst also acknowledging some conflicting findings and no statistically significant differences. The authors also report a “dose-dependent numerical benefit” (p102) but this is not statistically significant and should be reported more cautiously.	State clearly that there are conflicting results and no statistically significant differences therefore no firm conclusions can be drawn at present.	Appropriately cautious interpretation

Issue 18

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Professor Carsten Flohr) The reason why the NMA could not identify any trial evidence for ciclosporin is due to the decision to go with EASI-50 *plus* reduction in DLQI of at least 4 points as the combined primary outcome because that is what was used/recommended in TA534	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

and TA681. However, if the exercise of this assessment is to decide which drug gives best value-for-money per improvement in disease severity/QoL overall, then this is too limited an approach, not surprisingly resulting in limited evidence to appraise. The reports seems to partially admit this by stating *"…but they went on to caution that the subjective nature of the DLQI, as a patient-assessed tool that is open to recall bias, is also borne in mind and, consequently, their preference to assess clinical effectiveness is change in EASI by 75%"* (p253). I am not saying we should exclude categorical outcomes altogether, but they are in my opinion secondary outcomes to a % change from baseline-based assessment.		

Issue 19

Description of problem	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
Our living NMA (ref 80 in the report) used change in disease severity score from baseline as our main outcome for the NMA and, unlike the NMA conducted for this assessment, were therefore able to include ciclosporin in the first iteration. We found that the treatment efficacy of dupilumab was similar to high-dose ciclosporin (5 mg/kg/day). The NICE report, therefore, needs to clearly state what dose of ciclosporin they are referring to throughout.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 20

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The dearth of good quality data on conventional systemics is unlikely to change much in years to come, although the TREAT trial results (methotrexate vs. ciclosporin in children and young people), which will come out later this year, will contribute to filling this gap for children and adolescents.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 21

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
As the health economic modelling is key to this evaluation from an NHS perspective, I wonder whether NICE could approach Professor Tracey Sach from East Anglia University, as she is an expert on the health economic evaluation in atopic eczema trials. It would be very helpful to have her providing an independent critique of the presented calculations.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 22

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Cost per % change in physician-assessed severity (EASI/QoL) from baseline is preferable, as it will provide more data to appraise, even if improvement in EASI-50/DLQI is used for the decision around continuation of the drug at 16 weeks into therapy.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 23

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The aetiology section 1.1.2 only refers to concomitant allergic diseases in children. Adolescents and adults should be equally covered, and other co-morbid conditions at least briefly mentioned, including auto-immune and cardiovascular disease.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 24

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Top of page 44, it should say ‘mild’ (not ‘very mild’) for hydrocortisone and 1% needs to be stated.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the

		problem might have an impact on the result

Issue 25

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Figure 1. It would be helpful to state that phototherapy is not an option in all patients due to their skin type and reaction to NB-UVB.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 26

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There is very limited information about use of these technologies outside clinical trials. It would be extremely important for all people with atopic dermatitis who meet the eligibility criteria to be enrolled in A-STAR (https://astar-register.org/) when prescribed these agents to ensure capture of high-quality pharmacovigilance data and to allow relevant comparisons with other similar agents. A-STAR conducts health economic evaluations in addition to capturing data on treatment effectiveness and safety. If approved, we recommend featuring a future research recommendation in the final guidance, along the lines of that featured in the ustekinumab guidance for moderate-to-severe psoriasis (TA180) with respect to BADBIR (http://www.badbir.org/): *"The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR)."*	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

Issue 27

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
(Professor Michael Cork) An important perspective missing from the document is the order in which new therapies are/should be used in adults with moderate-to-severe atopic dermatitis. After failing one systemic (ciclosporin or methotrexate) the patient proceeds to dupilumab and in the future tralokinumab. Tralokinumab appears to be less effective than dupilumab, however, we do not know what happens in dupilumab failures – will such patients respond to tralokinumab? Maybe/probably, not but the field has been full of surprises. Apart from the exception of short-course therapy, a biologic has to be the first option over a JAK inhibitor based on safety. If a patient fails dupilumab or tralokinumab then a JAK inhibitor could be the next option. For dupilumab failures (and failed everything else before it) JAK inhibitors abrocitinib and upadacitinib can be highly effective and life-transforming.	Give details of any amendments/corrections made in sufficient detail to allow these to be reproduced	Insert ICER resulting from amended model. If the model has not been re-run, if appropriate, describe your expectations of how the problem might have an impact on the result

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

December 2021

Issue 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
We believe the analysis does not take into account fully the unmet need of adults with moderate-to-severe eczema. Patients deserve to be offered timely effective treatment, and not be expected to ensure many months of suffering trying a cheaper immunosuppressant drug first, which is known to be far less clinically effective. Some patients with more severe eczema are resistant to trying immunosuppressant treatments like ciclosporin, because of the known serious adverse effects. This means they will not be eligible, under NICE guidelines, for a JAK inhibitor or biologic treatment. Where there is a treatment option like upadacitinib, which research has shown to be clinically effective and cost effective, this should be made available routinely as a first-line treatment. The report recognises upadacitinib is more effective at both doses than ciclosporin as a first-line therapy. Many patients have been struggling for years with poorly controlled eczema and this has resulted in huge impacts on patents' physical and mental health and quality of life. To prevent people from accessing a significantly more clinically effective treatment, with superior safety profile, by insisting they try an established immunosuppressant drug first,	We propose making upadacitinib a first line treatment for both adults and adolescents. It should not be recommended as both a first and second line treatment for adults, as most clinicians will - in practice - be prevented from offering this as a first line treatment because of local funding constraints. The capability of drugs to achieve clear or near clear skin, i.e. EASI90 and EASI100, should be considered more prominently in the model. This is what patients want and allows them to stop using TCS, or only use TCS infrequently to manage periodic flare-ups. The success bar should be set higher. We understand the primary outcome of interest is EASI50 and DLQI greater than 4, and EASI75 where data is available, but that does not mean superior performance should not be recognised.	n/a

seems both perverse and cruel to patients.		

Issue 2

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
There are limited options for treating adolescents with more severe eczema, and for the reasons highlighted in Issue 1, preventing children and their parents from accessing a clinically effective treatment, with superior safety profile, by insisting they try an established immunosuppressant drug first, is both perverse and cruel. The impact of poorly controlled eczema for adolescents affects the health, quality of life and productivity of the whole family. We do not believe these wider impacts on the family have been adequately reflected in the analysis.	We propose making upadacitinib a first line treatment for adolescents. We would also like to see abrocitinib made available as a first line treatment for adolescents, as this performed well in this patient population at both lower and higher does.	n/a

Issue 3

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
This review is complex because it attempts to assess and compare three new treatments with existing treatments, some of which are relatively new as well, and considering these as used in mono therapy and combined therapy with TCS with different patient groups. Methotrexate,	To review the data assumptions and in particular ensure the report is not being conservative in the interpretation of the network meta-analysis findings. There is a natural tendency to build in allowances for significant uncertainties. This can underplay the real world clinical effectiveness of the drugs being assessed.	n/a

which many patients with moderate-to-severe disease are taking long-term and is the preferred immunosuppressant treatment for many dermatologists, is not included in the analysis because it is outside its marketing authorisation. Hence, the analysis does not fully reflect routine real world clinical practice. The studies considered in the MTA included mixed populations of people with moderate-to-severe eczema, some comprised both adolescents and adults, as well as a mix of people receiving systemic therapy as a first-line or second-line regimen. There is also a lack of head-to-head data. This means the report relies more heavily on data interpretation and modelling assumptions for how well the drugs perform longer term, or in wider cohorts of patients. There is high reliance in the modelling on Week 16 and Week 54 response and discontinuation data generated in the trials. The report acknowledges high uncertainty on the data for clinical effectiveness, as well as a lack of data for the primary outcome, and on occasions places an over reliance on upadacitinib the baseline data, which is regarded as representative of the eligible patient population in England. In particular, there appears to be conservative assumptions made regarding waning and discontinuation findings in the report.		

Issue 4

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
We do not recognise the assumptions made for combined therapy using TCS as reflecting real world patient experience and clinical practice. Many patients with moderate-to-severe eczema have needed to rely on extensive use of TCS, often at higher potencies, as well as periodic oral steroids. This carries a financial cost, but patients are rightly worried about the known adverse effects of long-term steroid use. This can have significant health impacts for patients, both while taking TCS and when stopping. Concerns and warnings about over-use of TCS and topical steroid withdrawal are growing. A huge attraction for patients of starting a systemic treatment is the possibility they will not need TCS, or not as much. Many patients continue taking TCS while they get established on the new treatment, and then taper off TCS use as the therapeutic benefits of the new treatment are realised. Many patients will be able to go steroid free for the first time in many years, other than occasional use to manage an exceptional flare-up. The trial and wider research data on the reduction in TCS use following starting a systemic treatment is limited, but anecdotal feedback indicates a significant reduction. We believe the analysis – both	Review and challenge assumptions of TCS use in the model (related to both cost effectiveness and clinical effectiveness measures) for patients starting on the newer systemic treatments, to more accurately reflect real world experience in the absence of conclusive research data.	n/a

the cost and clinical effectiveness elements - should reflect the expected lower use of TCS, which means in the real world they would be characterised more broadly as mono therapies.		

Issue 5

Description of problem	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
The way atopic eczema is described and characterised in the report does not fully represent the way people of colour can experience symptoms. In particular, the way presence of eczema in flexural areas can be different.	Review the report to ensure it is inclusive of the experiences of people of colour who have eczema.	n/a

(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Upadacitinib for treating moderate to severe atopic dermatitis in people aged 12 and over

ID3733

Document B

Company evidence submission

February 2021

File name	Version	Contains confidential information	Date
		Yes	

Contents

Tables and figures

Abbreviations

ACD	Appraisal Consultation Document
AD	Atopic Dermatitis
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
AE	Adverse Events
A&E	Accident and Emergency
AIC	Akaike's Information Criterion
BD	Twice Daily (Bis in Die)
BIC	Bayesian Information Criterion
BL	Baseline
BMI	Body Mass Index
BNF	British National Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
CCR	Chemokine Receptor
CDLQI	Children's Dermatology Life Quality Index
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CLA	Cutaneous Lymphocyte-Associated Antigen
CMH	Cochran-Mantel-Haenszel
CHMP	Committee for Medicinal Products for Human Use
CODA	Convergence Diagnosis and Output Analysis

COMBO	Combination Therapy
CPK	Creatine Phosphokinase
CPRD	Clinical Practice Research Datalink
CrI(s)	Credible Interval
CRTH2	Chemoattractant Receptor-homologous Molecule Expressed On Th2 Cell
CsA	Ciclosporin
CSR(s)	Clinical Study Reports
CUA	Cost Utility Analysis
CYP3A	Cytochrome P450 3A4
DC	Dendritic Cell
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DMARD(s)	Disease-modifying Anti-rheumatic Drugs
DSA	Deterministic Sensitivity Analysis
DSU	Decision Support Unit
DUP	Dupilumab
EADV	European Academy of Dermatology and Venereology
EASI	Eczema Area and Severity Index
EASI 50,70,90	Proportion of patients achieving percent improvement from baseline in EASI
EMA	European Medicines Agency
EO:	Eosinophil
EQ-5D	European Quality of Life-5 Dimensions

EQ-5D-3L	European Quality of Life-5 Dimensions 3 Levels
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
ERG	Evidence Review Group
FBC	Full Blood Count
FE	Fixed Effects
GLMM	Generalised Linear Model
H 1/4	Histamine 1/4
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
HRQOL	Health-related Quality of Life
HTA	Health Technology Assessment
ICD	International Classification of Disease
ICER(s)	Incremental Cost-Effectiveness Ratio(s)
IDEC	Inflammatory Dendritic Epidermal Cell
IEC	International Eczema Council
IFN	Interferon
IGA	Investigator Global Assessment
ILC	Innate Lymphoid Cell
INMB	Incremental Net Monetary Benefit
IQR	Interquartile Range
ISPOR	International Society for Pharmacoeconomic and Outcomes Research
ITC(s)	Indirect Treatment Comparison
ITT	Intention to Treat

JAK	Janus Kinase
KLK	Kallikrein-related Peptidase
LC	Lymphoid Cell
MACE	Major Adverse Cardiovascular Events
MC	Mast Cell
MCID	Minimal Clinically Important Difference
MI	Multiple Imputation
MMRM	Mixed-effect Model with Repeated Measures
MONO	Monotherapy
N/A	Not Applicable
NMA	Network Meta-analysis
NMF	Natural Moisturising Factor
NMSC	Non-Melanoma Skin Cancer
NRI	Non-Responder Imputation
NRI-C	Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19
NRS	Numerical Rating Scale
OLE	Open-Label Extension
ONS	Office for National Statistics
OP	Out-patient
OR(s)	Odds Ratios
OWSA	One-way Sensitivity Analyses
PAR2	Protease-activated Receptor 2
PAS	Patient Access Scheme

PBO	Placebo
PGA	Physician Global Assessment
POEM	Patient Oriented Eczema Measure
PP	Per Protocol
PSA	Probabilistic Sensitivity Analysis
PsA	Psoriatic Arthritis
PSS	Personal Social Services
PSRF	Potential Scale Reduction Factor
PUVA	Psoralen-ultraviolet A
Q1	Quarter 1
Q2	Quarter 2
Q2W	Every 2 Weeks
QALY(s)	Quality-adjusted Life Year
QD	Once Daily
QOL	Quality of Life
RA	Rheumatoid Arthritis
RAD	Revolutionizing Atopic Dermatitis
RCT(s)	Randomised Controlled Trial
RE	Random Effect
SAE	Serious Adverse Event
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SD	Standard Deviation

SE	Standard Error
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SOCS	Suppressor of Cytokine Signalling
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
STAT	Signal Transducer and Activator of Transcription
SUCRA	Surface Under the Cumulative Ranking Curve
TARC	Thymus and Activation-Regulated Chemokine
TA	Technology Appraisal
TB	Tuberculosis
TCI(s)	Topical Calcineurin Inhibitor
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
TEFF	Effector T Cell
TEM	Effector Memory T Cell
TH	T-Helper Cell
TPMT	Thiopurine Methyltransferase
TNAIVE	Naïve T Cell
TNF	Tumour Necrosis Factor
TRM	Tissue-Resident Memory T Cell
TSD	Technical Support Document

TSLP	Thymic Stromal Lymphopoietin
TX	Treatment
TYK2	Tyrosine Kinase 2
UMC	University Medical Centre
UPA	Upadacitinib
UVB	Ultraviolet B
VAS	Visual Analogue Scale
VBA	Visual Basic for Applications
vIGA-AD	Validated Investigator Global Assessment –Atopic Dermatitis
VTE	Venous Thromboembolism
WP-NRS	Worst Pruritus-Numerical Rating Scale
WTP	Willingness to Pay

Scales used in atopic dermatitis

EASI	**Eczema Area and Severity Index** Tool used to measure the extent (area) and severity of atopic dermatitis (AD). The body is divided into four regions (head and neck, trunk, upper limbs, lower limbs). Each region is given an area score from 0 (no active eczema) to 6 (90%-100% of the region is affected). Severity is evaluated using a four-point scale, from none (0) to severe (3), where each area is assessed for intensity of erythema (redness), oedema/papulation (swelling), excoriation (broken skin) and lichenification (thickening of the skin). The severity score is then multiplied by the area score and a multiplier for each region. Total of all four regions is the EASI score (maximum 72). Response to treatment is the % reduction in score, for example, EASI 75 is a reduction of 75% from baseline EASI score.
DLQI	**Dermatology Life Quality Index** DLQI is a simple, self-administered validated questionnaire. It consists of 10 questions concerning patients' perception of the impact of skin diseases (not specifically AD) on different aspects of their health related quality of life (HRQOL) over the last week. Each question is scored on a 4-point Likert scale from not at all (0) to very much (3). The maximum score is 30. Score >10 indicates the patient's life is being severely affected by their skin disease.
CDLQI	**Children's Dermatology Life Quality Index** CDLQI is a simple, self-administered validated questionnaire. The questionnaire is completed by the child with the help of an adult if necessary, preferably a parent. It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their HRQOL over the last week. The questionnaire also asks if AD has prevented attendance at school. Each question is scored on a 4-point Likert scale from not at all (0) to very much (3). The maximum score is 30. Score 7-12 indicates that skin disease has a moderate effect on the patient's life. Score 13-18 indicates that skin disease has a very large effect on the patient's life. Score 19-30 indicates that skin disease has an extremely large effect on the patient's life.
IGA **PGA**	**Investigator Global Assessment/ Physician Global Assessment** Five-point score from clear, no inflammatory scores of AD, (0), almost clear (1), mild (2), moderate (3) to severe (4). Moderate is described as clearly visible erythema (dull red) and clearly visible papulation/induration, and/or clearly perceptible thickening, oozing and crusting may be present. Severe is described as marked erythema (deep or bright red) and marked papulation/induration, disease is widespread and oozing and crusting may be present. Validated Investigator Global Assessment –Atopic Dermatitis (vIGA-AD) scale is a commonly used assessment in clinical trials and was used in the upadacitinib clinical trial programme, referred to as IGA in this document
POEM	**Patient Oriented Eczema Measure** POEM is a simple, self-administered validated AD questionnaire, focusing on the overall symptom burden as experienced by the patient. It consists of 7 questions about the frequency of eczema symptoms over the last week from no days (0), 1-2 days (1), 3-4 days (2), 5-6 days (3), to every day (4).

	The score is calculated by adding the scores for each question to a maximum of 28. Moderate eczema is defined as a score of 8-16, severe eczema 17-24 and very severe eczema 25-28.
Worst Pruritus NRS	**Worst Pruritus Numerical Rating Scale** WP-NRS is a self-reported, single-item questionnaire designed to measure peak pruritis or 'worst itch' using a numeric rating scale from no itch (0) to worst imaginable itch (10). It consists of one question: how was your worst itch in the past 24 hours?
SCORAD	**SCORing Atopic Dermatitis** A validated composite measure for assessing the severity (i.e. extent, intensity) of AD as objectively as possible as well as incorporating a patient reported component that assesses pruritus (itch) and sleep loss. The SCORAD index formula is: A/5 + 7B/2 + C. A is defined as the extent of disease (0-100), the sites affected by eczema are shaded on a drawing of a body with each part of the body assigned a different proportion (head and neck 9%, upper limbs 9% each, lower limbs 18% each, anterior trunk 18%, back 18% and genitals 1%). B is defined as the intensity (0-18) – six signs recorded on a 4-point scale from 0 (mild) to 3 (severe). Signs: redness, swelling, oozing/crusting, scratch marks, skin thickening and dryness. C is defined as the subjective symptoms (0-20). Itch and sleeplessness are scored on a visual analogue scale (VAS) from 0 (none) to 10 (worst imaginable) The maximum SCORAD score is 103. Disease is defined as a score of <25 (mild), 25-50 (moderate) and >50 (severe).
HADS	**Hospital Anxiety and Depression Scale** Used to determine levels of anxiety and depression, HADS is a 14-item questionnaire (seven of the questions relate to anxiety and seven relate to depression). Each item on the questionnaire is scored from 0 (not at all) to 3 (definitely/most of the time), meaning that a person can score between 0 and 21 for either anxiety or depression. A score of 8 and above indicates some anxiety or depression.
ADerm-IS	**Atopic Dermatitis Impact Scale** AbbVie-sponsored patient reported questionnaire developed and validated specifically for AD. Daily and weekly questions about sleep (daily) and impact on daily activities and emotional state (weekly). Each question scored on an 11-point scale from 0 (no) to 10 (worst imaginable)
ADerm-SS	**Atopic Dermatitis Symptom Scale** AbbVie-sponsored patient reported questionnaire developed and validated specifically for AD. Daily and weekly questions about sleep and skin pain (daily, x3 questions) and skin symptoms (weekly, x 8 questions). Each question scored on an 11-point scale from 0 (no) to 10 (worst imaginable)

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The anticipated marketing authorisation for upadacitinib (Rinvoq®) is for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. Upadacitinib may be used as a monotherapy or in combination with topical corticosteroids (TCS).

It is anticipated that upadacitinib will be used in two places in the treatment pathway, both aligned to the marketing authorisation.

- In people who are candidates for conventional systemic treatment. This population is referred to as 'systemic-eligible' throughout the submission.
- In people in whom the disease has not responded to at least one other conventional systemic therapy (ciclosporin [CsA], methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic therapy is not suitable. This population is referred to as 'systemic-exposed' throughout the submission.

Advice sought from clinical experts suggests that one conventional systemic therapy is likely to be initiated prior to upadacitinib in the majority of patients. If patients did not respond to conventional systemic therapies or these treatments were not suitable, then upadacitinib would be considered[1]. This places upadacitinib in the same position in the treatment pathway as the biologic, dupilumab[2].

Clinical advice also suggests there is a need for efficacious treatments, which are well tolerated and can be used long-term to target the cause of AD, rather than simply providing symptomatic relief, in patients who are candidates for systemic therapy. Therefore, upadacitinib could also provide an alternative option to conventional systemic therapies for some patients.

The company submission presented here is consistent with the final NICE scope and the NICE reference case, see Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years or over with moderate to severe AD	People aged 12 years or over with moderate to severe AD	
Intervention	Upadacitinib	Upadacitinib	
Comparator(s)	Phototherapy including with ultraviolet B (UVB) radiation or psoralen-ultraviolet A (PUVA) Oral corticosteroids Alitretinoin (in people with AD affecting the hands)	Not considered	Upadacitinib is expected to be used fourth and fifth-line in UK clinical practice in patients who are considered candidates for systemic treatment. These patients will have already been treated with topical treatments and with phototherapy if suitable. Oral steroids are only recommended as a short-term treatment option for patients with AD. European guidelines recommend that courses of systemic corticosteroids should not exceed 1 week due to long-term side effects[3]. Oral steroids are used in acute phases or flares and are therefore not an appropriate comparator for a chronic disease. Alitretinoin is not a relevant comparator based on its licensed indication and place in therapy is in the treatment of severe chronic hand eczema only[4].
	Immunosuppressive therapies (azathioprine, CsA, methotrexate and mycophenolate mofetil)	CsA only	Clinical advice suggests there is a need in patients who are candidates for systemic therapy for efficacious treatments, which are well tolerated and can be used long-term to target the cause of AD, rather than simply providing symptomatic relief. Therefore, upadacitinib could also provide an alternative option to conventional systemic therapies for some patients. This reflects the anticipated marketing authorisation and is our **systemic-eligible** population. CsA exposure is used as a proxy for systemic treatment, since azathioprine, methotrexate and mycophenolate mofetil are not licensed for AD and there is a paucity of data to support comparison with upadacitinib for these agents.

			It should be noted that: • CsA is not recommended for long-term use, guidelines recommend treatment for 3-6 months with a maximum of 2 years. • CsA requires careful monitoring for potentially severe side-effects including nephrotoxicity[3]. • CsA is only licensed in children aged over 16 years and adults.
	Dupilumab	Dupilumab	This is our **systemic-exposed** population.
	Best supportive care (BSC) (combination of emollients, low to mid potency TCS, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors [TCI]))	BSC	Represented by the placebo arm in the clinical trial programme.
	Baricitinib (subject to ongoing NICE appraisal)	Not considered	Baricitinib is not currently recommended by NICE in this indication and therefore is not considered part of established clinical practice.
Outcomes	Measures of disease severity Measures of symptom control Disease free period, maintenance of remission time to relapse, prevention of relapse Adverse effects (AE) of treatment Health-related quality of life (HRQOL)	Measures of disease severity (EASI, IGA) Measures of symptom control (WP-NRS, POEM) AE of treatment HRQOL (EQ-5D, DLQI, CDLQI) (see Scales used in atopic dermatitis for details)	Disease free periods, remission and relapse are not terms that are commonly used in clinical practice and are not defined for AD. Disease free periods, maintenance of remission time to relapse and prevention of relapse are represented by the following end-points in this submission. • Proportion of participants experiencing a flare, characterised as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from baseline. • Number of TCS free days with EASI 75 response up to week 16. • Time to first discontinuation of all TCS with EASI 75 response, discontinuation of all TCS is defined as cessation of TCS treatment for >7 consecutive days, up to week 16.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope and NICE reference case	
Subgroups to be considered	People with AD affecting the hands People for whom systemic therapies have been inadequately effective, not tolerated or contra-indicated Skin colour subgroups	People for whom systemic therapies have been inadequately effective or not tolerated	Hand eczema is a distinct condition in its own right. Although upadacitinib may provide benefit in hand eczema this was not a pre-specified subgroup in the clinical trial programme Unfortunately, the upadacitinib clinical trial programme does not provide outcomes specific to skin colour subgroups.

AD: Atopic Dermatitis, AE: Adverse Events, BSC: Best Supportive Care, CDLQI: Children's Dermatology Life Quality Life Index, Csa: Ciclosporin , DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EQ-5D: European Quality Of Life-5 Dimensions , HRQOL: Health-Related Quality of Life, IGA: Investigator Global Assessment, POEM: Patient Oriented Eczema Measure, PSS: Personal Social Services, PUVA: Psoralen-Ultraviolent A, QALY: Quality-Adjusted Life Year, TCI: Topical Calcineurin Inhibitor, TCS: Topical Corticosteroids, UVB: Ultraviolet B, WP-NRS: Worst Pruritus-Numerical Rating Scale,

B.1.2. Description of the technology being appraised

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2[5]

A summary description of upadacitinib, including details of its mechanism of action and expected marketing authorisation, is provided in Table 2.

A draft Summary of Product Characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Upadacitinib (Rinvoq®)
Mechanism of action	AD is a complex immune-mediated skin disease. In patients with established AD, disease is driven by a combination of skin barrier dysfunction and immune (T-cell) driven skin inflammation[6,7]. Multiple immune pathways are involved in AD, with key cytokines playing an important role in both inflammation and itch. Many of the cytokine signalling pathways central to the development of AD are mediated by JAK[8]. Upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2[5] Upadacitinib inhibits the kinase component of JAKs, thereby preventing phosphorylation and slowing intracellular signalling, thus minimising inflammation and itch[8].
Marketing authorisation/CE mark status	An application for upadacitinib in AD was filed to the European Medicines Agency (EMA) on 8th October 2020. Committee for Medicinal Products for Human Use (CHMP) opinion is expected in July 2021 with marketing authorisation expected in September 2021.
Indications and any restriction(s) as described in the SmPC	**Indications** Upadacitinib currently has marketing authorisation from the EMA in the following therapeutic indications[5]: • Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Upadacitinib may be used as monotherapy or in combination with methotrexate. • Rinvoq is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Upadacitinib may be used as monotherapy or in combination with methotrexate. • Rinvoq is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

	The anticipated marketing authorisation for upadacitinib in the indication of interest to this submission is: • The treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. **Special warnings and precautions for use** Combination with other potent immunosuppressants is not recommended as the risk of additive immunosuppression cannot be excluded. Serious and sometimes fatal infections have been reported in people taking upadacitinib. For more information, please see Appendix B.
Method of administration and dosage	Oral, once daily (QD) with or without food and may be taken at any time of the day. Tablets should be swallowed whole and not split, crushed or chewed[5]. Tablets presented as • Upadacitinib 15 mg: Purple 14 x 8 mm, oblong biconvex prolonged-release tablets imprinted on one side with 'a15'. • Upadacitinib 30 mg: Red 14 x 8 mm, oblong biconvex prolonged-release tablets imprinted on one side with 'a30'. The dosage is expected to be as follows: • The recommended dose of upadacitinib is 15 mg or 30 mg QD for adults. Consider [redacted] • The recommended dose of upadacitinib is 15 mg QD for adolescents weighing at least 40 kg (aged 12-17 years) Upadacitinib can be used with or without TCS. Topical calcineurin inhibitors (TCI) may be used for sensitive areas such as the face and neck.
Additional tests or investigations	Full blood count (FBC) to evaluate absolute neutrophil count, absolute lymphocyte count haemoglobin, hepatic transaminases at baseline and thereafter according to routine patient management. Lipids should be measured 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia.
List price and average cost of a course of treatment	The list price for upadacitinib 15 mg is £805.56 per 28-day pack. The cost per patient for 1 year of treatment is £10,508.24. The list price for upadacitinib 30 mg is [redacted] per 28-day pack. The cost per patient for 1 year of treatment is [redacted]
Patient access scheme (PAS) (if applicable)	For the existing NICE-approved indication for upadacitinib in RA the company has agreed a simple discount PAS with the Department of Health.

	The PAS price for upadacitinib 15 mg is [redacted] per 28-day pack. The PAS cost per patient for 1 year of treatment is [redacted] The PAS price for upadacitinib 30 mg is [redacted] per 28-day pack. The PAS cost per patient for 1 year of treatment is [redacted] The Department of Health considered that this PAS does not constitute an excessive administrative burden on the NHS.

AD: Atopic Dermatitis, CHMP: Committee for Medicinal Products for Human Use, DMARDs: Disease-modifying Anti-rheumatic Drugs, EMA: European Medicines Agency, JAK: Janus Kinase, PAS: Patient Access Scheme, PsA: Psoriatic Arthritis, QD: Once Daily, RA: Rheumatoid Arthritis, SmPC: Summary of Product Characteristics, TCS: Topical Corticosteroids

B.1.2.1 Changes in service provision and management

Upadacitinib provides a convenient QD oral option for patients who may otherwise be prescribed conventional systemic or an injectable biologic (dupilumab).

Systemic treatments are associated with additional health service needs including blood pressure monitoring and additional blood test monitoring at baseline including renal function, serum potassium, magnesium blood lipids, serum creatine and during treatment, see Table 4. Although monitoring is required for upadacitinib at baseline and throughout treatment, this is not as extensive as for conventional systemics

Dupilumab is associated with additional health service needs since it is a subcutaneous (SC) injection. Additional health service needs typically include patient training in self-injection techniques and approval from the relevant healthcare professional that their technique is appropriate.

Oral therapies, such as upadacitinib, allow for convenient self-administration, which is often preferred by patients. Home administration alleviates pressure on the healthcare systems and facilitates the out-patient management of immunosuppressed patients. This is particularly pertinent considering the ongoing COVID-19 pandemic.

Upadacitinib is effective without the need for TCS which represents a significant change for patients. Patients will not have the inconvenience of applying daily TCS, and the risk and concern over TCS AEs such as skin thinning will be removed. A TCS-free treatment regimen will be of great benefit to those patients with steroid phobia.

Therefore, upadacitinib is likely to have a positive impact on service provision compared to the current standard of care.

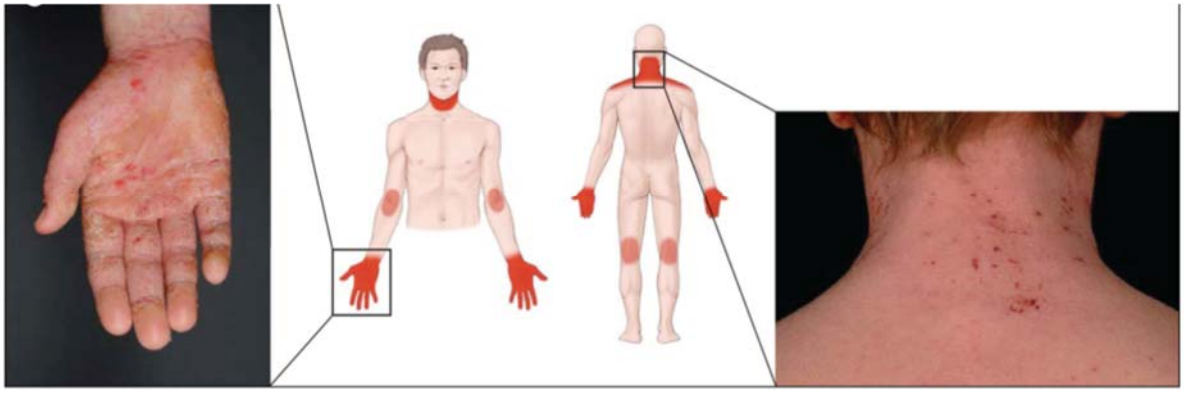
B.1.3. Health condition and position of the technology in the treatment pathway

- AD (also known as atopic eczema) is a long-term chronically relapsing, inflammatory skin condition, characterised by intense itching and eczematous lesions[7,9].
- It can appear anywhere (and everywhere) on the skin, although the most common sites in adolescents and adults are the flexures (behind the knees and elbows), eyelids, hands, head (face and scalp), upper trunk and shoulders[9].
- AD affects around 1 in 12 adults and 1 in 5 children in the UK[10]; around 50% of people with AD have moderate to severe disease[11]. A formal diagnosis of AD is made in 2.5% of adults[12] and 5.4% of adolescents[13].
- Moderate to severe AD has a considerable negative impact on physical, mental and psychosocial health, QOL, home, social, school and work life[7,9,14-16], with poorer outcomes seen in people with more severe disease or uncontrolled AD[15].
- There is no cure for AD at present; therefore, the aim of management is to improve symptoms and achieve long-term disease control by reducing inflammation and controlling disease flare[7,9]. Emollients with TCS are the mainstay of treatment, if AD is uncontrolled then additional treatments are used in a stepwise approach.
- AD is a complex disease with a genetic predisposition, driven by a combination of skin barrier dysfunction and immune driven skin inflammation[6,7].
- Multiple immune pathways are involved in AD, with cytokines playing a key role in both inflammation and itch. Many of the cytokine signalling pathways central to the development of AD are mediated by JAKs, which form pairs to facilitate cytokine signalling[8,17].
- Upadacitinib is an oral, once-daily, selective and reversible JAK inhibitor, which slows cytokine signalling thus minimising inflammation and itch[8].

AD (also known as atopic eczema) is a long-term chronically relapsing, inflammatory skin condition, characterised by intense itching and eczematous lesions[7,9]. In people with AD, the skin is red and inflamed (erythema), swollen (oedema/papulation), broken (excoriated), thickened and leathery (lichenification) and dry (xerosis) with scaly plaques, bleeding, oozing, cracking and flaking.

AD can appear anywhere (and everywhere) on the skin, although the most common sites in adolescents and adults are the flexures (behind the knees and elbows), eyelids, hands, head (face and scalp), upper trunk and shoulders[9].

Figure 1: Clinical appearance and location of AD in adolescents and adults[9]



AD is a relapsing/remitting condition; triggers include environmental allergens (house dust mites, pollen or animal dander), soaps, detergents and physical irritants. All of which can result in rapid worsening of disease known as flare or flare up[7,18].

B.1.3.1 Aetiology

AD is a complex disease with a genetic predisposition strongly influenced by innate and adaptive immune responses. Environmental factors, including allergen exposure, irritants and microbiota, play a role. Diet and stress are also important and are worsened by modern lifestyles[6].

In patients with established AD, disease is driven by a combination of skin barrier dysfunction and immune (T-cell) driven skin inflammation[6,7].

Multiple immune pathways are involved in AD, with cytokines playing a key role in both inflammation and itch. Type 2 cytokines (interleukin-4 [IL-4], IL-13, thymic stromal lymphopoietin [TSLP] and IL-31) are particularly important since they directly activate sensory nerves, promoting itching[7].Figure 2 illustrates the pathogenesis and development of AD.

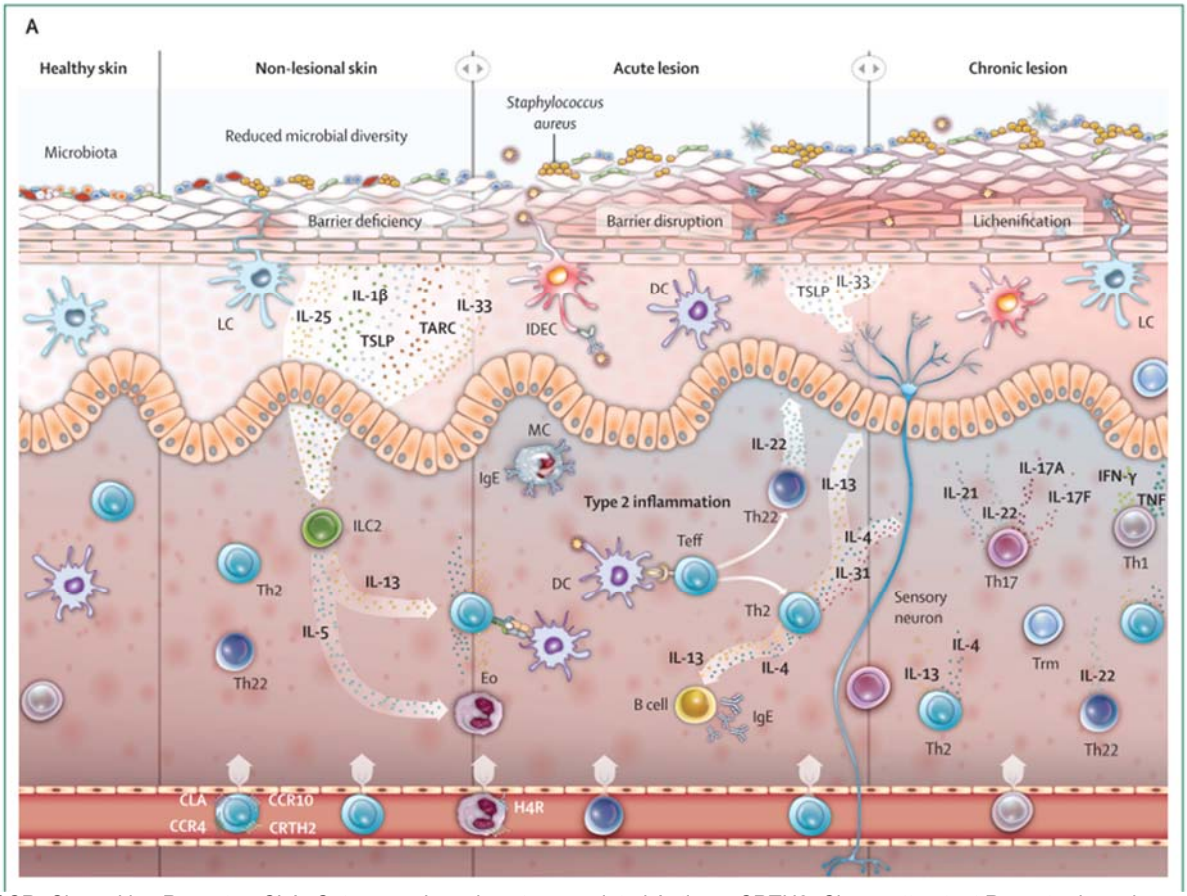
Clinically unaffected skin shows some epidermal barrier dysfunction with reduced microbial diversity.

In skin with eczematous lesions, the defective skin barrier facilitates penetration of allergens and antigens, which are then taken up by skin dendritic cells (Langerhans cells, inflammatory epidermal dendritic cells and dermal dendritic cells), which migrate to the lymph node and prime a type 2 inflammatory immune response. The type 2 cytokines IL-4, IL-13, IL-31 and TSLP directly activate sensory nerves

promoting itch and additionally cause down-regulation of key epidermal proteins which results in further barrier dysfunction.

As the disease becomes chronic, there is a progressive increase in cytokines derived from keratinocytes and T cells. Itch is further induced by antigens and by molecular mediators such as histamine and mediated by sensory nerves.

Figure 2: Pathogenesis, main mechanisms, and pathophysiology of AD[7]



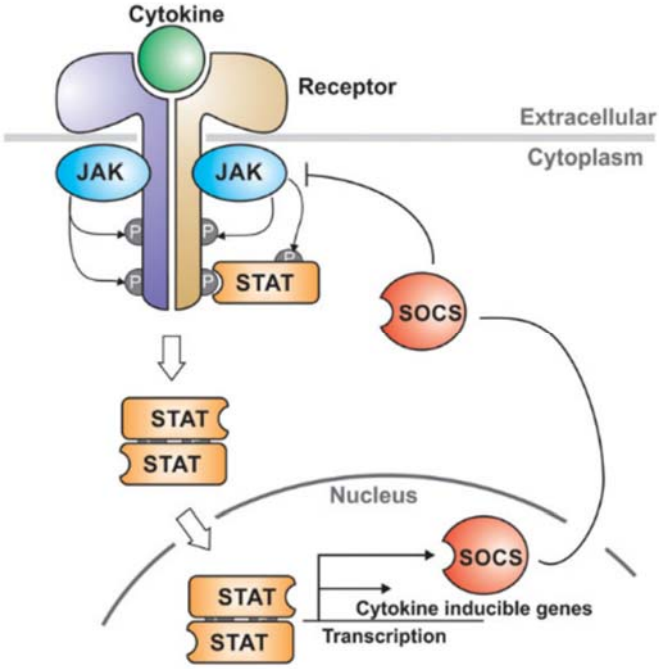
CCR: Chemokine Receptor, CLA: Cutaneous Lymphocyte-associated Antigen, CRTH2: Chemoattractant Receptor-homologous Molecule Expressed on Th2 Cell, DC: Dendritic Cell, Eo: Eosinophil, H1/4: Histamine 1/4, IDEC: Inflammatory Dendritic Epidermal Cell, IFN: Interferon, IL: Interleukin, ILC: Innate Lymphoid Cell, KLK: Kallikrein-related Peptidase, LC: Lymphoid Cell, MC: Mast Cell, NMF: Natural Moisturising Factor, PAR2: Protease-activated Receptor 2, TARC: Thymus and Activation-Regulated Chemokine, Teff: Effector T Cell, Tem: Effector Memory T Cell, Th: T-Helper Cell, Tnaive: Naive T Cell, TNF: Tumour Necrosis Factor, Trm: Tissue-resident Memory T Cell, TSLP: Thymic Stromal Lymphopoietin.

The JAK and signal transducer and activator of transcription (STAT) pathway mediates the inflammatory and pruritic cytokines involved in the pathogenesis of AD[8]. AD is associated with increased signalling through all four JAKs (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2])[8]. JAKs signal in pairs and JAK1 is one of each pair in cytokine signalling in AD[17], see Figure 3.

Activation of JAK leads to a phosphorylation cascade, which ultimately activates the STAT pathway which modulates gene expression and cellular function[19].

Suppressor of cytokine signalling (SOCS) proteins are direct targets of STAT and act as negative feedback inhibitors to switch off the signalling cascade[17].

Figure 3: The JAK/STAT pathway[17]



JAK: Janus Kinase, SOCS: Suppressor of Cytokine Signalling, STAT: Signal Transducer and Activator Of Transcription

B.1.3.2 Symptoms and impact of AD

Itching (pruritus) is the hallmark of AD and a requirement for diagnosis. It is the most disruptive symptom and can be unrelenting, frequent and intense: 42% of adults with moderate to severe AD report itching for 18 hours a day or more, which is unbearable in 14% of cases[20].

The sensation of itch and subsequent scratching in AD impacts on physical symptoms by compromising the skin barrier leading to further irritation and inflammation, resulting in more itching and scratching, often referred to as the 'itch-scratch cycle'. Breaking the skin barrier can also lead to infection[9]. Patients with AD have a 2.7x higher risk of infection than the general population[21]. Recent UK data derived from Hospital Episode Statistics (HES) and Clinical Practice Research Datalink (CPRD) data suggests that around one-third of patients will have a skin infection, rising from 0.2 infections per patient in mild disease to 0.44 in severe disease over a 5-year period[11].

The skin of people with AD shows a less diverse microbiome, with a relative abundance of *Staphylococcus aureus*, than healthy individuals[7].

Itching has a considerable impact on sleep, with almost 70% of people with moderate to severe AD reporting that itch delays falling asleep and results in waking during the night; sleep is disrupted in 55% of people[20]. Sleep disorders are reported significantly more in people with uncontrolled AD than in those with controlled disease (40% vs 22% in a 2016 European survey, p=0.003)[15].

Lack of sleep contributes to daytime sleepiness and fatigue, reducing patient's ability to go about their daily life at home and at work/school. It also has a negative impact on mental health and wellbeing. Anxiety and depression are common in people with AD – anxiety is reported by 32% of people with moderate disease and 55% of people with severe disease, with depression reported by 20% of people with moderate or severe disease[22]. Adolescents with AD have an increased risk of attention-deficit hyperactivity disorder, thought to be driven by lack of sleep[23,24]. Anxiety, depression, behavioural problems and autism are also increased in adolescents with AD, with the highest rates seen in those with severe disease[24].

There is a profound impact on QOL. Moderate to severe AD is associated with worse QOL outcomes than many common chronic illnesses, including heart disease and diabetes in adults[14]. In adolescents, the impact of AD on QOL is comparable to asthma or cystic fibrosis[25].

AD impacts on people's home, social and work lives. A recent survey of people with AD in the UK by the National Eczema Society carried out in 2020, found that that AD negatively impacted on their home and work life. For those patients with moderate disease 66% and 56% reported a negative impact on home and work life, increasing to 79% and 78% for those with severe disease[16].

For people with moderate disease, 72% reported that AD impacts on their social life, 67% reported that their disease impacts on sexual intimacy and relationship with their partner and 33% reported that AD limits choice of hobbies. For people with severe disease, rates are higher at 86%, 86% and 42%, respectively[16]. Other work has shown that people with uncontrolled AD report significantly more interference with activity vs all people with AD (52% vs 32%, p<0.001)[15].

People with moderate to severe disease may become socially isolated due to self-consciousness, low self-esteem and embarrassment attached to their skin condition, which can contribute to adverse psychosocial and health outcomes[7]. Indeed, in a recent UK survey, 92% of people with moderate AD and 96% with severe AD reported feeling self-conscious or embarrassed about their condition and 77% and 93% reported feeling lonely or socially isolated[16].

AD impacts on school and work, in a survey of UK patients, over half of patients reported that eczema affected their education (54% with moderate disease and 75%

with severe) and 17% with moderate disease and 22% with severe reported that AD has had a negative impact on their career[16].

People with AD are significantly more likely to report absence from work and work impairment, compared to people without AD, with the highest rates seen in those with uncontrolled disease[15]: overall work impairment is reported by 57% of people with uncontrolled AD, 27% of people with AD and 24% of people without AD, p=0.009 AD vs no AD, p<0.001 uncontrolled AD vs AD[15].

AD is associated with considerable healthcare resource. A European survey revealed that people with AD reported significantly more healthcare resource use than those without AD, with the highest rates in people with uncontrolled disease: 21.6% of people with AD and 37.9% of those with uncontrolled AD reported one or more unscheduled accident and emergency visit in the previous 6 months vs 16.5% of people without AD, p<0.001[15].

People with AD were also more likely to visit their GP (AD: 93.1% and uncontrolled AD: 94.8%) than those without AD (84.2%) in the previous 6 months. People with uncontrolled AD had almost twice as many visits over 6 months than those with AD, and people with AD had 1.6x more visits than those without AD: mean number of visits, 7.4 ± 11.2 vs 13.9 ± 17.8 vs 4.5 ± 7.2, p<0.001 for all[15].

Work carried out using CPRD-HES data revealed that adolescents and adults with moderate AD attend a median of 12.74 (interquartile range [IQR] 6.83, 22.47) GP appointments per year and 1.86 (0.61, 4.69) out-patient appointments[26]. Rates are even higher in people with severe AD: 18.76 (9.69, 34.33) GP appointments and 4.61 (1.74, 9.34) out-patient appointments.

B.1.3.3 Epidemiology

AD is the most common chronic inflammatory skin disease[6] and affects around 1 in 12 children and 1 in 5 adults in the UK[10]. A formal diagnosis of AD is made in 5.4% of adolescents[13] and 2.5% of adults[12].

Around 50% of cases of AD are mild and transient and can be managed using simple emollients and TCS[27].

However, 50% of people with AD will have moderate to severe disease[11] which has a considerable negative impact on their physical health, mental health and QOL[9]. AD is the leading non-fatal health burden attributable to skin disease[9].

B.1.3.4 Management strategies

There is no cure for AD at present; therefore, the aim of management is to improve symptoms and achieve long-term disease control[9].

Management plans should be individualised to the person with AD and should include avoidance of individual triggers, restoration of the skin barrier using emollients and a stepwise approach aimed at reducing inflammation and controlling disease flares, according to the severity of disease[7].

B.1.3.4.1 Treatment pathway

The most recent UK guidelines for the treatment of AD were issued in 2019 by the Primary Care Dermatology Society[28], with European consensus guidelines published in 2018[3,18].

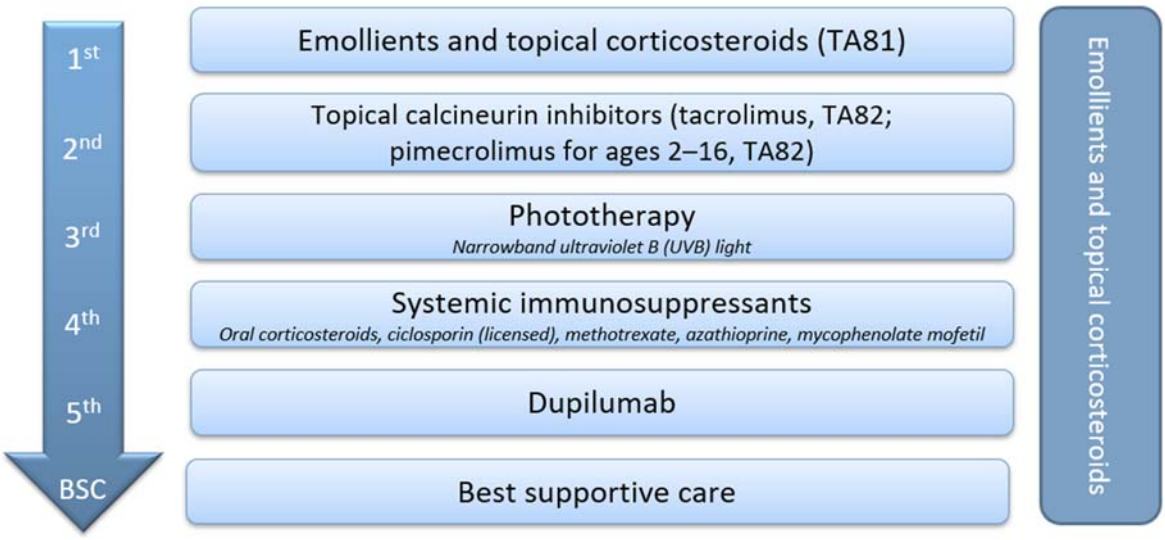
NICE have issued guidance on a number of treatments used in AD, see Table 3. The NICE website details all NICE AD-related guidance in a pathway.

Table 3: NICE guidance in AD

Year	Title	Appraisal number
All people aged 12 and over with AD		
2004	Frequency of application of topical corticosteroids for atopic eczema	TA81
People aged 12-16 with AD		
2004	Tacrolimus and pimecrolimus (moderate atopic eczema on face and neck in people aged 2-16) for atopic eczema	TA82
In development Expected: TBC	Crisaborole for treating mild to moderate atopic dermatitis in people aged 2 years and older	ID1195
In development Expected: TBC	Tralokinumab for treating moderate to severe atopic dermatitis in people aged 12 and over	ID3823
In development Expected: TBC	Abrocitinib for treating moderate to severe atopic dermatitis in people aged 12 and over	ID3768
Adults with AD		
2004	Tacrolimus for atopic eczema	TA82
2018	Dupilumab for treating moderate to severe atopic dermatitis	TA 534
In development Expected: TBC	Crisaborole for treating mild to moderate atopic dermatitis in people aged 2 years and older	ID1195
In development Expected: March 2021	Baricitinib for treating moderate to severe atopic dermatitis	ID1622
In development Expected: Dec 2021	Tralokinumab for treating moderate to severe atopic dermatitis	ID3734
In development Expected: TBC	Abrocitinib for treating moderate to severe atopic dermatitis in people aged 12 and over	ID3768
Adults with severe hand eczema		
2009	Alitretinoin for the treatment of severe chronic hand eczema	TA177

All guidelines follow a similar treatment pathway as outlined in Figure 4.

Figure 4: Treatment pathway for moderate to severe AD



Emollients should be used liberally, two or three times each day. For flares, or AD that does not respond, TCS are normally prescribed once or twice daily plus emollients[7,29].

The duration of treatment with TCS depends on the diagnosis. Generally, very potent TCS should not be used at any site for more than 4 weeks continuously and potent TCS should not be used continuously at any site for longer than 8 weeks. If treatment is indicated for longer, intermittent dosing and gradual tapering of the dose should be considered, and more frequent monitoring for AE should be arranged. Adults using intermittent or short term courses of potent or very potent TCS and children using TCS of any potency should be offered an annual review to assess for steroid-induced atrophy and other AE.

For people with moderate to severe AD, TCI (tacrolimus and pimecrolimus) are the next step in the treatment pathway. TCIs are mainly considered for the treatment of flares that affect the face and neck.

Tacrolimus is recommended in both adults and adolescents if TCS at maximal appropriate potency do not control disease or there is a risk of important AE from further TCS use (particularly irreversible skin atrophy).

Pimecrolimus is recommended as an option for moderate AD on the face and neck in children aged 2 to 16 years that has not been controlled by TCS, where there is a serious risk of important AE from further TCS use (particularly irreversible skin atrophy)[30].

For people who do not respond to topical treatments, short-term phototherapy (usually 4–8 weeks) should be considered[9]. Because of a potentially increased cumulative risk of skin cancer, phototherapy should not be combined with TCI or systemic CsA treatment and should be used with caution in children.

When topical therapy and phototherapy are inadequate to control disease symptoms or unsuitable, treatment steps up to systemic immunosuppressive drugs. The most widely used agents are methotrexate, CsA, azathioprine and mycophenolate mofetil[7]. All of these agents are used off licence, except CsA, which is only licensed for people aged over 16 years[7].

CsA is not recommended for long-term use due to known safety concerns; guidelines recommend treatment for 3-6 months with a maximum of 2 years[3]. Patients receiving CsA commonly discontinue due to AE, 20% in one recent Spanish registry[31].

CsA requires careful monitoring for potentially severe side-effects including nephrotoxicity[3]. The monitoring requirements are a considerable burden: dermatological and physical examination, including blood pressure and renal function measurement is required at least twice prior to starting treatment for AD and blood lipids should be measured before treatment and after the first month of treatment. Serum creatinine must be measured every 2 weeks (Q2W) for the first 3 months of treatment and monthly thereafter. Regular monitoring of blood pressure, renal function, full blood count (FBC) and liver function is recommended[32].

Other conventional systemic immunosuppressive drugs are also limited by AEs which increase with longer term exposure in a number of cases and monitoring that can be onerous, see Table 4[32].

Table 4: AE and monitoring requirements of unlicensed conventional systemic immunosuppressive drugs[32]

Common AE	Monitoring requirements	Other
Methotrexate		
Anaemia; appetite decreased; diarrhoea; drowsiness; fatigue; gastrointestinal discomfort; headache; increased risk of infection; leucopenia; nausea; oral disorders; respiratory disorders; skin reactions; throat ulcer; thrombocytopenia; vomiting	FBC and renal and liver function tests prior to initiation and repeated every 1-2 weeks until therapy stabilised, thereafter patients should be monitored every 2-3 months Report all symptoms and signs suggestive of infection, especially sore throat	Contraception required during and for at least 6 months after treatment for men and women Avoid in pregnancy Discontinue breast feeding Avoid in hepatic or renal impairment
Azathioprine		
Bone marrow depression (dose-related); increased risk of infection; leucopenia; pancreatitis; thrombocytopenia Nausea with oral use	Measure thiopurine methyltransferase (TPMT) prior to initiation, since risk of myelosuppression is increased in	Contra-indicated in patients with AD with absent TPMT activity; very low TPMT activity Avoid in pregnancy

	patients with reduced TPMT activity Monitor for toxicity throughout treatment. Monitor FBC weekly for first 4 weeks, thereafter reduce frequency of monitoring to at least every 3 months. Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment.	Continue breast feeding if benefits outweigh risk Use with caution in patients with hepatic or renal impairment
Mycophenolate mofetil		
Acidosis; alopecia; anaemia; appetite decreased; arthralgia; asthenia; bone marrow disorders; chills; constipation; cough; depression; diarrhoea; drowsiness; dyslipidaemia; dyspnoea; electrolyte imbalance; fever; gastrointestinal discomfort; gastrointestinal disorders; gastrointestinal haemorrhage; headache; hyperglycaemia; hypertension; hypotension; increased risk of infection; insomnia; leucocytosis; leucopenia; malaise; nausea; neoplasms; oedema; oral disorders; pain; pancreatitis; paraesthesia; renal impairment; respiratory disorders; seizure; sepsis; skin reactions; tachycardia; thinking abnormal; thrombocytopenia; tremor; vomiting; weight decreased Anxiety; burping; confusion; dizziness; gout; hepatic disorders; hyperbilirubinaemia; hyperuricaemia; neuromuscular dysfunction; taste altered; vasodilation with oral use	Monitor FBC every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops) Warn patients to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding	Contraception required during and for at least 6 months after treatment for men and women Avoid in pregnancy Discontinue breast feeding

AD: Atopic Dermatitis, AE: Adverse Events, FBC: Full Blood Count, TPMT: Thiopurine Methyltransferase

Systemic corticosteroids should only be used for short-term management of flares[7]. European guidelines recommend that courses of systemic corticosteroids should not exceed 1 week due to long-term side-effects[3].

Dupilumab is a biologic treatment which blocks receptor binding of two of the key cytokines involved in the pathogenesis of AD (IL-4 and IL-13)[19]. It is recommended by NICE in TA534 as an option for treating moderate to severe AD in adults if the disease has not responded to at least one other systemic therapy, such as CsA, methotrexate, azathioprine and mycophenolate mofetil, or these are contra-indicated or not tolerated[2]. Dupilumab is funded for use in adolescents, within licence, under the NHS England Medicines for Children Policy as part of specialised commissioning if the patient is seen within a specialised treatment centre and they meet the criteria set out within the NICE Technology Appraisal (TA) for dupilumab in adults[33].

Dupilumab is given by SC injection Q2W, after an initial loading dose, and can be used with or without TCS[2].

B.1.3.5 Unmet need

AD is a chronic disease and topical treatments - in particular emollients, the mainstay of AD management - are used over the long-term throughout the treatment pathway. Adherence to topical treatments is often poor, due to the inconvenience of using a messy and sticky emollient cream multiple times each day, frustration with lack of efficacy and fear of side effects such as skin thinning with TCS[34].

It is not uncommon for patients to express fear and anxiety about using TCS, which in some patients can lead to steroid phobia and poor adherence[34,35]. A UK survey of 200 dermatology out-patients with AD found that almost three-quarters of respondents were concerned about using TCS on their own or their child's skin; respondents were particularly concerned about skin atrophy and the potential for systemic effects on growth and development. Furthermore, 33% of respondents admitted to non-adherence with TCS treatment due to their fear of AE[35].

Poor adherence is reflected by recent work using the CPRD-HES database which indicates that prescribing of emollients and TCS per patient in Primary Care is considerably lower the recommended quantities outlined in respective guidelines, suggesting that people with AD are not applying sufficient amounts of emollients and TCS to control disease[26].

Furthermore, the use of topical treatments has a detrimental impact on QOL, which increases with the duration and frequency of applications, which is likely to discourage adherence. In a recent study, the most intense regimen (TCS twice a day and emollient four times a day) was associated with the largest detrimental impact on QOL, and the addition of TCS was significantly more likely to impact on QOL than the use of emollient alone[36].

Sub-optimal use of topical treatments impacts on disease control and the majority of people with moderate to severe AD remain uncontrolled on current treatments, including conventional systemic treatments and biologics. A survey carried out in the UK, Germany and France found that 70% of people with moderate AD and 85% of those with severe AD had uncontrolled disease, despite use of conventional systemic treatments or phototherapy in around one-third of patients[37].

People with moderate and severe AD are dissatisfied with current topical and conventional systemic treatments, and dissatisfaction increases with the severity of disease, rising from 23% to 46%, driven by poor symptom relief (36% of people with moderate disease and 59% of those with severe disease) and the length of time treatments take to work (38% and 63%)[38]. Indeed, people with moderate and severe AD rank reduction in itch, control of AD flares and rapid skin clearance as the most important clinical attributes for treatment for moderate to severe AD[39].

Other conventional systemic immunosuppressive drugs are also limited by AE which increase with longer term exposure in a number of cases and monitoring that can be onerous, see Table 4. Conventional systemic therapies are usually given for a limited period due to short-term clinical benefits and high rates of safety-related discontinuation. There is limited clinical evidence to support use of these therapies in AD, therefore efficacy and tolerability is difficult to predict and both clinicians and patients may face concerns when initiating a new treatment.

Dupilumab is given as a SC injection and must be stored in a refrigerator (between 2 to 8°C), which some patients may find inconvenient. It is difficult to ensure that patients store their medication at home according to storage recommendations which may affect safety and effectiveness. Furthermore, patients may find it difficult to keep medicine refrigerated while travelling or being away from home for extended period of time (for example, long flights, limited access to refrigeration).

A proportion of patients will not be able to self-inject and will require out-patient visits to hospital or home administration with a nurse, family member or carer.

Additionally, needle phobia is relatively common (20%-50%) in adolescents and continues into adulthood for some people, which makes SC injection challenging for some[40]. Indeed, a survey carried out in the UK and US in 320 people with moderate to severe AD found that respondents preferred oral treatment over injectable treatment and that mode of administration was the second most important attribute in a treatment for AD[39].

Conjunctivitis is a well-known AE associated with dupilumab, which can be debilitating for patients and may lead to discontinuation of treatment[41]. Recent real world UK data reveals that 35% (36/102) of patients receiving dupilumab reported worsening ocular symptoms, 36% (13/36) of whom required steroid eye drops and 11% (4/36) stopped treatment with dupilumab due to their eye symptoms[42].

Despite treatment advances in AD, including biologic therapies, data from the dupilumab clinical trial programme suggests that 62-64% of people receiving dupilumab did not achieve disease control[43], either because of non-response, a partial response or loss of response over time, highlighting that a significant unmet need still exists in AD. Such patients may require additional treatments such as TCS, phototherapy or conventional systemic immunosuppressive drugs in order to achieve disease control[43].

Uncontrolled AD has a significant negative impact on patient QOL[37] and on symptoms[20]: 68% of people with uncontrolled AD report a DLQI>10, indicating that the patient's life is being severely affected by their skin disease[37], 85.8% report daily itching with an average severity of 6.5/10 on a 10-point severity scale, 41.5% report

itching for 18 hours or more each day and 55% report sleep disturbances 5 or more days a week[20].

The burden of AD and unmet need is particularly high in adolescents. AD has a significant impact on school attendance and achievement at school[16]. The National Eczema Society survey revealed that of the parents surveyed, more than half said their child had to take time off school due to their eczema and one in seven children took more than 10 days off during the last year. One-fifth of parents in the survey said their child limited their activities at school and regularly mentions difficulty concentrating in class because of their AD[16]. Additionally the psychological impact of living with AD can be overwhelming for this age group in coping with their AD, in addition to teasing, bullying and managing emollients at school[44].

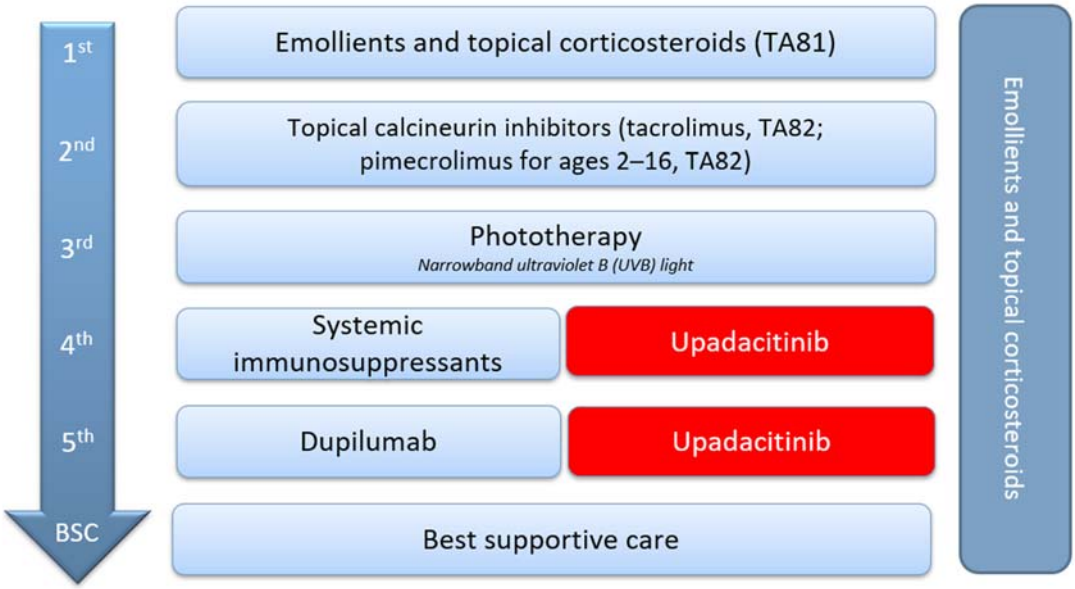
B.1.3.6 Place in therapy for upadacitinib

The indication for upadacitinib is for the treatment of moderate to severe atopic dermatitis in patients 12 years of age and older who are candidates for systemic therapy.

It is anticipated, based on clinical opinion, that upadacitinib will be used in adolescents and adults in two places in the treatment pathway,

- In people who are candidates for conventional systemic treatment. This population is referred to as **'systemic-eligible'** and in this instance, upadacitinib provides an alternative option to conventional systemic therapy.
- In people in whom the disease has not responded to at least one other conventional systemic therapy (CsA, methotrexate, azathioprine or mycophenolate mofetil) or these treatments are not suitable. This places upadacitinib in the same position in the treatment pathway as dupilumab. This population is referred to as '**systemic-exposed'.**

Figure 5: Place in the treatment pathway for upadacitinib



B.1.4. Equality considerations

We do not believe that the use of upadacitinib in AD will raise any equality issues.

B.2 Clinical effectiveness

- Upadacitinib is being studied in adolescents and adults (12-75 years) with moderate to severe AD who are candidates for systemic therapy. Three phase III registration studies compare upadacitinib with placebo: two using upadacitinib as monotherapy (Measure UP 1, Measure UP 2) and one using upadacitinib in combination with TCS (AD UP)[45-47]. A phase IIIb head to head study compares upadacitinib monotherapy with dupilumab monotherapy (Heads UP)[48].
- The three placebo-controlled registration studies randomised patients to upadacitinib (15 mg or 30 mg) or placebo for 16 weeks, followed by a long-term extension period for a further 120 weeks. Efficacy data is available for the first 16 weeks of the placebo-controlled studies[45-47].
- Upadacitinib rapidly clears skin and relieves itch. Symptomatic control of AD with upadacitinib results in significant improvements in sleep, mental health and QOL[45-47].
- Significantly more patients achieved 75% skin clearance (improvement in the area covered by AD and its severity as measured by the EASI score) with upadacitinib vs placebo at week 16. In the monotherapy studies, 60%-70% of patients receiving upadacitinib 15 mg, 73%-80% of patients receiving upadacitinib 30 mg vs 13%-16% of patients receiving placebo achieved 75% skin clearance. In combination with TCS, the proportions of patients were 65%, 77% and 26% respectively, $p<0.001$ for all[45-47].
- Significantly more patients achieved 90% skin clearance (improvement in the area covered by AD and its severity as measured by the EASI score) with upadacitinib vs placebo at week 16. In the monotherapy studies, 42%-53% of patients receiving upadacitinib 15 mg, 58%-66% of patients receiving upadacitinib 30 mg vs 5%-8% of patients receiving placebo achieved 90% skin clearance. In combination with TCS, the proportions of patients were 43%, 63% and 13% respectively, $p<0.001$ for all[45-47].
- Significantly more patients achieved clear/almost clear skin (0/1) as measured by vIGA-AD with upadacitinib vs placebo at week 16. In the monotherapy studies, 39%-48% of patients receiving upadacitinib 15 mg, 52%-62% of patients receiving upadacitinib 30 mg vs 5%-8% of patients receiving placebo achieved clear/almost clear skin. In combination with TCS, the proportions of patients were 40%, 59% and 11% respectively, $p<0.001$ for all[45-47].
- Significantly more patients achieved an improvement in itch of ≥4 on the Worst Pruritus Numerical Rating Score (WP-NRS) (0-10) with upadacitinib vs placebo at week 16. In the monotherapy studies, 42%-52% of patients receiving upadacitinib 15 mg, 60% of patients receiving upadacitinib 30 mg vs 9%-12% of

patients receiving placebo achieved an improvement in itch of ≥4 points. In combination with TCS, the proportions of patients were 52%, 64% and 15% respectively, p<0.001 for all[45-47].

- Onset of action is rapid, patients achieve 75% skin clearance (EASI 75) as early as week 1 with 90% skin clearance (EASI 90) as early as week 2, all of which are significantly faster than with placebo[45-47].
- Clinically meaningful reductions in itch are seen as early as 1 day after initiation of treatment with upadacitinib 30 mg and within 2 days with upadacitinib 15 mg[45,46].
- [redacted][45-47].
  [redacted][45].
- Upadacitinib reduced the need for TCS, in the 16-week double-blind period of AD UP, both doses of upadacitinib increased the number of steroid free days while maintaining a 75% reduction in EASI vs placebo (mean of 34 steroid-free days with upadacitinib 15 mg, 48 days with upadacitinib 30 mg vs 8 days with placebo, p<0.001)[47].
- Heads UP randomised patients to upadacitinib 30 mg or dupilumab 300 mg for 24 weeks. The primary end-point was achievement of EASI 75 at 16 weeks[49].
- Significantly more patients achieved the primary end-point (achievement of EASI 75 by 16 weeks) with upadacitinib 30 mg vs dupilumab (71.1% vs 61.1%, p=0.006). Onset of action was significantly quicker with upadacitinib than with dupilumab[49].
- In the studied measures of disease activity (skin clearance [EASI 90 and EASI 100] and pruritus),
  [redacted][49].
- Initial 16-week data from the phase III placebo-controlled studies, revealed that AE were generally mild to moderate, with acne, upper respiratory tract infection and nasopharyngitis being the most common AE. Serious AE occurred in 1.3%-2.8% of patients depending on the study and the dose[45-47].
- The safety profile for upadacitinib meant that patients were able to continue treatment with upadacitinib, discontinuation due to AE was low; ranging from 1.3% to 4.0% depending on the study and the dose[45-47].

- The head to head study vs dupilumab, Heads UP, showed a similar safety profile to the phase III registration studies[49].

B.2.1. Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

The clinical trial programme for upadacitinib in AD is comprehensive and detailed below and in Table 6.

- The three phase III registration trials: Measure UP 1, Measure UP 2 and AD UP compare upadacitinib 15 mg and 30 mg with placebo over a 16-week double-blind period with a 120-week blinded extension period. Measure UP 1 and 2 study upadacitinib as monotherapy and AD UP studies upadacitinib in combination with TCS.
- One phase IIIb trial, Heads UP, compares upadacitinib 30 mg monotherapy with dupilumab 300 mg Q2W monotherapy over a 24-week double-blind period.

Two other studies have also been carried out:

- Guttman-Yassky, 2020[50], 16-week phase II dose finding study comparing upadacitinib 7.5 mg, 15 mg and 30 mg vs placebo in people with mild to moderate AD.
- Rising UP, Japanese randomised controlled trial (RCT) in 272 people, 16-week double-blind period followed by a long-term extension. The study compares upadacitinib 15 mg/30 mg plus TCS with placebo plus TCS. The primary end-point is the number of patients experiencing AE. This study has been submitted for publication.

Guttman-Yassky, 2020 and Rising UP will not be included in this submission, since Guttman-Yassky, 2020 is a phase II study and Rising UP is in Japanese patients. The large RCTs detailed in Table 6 provide robust evidence for upadacitinib in European populations at the licensed dose.

Since AD is a multifactorial disease and has such a negative impact on patients' lives the studies considered numerous end-points, assessing skin clearance and disease activity measures, impact of upadacitinib on pruritus, QOL, patient reported outcomes and mental health. These are detailed in Table 8.

Measure UP 1, Measure UP 2, AD UP and Heads UP were not identified in the systematic literature review (SLR) detailed in Appendix D, since they were not

published at the time of the review (October 2020). The studies are still underway, and much of the data presented in this submission is taken from clinical study reports (CSR).

Table 5: Publication plan for the clinical study programme

Date	Study	Publication
16-week data		
Nov 2020	Measure UP 1 & 2	Oral presentation at EADV Guttman-Yassky 2020[51]
Quarter 1 2021	Measure UP 1 & 2	Publication expected
Quarter 1 2021	AD UP	Publication expected
Dec 2020	AD UP	Poster and abstract presented at RAD, Reich 2020[52,53]
24 week data		
Quarter 2 2021	Heads UP	Publication expected
April 2021	Heads UP	To be presented at ISAD
52 week data		
Quarter 2 2021	Measure UP 1	Publication expected
Quarter 3 2021	Measure UP 2	Publication expected
Quarter 2 2021	AD UP	Publication expected

AD: Atopic Dermatitis, EADV: European Academy of Dermatology and Venereology, ISAD: International Symposium on Atopic Dermatitis, RAD: Revolutionizing Atopic Dermatitis

All four studies were used in the economic modelling and are detailed below. The registration studies (Measure UP 1, Measure UP 2 and AD UP) were used in the economic base cases. Use of the head to head study vs dupilumab, Heads UP, was limited in the economic modelling. Heads UP only includes upadacitinib 30 mg used as monotherapy and does not report DLQI, which is used to determine response criteria in the base case. Therefore, Heads UP was used in scenario analyses where appropriate.

Table 6: Clinical effectiveness evidence

Study	Measure UP 1 M16-045 NCT03569293	Measure UP 2 M18-891 NCT03607422	AD UP M16-047 NCT03661138	Heads UP M16-046 NCT03738397
Study design	RCT, 16-week double-blind, 120-week blinded extension period			RCT, 24-week double-blind
Population	Moderate to severe AD Candidates for systemic therapy or have recently required systemic therapy IGA ≥3 EASI ≥16 BSA involvement ≥ 10% WP-NRS ≥4			
Age groups	Adolescents and adults aged 12-75 years			Adults aged 18-75 years
Intervention(s)	Upadacitinib 15 mg QD Upadacitinib 30 mg QD	Upadacitinib 15 mg QD Upadacitinib 30 mg QD	Upadacitinib 15 mg QD +TCS Upadacitinib 30 mg QD +TCS	Upadacitinib 30 mg QD
Comparator(s)	Placebo	Placebo	Placebo + TCS	Dupilumab 300 mg Q2W
Indicate if trial supports application for marketing authorisation	Yes ✓ / No Used in economic model: Yes ✓ / No	Yes ✓ / No Used in economic model: Yes ✓ / No	Yes ✓ / No Used in economic model: Yes ✓ / No	No / No ✓ Used in economic model: Yes ✓ / No
Rationale for use/non-use in the model	All trials were included in the model because they supported the application for marketing authorisation and include the populations relevant to the decision problem.			Heads UP is used in scenario analyses*
Reported outcomes specified in the decision problem	**IGA 0/1 (%)** **EASI 75 (%)** Measures of disease severity (EASI) Measures of symptom control (WP-NRS, POEM, % of patients experiencing flare) AE of treatment	**IGA 0/1 (%)** **EASI 75 (%)** Measures of disease severity (EASI) Measures of symptom control (WP-NRS, POEM, % of patients experiencing flare) AE of treatment	**IGA 0/1 (%)** **EASI 75 (%)** Measures of disease severity (EASI) Measures of symptom control (WP-NRS, POEM, % of patients experiencing flare) AE of treatment	**EASI 75 (%)** Measures of disease severity (EASI) Measures of symptom control (WP-NRS) AE of treatment

Study	Measure UP 1 M16-045 NCT03569293	Measure UP 2 M18-891 NCT03607422	AD UP M16-047 NCT03661138	Heads UP M16-046 NCT03738397
	HRQOL (EQ-5D, DLQI, CDLQI)	HRQOL (EQ-5D, DLQI, CDLQI)	HRQOL (EQ-5D, DLQI, CDLQI)	
All other outcomes in the economic model	Composite of EASI 50 and DLQI ≥4 EASI 50	Composite of EASI 50 and DLQI ≥4 EASI 50	Composite of EASI 50 and DLQI ≥4 EASI 50	EASI 50
Status	16-week data published in CSR 52-week data due Q2 2021	16-week data published in CSR 52-week data due Q2 2021	16-week data published in CSR 52-week data due Q2 2021	16 and 24-week data provided, in topline memo, CSR due Q1 2021

AD: Atopic Dermatitis, AE: Adverse Events, BSA: Body Surface Area, CDLQI : Children's Dermatology Life Quality Index, CSR: Clinical Study Report, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EQ-5D: European Quality Of Life-5 Dimensions HRQOL: Health-related Quality Of Life, IGA: Investigator Global Assessment, POEM: Patient Oriented Eczema Measure, Q1: Quarter 1, Q2: Quarter 2, QD: Once Daily, Q2W: Every 2 Weeks, RCT: Randomised Controlled Trial, TCS: Topical Corticosteroids, WP-NRS: Worst Pruritus Numerical Rating Scale.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Table 7: Study design for Measure UP 1, Measure UP 2, AD UP and Heads UP

	Measure UP 1 **M16-045** **NCT03569293**	**Measure UP 2** **M18-891** **NCT03607422**	**AD UP** **M16-047** **NCT03661138**	**Heads UP** **M16-046** **NCT03738397**
Location	151 sites in 24 countries UK (4 sites: 3 x London, Manchester,) Bosnia & Herzegovina, Bulgaria, Croatia, Denmark, Finland, France, Germany, Italy, Romania, Turkey, Switzerland Canada, US (including Puerto Rico) Argentina, Columbia Australia, New Zealand Ukraine, Russia, Estonia China Japan Malaysia	154 sites in 23 countries UK (4 sites: London, Newcastle, Plymouth, Southampton) Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Spain Canada, US Australia, New Zealand Singapore, South Korea, Taiwan	171 sites in 22 countries UK (5 sites: Dundee, Leeds, 2 x London, Oxford) Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Slovakia, Spain, Sweden Canada, US (including Puerto Rico) Australia, New Zealand China Japan	142 sites in 23 countries UK (6 sites: Brighton, Cardiff, Glasgow, 2 x London, Fife) Croatia, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Spain, Sweden, Ukraine Canada, US Australia, New Zealand Malaysia, Singapore, Taiwan
Trial design	RCT, 16-week double-blind, 120-week blinded extension period			
Eligibility criteria	Moderate to severe AD who are candidates for systemic therapy or have recently required systemic therapy IGA ≥3, EASI ≥16, BSA involvement ≥ 10%, WP-NRS ≥4			
Age groups	Adolescents and adults aged 12-75 years			Adults aged 18-75 years
Settings and locations where data were collected	Screening Baseline (day 1) Week 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, 64, 76, 88, 100, 112, 124, 136 Follow-up visit 30 days after last dose of study drug		Screening Baseline (day 1) Week 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, 64, 76, 88, 100, 112, 124, 136 Follow-up visit 30 days after last	Screening Baseline (day 1) Week 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 Follow-up 12 weeks after last injection (week 24)

			dose of study drug	
Trial drugs	Upadacitinib 15 mg QD (n=281) Upadacitinib 30 mg QD (n= 285) Placebo QD (n=281)	Upadacitinib 15 mg QD (n=276) Upadacitinib 30 mg QD (n=282) Placebo QD (n=278)	Upadacitinib 15 mg QD + TCS (n=300) Upadacitinib 30 mg QD + TCS (n=279) Placebo QD + TCS (n=304)	Upadacitinib 30 mg QD + dummy SC injection Q2W Dupilumab 300 mg SC Q2W + dummy tablet QD
Permitted medication	Emollient BD	Emollient BD	Emollient BD TCS	Emollient BD
Disallowed medication	Prior and concomitant use of JAK inhibitors, biologic therapies, DMARDs, systemic corticosteroids, phototherapy and topical treatment Vaccination using live vaccination Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers		As Measure UP 1 and 2, except TCS allowed	As Measure UP 1 and 2
Primary outcomes	IGA 0/1 (%) with at least two grades of reduction from baseline at week 16 EASI 75 (%) at week 16			EASI 75 (%) at week 16
Pre-planned subgroups	Age: adolescents vs adults <18 years, ≥18 years Age: <18 years, ≥18 to <40 years, ≥40 to <65 years, ≥65 years Gender: male, female BMI: normal (<25), overweight (≥ 25 to <30), obese (≥ 30) Race: White, Asian, Black, other Weight: <median, ≥median Geographic region: US/Puerto Rico/Canada and other Baseline IGA-AD: <4, ≥4) Baseline EASI: <median, ≥median High-sensitivity C-reactive protein: <median, ≥median Previous systemic therapy: with, without Participants who reported an intolerance to at least one prior TCS or TCI therapy Participants who reported an inadequate response to at least one prior topical treatment.			Age: <40 years, ≥40 to <65 years, ≥65 years Gender: male, female BMI: normal (<25), overweight (≥25 to <30), obese (≥30) Race: White, Asian, Black, other Weight: <median, ≥median Geographic region: US/Puerto Rico/Canada and other Baseline IGA-AD: <4, ≥4 Baseline EASI: <median, ≥median High-sensitivity C-reactive protein: <median, ≥median Previous systemic therapy: with, without

AD: Atopic Dermatitis, BD: Twice Daily, BMI: Body Mass Index, BSA: Body Surface Area, CYP3A: Cytochrome P450 3A4, DLQI: Dermatology Life Quality Index, DMARDs: Disease-modifying Anti-rheumatic Drugs, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, JAK: Janus Kinase, Q2W: Every 2 Weeks, QD: Once Daily, RCT: Randomised Controlled Trial, SC: Subcutaneous, TCS: Topical Corticosteroids, TCI: Topical Calcineurin Inhibitor, WP-NRS: Worst Pruritis-Numerical Rating Scale

B.2.3.1 Study design

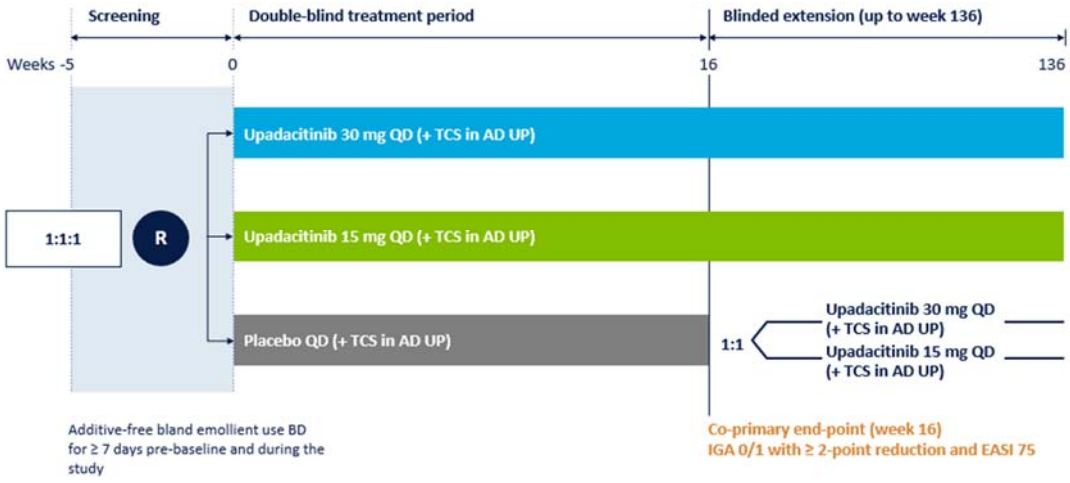
B.2.3.1.1 Registration studies

Measure UP 1, Measure UP 2 and AD UP had a common study design[45-47].

All three studies were phase III RCTs, comprised of a main study (adults and adolescents) and an adolescent sub-study (adolescents only). The main study and the adolescent sub-study were composed of a 5-week screening period, a 16-week double-blind period, a 120-week blinded extension period and a 30-day follow-up.

Participants in the main study and adolescent sub-study were randomised 1:1:1 to upadacitinib 15 mg, upadacitinib 30 mg or placebo followed by a 120-week blinded extension period, where patients on placebo were randomised 1:1 to upadacitinib 15 mg or upadacitinib 30 mg. The study ended with a 30-day follow-up visit. Patients in Measure UP 1 and Measure UP 2 received upadacitinib or placebo alone, whereas those in AD UP received upadacitinib or placebo plus TCS.

Figure 6: Study design for Measure UP 1, Measure UP 2 and AD UP



AD: Atopic Dermatitis Atopic Dermatitis, BD: Twice Daily, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, QD: Once Daily, TCS: Topical Corticosteroids

Study sites and participants remained blinded to treatment assignments for the duration of the study.

Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.

Once 810 participants were enrolled into the main study, the supplementary study opened to ensure enrolment of 180 adolescent participants in the overall study (main study plus adolescent sub-study).

Randomisation was stratified by baseline disease severity (moderate [IGA 3] vs severe [IGA 4]), by geographic region (US/Puerto Rico/Canada, Japan, China, and other), and by age (adolescent [ages 12 to 17] vs adult [ages 18 to 75]). The adolescent sub-study was stratified by baseline disease severity (moderate [IGA 3] vs. severe [IGA- 4]) and by geographic region (US/Puerto Rico/Canada and other).

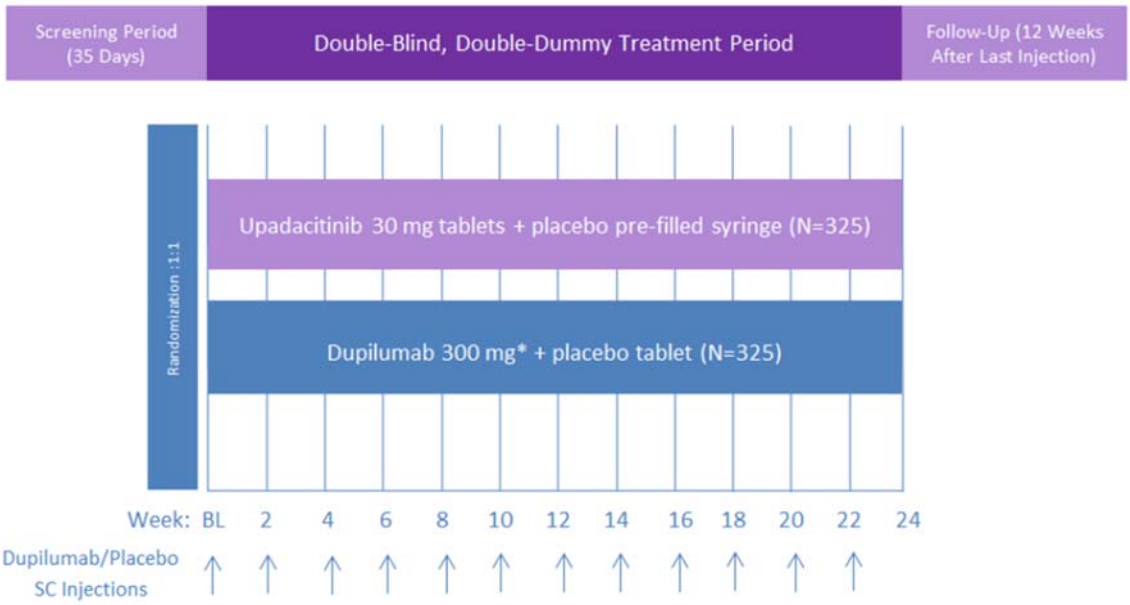
The primary analysis for the main study was conducted after all ongoing participants completed week 16.

After the primary analysis, an additional analysis for the main study will be conducted when the required safety exposure target is reached. Other planned analyses include overall population at week 52, together with adolescents at week 16 and week 52.

B.2.3.1.2 Head to head study vs dupilumab

Heads UP, the head to head trial vs dupilumab, is a 24-week double-blind phase IIIb RCT[48]. The study consists of a 5-week screening period, followed by a 24-week double-blind, double-dummy treatment period and 12-week follow-up.

Figure 7: Study design for Heads UP



BL: Baseline, SC: Subcutaneous
*Dupilumab 300 mg SC injection will be administered every other week starting at the week 2 visit and until the week 22 visit, after an initial loading dose of 600 mg at the baseline visit

Participants were randomised in a 1:1 ratio to upadacitinib 30 mg + placebo pre-filled syringe (n=325) or dupilumab 300 mg + placebo tablets (n=325). Randomisation was stratified by baseline disease severity (moderate [IGA 3] vs severe [IGA 4]) and age (<40, ≥40 to 65, ≥65 years).

Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.

The primary end-point was the % of participants achieving EASI 75 at week 16.

B.2.3.2 Eligibility criteria

Eligibility criteria for all four studies were the same, with the exception that participants were aged 12-75 years in Measure UP 1, Measure UP 2 and AD UP and 18-75 years in Heads UP.

- Aged 12 to 75 years (Measure UP 1, Measure UP 2 and AD UP) or 18-75 years (Heads UP) with moderate to severe AD (diagnosis of AD according to the Hanifin and Rajka criteria: ≥3 of 4 major features and ≥3 of 23 minor features)
- Body weight ≥40 kg at baseline for participants aged ≥12 and <18 years
- AD symptoms ≥3 years
- ≥ 10% BSA
- EASI ≥16
- IGA ≥3
- Baseline weekly average of daily WP-NRS ≥4
- Inadequate response to TCS or TCI within the 6 months prior to baseline

Patients were excluded if they had

- Topical treatments (other than emollients) within the 7 days prior to baseline (excluding AD UP in which TCS were mandated)
- Systemic therapy for AD or phototherapy or traditional Chinese medicine or any investigational drug within the 4 weeks prior to baseline
- Prior exposure to dupilumab or systemic JAK inhibitors

B.2.3.3 Locations

All four studies were multicentre, with patients enrolled globally.

B.2.3.4 Trial drugs, concomitant and prohibited medications

- Measure UP 1 and Measure UP 2 randomised participants to upadacitinib 15 mg, upadacitinib 30 mg or placebo.
- AD UP randomised participants to upadacitinib 15 mg, upadacitinib 30 mg or placebo with concomitant TCS.
- Heads UP randomised participants to upadacitinib 30 mg or dupilumab 300 mg.

Upadacitinib and placebo were both taken as an oral tablet QD at approximately the same time each day, with or without food. Patients were advised that upadacitinib and placebo tablets should be swallowed whole and not split, crushed or dissolved.

Dupilumab or placebo pre-filled syringe was administered SC on study visit 1 and Q2W until week 22.

All participants were required to apply a bland, additive-free emollient BD from at least 7 days before baseline and for the duration of the study.

Rescue therapy could be provided from week 4 at the discretion of the investigator if participants had EASI response of <50% at any two consecutive study visits. The first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. Study drug was discontinued if a systemic treatment or phototherapy was required.

Prior and concomitant use of JAK inhibitors, biologic therapies, DMARDs, systemic corticosteroids, phototherapy and topical treatment (except for TCS in AD UP) was prohibited.

Vaccination using live vaccines was prohibited for the duration of the studies. If patients required a vaccination it was given at least 4 weeks prior to the first dose of study drug.

Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers was prohibited.

No elective surgery was allowed during the study.

B.2.3.5 End-points

The pre-specified co-primary end-points for Measure UP 1, Measure UP 2 and AD UP were % of participants achieving IGA 0/1 and % of participants achieving EASI 75.

The pre-specified primary end-point for Heads UP was % of participants achieving EASI 75.

The results of the primary end-points can be found in Table 13.

End-points of particular interest are detailed in Table 8. We have noted in Table 8 whether the end-point results are to be found in the main dossier or in Appendix B.

Those in *red italics* are used in the economic model and results can be found in Section B.2.6.3 for the registration studies and Section B.2.6.4 for Heads UP.

An asterisk denotes that the secondary end-point is a key secondary end-point in the CSR.

.

Table 8: Study end-points in Measure UP 1, Measure UP 2, AD UP and Heads UP

	Measure UP 1 M16-045 NCT03569293	Measure UP 2 M18-891 NCT03607422	AD UP M16-047 NCT03661138	Heads UP M16-046 NCT03738397	Place in submission
Primary end-point					
IGA 0/1 (%) with at least two grades of reduction from baseline at week 16	✓	✓	✓		Dossier
EASI 75 (%) at week 16	✓	✓	✓	✓	*Dossier*
Skin clearance and disease activity measures					
% change in EASI from baseline at week 16	✓*	✓*	✓*		Dossier
% of participants achieving EASI 50 at week 16	✓	✓	✓	✓ (not reported yet)	Dossier
% of participants achieving EASI 75 at week 2	✓*	✓*	✓	✓*	Dossier
% of participants achieving EASI 75 at week 4	✓	✓	✓*	✓	Dossier
% of participants achieving EASI 90 at week 4	✓	✓	✓*	✓	Dossier
% of participants achieving EASI 90 at week 16	✓*	✓*	✓	✓*	Dossier
% of participants achieving EASI 100 at week 16	✓*	✓*	✓*	✓*	Appendix
Flares (EASI ≥6.6 points) % of participants experiencing a flare (increase of EASI by ≥6.6 from baseline) during double-blind period prior to use of rescue medication for participants with EASI ≤65.4 at baseline	✓*	✓*	✓		Dossier
% of participants achieving IGA of **0** (clear skin) with a reduction from baseline of ≥ 2 points at week 16	✓	✓	✓		Dossier
% change from baseline in SCORAD at week 16	✓*	✓*	✓		Dossier
% of participants achieving EASI 75 in the head and neck body region at week 16				✓	Dossier
% of participants achieving EASI 75 in each body region (other than head and neck) at week 16				✓	Dossier
Patient reported disease symptom scores: pruritus					
Improvement (% change) from baseline of WP-NRS at week 16	✓*	✓*	✓*	✓*	Dossier
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at day 2 for participants with WP-NRS ≥ 4 at baseline	✓*	✓*	✓		Dossier

% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at day 3 for participants with WP-NRS ≥ 4 at baseline	✓*	✓*			Appendix
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 1 for participants with WP-NRS ≥ 4 at baseline	✓*	✓*	✓*		Dossier
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 16 for participants with WP-NRS ≥ 4 at baseline	✓*	✓*	✓*	✓*	Dossier
Improvement (% change) from baseline of WP-NRS at week 1				✓*	Dossier
Improvement (% change) from baseline of WP-NRS at week 4				✓*	
Patient reported disease symptom scores: POEM					
% of participants achieving an improvement (reduction) in POEM ≥ 4 from baseline at week 16 for participants with POEM ≥4 at baseline	✓*	✓*	✓		Dossier
Change from baseline in POEM at week 16	✓	✓	✓		Dossier
% change from baseline in POEM at week 16	✓	✓	✓		Appendix
QOL					
% of participants aged ≥16 years old at screening achieving score of 0/1 in DLQI among participants with DLQI >1 at baseline at week 16	✓	✓	✓		Dossier
Change from baseline in DLQI among participants aged ≥16 years old at screening at week 16	✓	✓	✓		Dossier
% change from baseline in DLQI among participants aged ≥16 years old at screening at week 16	✓	✓	✓		Appendix
% of participants aged <16 years old at screening achieving score of 0/1 in CDLQI among participants with CDLQI >1 at baseline at week 16	✓	✓	✓		Dossier
Change from baseline in CDLQI among participants aged <16 years old at screening at week 16	✓	✓	✓		Dossier
% change from baseline in CDLQI among participants aged <16 years old at screening at week 16	✓	✓	✓		Appendix
% of participants aged ≥ 16 years old at screening achieving an improvement (reduction) in DLQI ≥ 4 from baseline at week 16 for participant with DLQI ≥ 4 at baseline	✓*	✓*	✓		Dossier
Change from baseline in EQ-5D-5L at week 16	✓	✓	✓		Dossier
% change from baseline in EQ-5D-5L at week 16	✓	✓	✓		Appendix
Mental health					
Change from baseline in HADS total score at week 16	✓	✓	✓		Dossier

% change from baseline in HADS total score at week 16	✓	✓	✓		Appendix
Symptoms and impact on the patient					
% of participants achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥12 (minimal clinically important difference [MCID]) from baseline at week 16 for participants with ADerm-IS sleep domain score ≥ 12 at baseline	✓*	✓*	✓		Dossier
% of participants achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥4 (MCID) from baseline at week 16 for participants with ADerm-SS skin pain score ≥4 at baseline	✓*	✓*	✓		Dossier
TCS sparing					
Reduction in TCS use Mean (median) number of days off all TCS and achieving EASI 75			✓		Dossier
TCS free days with EASI 75 at week 16			✓		Dossier
Median time to first discontinuation with EASI 75 response			✓		Dossier

AD: Atopic Dermatitis: ADerm-IS: Atopic Dermatitis Impact Scale, ADerm-SS: Atopic Dermatitis Symptom Scale, CDLQI: Children's Dermatology Life Quality Index, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EQ-5D-5L: European Quality Of Life-5 Dimensions 5 Levels HADS: Hospital Anxiety and Depression Scale, IGA: Investigator Global Assessment, MCID: Minimal Clinically Important Difference, POEM: Patient Oriented Eczema Measure, QOL: Quality of Life, SCORAD: Scoring Atopic Dermatitis, TCS: Topical Corticosteroids, WP-NRS: Worst Pruritus Numerical Rating Scale

B.2.3.6 Baseline characteristics

Baseline characteristics for each study are shown below in Table 9 (overall population) and Table 10 (adolescent population).

For Measure UP 1, demographics were balanced between all groups. Just over one-half (53.8%) were male, [redacted] were white, with a mean age of 34 years. For the adolescent subgroup, [redacted] were female, [redacted] were white and [redacted] had a BMI <25 kg/m^2. Participants had been diagnosed with AD for a mean of approximately [redacted] years overall and [redacted] years for adolescents. Disease activity consistently reflected moderate to severe AD across all treatment groups.

For Measure UP 2, demographics were balanced between all groups. Over one-half (56.3%) were male, [redacted] were white, with a mean age of 33.6 years. For the adolescent subgroup, [redacted] were female, [redacted] were white and [redacted] had a BMI <25 kg/m^2. Participants had been diagnosed with AD for a mean of approximately [redacted] years overall and [redacted] years for adolescents. Disease activity consistently reflected moderate to severe AD across all treatment groups.

For AD UP, demographics were balanced between all groups. More than half (60.7%) were male, [redacted] were white, with a mean age of 34.1 years. For the adolescent subgroup, [redacted] were female, [redacted] were white and [redacted] had a BMI <25 kg/m^2. Participants had been diagnosed with AD for a mean of approximately [redacted] years overall and [redacted] years for adolescents. Disease activity consistently reflected moderate to severe AD across all treatment groups.

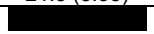
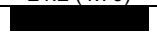
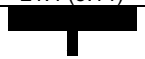
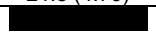
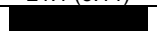
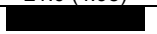
In terms of prior exposure to systemic therapy, [redacted] of participants in Measure UP 1, [redacted] in Measure UP 2 and [redacted] in AD UP had received prior systemic therapy.

Early data is available from Heads UP, the head to head trial of upadacitinib 30 mg vs dupilumab 300 mg[49], see Table 11. Demographics were balanced between all groups. [redacted] were male, [redacted] were white and all participants were aged over 18 years. The mean age was [redacted] years. Participants had been diagnosed with AD for a mean of approximately [redacted] years. Disease activity consistently reflected moderate to severe AD across all treatment groups, with around [redacted] of participants having severe disease (IGA=4). Around [redacted] of patients had received prior systemic therapy.

Feedback from UK clinicians confirms that these patient characteristics are representative of patients in the UK[1].

Table 9: Measure UP 1, Measure UP 2, AD UP: baseline characteristics in the overall populations

Characteristic	Measure UP 1			Measure UP 2			AD UP		
	Placebo (n=281)	UPA 15 mg (n=281)	UPA 30 mg (n=285)	Placebo (n=278)	UPA 15 mg (n=276)	UPA 30 mg (n=282)	Placebo (n=304)	UPA 15 mg (n=300)	UPA 30 mg (n=297)
Male sex, n (%)	144 (51.2%)	157 (55.9%)	155 (54.4%)	154 (55.4%)	155 (56.2%)	162 (57.4%)	178 (58.6%)	179 (59.7%)	190 (64.0%)
Age									
Mean (SD)	34.4 (15.50)	34.1 (15.72)	33.6 (15.84)	33.4 (14.79)	33.3 (15.70)	34.1 (15.95)	34.3 (15.12)	32.5 (14.02)	35.5 (15.79)
<18	40 (14.2%)	42 (14.9%)	42 (14.7%)	36 (12.9%)	33 (12.0%)	35 (12.4%)	40 (13.2%)	39 (13.0%)	37 (12.5%)
>18	241 (85.8%)	239 (85.1%)	243 (85.3%)	242 (87.1%)	243 (88.0%)	247 (87.6%)	264 (86.8%)	261 (87.0%)	260 (87.5%)
Race n (%)									
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American									
Asian									
American Indian/Alaska Native									
Native Hawaiian or other Pacific islander									
Other									
Multiple									
Weight (kg)									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median									
Min, Max									
Geographic region									
Europe	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
UK									
Previous systemic therapy - n (%)									
With	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without									
Baseline IGA, n (%)									
3 (moderate)	156 (55.5%)	154(54.8%)	154 (54.0%)	125 (45.0%)	126 (45.7%)	126 (44.7%)	141 (46.4%)	143 (47.7%)	140 (47.1%)
4 (severe)	125 (44.5%)	127 (45.2%)	131 (46.0%)	153 (55.0%)	150 (54.3%)	156 (55.3%)	163 (53.6%)	157 (52.3%)	157 (52.9%)
Baseline EASI - n (%)									
< Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ Median									

EASI Mean (SD)	28.84 (12.62)	30.57 (12.76)	28.98 (11.11)	29.08 (12.13)	28.60 (11.69)	29.65 (12.19)	30.26 (12.97)	29.16 (11.83)	29.72 (11.78)
Percentage BSA Mean (SD)	45.67 (21.60)	48.52 (22.23)	47.00 (21.97)	47.61 (22.69)	45.12 (22.35)	47.02 (23.18)	48.57 (23.11)	46.68 (21.65)	48.53 (23.09)
Overall SCORAD Mean (SD)									
DLQI n Mean (SD)	252 17.0 (6.85)	259 16.2 (7.00)	261 16.4 (6.97)	257 17.1 (7.17)	253 16.9 (7.04)	256 16.7 (6.93)	276 16.3 (6.99)	276 16.4 (7.20)	273 17.1 (7.00)
CDLQI n Mean (SD)									
WP-NRS Weekly average, Mean (SD)	7.27 (1.67)	7.23 (1.62)	7.28 (1.54)	7.34 (1.58)	7.15 (1.55)	7.26 (1.55)	7.14 (1.63)	7.06 (1.76)	7.36 (1.65)
POEM Mean (SD)	21.5 (5.35)	21.2 (4.76)	21.4 (5.14)	21.9 (5.24)	21.2 (5.13)	21.8 (4.76)	21.1 (5.14)	21.0 (4.98)	21.5 (5.27)
Disease Duration since Diagnosis (years)									

AD: Atopic Dermatitis, BSA: Body Surface Area, CDLQI: Children's Dermatology Life Quality Index, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, POEM: Patient Oriented Eczema Measure, SD: Standard Deviation, SCORAD: Scoring Atopic Dermatitis, UPA: Upadacitinib, WP-NRS: Worst Pruritus Numerical Rating Scale

Table 10: Measure UP 1, Measure UP 2, AD UP: baseline characteristics in the adolescent populations

Characteristic	Measure UP 1			Measure UP 2			AD UP		
	Placebo (n=40)	UPA 15 mg (n=42)	UPA 30 mg (n=42)	Placebo (n=36)	UPA 15 mg (n=33)	UPA 30 mg (n=35)	Placebo (n=40)	UPA 15 mg (n=39)	UPA 30 mg (n=47)
Male sex, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race									
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian/Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous systemic therapy - n (%)									
With	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA, n (%)									
3 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 (severe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EASI - n (%)									
< Median (25.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= Median (25.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage BSA									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall SCORAD									
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLQI n Mean (SD) **CDLQI** n Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WP-NRS Weekly average, Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POEM Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration since diagnosis (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AD: Atopic Dermatitis, BSA: Body Surface Area, CDLQI: Children's Dermatology Life Quality Index, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, POEM: Patient Oriented Eczema Measure, SD: Standard Deviation, SCORAD: Scoring Atopic Dermatitis, UPA: Upadacitinib, WP-NRS: Worst Pruritus Numerical Rating Scale

Table 11: Heads UP: baseline characteristics in the overall populations

Characteristic	Dupilumab 300 mg Q2W (n=344)	Upadacitinib 30 mg QD (n=348)
Male sex, n (%)	[redacted]	[redacted]
Age Mean (SD)	[redacted]	[redacted]
Race n (%) White Black or African American Asian American Indian/Alaska Native Native Hawaiian or other Pacific islander Other Multiple	[redacted]	[redacted]
Weight (kg) Mean (SD) Median Min, Max	[redacted]	[redacted]
Geographic region US//Puerto Rico/Canada Other	[redacted]	[redacted]
Previous systemic therapy - n (%) With Without	[redacted]	[redacted]
Baseline IGA, n (%) <4 (clear, almost clear, mild or moderate) 4 (severe)	[redacted]	[redacted]
Baseline EASI - n (%) < Median (26.4) ≥ Median (26.4)	[redacted]	[redacted]
EASI Mean (SD)	[redacted]	[redacted]
Percentage BSA Mean (SD)	[redacted]	[redacted]
WP-NRS Weekly average, Mean (SD)	[redacted]	[redacted]
Disease duration since diagnosis (years)	[redacted]	[redacted]

BSA: Body Surface Area, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, Q2W: Every 2 Weeks, QD: Once Daily, SD: Standard Deviation, WP-NRS: Worst Pruritus Numerical Rating Scale

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 12: Summary of statistical analyses

	Measure UP 1	Measure UP 2	AD UP	Heads UP
Hypothesis objective	Upadacitinib is expected to provide better efficacy compared to placebo and be well tolerated in adolescent and adults with moderate to severe AD. This hypothesis was tested by co-primary end-points which aimed to demonstrate superiority of each upadacitinib dose vs placebo: • Proportion (%) of participants achieving at least a 75% reduction in EASI from baseline at week 16 • Proportion (%) of participants achieving validated IGA of 0 or 1 with at least two grades of reduction from baseline at week 16.			Upadacitinib is expected to provide better efficacy compared to dupilumab and be well tolerated in adolescent and adults with moderate to severe AD. This hypothesis was tested by the primary end-point which aimed to demonstrate superiority of upadacitinib vs dupilumab: • Proportion (%) of participants achieving at least a 75% reduction in EASI from baseline at week 16.
Statistical analysis	Primary analysis at 16 weeks. Comparison of the primary endpoints will be made between each upadacitinib group and the placebo group in the intention to treat (ITT) population using the Cochran-Mantel-Haenszel (CMH) test, adjusting for IGA categories and age (adolescent vs adult). Primary end-point(s) will also be evaluated in the per protocol (PP) population.			
Sample size, power calculation	Approximately 810 adolescent and adult participants will be randomised to upadacitinib 30 mg, upadacitinib 15 mg or placebo in a ratio of 1:1:1 in the main study (270 subjects per treatment group). Sample size is determined by regulatory requirements to adequately characterise the safety profile. Assuming an EASI 75 response rate of 15%, and IGA 0/1 with at least a 2-point reduction response rate of 10% in the placebo arm, this sample size will also provide more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above two end-points simultaneously using two-sided test at a 0.05 significant level. The assumptions of placebo response rates for EASI 75 and IGA 0/1 were based on the maximum placebo rate in upadacitinib AD phase IIb[50] study and dupilumab phase III monotherapy studies (SOLO 1 and SOLO 2)[54]. The studies will also enrol 180 adolescent participants in an adolescent sub-study. This sample size was determined to ensure that a total of 225 subjects per dose across the three pivotal studies will provide 1 year of data.			Approximately 650 participants will be randomised to upadacitinib 30 mg or dupilumab in a ratio of 1:1 (325 per treatment group). Assuming an EASI 75 response rate of 50% in the dupilumab arm, this sample size will provide more than 80% power to detect at least a 12% treatment difference using two-sided test at a 0.05 significant level.
Data management, patient withdrawals	Missing values will be managed using non-responder imputation (NRI)* as the primary approach, with multiple imputation (MI) and tipping point analysis as sensitivity approaches. During the double-blind period, missing values and visits after the rescue will be handled by NRI for categorical variables or mixed effect model with repeated measures (MMRM) for continuous variables.			

	Logistical restrictions in hospital due to the COVID-19 pandemic led to patients being unable to attend their trial visits resulting in additional missing data. Missing values due to COVID-19 will be managed using NRI incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C). The results presented in the primary analysis are NRI-C wherever possible.

AD: Atopic Dermatitis, CMH: Cochran-Mantel-Haenszel, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, ITT: Intention to Treat, MI: Multiple Imputation, MMRM: Mixed-effect Model with Repeated Measures, NRI: Non-Responder Imputation, NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to Covid-19, PP: Per Protocol

*NRI analysis will categorise any participant who does not have evaluation during a specific visit window as a non-responder for that visit. The exception is when the participant is a responder both before and after a specific visit window, in which case the participant will be categorised as a responder for the visit. Only observations within the same analysis period will be used. NRI will be the primary approach in the analyses of categorical variables in the double-blind period and period up to Week 52 (primary and secondary variables only).

B.2.4.1 Censoring

In the upadacitinib trials data have been analysed according to two censoring rules for all efficacy and health outcome end-points:

Primary analysis: data were censored as missing or NRI after permanent study drug discontinuation or following initiation of rescue therapy with TCS, oral corticosteroids or systemic therapy.

'All observed' analysis: data were censored as missing or NRI after permanent study drug discontinuation, initiation of systemic rescue therapy or use of oral corticosteroid for over 2 weeks. Patients receiving rescue therapy with TCS or oral corticosteroids for less than 2 weeks were not censored at the time of rescue.

Data presented in the clinical effectiveness section (see Section B.2.6) are for the primary (ITT) analysis in which responders receiving rescue medication are censored from analysis. This is the standard approach for clinical trials in this disease area and consistent with primary publications and the CSR.

The base cases in the economic modelling use the 'all observed' dataset in which patients responding and receiving rescue medication or withdrawing are considered responders, which reflects clinical practice. This approach was validated by UK clinicians, who agreed that medication received for flares do not lead to active treatment discontinuation or define non-response[1]. Therefore, the 'all observed' data set is more reflective of clinical practice than the primary analysis. The primary analysis is presented in the economic modelling as a scenario analysis, where available.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

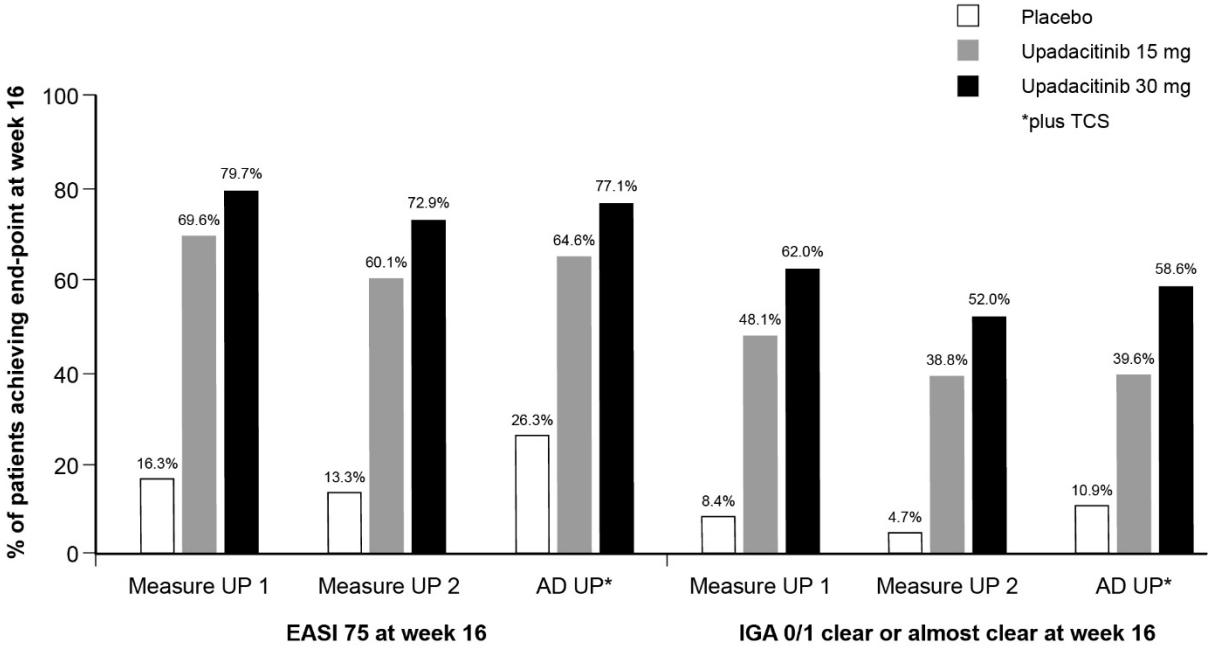
Complete quality assessment for each trial can be found in Appendix D (Section D.4)

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 Primary end-points vs placebo

The co-primary end-points of EASI 75 (reduction of 75% from baseline EASI score) and IGA score of 0/1 (clear/almost clear) with a clinically meaningful reduction (at least two grade reductions from baseline) were achieved in all three RCT vs placebo, see Figure 8 and Table 13.

Figure 8: Measure UP 1, Measure UP 2, AD UP: Co-primary end-points EASI 75 and IGA 0 or 1 at week 16 (ITT population), all differences from placebo p<0.001



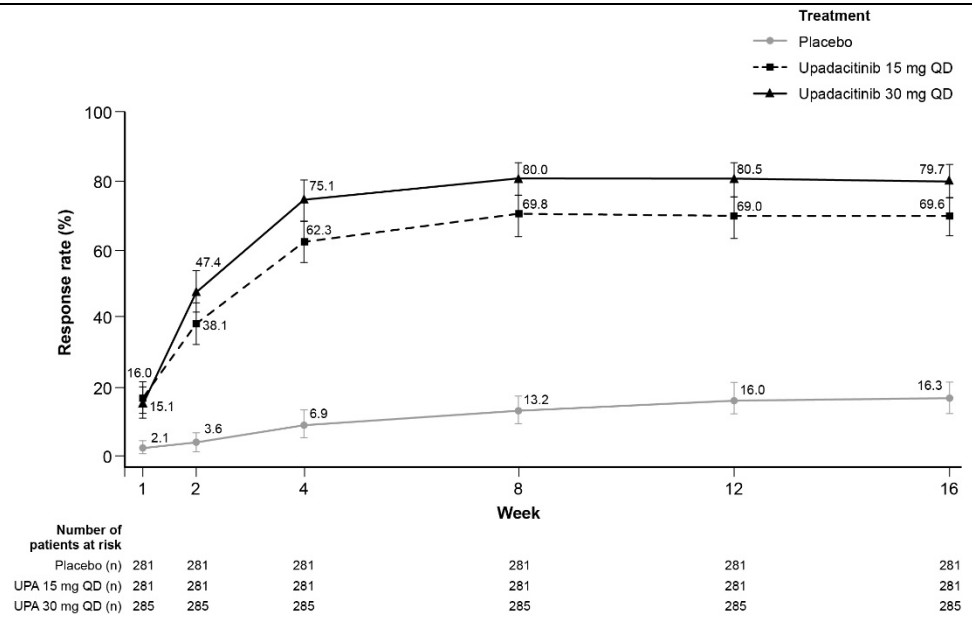
EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, TCS: Topical Corticosteroids

Onset of action with upadacitinib is rapid as demonstrated in Figure 9. There is a significant improvement vs placebo in EASI 75 (seen as early as week 1) and IGA 0/1 clear or almost clear (seen by week 2). An extremely rapid onset of action was seen in all three studies, regardless of concomitant TCS use.

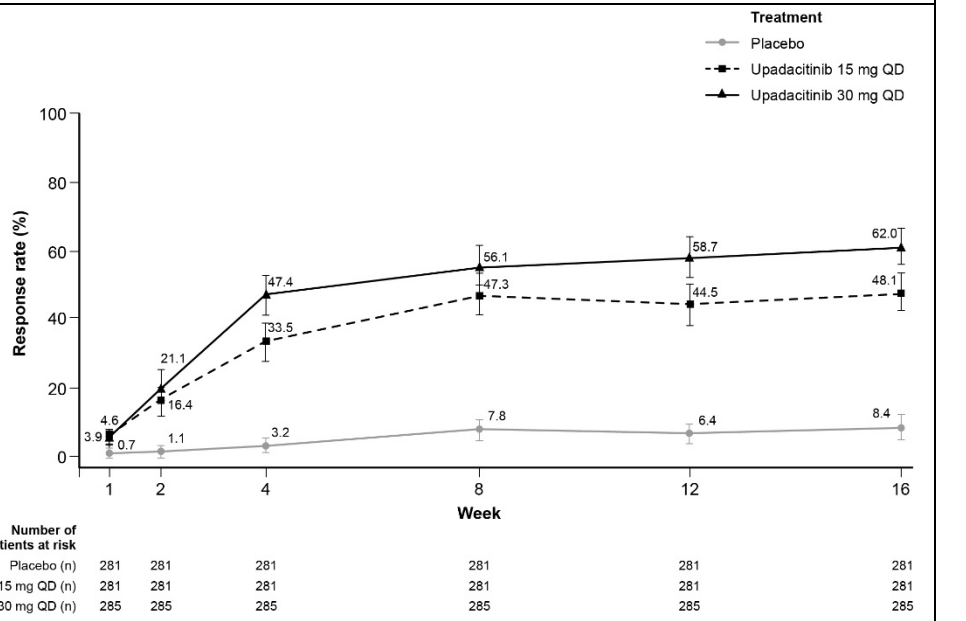
.

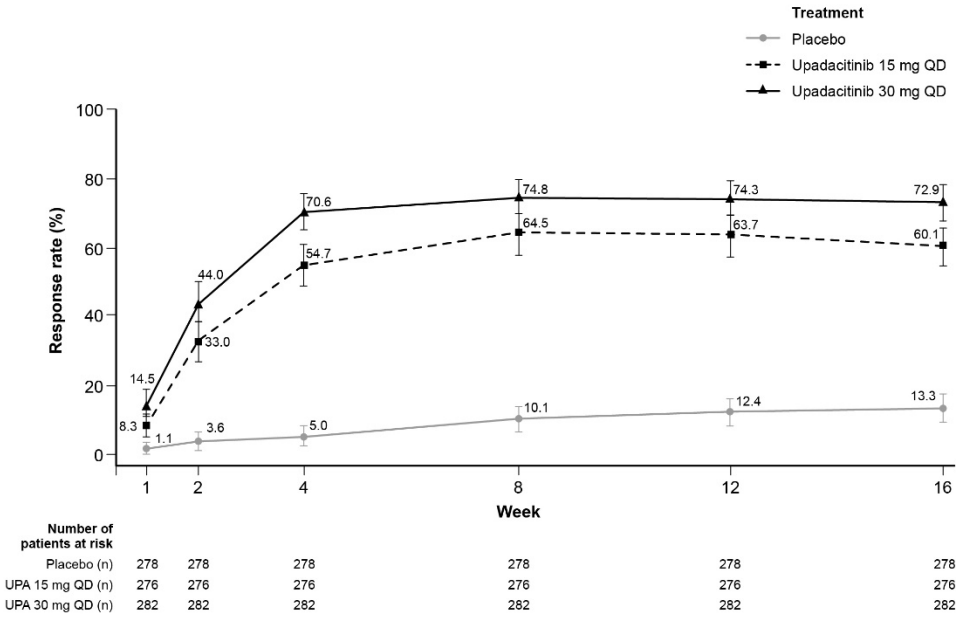
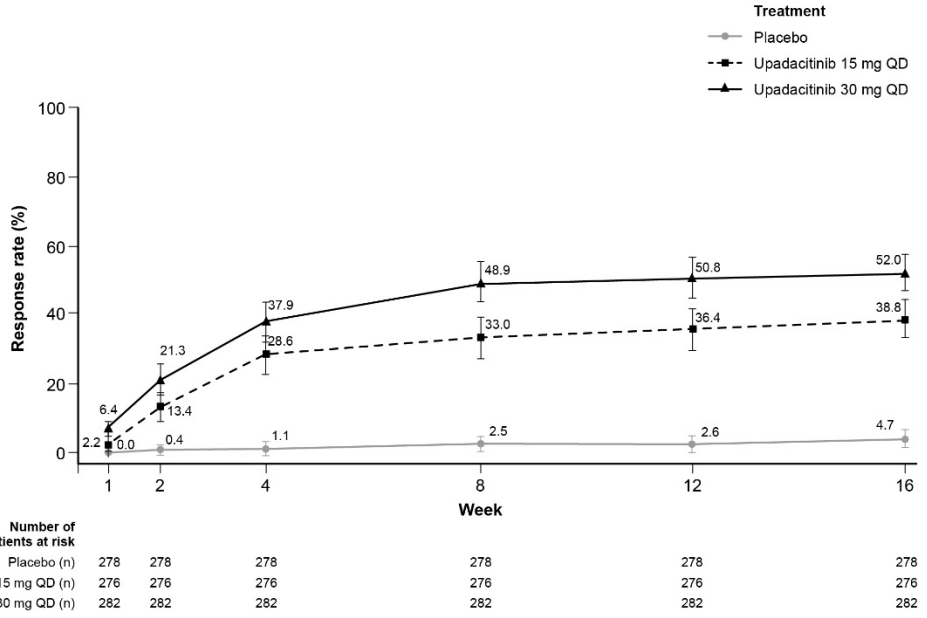
Figure 9: Measure UP 1, Measure UP 2 and AD UP: Primary end-points by visit during the double-blind period (ITT population), all differences from placebo p<0.001

Measure UP 1 –% of patients achieving EASI 75



Measure UP 1 –% of patients achieving IGA 0/1 clear or almost clear



Measure UP 2 –% of patients achieving EASI 75	Measure UP 2 –% of patients achieving IGA 0/1 clear or almost clear
	

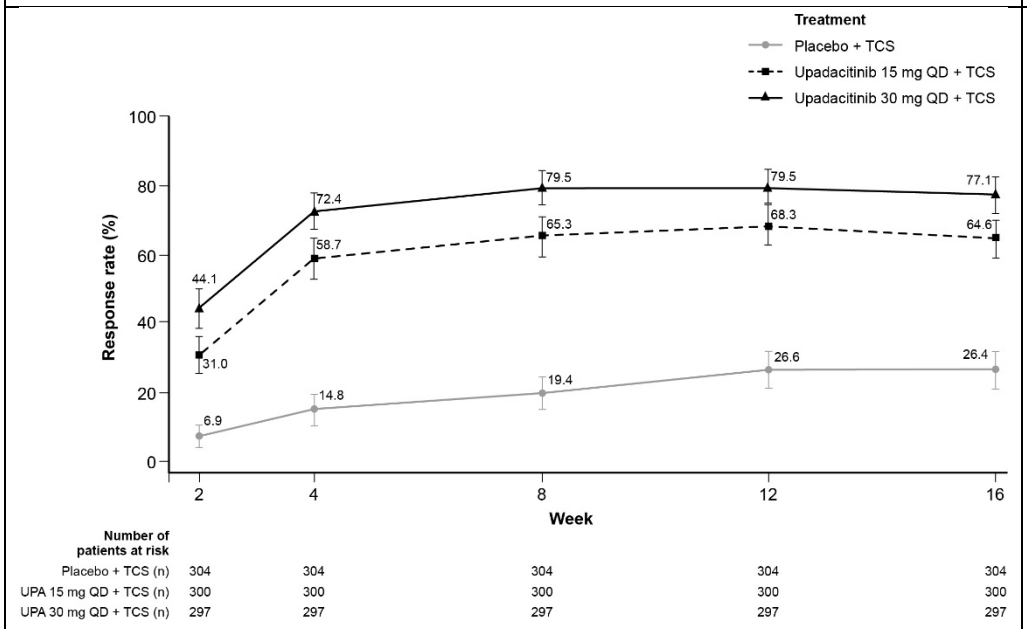
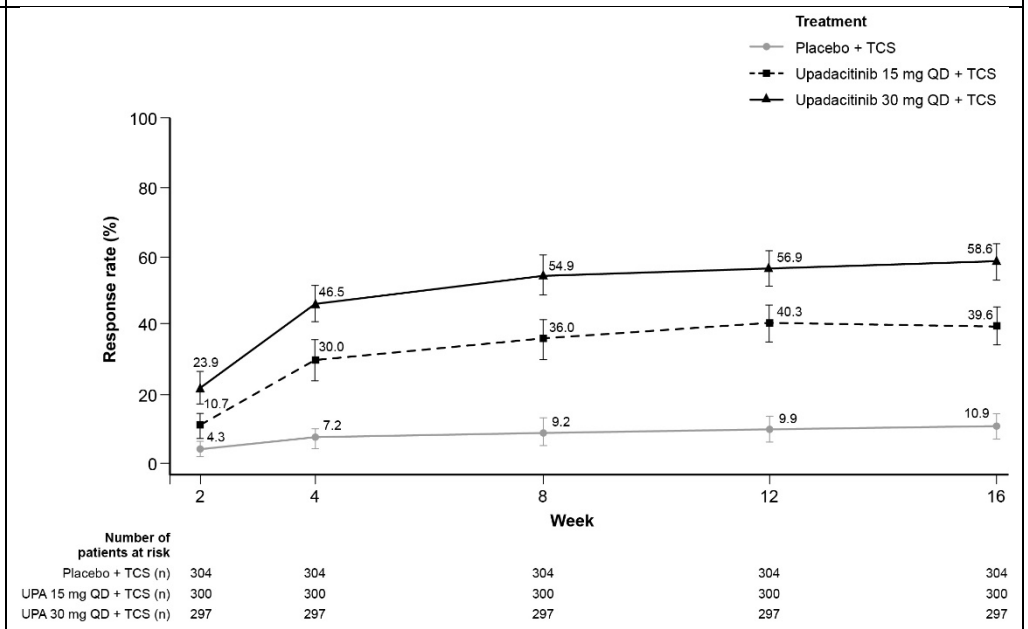
AD UP 1 –% of patients achieving EASI 75	AD UP 1 –% of patients achieving IGA 0/1 clear or almost clear
	

Table 13: Measure UP 1, Measure UP 2 and AD UP – Co-primary end-points EASI 75 and IGA 0 or 1 at week 16 (ITT population)

	EASI 75 at week 16			**IGA 0/1 clear or almost clear at week 16**		
Measure UP 1	Placebo	Upadacitinib 15 mg n (%) Adjusted difference, (95% CI), p value	Upadacitinib 30 mg n (%) Adjusted difference, (95% CI), p value	Placebo	Upadacitinib 15 mg n (%) Adjusted difference, (95% CI), p value	Upadacitinib 30 mg n (%) Adjusted difference, (95% CI), p value
All	N=281 46 (16.3%)	N=281 196 (69.6%) 53.3 (46.4, 60.2) p<0.001	N=285 227 (79.7%) 63.4 (57.1, 69.8) p<0.001	N=281 24 (8.4%)	N=281 135 (48.1%) 39.8 (32.2, 46.4) p<0.001	N=285 177 (62.0%) 53.6 (47.2, 60.0) p<0.001
Adolescents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Measure UP 2	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
All	N=278 37 (13.3%)	N=276 166 (60.1%) 46.9 (39.9, 53.9), p<0.001	N=282 206 (72.9%) 59.6 (53.1, 66.2), p<0.001	N=278 13 (4.7%)	N=276 107 (38.8%) 34.0 (27.8, 40.2), p<0.001	N=282 147 (52.0%) 47.4 (41.0, 53.7), p<0.001
Adolescents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AD UP	Placebo +TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg +TCS	Placebo +TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg +TCS
All	N=304 80 (26.3%)	N=300 194 (64.6%) 38.1 (30.8, 45.4), p<0.001	N=297 229 (77.1%) 50.6 (43.8, 57.4), p<0.001	N=304 33 (10.9%)	N=300 119 (39.6%) 28.5 (22.1, 34.9), p<0.001	N=297 174 (58.6%) 47.6 (41.1, 54.0), p<0.001
Adolescents	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AD: Atopic Dermatitis, CI: Confidence Interval, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, TCS: Topical Corticosteroids.

B.2.6.2 Primary end-points vs dupilumab

The primary end-point of achievement of EASI 75 at week 16 was achieved in Heads UP: significantly more participants achieved an EASI 75 response at week 16 (71.0% vs 61.1%, p=0.006)[49].

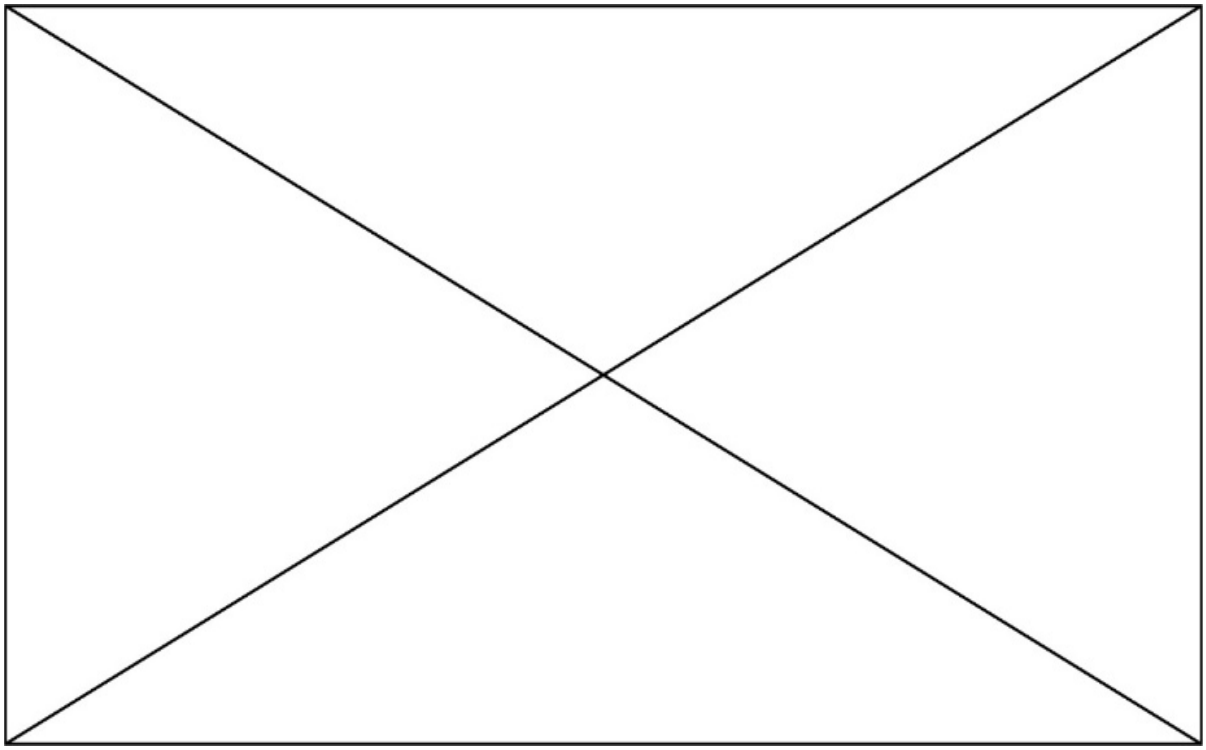
Table 14: Heads UP – Primary end-point EASI 75 at week 16 (ITT population)

	Dupilumab 300 mg n (%)	**Upadacitinib 30 mg n (%) Adjusted difference, (95% CI), p value**
Heads UP	N=344 210 (61.1%)	N=348 247 (71.0%) 10.0 (2.9, 17.0) p=0.006

CI: Confidence Interval

Onset of action with upadacitinib was rapid as demonstrated in Figure 10. There was a significant difference in response rate between upadacitinib and dupilumab as early as week 1.

Figure 10: Heads UP: primary end-point EASI 75 by visit during the double-blind period (ITT population)

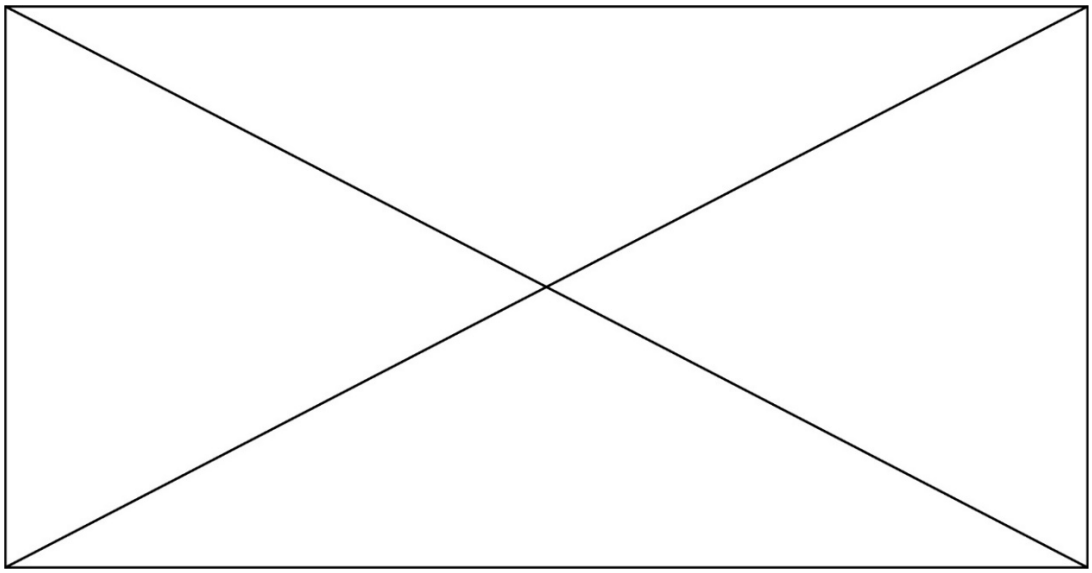


B.2.6.3 Key secondary efficacy end-points vs placebo

Table 18 lists the results of the key secondary end-points for Measure UP 1 and for AD UP. In the interests of space results for Measure UP 2 and additional end-points may be found in Appendix B, Section B.2.1.

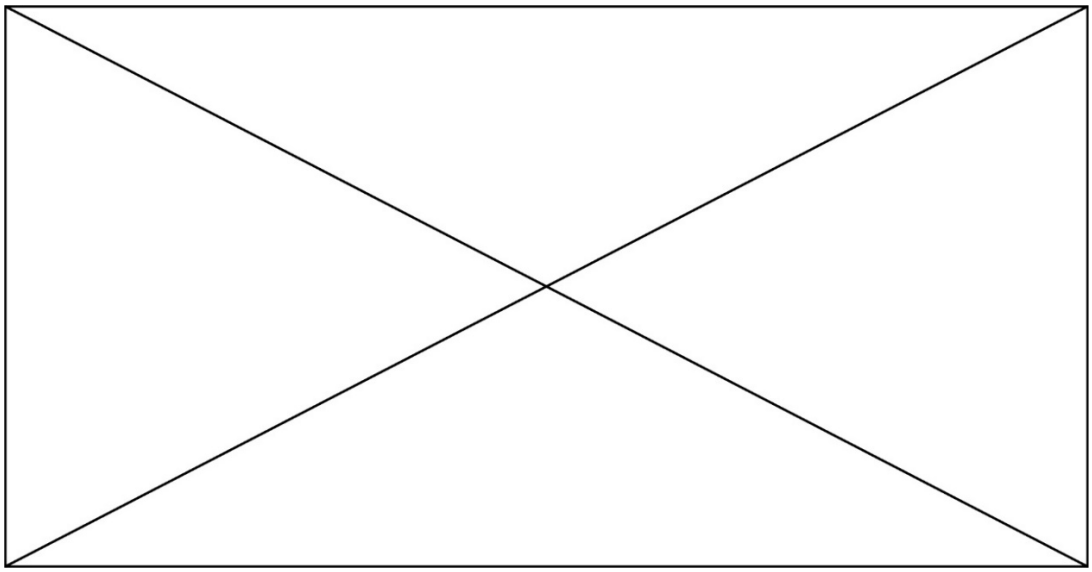
Improvements in the signs and symptoms of AD over the double-blind period are shown below in for each of the three registration studies, with further details for each end-point following in the copy below.

Figure 11: Measure UP 1: % of participants achieving end-point at the end of the double-blind period (16 weeks), all differences from placebo p<0.001



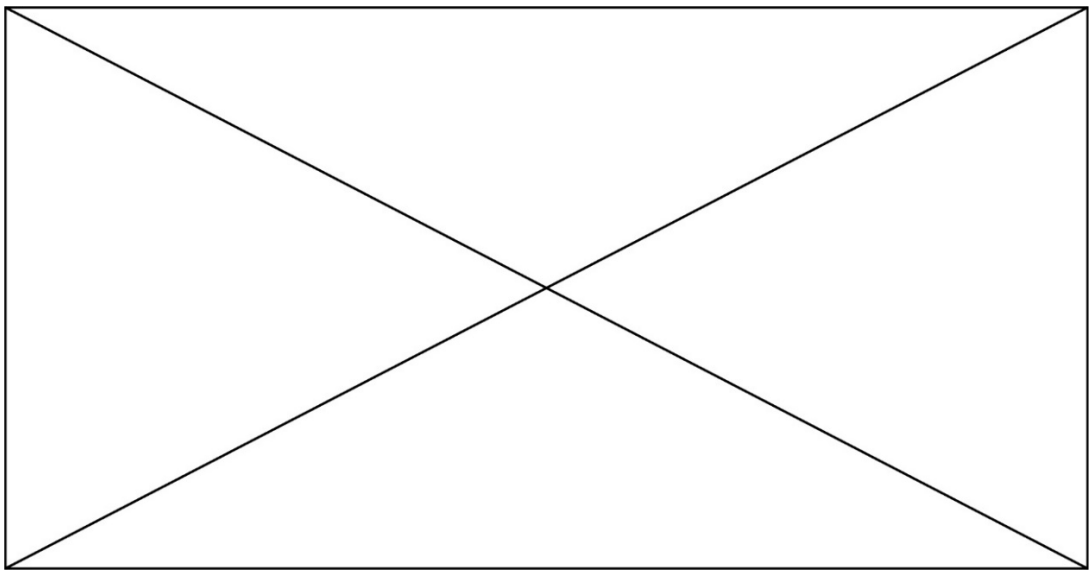
DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, POEM: Patient Oriented Eczema Measure

Figure 12: Measure UP 2: % of participants achieving end-point at the end of the double-blind period (16 weeks), all differences from placebo p<0.001



DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, POEM: Patient Oriented Eczema Measure

Figure 13: AD UP: % of participants achieving end-point at the end of the double-blind period (16 weeks), all differences from placebo p<0.001



DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, POEM: Patient Oriented Eczema Measure, TCS: Topical Corticosteroids

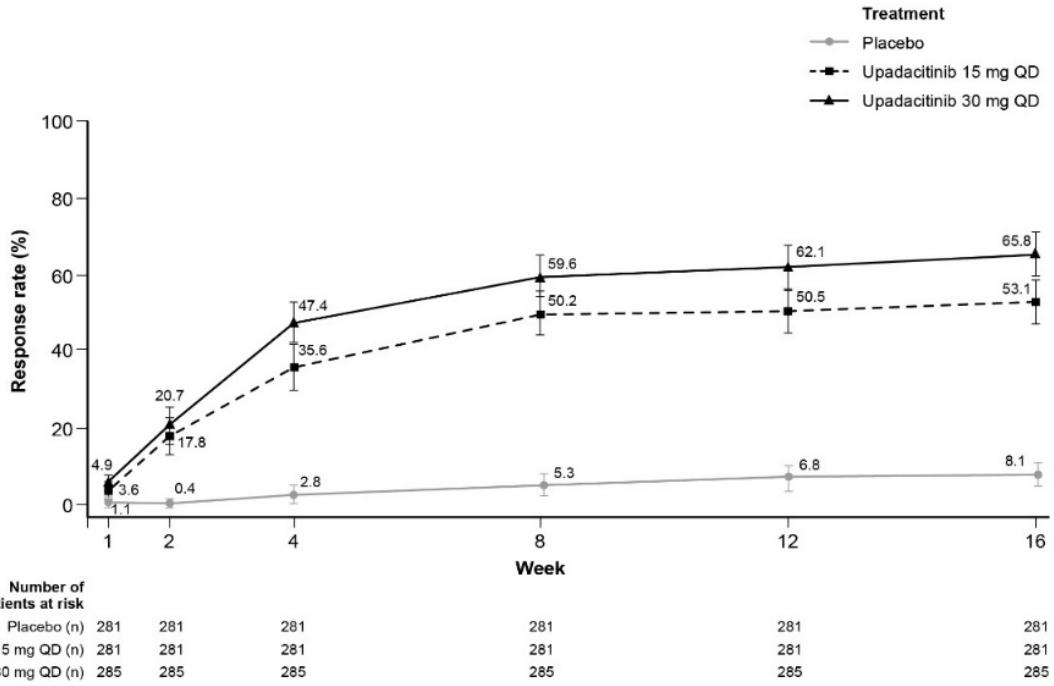
B.2.6.3.1 Skin clearance and disease activity measures

Results for the secondary end-points support the results of the co-primary end-points. Upadacitinib 15 mg or 30 mg rapidly clears skin and reduces disease flare as demonstrated by a significant improvement in skin clearance and reduction in the % of patients experiencing flare from around [redacted] in the monotherapy studies and from [redacted] in AD UP.

Figure 14 illustrates the rapid onset of action of both doses of upadacitinib, with a significant difference in the proportion of patients achieving EASI 90 (reduction in EASI score from baseline of 90%) seen by week 2. Figures illustrating achievement of EASI 100 may be found in Appendix B (Section B.2.2). Improvements in skin clearance were maintained for the duration of the double-blind period.

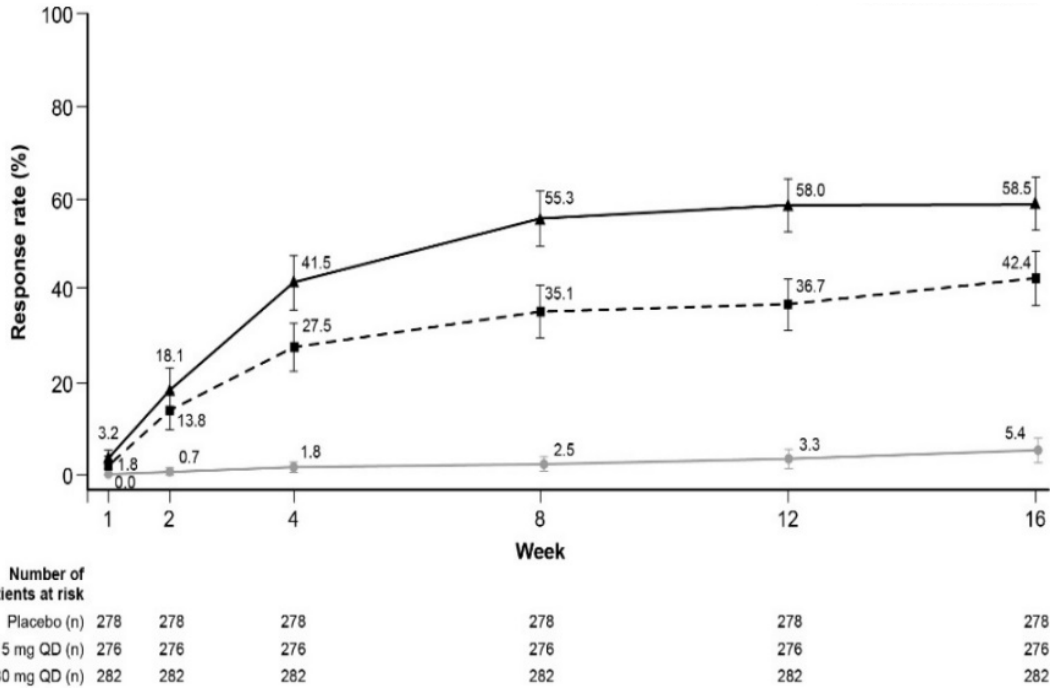
Figure 14: % of participants achieving EASI 90 by visit during the double-blind period, all differences from placebo p<0.001 from week 2

Measure UP 1



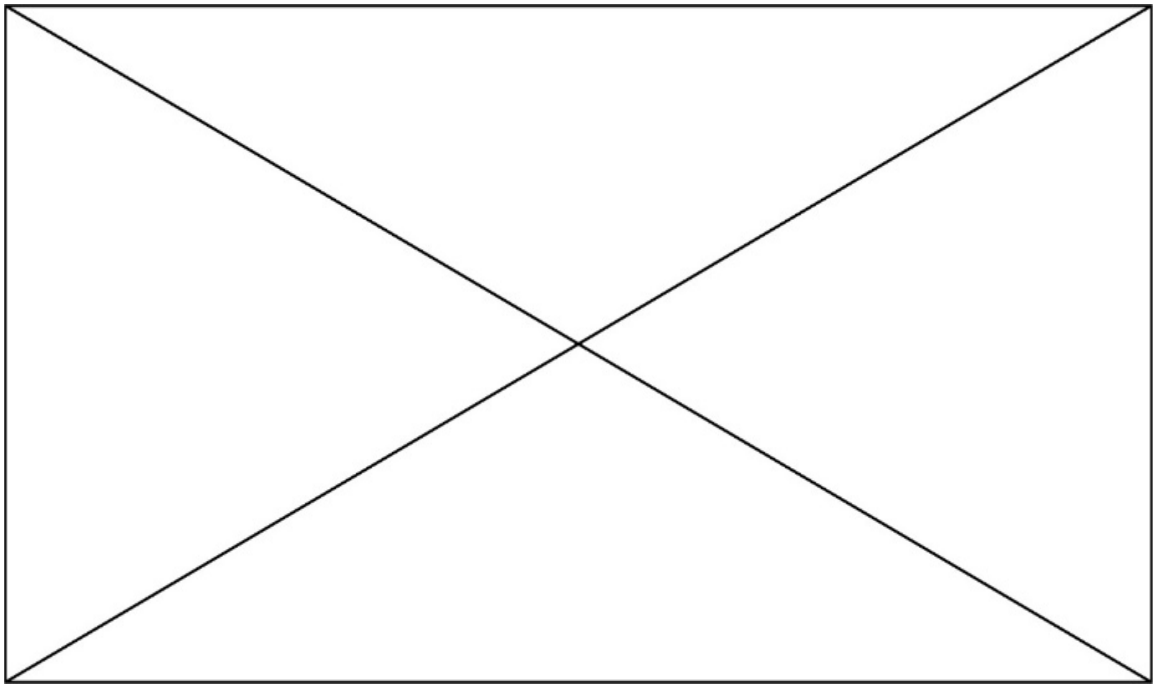
Number of patients at risk						
Placebo (n)	281	281	281	281	281	281
UPA 15 mg QD (n)	281	281	281	281	281	281
UPA 30 mg QD (n)	285	285	285	285	285	285

Measure UP 2



Number of patients at risk						
Placebo (n)	278	278	278	278	278	278
UPA 15 mg QD (n)	276	276	276	276	276	276
UPA 30 mg QD (n)	282	282	282	282	282	282

AD UP 2



B.2.6.3.2 Patient reported disease symptom scores: pruritus

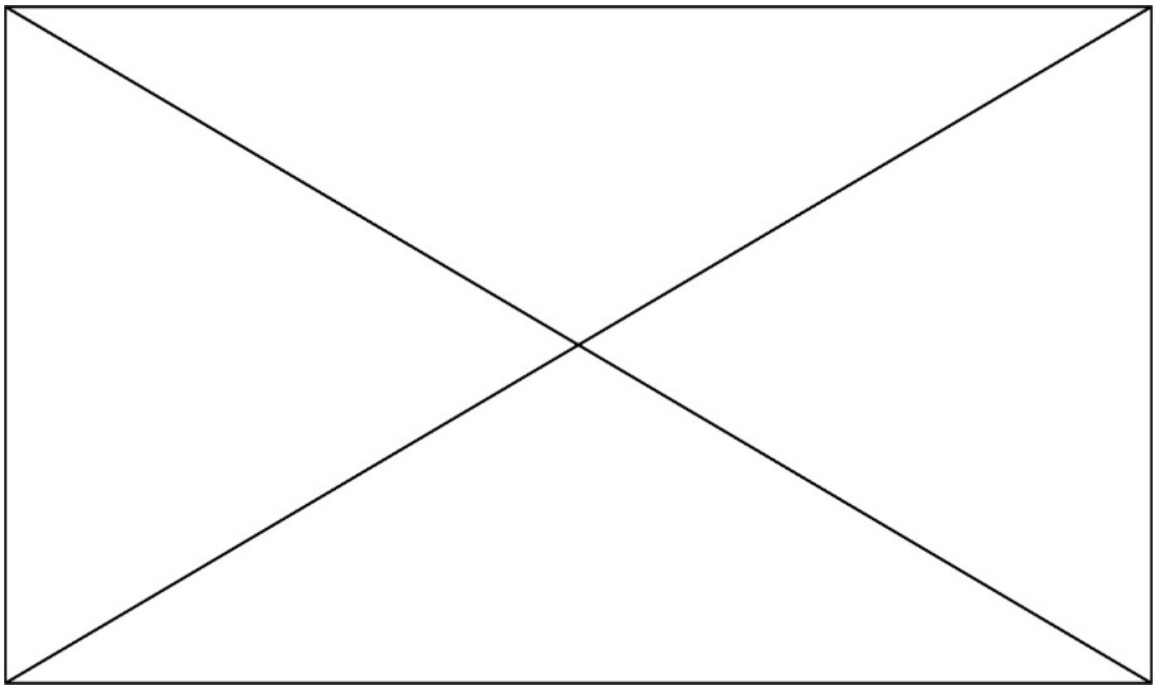
WP-NRS considers itch on a scale from no itch (0) to worst imaginable itch (10), over the previous 24 hours. The MCID for WP-NRS is between 3 and 4[55].

Upadacitinib 15 mg or 30 mg minimises itch within days; there is a significant reduction in itch within 1 day of starting treatment for patients receiving upadacitinib 30 mg and within 2 days for those receiving 15 mg.

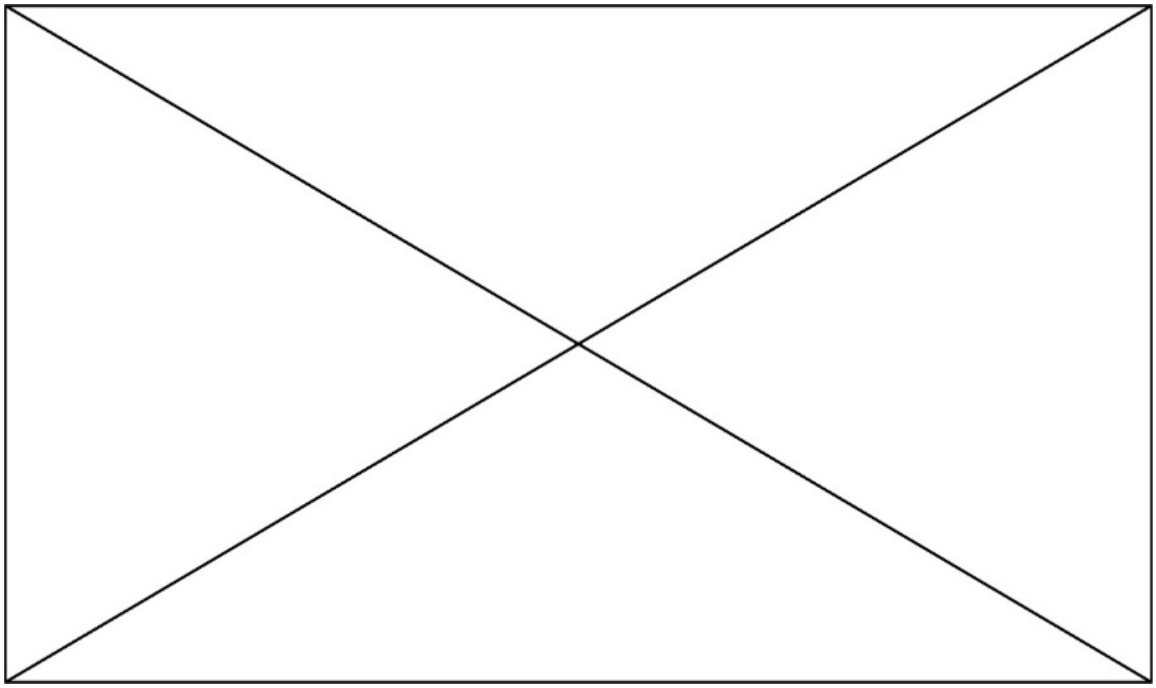
Figure 15 illustrates the reduction in itch and shows a rapid reduction which was sustained for the duration of the double-blind period. Figures illustrating the achievement of a reduction in WP-NRS ≥4 from baseline may be found in Appendix B.

Figure 15: % change from baseline in WP-NRS (weekly average) by visit during the double-blind period, all differences from placebo p<0.001

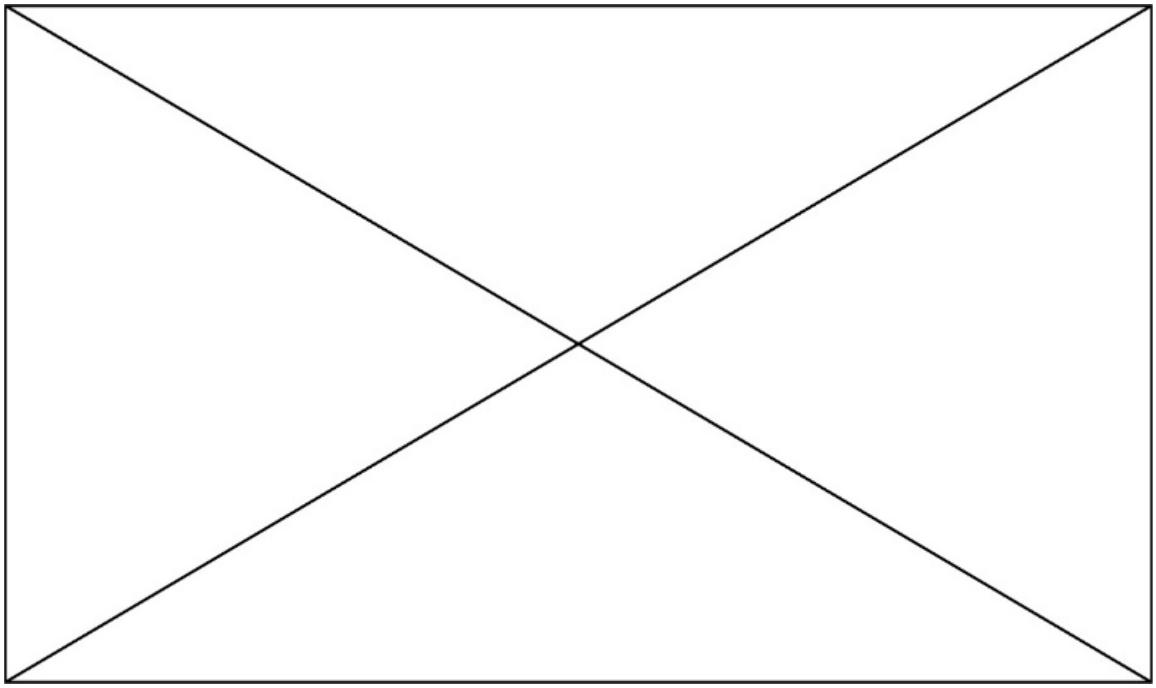
Measure UP 1



Measure UP 2



AD UP



B.2.6.3.3 Quality of life

QOL was measured using skin-specific QOL measures: DLQI in participants aged ≥16 years and CDLQI for those younger than 16. UK data recommends that a MCID of 4 is used in inflammatory skin diseases, for both adults and adolescents[56]. The study programme also used EQ-5D in the overall population to examine the impact of upadacitinib on general QOL.

The improvement in symptoms and impact of AD on the patient is reflected in a significant improvement in all measures of QOL in both the overall and adolescent populations with both doses of upadacitinib.

A significant improvement in QOL was seen as early as the first post-baseline assessment (week 2) for DLQI (LS: Least Squares, SE: Standard Error

Figure 16) and for CDLQI (see Appendix B, Section B.2.2) and maintained for the duration of the double-blind period.

A significant improvement in EQ-5D was observed at week 16, as shown below in Table 15.

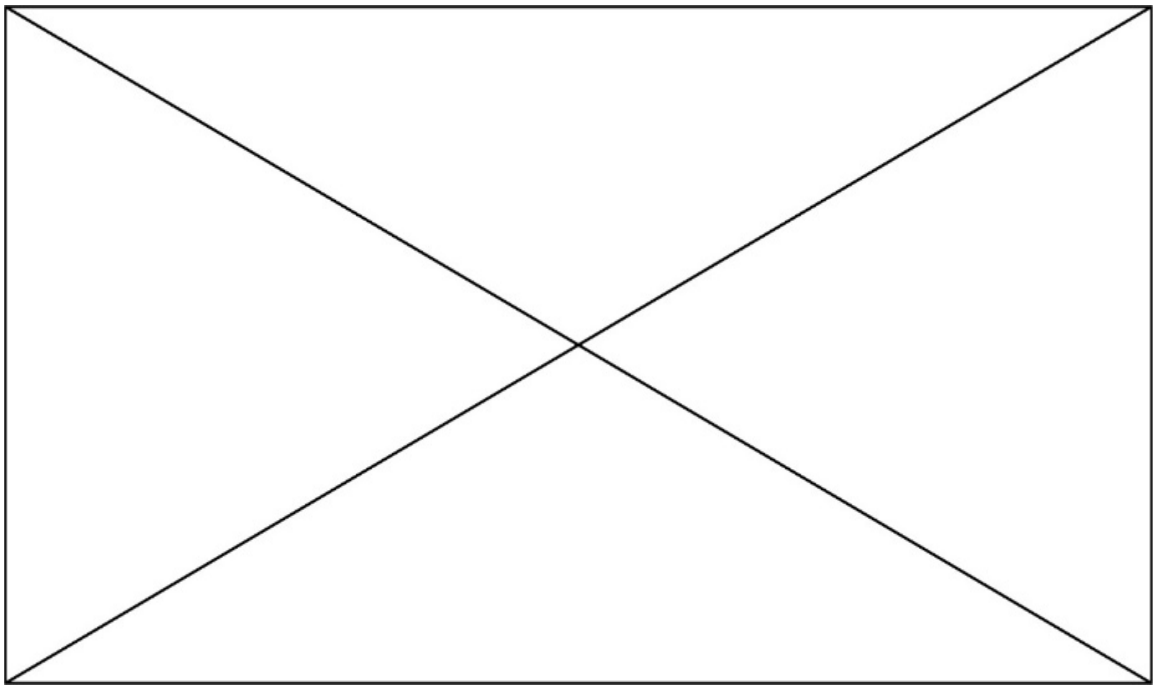
Table 15: Change from baseline in EQ-5D-5L at week 16

	Placebo (N) LS mean (SE)	Upadacitinib 15 mg (N) LS mean (SE) LS mean difference (SE) p value	Upadacitinib 30 mg (N) n (%) LS mean difference (SE) p value
Measure UP 1	[redacted]	[redacted]	[redacted]
Measure UP 2	[redacted]	[redacted]	[redacted]
Heads UP	[redacted]	[redacted]	[redacted]

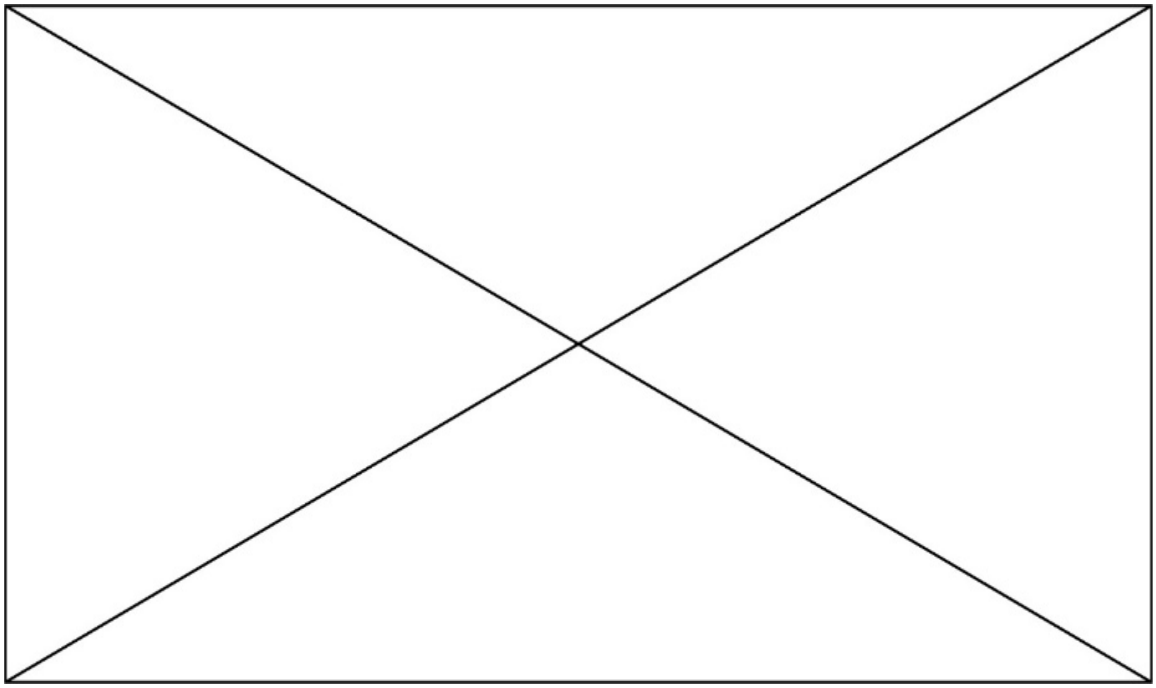
LS: Least Squares, SE: Standard Error

Figure 16: % change from baseline in DLQI by visit during the double-blind period

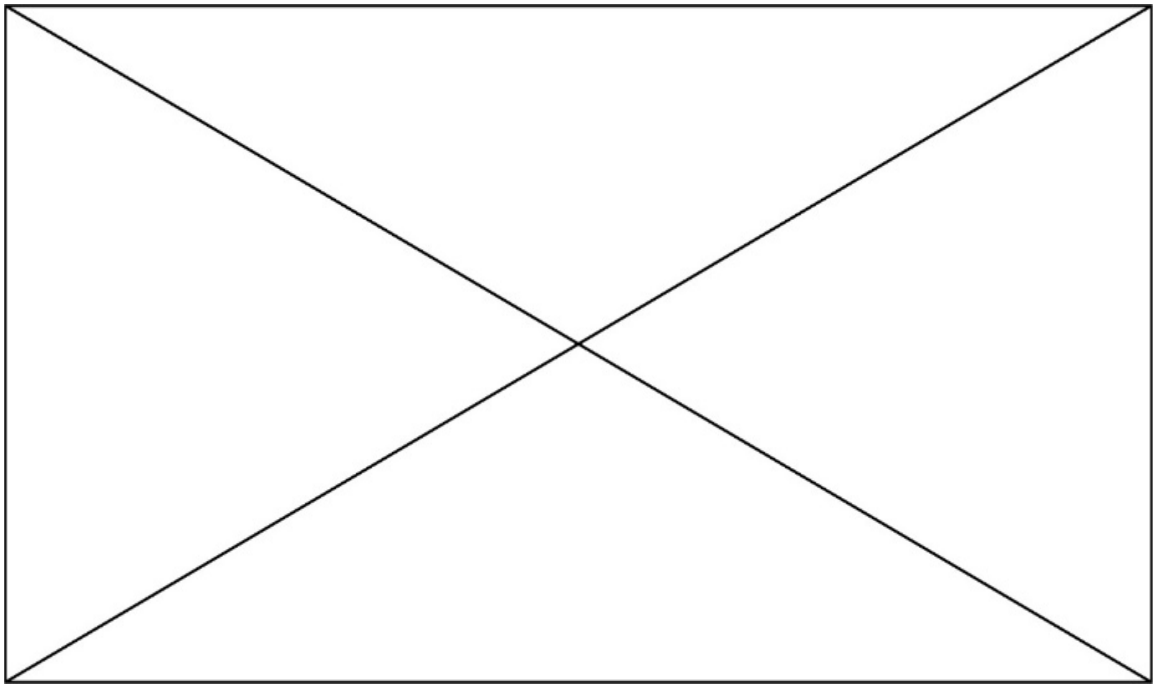
Measure UP 1



Measure UP 2



AD UP



B.2.6.3.4 Mental health

Anxiety and depression as measured by HADS total score significantly improved with both doses of upadacitinib. The first available data was at 12 weeks and showed a significant improvement in anxiety and depression, which was maintained to 16 weeks.

Table 16: Change from baseline in HADS total score at week 16

	Placebo **(N)** **LS mean (SE)**	**Upadacitinib 15 mg** **(N)** **LS mean (SE)** **LS mean difference (SE)** **p value**	**Upadacitinib 30 mg** **(N)** **n (%)** **LS mean difference (SE)** **p value**
Measure UP 1	[redacted]	[redacted]	[redacted]
Measure UP 2	[redacted]	[redacted]	[redacted]
AD UP	[redacted]	[redacted]	[redacted]

LS: Least Squares, SE: Standard Error

B.2.6.3.5 Symptoms and impact on the patient

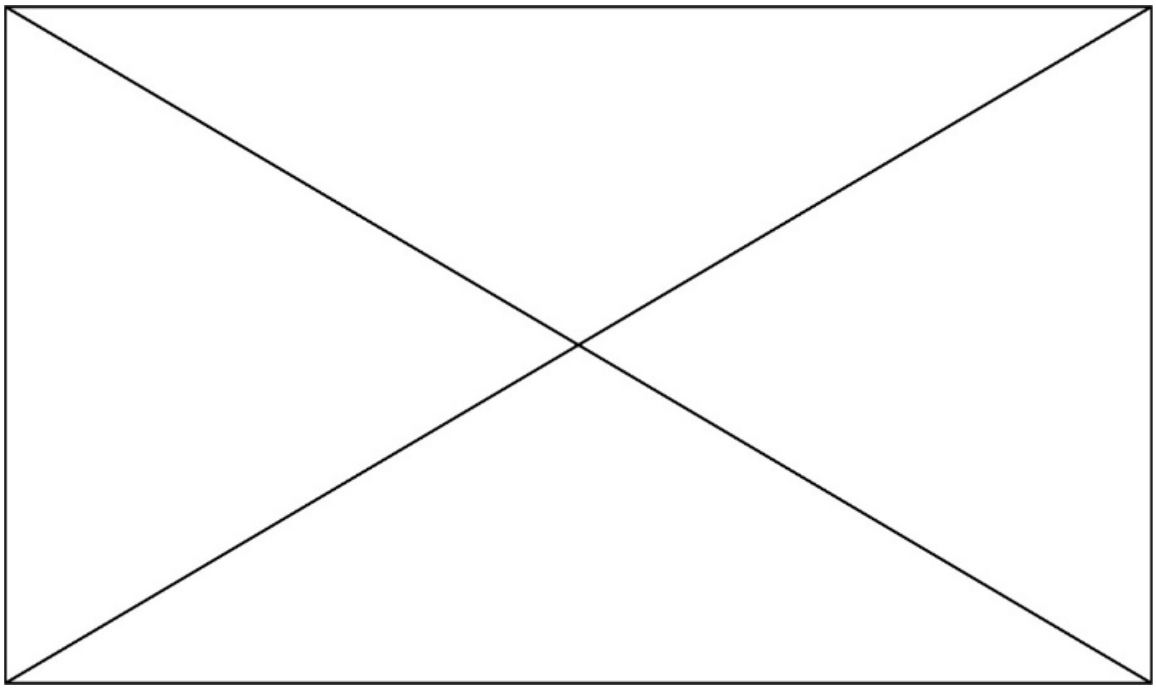
B.2.6.3.5.1 POEM

POEM is a simple, self-administered AD validated questionnaire, focusing frequency of symptoms and sleep disturbance as experienced by the patient. The MCID of POEM is reported as between 3 and 4 points[57].

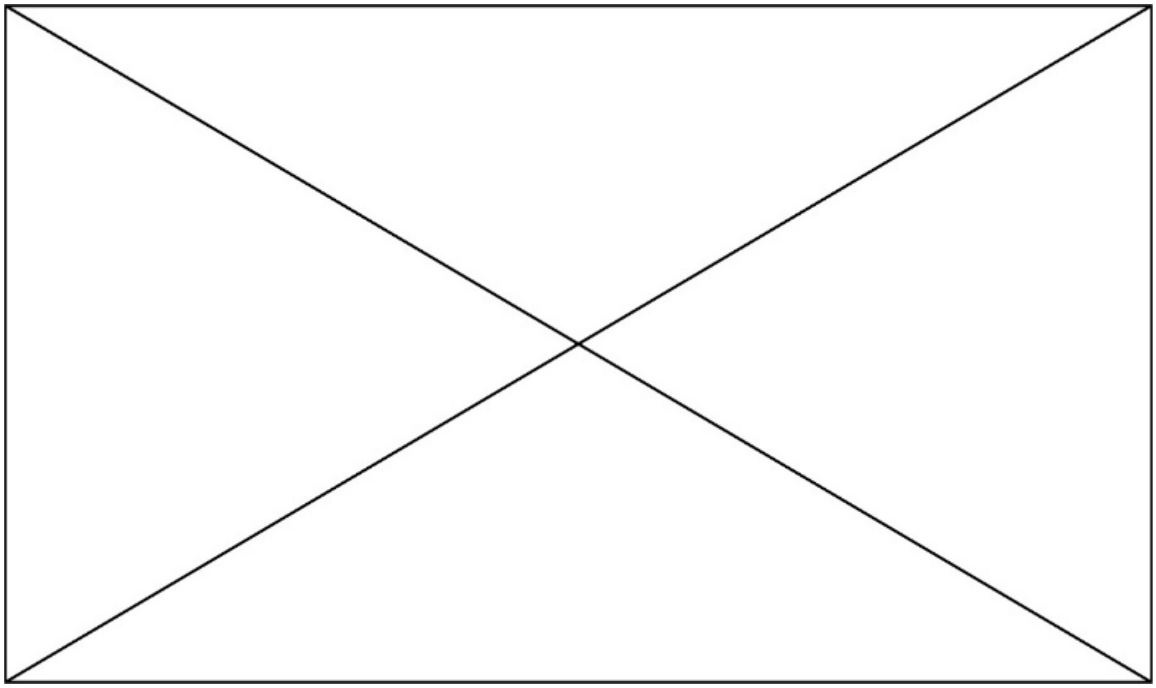
[redacted]

Figure 17: % change from baseline in POEM by visit during the double-blind period

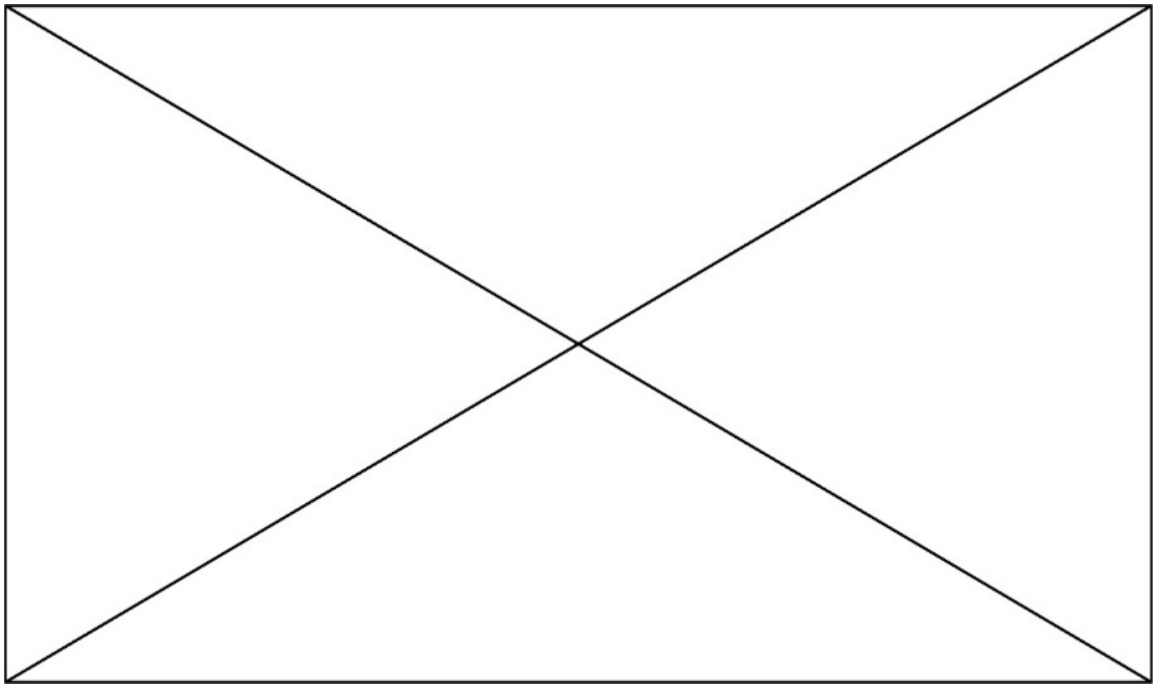
Measure UP 1



Measure UP 2



AD UP



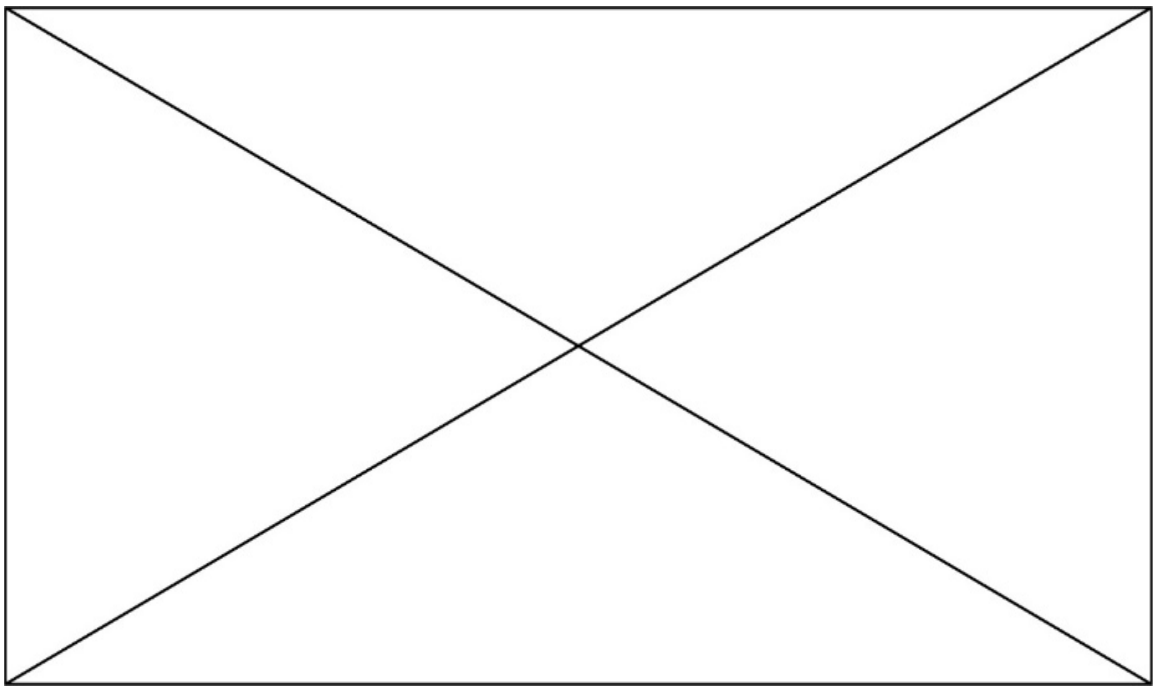
B.2.6.3.5.2 ADerm-IS and ADerm-SS

The ADerm-SS and ADerm-IS assess the patient-reported symptoms of AD and the impact of AD, respectively, and were included in the registration studies. Included in these instruments is an assessment of skin pain (ADerm-SS Skin Pain; MCID=4 points) and the impact of AD on sleep (ADerm-IS Sleep; MCID=12 points).

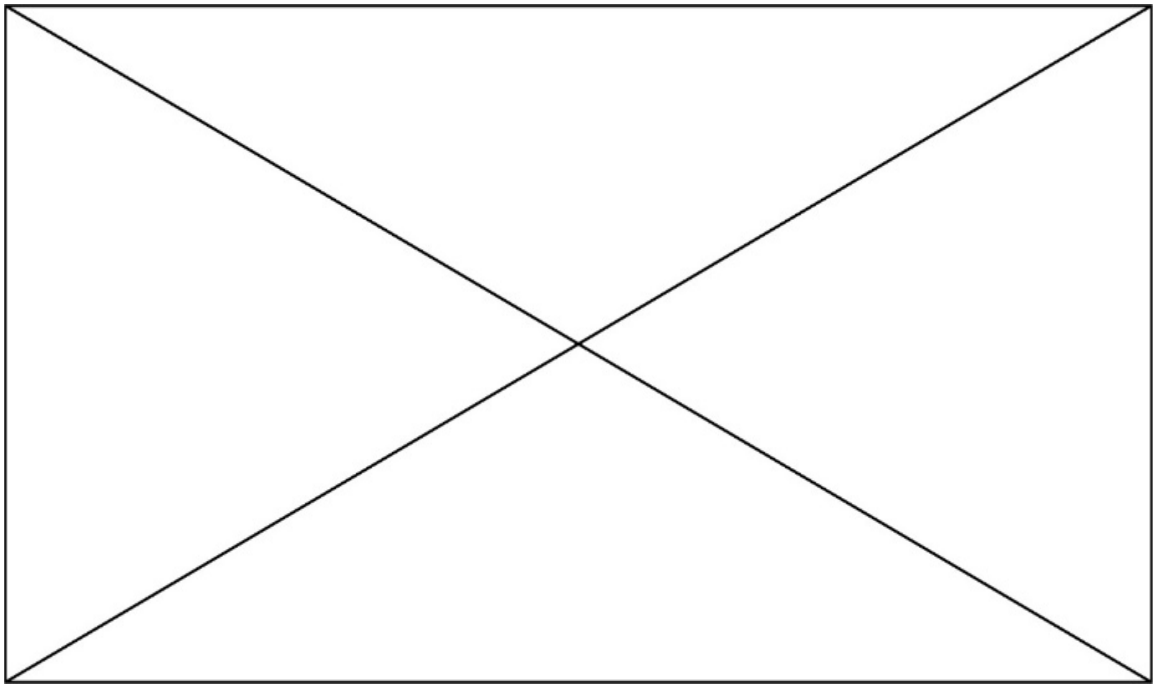
A significant improvement in sleep and skin pain was seen with upadacitinib 15 mg and 30 mg as early as week 1 of treatment and this improvement was maintained for the duration of the double-blind period (Figure 18 for sleep and Figure 19 for skin pain).

Figure 18: % of participants achieving an improvement (reduction) in ADerm-IS Sleep Domain ≥12 from baseline at week 16 for participants with ADerm-IS Sleep Domain ≥ 12 at baseline by visit during the double-blind period

Measure UP 1



Measure UP 2



AD UP

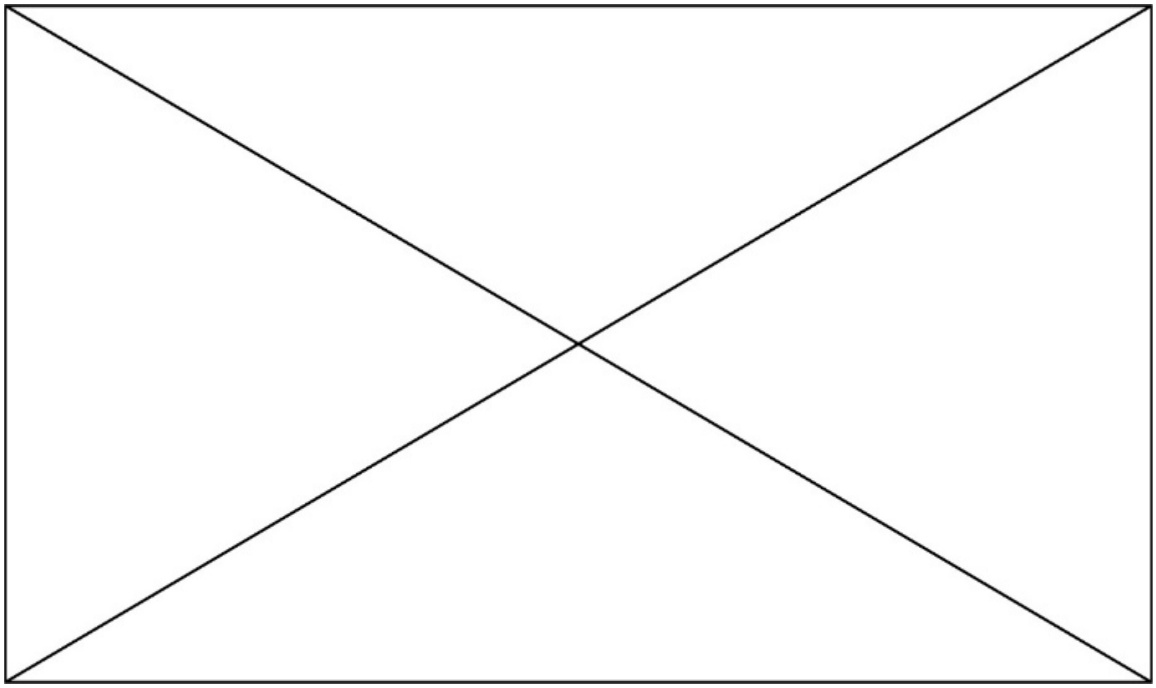
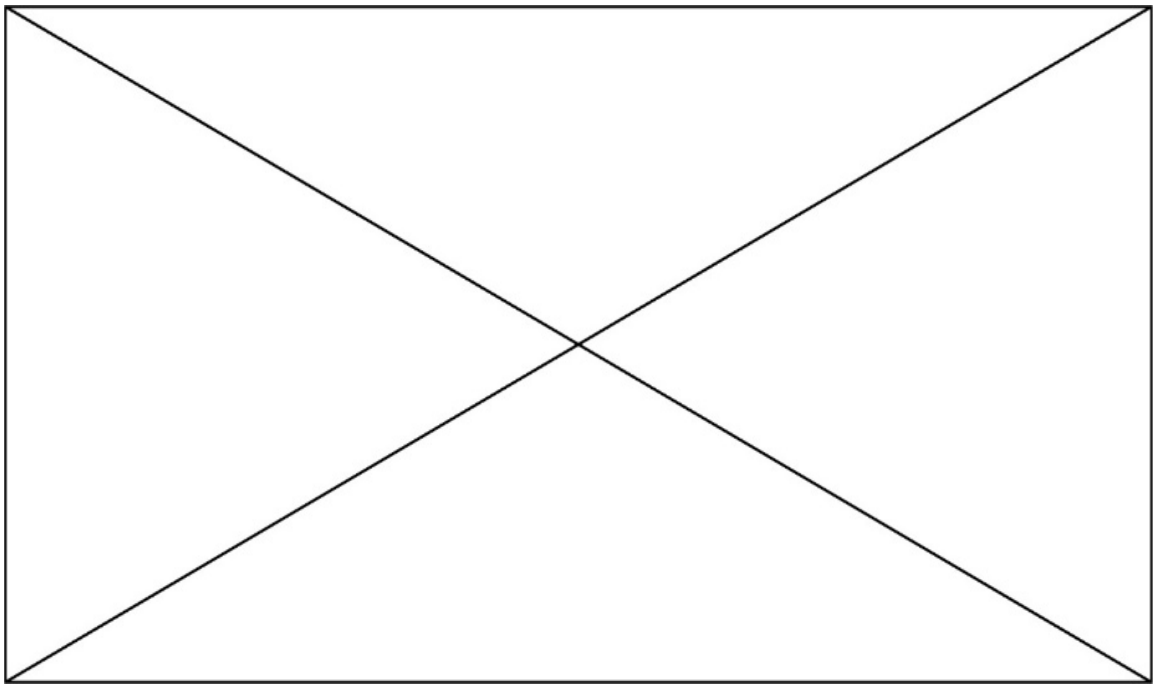
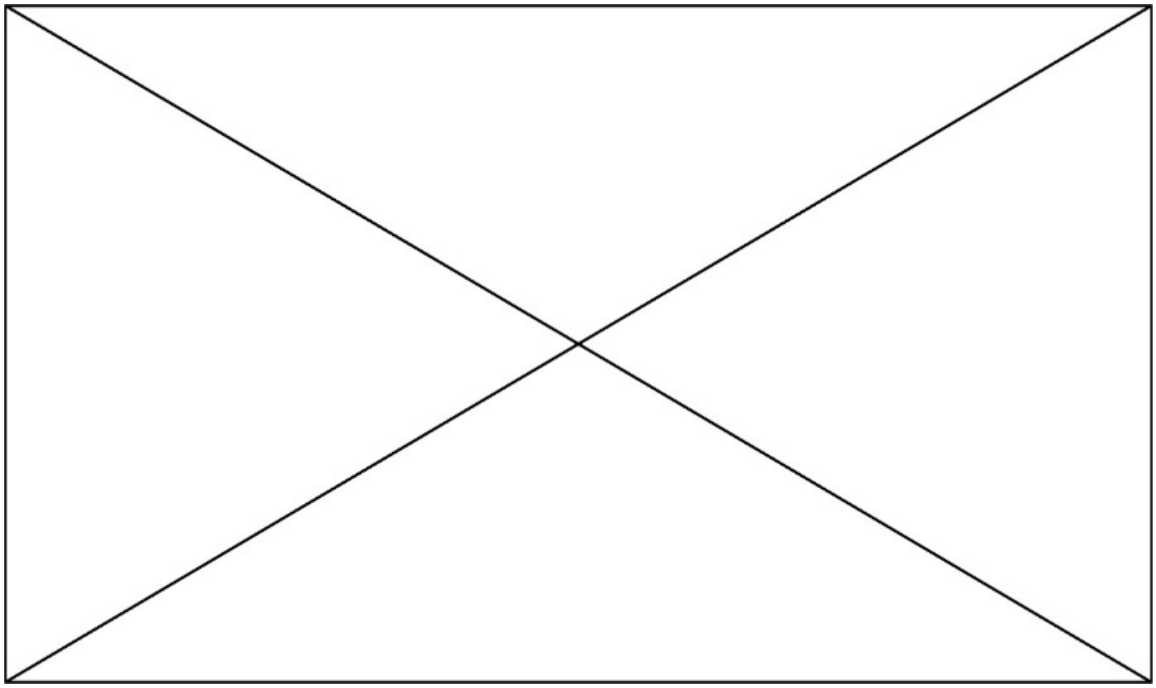


Figure 19: % of participants achieving an improvement (reduction) in ADerm-SS Skin Pain ≥4 from baseline at week 16 for participants with ADerm-SS Skin Pain ≥4 at baseline

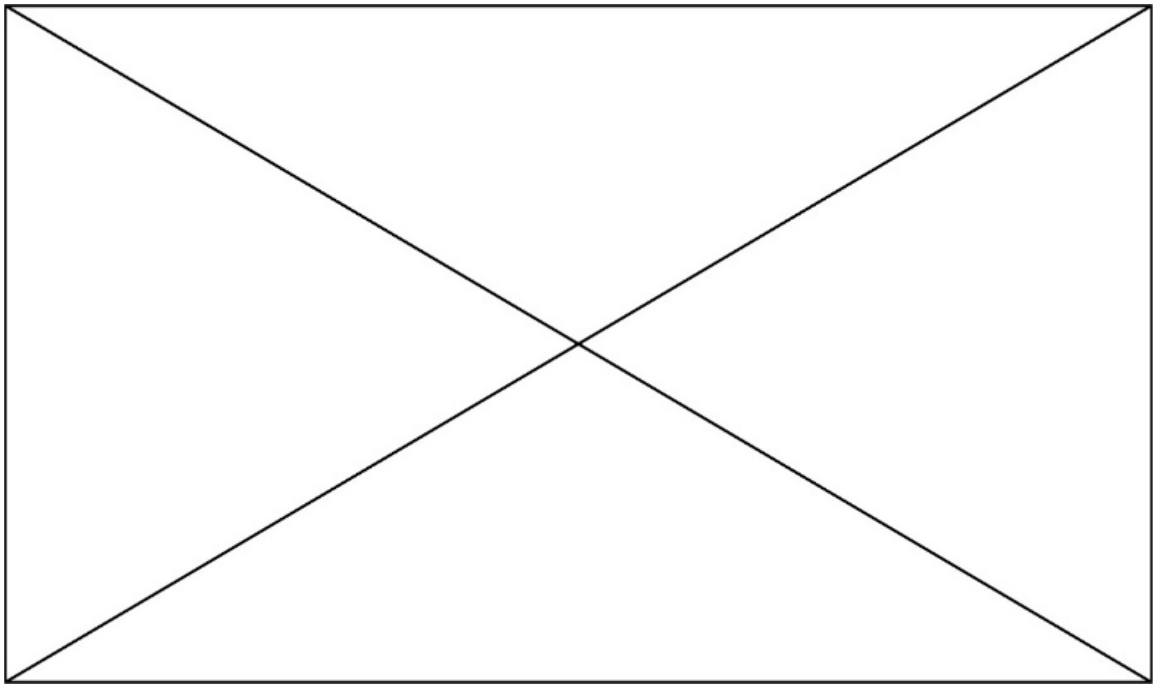
Measure UP 1



Measure UP 2



AD UP



B.2.6.3.6 Use of rescue medication

The use of rescue medication was significantly reduced in patients receiving upadacitinib vs placebo.

In the monotherapy studies [redacted] of patients receiving placebo in Measure UP 1 and [redacted] in Measure UP 2 required at least one rescue medication during the double-blind period. In contrast, [redacted] of patients receiving upadacitinib 15 mg and [redacted] receiving upadacitinib 30 mg in Measure UP 1 and [redacted] and [redacted] in Measure UP 2 required rescue mediation.

In AD UP, the combination study, [redacted] of patients receiving placebo + TCS required rescue therapy, vs [redacted] and [redacted] of patients receiving upadacitinib 15 mg and 30 mg respectively.

TCS were the most common form of rescue medication, followed by systemic therapy.

Table 17: Use of rescue medication during the double-blind period

	Measure UP 1			Measure UP 2			AD UP		
	Placebo n=281	**UPA 15 mg n=281**	**UPA 30 mg n=285**	**Placebo n=278**	**UPA 15 mg n=276**	**UPA 30 mg n=282**	**Placebo +TCS n=304**	**UPA 15 mg + TCS n=300**	**UPA 30 mg + TCS N=297**
Any rescue mediation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of rescue medication (patients may receive more than one type of treatment)									
	Placebo n=173	UPA 15 mg n=35	UPA 30 mg n=22	Placebo n=155	UPA 15 mg n=31	UPA 30 mg n=23	Placebo +TCS n=91	UPA 15 mg + TCS n=18	UPA 30 mg + TCS N=16
TCS (Measure UP 1 and 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High potency TCS (AD UP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other topical therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-biologic immunomodulating systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TSC: Topical Corticosteroids, TCI: Topical Calcineurin Inhibitors, UPA: Upadacitinib

B.2.6.3.7 TCS sparing

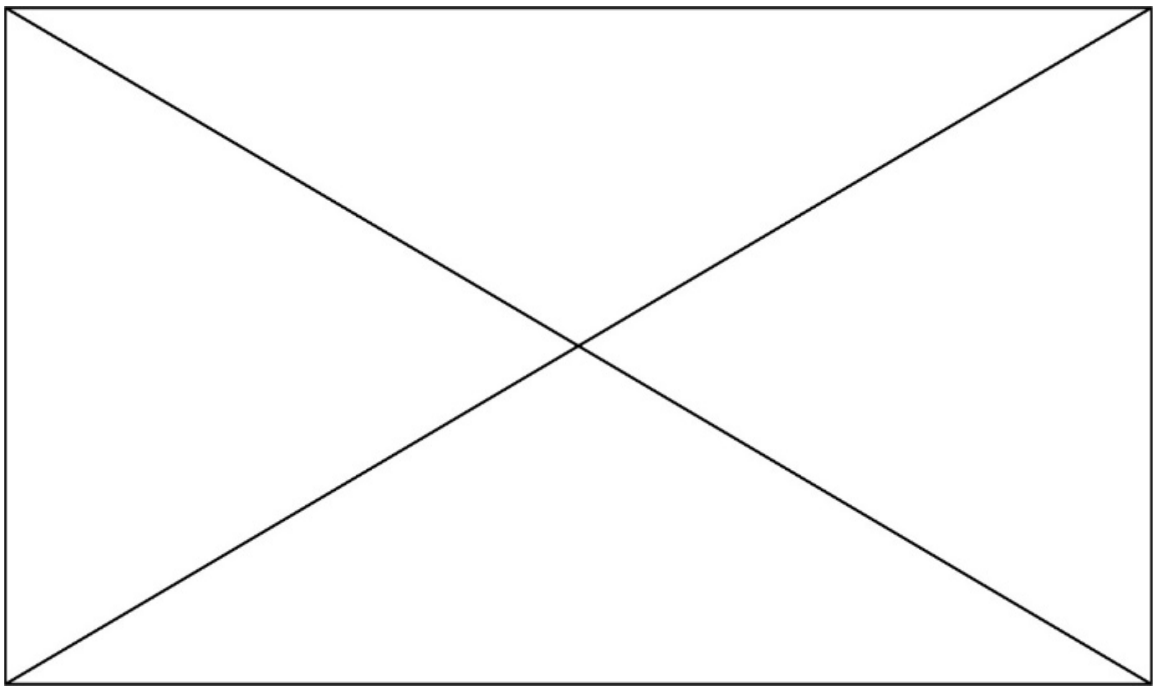
Participants in AD UP were treated with concomitant TCS. Overall results for skin clearance, pruritus, QOL, mental health and impact of symptoms on the patient were similar between the monotherapy studies (Measure UP 1 and Measure UP 2) and the combination study (AD UP), indicating that TCS may not be required to improve the efficacy of upadacitinib treatment.

AD UP also assessed whether upadacitinib could reduce the use of TCS, whilst still achieving symptomatic control. During the double-blind period the mean number of days free from all TCS and achieving an EASI 75 response was 47 days (median: [redacted] days) with upadacitinib 30 mg, 33.53 days (median [redacted] days) with upadacitinib 15 mg and 7.88 days (median: [redacted] days) with placebo.

Looking specifically at patients using medium and high potency TCS and achieving an EASI 75 response, the mean number of TCS-free days was [redacted] days(median: xx days) with upadacitinib 30 mg, [redacted] days (median: [redacted] days) with upadacitinib 15 mg group and [redacted] days (median [redacted] days) with placebo.

Median time to first discontinuation of all TCS with an EASI 75 response during the double-blind period was 57 days with upadacitinib 30 mg, 88 days with upadacitinib 15 mg and not reached for the placebo group, see Figure 20.

Figure 20: Time to first discontinuation of all TCS in patients with an EASI 75 response during the double-blind period



CI: Confidence Interval, EASI: Eczema Area and Severity Index, PBO: Placebo, QD: Once daily, TCS: Topical Corticosteroids, UPA: Upadacitinib

Table 18: Measure UP 1: secondary efficacy end-points (overall population)[45]

Measure UP 1	Placebo (n=281) n (%) or LS mean (SE)	Upadacitinib 15 mg (n=281) n (%) or LS mean (SE) Adjusted diff (95% CI) or LS mean difference (SE) p value	Upadacitinib 30 mg (n=285) n (%) Adjusted diff (95% CI) or LS mean difference (SE) p value	page in CSR
Skin clearance and disease activity measures				
% change in EASI from baseline at week 16	[redacted]	[redacted]	[redacted]	1162
% of participants achieving EASI 50 at week 16	[redacted]	[redacted]	[redacted]	907
% of participants achieving EASI 75 at week 2	N=281 10 (3.6%)	N=281 107 (38.1%) 34.5 (28.6, 40.5), p<0.001	N=285 135 (47.4%) 43.9 (37.7, 50.0), p<0.001	681
% of participants achieving EASI 75 at week 4	N=281 25 (8.9%)	N=281 175 (62.3%) 53.4 (46.9, 59.9), p<0.001	N=285 214 (75.1%) 66.3 (60.3, 72.2), p<0.001	684
% of participants achieving EASI 90 at week 4	N=281 8 (2.8%)	N=281 100 (35.6%) 32.8 (27.0, 38.7), p<0.001	N=285 135 (47.4%) 44.5 (38.4, 50.6), p<0.001	961
% of participants achieving EASI 90 at week 16	N=281 23 (8.1%)	N=281 149 (53.1%) 45.1 (38.6, 51.7), p<0.001	N=285 187 (65.8%) 57.8 (51.5, 64.1), p<0.001	970
% of participants experiencing a flare (Increase of EASI by ≥6.6 points from baseline) prior to use of rescue medication for participants with EASI ≤65.4 at baseline	[redacted]	[redacted]	[redacted]	1115

% of participants achieving IGA of **0** (clear skin) with a reduction from baseline of ≥2 points at week 16	[redacted]	[redacted]	[redacted]	1524
% change from baseline in SCORAD at week 16	[redacted]	[redacted]	[redacted]	2950
Patient reported disease symptom scores: pruritus				
Improvement (% change) from baseline of WP-NRS at week 16	[redacted]	[redacted]	[redacted]	2235
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at day 2 for participants with WP-NRS ≥ 4 at baseline	N=270 10 (3.7%)	N=275 29 (10.5%) 6.8 (2.5, 11.0), p=0.002	N=279 33 (11.8%) 8.1 (3.8, 12.5), p<0.001	1911
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 1 for participants with WP-NRS ≥ 4 at baseline	N=272 1 (0.4%)	N=274 41 (15.0%) 14.6 (10.3, 18.8), p<0.001	N=280 55 (19.6%) 19.2 (14.6, 23.9), p<0.001	1566
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 16 for participants with WP-NRS ≥ 4 at baseline	N=272 32 (11.8%)	N=274 143 (52.2%) 40.5 (33.5, 47.5), p<0.001	N=280 168 (60.0%) 48.2 (41.3, 55.0), p<0.001	1611
Patient reported disease symptom scores: POEM				
% of participants achieving an improvement (reduction) in POEM ≥ 4 from baseline at week 16 for participants with POEM ≥4 at baseline	N=276 63 (22.8%)	N=278 209 (75.0%) 52.3 (45.2, 59.4), p<0.001	N=280 228 (81.4%) 58.6 (51.9, 65.3), p<0.001	2458
Change from baseline in POEM at week 16	[redacted]	[redacted]	[redacted]	2576
QOL				
% of participants aged ≥ 16 years old at screening achieving an improvement (reduction) in DLQI ≥ 4 from baseline at week 16 for participants with DLQI ≥ 4 at baseline	[redacted]	[redacted]	[redacted]	2619

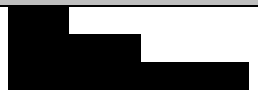
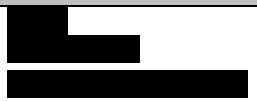
% of participants aged ≥16 years old at screening achieving score of 0/1 in DLQI among participants with DLQI >1 at baseline at week 16	[redacted]	[redacted]	[redacted]	2661
Change from baseline in DLQI among participants aged ≥16 years old at screening at week 16	[redacted]	[redacted]	[redacted]	2746
% of participants aged <16 years old at screening achieving score of 0/1 in CDLQI among participants with CDLQI >1 at baseline at week 16	[redacted]	[redacted]	[redacted]	2789
Change from baseline in CDLQI among participants aged <16 years old at screening at week 16	[redacted]	[redacted]	[redacted]	2865
Change from baseline in EQ-5D-5L at week 16	[redacted]	[redacted]	[redacted]	6362
Mental health				
Change from baseline in HADS total score at week 16	[redacted]	[redacted]	[redacted]	3126
Symptoms and impact on the patient				
% of participants achieving an improvement (reduction) in ADerm-IS sleep domain score ≥12 (MCID) from baseline at week 16 for participants with ADerm-IS sleep domain score ≥ 12 at baseline	[redacted]	[redacted]	[redacted]	3279
% of participants achieving an improvement (reduction) in ADerm-SS skin pain score ≥4 (MCID) from baseline at week 16 for participants with ADerm-SS skin pain score ≥4 at baseline	[redacted]	[redacted]	[redacted]	4695

ADerm-IS: Atopic Dermatitis Impact Scale, ADerm-SS: Atopic Dermatitis Symptom Scale, CI: Confidence Interval, CSR: Clinical Study Report, CDLQI: Children's Dermatology Life Quality Index, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EQ-5D-5L:European Quality of Life-5 Dimensions 5 Levels, HADS: Hospital Anxiety and Depression Scale, IGA: Investigator Global Assessment, MCID: Minimal Clinically Important Difference, , POEM: Patient Oriented Eczema Measure, QOL: Quality of Life, SE: Standard Error, SCORAD: Scoring Atopic Dermatitis, WP-NRS: Worst Pruritus Numerical Rating Scale

Table 19: AD UP: secondary efficacy end-points (overall population)[47]

AD UP	Placebo +TCS (n=304) n (%) or LS mean (SE)	Upadacitinib 15 mg +TCS (n=300) n (%) or LS mean (SE) Adjusted diff (95% CI) or LS mean difference (SE) p value	Upadacitinib 30 mg +TCS (n=297) n (%) Adjusted diff (95% CI) or LS mean difference (SE) p value	page in CSR
Skin clearance and disease activity measures				
% change in EASI from baseline at week 16	[redacted]	[redacted]	[redacted]	1159
% of participants achieving EASI 50 at week 16	[redacted]	[redacted]	[redacted]	859
% of participants achieving EASI 75 at week 2	N=304 21 (6.9%)	N=300 93 (31.0%) 24.0 (18.1, 29.9), p<0.001	N=297 131 (44.1%) 37.2 (31.0, 43.3), p<0.001	639
% of participants achieving EASI 75 at week 4	N=304 45 (14.8%)	N=300 176 (58.7%) 43.8 (37.0, 50.5), p<0.001	N=297 215 (72.4%) 57.6 (51.2, 63.9), p<0.001	642
% of participants achieving EASI 90 at week 4	[redacted]	[redacted]	[redacted]	901
% of participants achieving EASI 90 at week 16	N=304 40 (13.2%)	N=300 128 (42.8%) 29.5 (22.8, 36.3), p<0.001	N=297 187 (63.1%) 49.9 (43.3, 56.4), p<0.001	910
% of participants experiencing a flare (Increase of EASI by ≥6.6 points from baseline) prior to use of rescue medication for participants with EASI ≤65.4 at baseline	[redacted]	[redacted]	[redacted]	1040

% of participants achieving IGA of **0** (clear skin) with a reduction from baseline of ≥2 points at week 16	[redacted]	[redacted]	[redacted]	1432
% change from baseline in SCORAD at week 16	[redacted]	[redacted]	[redacted]	2681
Patient reported disease symptom scores: pruritus				
Improvement (% change) from baseline of WP-NRS at week 16	[redacted]	[redacted]	[redacted]	1994
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at day 2 for participants with WP-NRS ≥ 4 at baseline	N=267 2 (0.7%)	N=269 20 (7.4%) 6.7 (3.4, 10.0), p<0.001	N=278 22 (7.9%) 7.2 (3.8, 10.5), p<0.001	1776
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 1 for participants with WP-NRS ≥ 4 at baseline	N=294 9 (3.1%)	N=288 35 (12.2%) 9.2 (4.9, 13.4), p<0.001	N=291 56 (19.2%) 16.2 (11.3, 21.1), p<0.001	1471
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 16 for participants with WP-NRS ≥ 4 at baseline	N=294 44 (15.0%)	N=288 149 (51.7%) 36.8 (29.7, 43.8), p<0.001	N=291 186 (63.9%) 48.8 (41.9, 55.7), p<0.001	1516
Patient reported disease symptom scores: POEM				
% of participants achieving an improvement (reduction) in POEM ≥ 4 from baseline at week 16 for participants with POEM ≥4 at baseline	[redacted]	[redacted]	[redacted]	2219
Change from baseline in POEM at week 16	[redacted]	[redacted]	[redacted]	2332
QOL				
% of participants aged ≥ 16 years old at screening achieving an improvement (reduction) in DLQI ≥ 4 from baseline at week 16 for participants with DLQI ≥ 4 at baseline	[redacted]	[redacted]	[redacted]	2377
% of participants aged ≥16 years old at screening achieving score of 0/1 in DLQI among participants with DLQI >1 at baseline at week 16	[redacted]	[redacted]	[redacted]	2413

Change from baseline in DLQI among participants aged ≥16 years old at screening at week 16				2490
% of participants aged <16 years old at screening achieving score of 0/1 in CDLQI among participants with CDLQI >1 at baseline at week 16				2533
Change from baseline in CDLQI among participants aged <16 years old at screening at week 16				2601
% change from baseline in CDLQI among participants aged <16 years old at screening at week 16				2563
Change from baseline in EQ-5D-5L at week 16				5749
Mental health				
Change from baseline in HADS total score at week 16				2851
Symptoms and impact on the patient				
% of participants achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥12 (minimal clinically important difference [MCID]) from baseline at week 16 for participants with ADerm-IS sleep domain score ≥ 12 at baseline				3004
% of participants achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥4 (MCID) from baseline at week 16 for participants with ADerm-SS skin pain score ≥4 at baseline				4228
TCS sparing				
Reduction in TCS use at week 16 Mean (median) number of days off all TCS and achieving EASI 75	N=115 7.88 days (0 days)	N=254 33.53 days (26 days)	N=265 47.47 days (57 days)	142

TCS free days with EASI 75 at week 16	[redacted]	[redacted]	[redacted]	5800
Median time to first discontinuation with EASI 75 response	Not observed	88 days	57 days	142

ADerm-IS: Atopic Dermatitis Impact Scale, ADerm-SS: Atopic Dermatitis Symptom Scale, CI: Confidence Interval, CSR: Clinical Study Report, CDLQI: Children's Dermatology Life Quality Index, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, EQ-5D-5L:European Quality of Life-5 Dimensions 5 Levels, HADS: Hospital Anxiety and Depression Scale, IGA: Investigator Global Assessment, MCID: Minimal Clinically Important Difference, , POEM: Patient Oriented Eczema Measure, QOL: Quality of Life, SE: Standard Error, SCORAD: Scoring Atopic Dermatitis, TCS: Topical corticosteroids, WP-NRS: Worst Pruritus Numerical Rating Scale

B.2.6.4 Key secondary efficacy end-points vs dupilumab

Table 20 lists the secondary end-points for Heads UP. Those with an asterisk are ranked secondary end-points.

Improvements in EASI score and pruritus are clear, with upadacitinib showing significant benefit over dupilumab. Heads UP also considered the impact of treatment on EASI 75 by body region.

[redacted]49.

Table 20: Heads UP: secondary efficacy end-points (overall population)

	Dupilumab 300 mg n (%) or LS mean (SE)	Upadacitinib 30 mg n (%) or LS mean (SE) Adjusted difference, (95% CI), p value	Reference Table 14.2_1
Skin clearance and disease activity measures			
% of participants achieving EASI 75 at week 2	N=344 60 (17.5%)	N=348 152 (43.6%) 26.0 (19.5, 32.6), p<0.001	Page 5
% of participants achieving EASI 75 at week 4	[redacted]	[redacted]	Page 7
% of participants achieving EASI 90 at week 4	[redacted]	[redacted]	Page 85
% of participants achieving EASI 90 at week 16*	N=344 133 (38.8%)	N=348 211 (60.6%) 21.8 (14.5, 29.1), p<0.001	Page 91
% of participants achieving EASI 100 at week 16*	N=344 26 (7.6%)	N=348 97 (27.9%) 20.3 (14.9, 25.8), p<0.001	Page 139
% of participants achieving EASI 75 in the head and neck body region at week 16	[redacted]	[redacted]	Page 187
% of participants achieving EASI 75 in the trunk body region at week 16	[redacted]	[redacted]	Page 203
% of participants achieving EASI 75 in the upper limbs body region at week 16	[redacted]	[redacted]	Page 219
% of participants achieving EASI 75 in the lower limbs body region at week 16	[redacted]	[redacted]	Page 235
Patient reported disease symptom scores: pruritus			
Improvement (% change) from baseline of WP-NRS at week 1	[redacted]	[redacted]	Page 439

Improvement (% change) from baseline of WP-NRS at week 4	[redacted]	[redacted]	Page 448
Improvement (% change) from baseline of WP-NRS at week 16*	[redacted]	[redacted]	Page 484
% of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 16 for participants with WP-NRS ≥ 4 at baseline	[redacted]	[redacted]	Page 335

CI: Confidence Interval, EASI: Eczema Area and Severity Index, SE: Standard Error, WP-NRS: Worst Pruritus-Numerical Rating Scale

B.2.6.4.1 Skin clearance and disease activity measures

Results for the secondary end-points support the results of the primary end-point. Upadacitinib rapidly clears skin as demonstrated by a significant improvement in skin clearance.

Figure 21 and Figure 22 illustrate the rapid onset of action of upadacitinib 30 mg, with a [redacted].

Figure 21: Heads UP: % of participants achieving EASI 90 by visit during the double-blind period

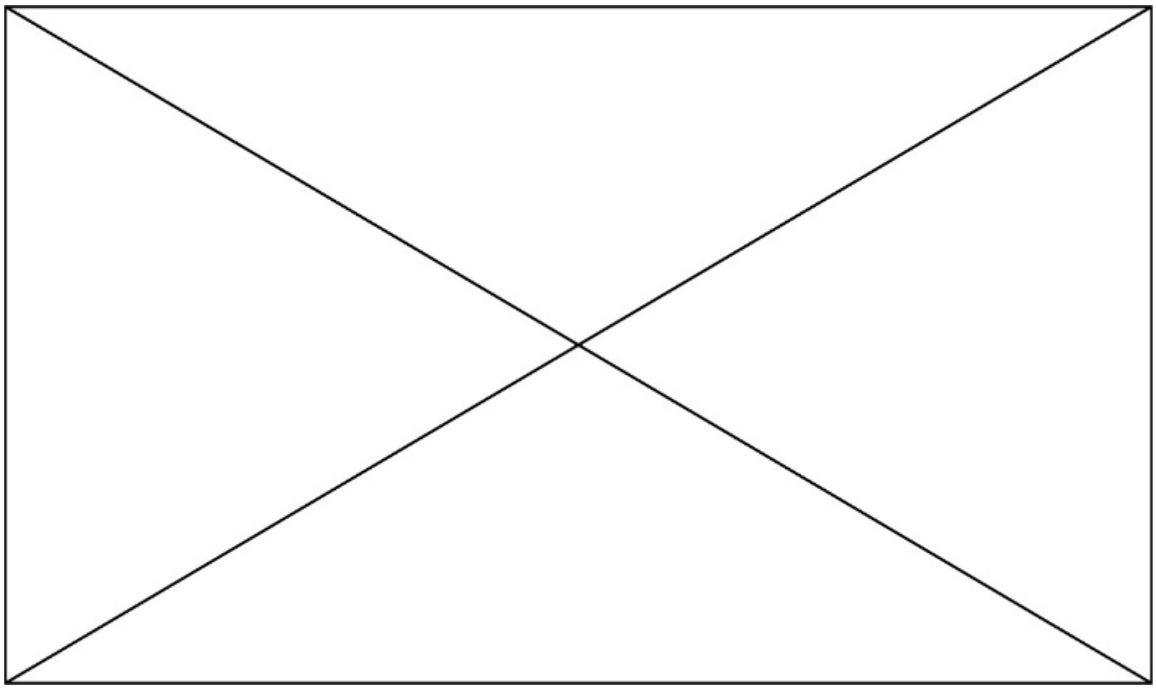
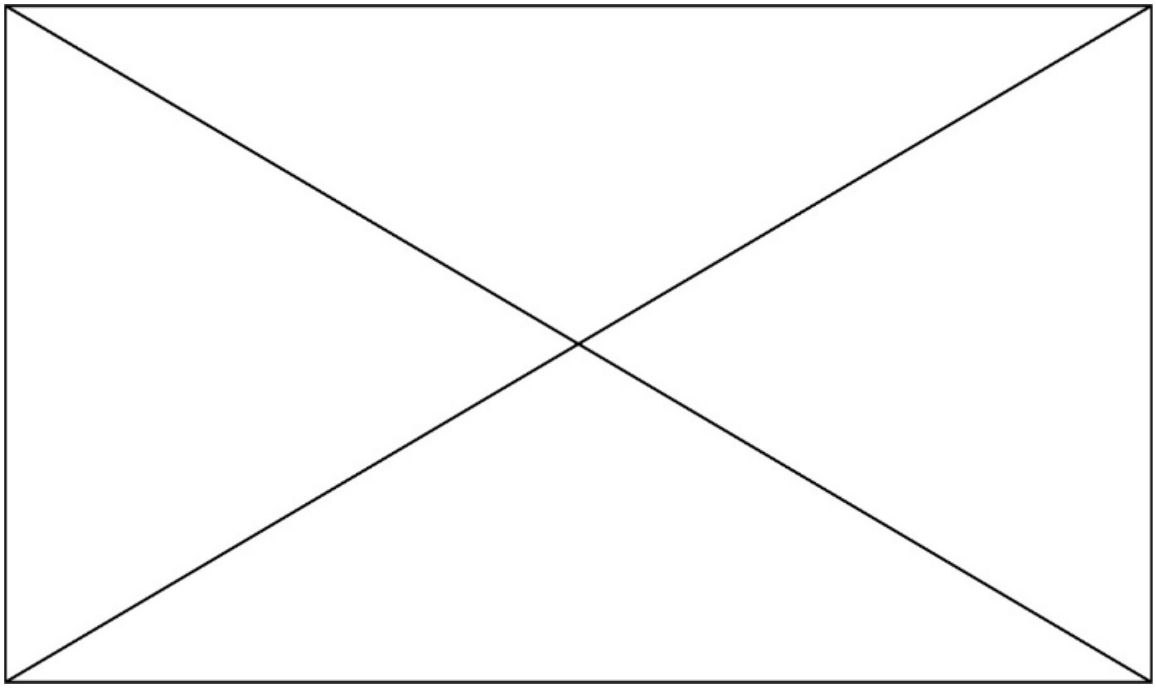


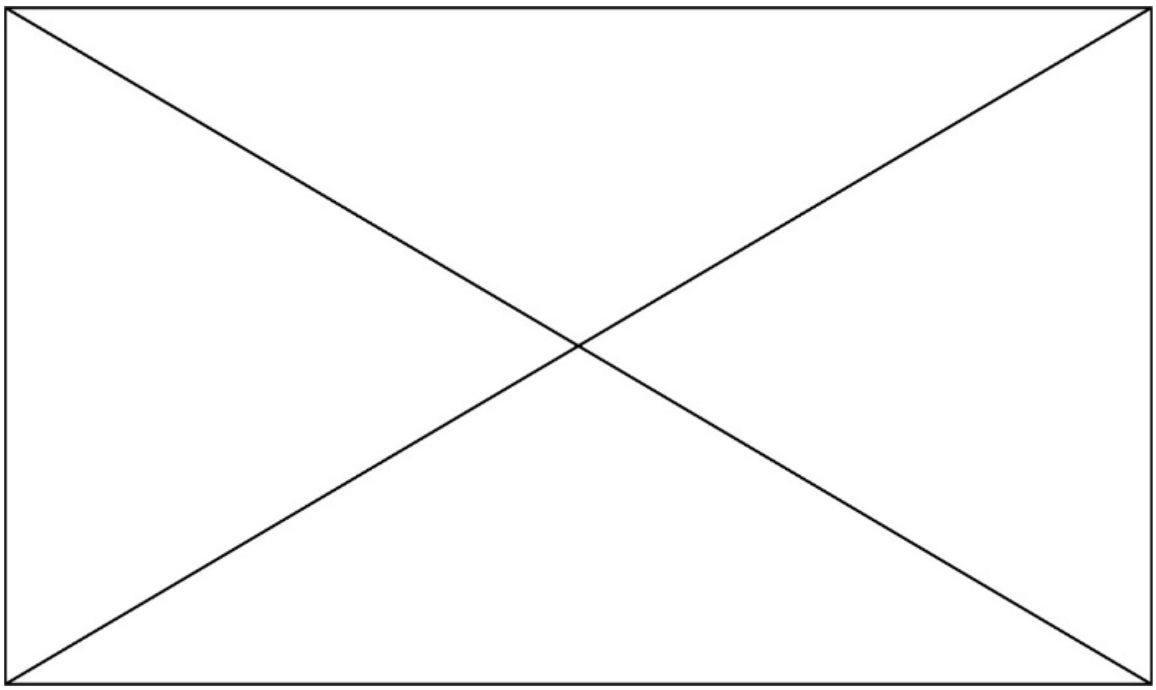
Figure 22: Heads UP: % of participants achieving EASI 100 by visit during the double-blind period



B.2.6.4.2 Patient reported disease symptom scores: pruritus

[redacted]

Figure 23: Heads UP: % of participants achieving an improvement (reduction) in WP-NRS ≥ 4 from baseline at week 16 for participants with WP-NRS ≥ 4 at baseline



B.2.6.5 Long-term data

For Measure UP 1, early data for the co-primary end-points is available with robust data out to 52 weeks [redacted]

[redacted]

Long-term data for Measure UP 2 is also available, with similar long-term results to Measure UP 1, and can be found in Appendix B, Section B.2.3.

[redacted]

[redacted]

Please note that the long-term data plots have numerically different results at 16 weeks from the 16-week results for the primary end-points due to the use of observed case data rather than NRI-C.

Figure 24: Measure UP 1: Primary end-points at week 52 (ITT population)

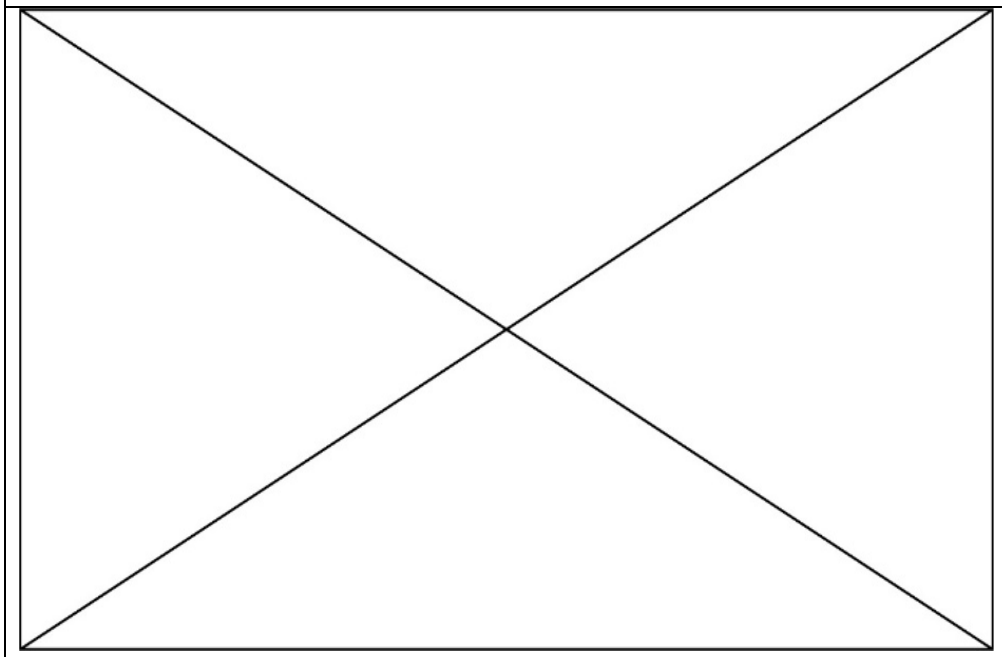
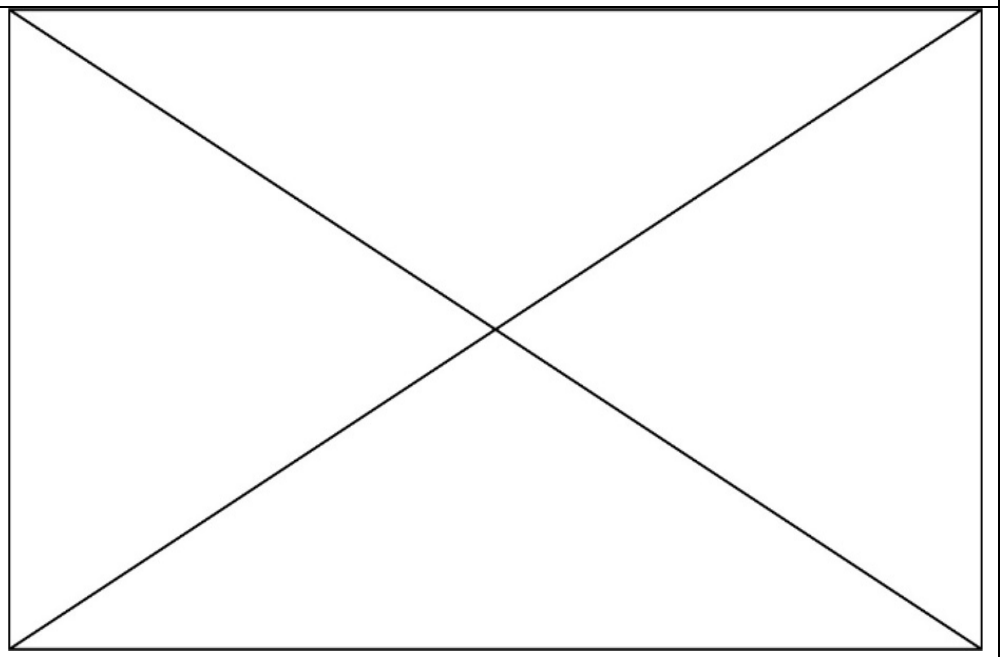
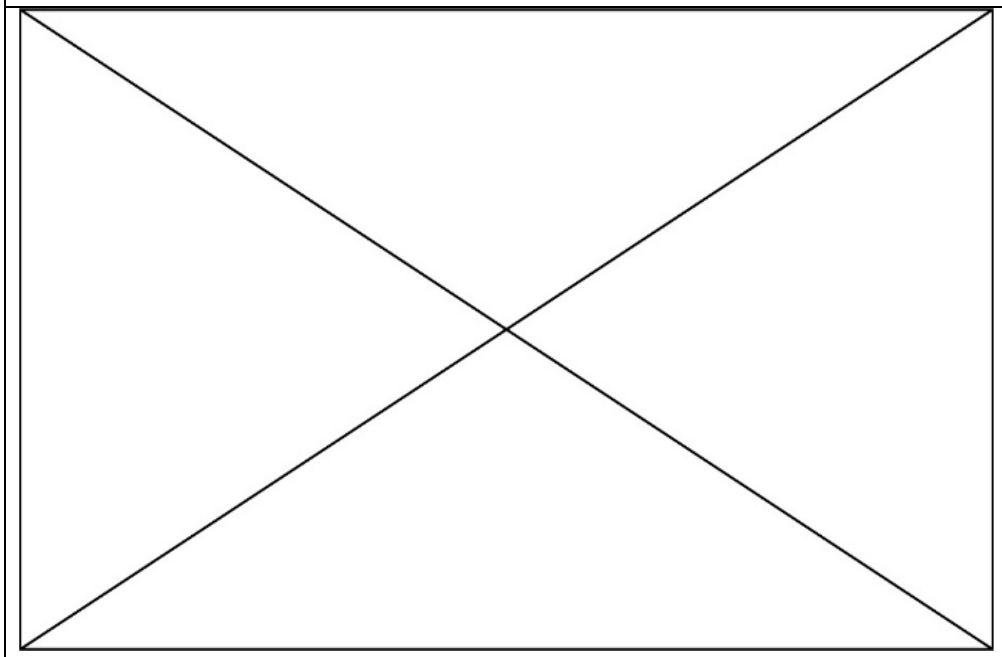
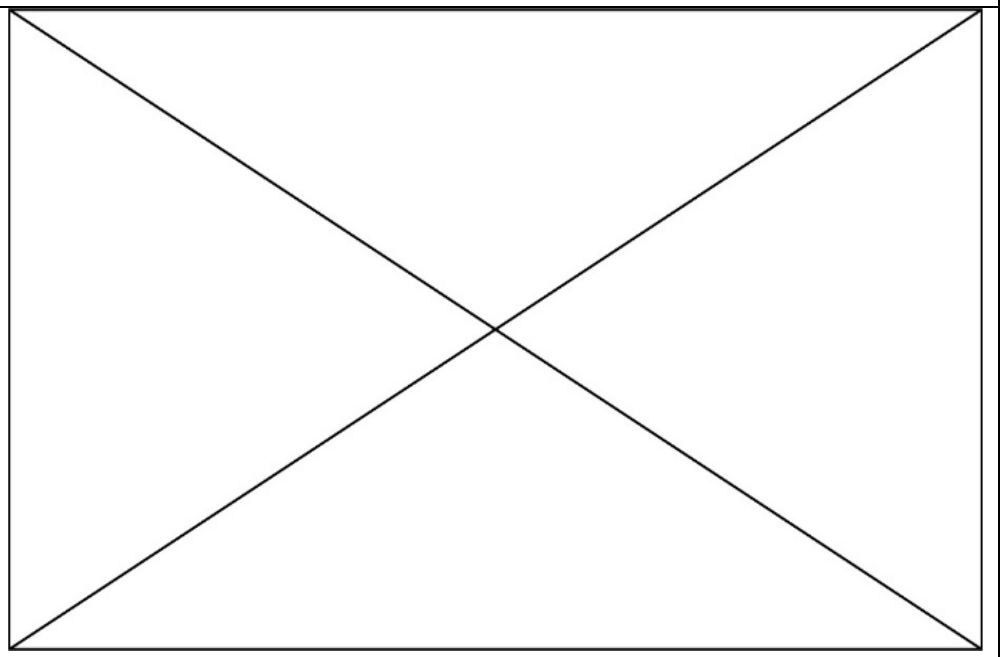
Measure UP 1 –% of patients achieving EASI 75 (52 weeks)	Measure UP 1 –% of patients achieving IGA 0/1 clear or almost clear (52 weeks)
	

Figure 25: AD UP: Primary end-points at week 52 (ITT population)

AD UP –% of patients achieving EASI 75 (52 weeks)	AD UP –% of patients achieving IGA 0/1 clear or almost clear (52 weeks)
	

B.2.6.6 End-points used in the economic model

The end-points used in the base case cost-effectiveness analysis are derived from data in the three registration trials: Measure UP 1, Measure UP 2 and AD UP. Heads UP, the head to head study vs dupilumab is used in several scenario analyses. Use of Heads UP in the economic modelling is limited since the study only included upadacitinib 30 mg as monotherapy in adults and did not collect data on the DLQI endpoint which is part of the response definition in the economic model.

B.2.6.6.1 Data sources

The end-points for the base case economic analysis differ from data presented earlier in this clinical section. Data presented earlier in this section are for the primary (ITT) analysis in which responders receiving rescue medication are censored from analysis. This is the standard approach for clinical trials in this disease area and consistent with primary publications and the CSR.

However, the base cases in the economic modelling use the 'all observed' dataset in which patients responding and receiving rescue medication are considered responders, which reflects clinical practice.

This approach was validated by UK clinicians, who agreed that the 'all observed' data set is more reflective of clinical practice than the primary analysis. They confirmed that the treatment of flares in AD does not define non-response[1]. This approach also enables a robust comparison with the dupilumab data, which showed higher response rates in the 'all observed' dataset than in the primary data set. The primary analysis is presented in the economic modelling as a scenario analysis, where available.

The end-points chosen for the economic modelling were assessed at 16 weeks, which was the primary end-point in the upadacitinib clinical trials and is also the time cut off for the stopping rule for dupilumab.

B.2.6.6.2 Subgroups considered in the economic model

As described in Section B.1.1 it is anticipated that upadacitinib could be used in two places in the treatment pathway. Advice from clinicians working in the field suggests that one conventional systemic therapy is likely to be initiated prior to upadacitinib in the majority of patients, and if patients did not respond to conventional systemic therapies or it was not tolerated then upadacitinib would be considered.

Clinical advice also suggests there is a need for efficacious treatments, which are well tolerated and can be used long-term to target the cause of AD rather than simply provide symptomatic control in patients who are candidates for systemic

therapy. Therefore, upadacitinib could also provide an alternative option to conventional systemic therapies for some patients.

For modelling purposes three populations are presented within this submission:

1. Adults previously exposed to conventional systemics, referred to as **adult systemic-exposed**

2. Adolescents who are eligible for treatment with conventional systemics, referred to as **adolescent systemic-eligible**

3. Adults who are eligible for treatment with conventional systemics, referred to as **adult systemic-eligible**

These groups are further described below.

B.2.6.6.2.1 Adult systemic-exposed

The first base case population is adults with moderate to severe AD whose disease has not responded to at least one systemic therapy, or in whom systemic therapy is not suitable. This is a sub-population of the full licensed indication for upadacitinib. This positioning is supported by UK clinical experts [1] and is in line with the position in which dupilumab is recommended by NICE[2].

The upadacitinib studies included a pre-specified subgroup of patients with prior exposure to systemic therapy. However, to align with TA534 we have identified a subgroup of patients who had prior exposure to CsA (the only licensed systemic therapy in the UK for people aged 16 years and over). This does not fully align with the sub-population used in the TA534 (inadequate efficacy response to oral CsA, were intolerant to oral CsA or patients who did not receive prior oral CsA treatment because CsA was contra-indicated or otherwise medically inadvisable) since patients with a contra-indication to CsA were not identified in the upadacitinib data. However, UK experts felt that this was an appropriate approach since contra-indication to CsA would not affect response as it is not a treatment effect modifier[1].

Data from Measure UP 1 and Measure UP 2 provide evidence for upadacitinib as monotherapy, therefore, data was pooled to form the MUP-sys-exp group. Data from AD UP provides evidence for upadacitinib in combination with TCS and forms the ADUP-sys-exp group. Baseline demographics can be found in Appendix D, Tables 44-46.

We have assumed that prior CsA use can be considered as a proxy for prior systemic treatment (methotrexate, mycophenolate mofetil, azathioprine) since they are considered at the same place in the treatment pathway.

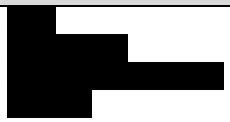
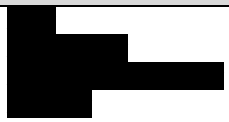
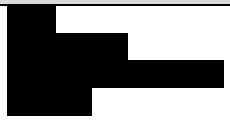
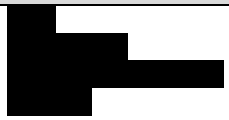
In practice, clinicians use a combination of outcomes assessing signs and symptoms of AD to determine response[1].

DLQI is regularly used to assess the impact of AD on QOL and EASI to measure skin involvement. In the NICE submission for dupilumab (TA534)[58] response to treatment was defined as at least a 50% reduction in the EASI score (EASI 50) from when treatment started and at least a 4-point reduction in DLQI from when treatment started (DLQI ≥4). Clinicians consulted by AbbVie to support this submission confirmed that they regularly use a combination of outcomes when assessing response and that EASI 50 combined with an DLQI improvement of at least 4 points is a suitable composite outcome for adult patients[1].

Scenario analyses consider alternative response definitions based on EASI 50 and EASI 75 as single end-points.

The base case response criteria for the systemic-exposed adult population is the composite of EASI 50 + DLQI ≥4, using 'all observed' data, as shown in *red italics* in Table 22 and Table 21 below. The base case population will be combination therapy using data from AD UP, since AD treatments are commonly used in combination with TCS. Furthermore, this approach aligns with the committee preference in TA534. Analyses will be carried out for both doses of upadacitinib ± TCS.

Table 21: End-points used in the economic model (adult systemic-exposed): combination therapy

	Combination therapy (ADUP-sys-exp)			
	Placebo + TCS **n (%)**	**UPA 15 mg +TCS** **n (%)** **Adjusted diff (95% CI)** **p value**	**UPA 30 mg + TCS** **n (%)** **Adjusted diff (95% CI)** **p value**	**Ref**
All observed				
% of participants achieving EASI 50 and DLQI ≥4 at week 16				t_4.2.3
% of participants achieving EASI 75 at week 16				t_6.5.3
% of participants achieving EASI 50 at week 16				t_5.5.3
Primary analysis				
% of participants achieving EASI 50 and DLQI ≥4 at week 16				t_1.2.3
% of participants achieving EASI 75 at week 16				t_3.2.3
% of participants achieving EASI 50 at week 16				t_2.2.3

CI: Confidence Interval, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, TCS: Topical Corticosteroids, UPA: Upadacitinib

Table 22: End-points used in the economic model (adult systemic-exposed): monotherapy

	Monotherapy (MUP-sys-exp)							
	Measure UP 1				Measure UP 2			
	Placebo n (%)	UPA 15 mg n (%) Adjusted diff (95% CI) p value	UPA 30 mg n (%) Adjusted diff (95% CI) p value	Ref	Placebo n (%)	UPA 15 mg n (%) Adjusted diff (95% CI) p value	UPA 30 mg n (%) Adjusted diff (95% CI) p value	Ref
All observed								
% of participants achieving EASI 50 and DLQI ≥4 at week 16				t_4.2.1				t_4.2.2
% of participants achieving EASI 75 at week 16				t_6.5.1				t_6.5.2
% of participants achieving EASI 50 at week 16				t_5.5.1				t_5.5.2
Primary analysis								
% of participants achieving EASI 50 and DLQI ≥4 at week 16				t_1.2.1				t_1.2.2
% of participants achieving EASI 75 at week 16				t_3.2.1				t_3.2.2
% of participants achieving EASI 50 at week 16				t_2.2.1				t_2.2.2

CI: Confidence Intervals, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, UPA: Upadacitinib.

.

B.2.6.6.2.2 Adolescent systemic-eligible

The second base case population is adolescents with moderate to severe AD.

The SLR identified one phase III clinical trial, AD ADOL (Simpson 2019[59]) evaluating dupilumab monotherapy in adolescents with uncontrolled moderate to severe AD. Results were reported for monotherapy only, therefore the economic analysis is limited to monotherapy in systemic-eligible patients vs dupilumab and BSC.

Limited evidence was available on systemic therapies and no data was identified in the literature evaluating the efficacy of CsA in adolescent patients. An abstract presented data for the subset of adolescent patients with a history of inadequate response or intolerance to CsA in AD ADOL[60]. However, the sample size was very small (n=11 for dupilumab Q2W) and not considered robust enough for analysis. Therefore, it was not possible to conduct two separate analyses of upadacitinib in adolescent patients: one in the systemic-eligible population vs CsA and one in the systemic-exposed population vs dupilumab and BSC.

The only end-point reported for the all observed population in AD ADOL was EASI 75[59] which was used in the network meta-analysis (NMA) to estimate comparative data for upadacitinib vs dupilumab and this was used as the base case end-point.

UK clinical experts consulted for this submission advised that EASI 50 would be the most appropriate end-point for the economic model in the adolescent population[1]. However, the all observed dataset is more reflective of UK clinical practice and therefore outcomes available in this dataset have been preferentially selected. Given that AD ADOL reported EASI 50 and EASI 75 for the primary population, a scenario analysis in the primary population considers EASI 50 as an alternative end-point.

QOL in the adolescent population was measured using either CDLQI in patients aged 12-15 years or DLQI in those aged 16-17 years, which is consistent with UK clinical practice and confirmed by UK clinical experts[1]. Studies suggest that CDLQI and DLQI should not be combined and no mapping algorithms were identified in the literature[61]. Therefore, the composite end-point of EASI 50 + DLQI ≥4 cannot be applied to the adolescent population. Furthermore, no data on the EASI 50 + DLQI ≥4 score was identified for dupilumab in the adolescent population.

Systemic treatments are used in adolescents; however, no data is available to support the efficacy and/or safety of conventional systemic treatment in the adolescent population. Furthermore, it should be noted that CsA is not licensed for use in children aged under 16 years. Therefore, if adolescents aged under 16 years receive a conventional systemic treatment then it is unlicensed.

The base case response criteria for the adolescent population is EASI 75, using all observed data, as shown in *red italics* in Table 23. Analysis will be carried out for the 15 mg dose as monotherapy, since the anticipated licensed dose in the label for upadacitinib is 15 mg in adolescent patients.

Table 23: End-points used in the economic model (adolescent)

	Measure UP 1			Measure UP 2		
	Placebo n (%)	**UPA 15 mg n (%) Difference (95% CI) p value**	**Ref**	**Placebo n (%)**	**UPA 15 mg n (%) Difference (95% CI) p value**	**Ref**
All observed						
% of participants achieving EASI 75 at week 16	[redacted]	[redacted]	*t_6.2.1*	[redacted]	[redacted]	*t_6.2.2*
Primary analysis						
% of participants achieving EASI 50 at week 16	[redacted]	[redacted]	M16-045/ 14.2_2.2.1	[redacted]	[redacted]	M18-891/ 14.2_2.2.1
% of participants achieving EASI 75 at week 16	[redacted]	[redacted]	M16-045/ 14.2_2.1.1	[redacted]	[redacted]	M18-891/ 14.2_2.1.1

CI: Confidence Interval, EASI: Eczema Area and Severity Index, UPA: Upadacitinib.

B.2.6.6.2.3 Adult systemic-eligible

The third base case population matches the expected marketing authorisation and includes patients who have yet to receive systemic treatment as well as those who have already received treatment with a systemic therapy and had an inadequate response or those unsuitable for treatment. This group is referred to as 'adult systemic-eligible'.

For some patients, conventional systemic therapy (CsA, methotrexate, mycophenolate mofetil, azathioprine) may not be appropriate due to the known AE profile and an alternative treatment choice would be welcomed by both patients and clinicians. Upadacitinib can be used long-term to target the cause of AD, rather than simply providing symptomatic relief, preventing the need for patients to switch to alternative systemic therapies which requires significant monitoring on treatment initiation. Two independent groups of clinical advisors consulted with by AbbVie to inform this submission confirmed that they would appreciate having the option of upadacitinib to treat patients in this population[1,62].

As detailed above we have used CsA exposure as a proxy for systemic exposure. Comparative data for upadacitinib vs CsA is available from an NMA carried out for this submission. Data is not available for the composite end-point, however, comparative data on EASI 50 and EASI 75 has been computed (see Section B.2.9.5).

The base case response criteria for the systemic-eligible adult population is EASI 75, using all observed data, as shown in *red italics* in Table 24 below. Analyses will be carried out for both doses as combination therapy (upadacitinib + TCS), since the studies used to form the network in the NMA all used systemic treatment in combination with TCS.

Table 24: End-points used in the economic model (adult systemic-eligible): combination therapy

	Combination therapy (ADUP-sys-eligible)			
	Placebo + TCS **n (%)**	**UPA 15 mg +TCS** **n (%)** **Adjusted diff (95% CI)** **p value**	**UPA 30 mg + TCS** **n (%)** **Adjusted diff (95% CI)** **p value**	**Ref**
All observed				
% of participants achieving EASI 50 at week 16	[redacted]	[redacted]	[redacted]	t_5.5.3
% of participants achieving EASI 75 at week 16	[redacted]	[redacted]	[redacted]	t_6.5.3

CI: Confidence Interval, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, TCS: Topical Corticosteroids, UPA: Upadacitinib

B.2.7. Subgroup analysis

For Measure UP 1, Measure UP 2 and AD UP[45-47], subgroup analyses were pre-planned and are listed below:

- Age: adolescents vs adults <18 years (12-18 years), ≥18 years
- Age: <18 years, ≥18 to <40 years, ≥40 to <65 years, ≥65 years
- Gender: male, female
- BMI: normal (<25), overweight (≥25 to <30), obese (≥30)
- Race: white, Asian, Black, other
- Weight: <median, ≥median
- Geographic region: US/Puerto Rico/Canada, Japan, China (mainland) and other
- Baseline IGA-AD: <4, ≥4)
- Baseline EASI: <median, ≥median
- High-sensitivity C-reactive protein: <median, ≥median
- Previous systemic therapy: with, without
- Participants who reported an intolerance to at least one prior TCS or TCI therapy
- Participants who reported an inadequate response to at least one prior topical treatment.

For Heads UP, the following subgroup analyses were pre-planned:

- Age: <40 years, ≥40 to <65 years, ≥65 years
- Gender: male, female
- BMI: normal (<25), overweight (≥25 to <30), obese (≥30)
- Race: white, Asian, Black, other
- Weight: <median, ≥median
- Geographic region: US/Puerto Rico/Canada and other
- Baseline IGA-AD: <4, ≥4
- Baseline EASI: <median, ≥median
- High-sensitivity C-reactive protein: <median, ≥median
- Previous systemic therapy: with, without

Categorical variables were analyzed using the CMH test as per the main analysis.

[redacted]

A summary of the results is provided in Appendix E.

Post-hoc subgroup analysis was conducted to generate patient data for the economic modelling in the systemic-exposed population for the composite end-point of EASI 50 + DLQI ≥4 and in the systemic-exposed population (participants who reported inadequate response to or were intolerant to CsA), see Section B.3.2.1.

B.2.8. Meta-analysis

B.2.9. Indirect and mixed treatment comparisons

Appendix D includes full details of the methodology for the NMAs, see Section D.2.2.

B.2.9.1 Background

Other than the head to head comparison with dupilumab in the Heads Up trial, the SLR did not identify any studies that investigated upadacitinib vs relevant comparators in the base case populations considered in the economic modelling. Heads UP provides evidence for upadacitinib 30 mg vs dupilumab 300 mg monotherapy in adult patients for the EASI 50 and EASI 75 end-points, thereby providing data for scenario analyses in the adult systemic-exposed population.

Therefore, three separate NMAs were conducted in the base case populations of:

- Adult systemic-exposed
- Adolescent systemic-eligible
- Adult systemic-eligible

B.2.9.2 Objective

The primary objective of the NMA was to compare the relative efficacy of upadacitinib, dupilumab or CsA at week 16 for the treatment of moderate to severe AD in adult systemic-exposed, adolescent and adult systemic-eligible patients, measured by the following end-points:

- Proportion of patients achieving an EASI 50 + DLQI ≥4 response (informing economic modelling in the adult systemic-exposed population)

- Proportion of patients achieving an EASI 50 or EASI 75 response (informing economic modelling for adult systemic-exposed, adolescent and adult systemic-eligible populations)

B.2.9.3 Methods

An SLR was conducted to identify clinical evidence on the efficacy of treatments used for adult and adolescent patients with moderate to severe AD (see Appendix D.1). The studies identified by the SLR were used to inform the NMA, which included RCTs with upadacitinib or treatments currently licensed by the EMA for adult and adolescent patients with moderate to severe AD.

The NMA was performed separately for three sub-populations:

1. Adult systemic-exposed: defined as patients who have previously received CsA (proxy for systemic therapies) and comparing upadacitinib 30 mg and 15 mg with dupilumab and BSC. We have called this the 'adult systemic-exposed NMA'.

2. Adolescent systemic-eligible: defined as adolescent patients aged 12-17 years, eligible for conventional systemic treatment who may or may not have received prior conventional systemic treatment(s). The NMA compares upadacitinib 15 mg with dupilumab and BSC. We have called this the 'adolescent NMA'.

3. Adult systemic-eligible: defined as adult patients eligible for conventional systemic treatment. This population includes patients who have yet to receive systemic treatment as well as those who have already received treatment with conventional systemic treatment(s) and had an inadequate response or were unsuitable for treatment. The NMA compares upadacitinib 15 mg and 30 mg with CsA. We have called this the 'adult systemic-eligible NMA'.

Table 25: NMA carried for this submission

NMA name	Population	Comparators	Intervention
Adult systemic-exposed NMA	Adult systemic-exposed	Dupilumab, BSC	Upadacitinib 15 mg Upadacitinib 30 mg Monotherapy and combination therapy
Adolescent NMA	Adolescent systemic-eligible	Dupilumab, BSC	Upadacitinib 15 mg Monotherapy
Adult systemic-eligible NMA	Adult systemic-eligible	CsA	Upadacitinib 15 mg Upadacitinib 30 mg Combination therapy

BSC: Best Supportive Care, CsA: Ciclosporin, NMA: Network Meta-Analysis

The statistical methods followed the recommended methods in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 2 and 3[63,64], conducted

under a Bayesian generalised linear model (GLMM) framework. Per the NICE DSU TSD 2[63], binary outcomes were modelled with a *binomial* likelihood and *logit* link function.

For all networks, both fixed effect (FE) and random effect (RE) models were tested, and for each selected model a baseline risk-adjusted sensitivity analysis was considered if feasible and where between-trial heterogeneity was observed among placebo response rates.

Outcomes from dupilumab studies were reported for within pooled study estimates. Upon availability, individual study results were removed from pooled results to capture between-study heterogeneity as accurately as possible. Where this was not feasible, pooled studies results were considered as a single study. All data imputation was made prior to assessing the NMA feasibility.

B.2.9.4 Adult systemic-exposed and adolescent NMA

B.2.9.4.1 Study selection from SLR

B.2.9.4.1.1 Adult systemic-exposed

The dupilumab submission to NICE (TA534)[58] used a composite of EASI 50 + DLQI ≥4 as the response definition for their cost-effectiveness analysis (CEA) in an adult systemic-exposed population. On clinical advice the same end-point was used to inform the adult systemic-exposed population base case CEA[1].

Data for dupilumab was extracted from the CAFÉ study which evaluated dupilumab vs placebo in combination with TCS in adults with an inadequate response or contra-indication to CsA[65] and from TA534. TA534 provided data from post-hoc analyses of the SOLO 1 & 2 (monotherapy) and CHRONOS trial (combination therapy with TCS) for the CsA-exposed populations (CAFÉ-like).

Data were presented in TA534 using the following definitions:

- SOLO CAFÉ-like: Pooled analysis of subgroup of patients from SOLO 1 and SOLO 2 who showed an inadequate efficacy response to oral CsA or were intolerant to oral CsA or patients who did not receive prior oral CsA treatment because CsA was contra-indicated or otherwise medically inadvisable.
- CAFÉ+CHRONOS CAFÉ-like: Pooled analysis which included all patients from CAFÉ and CHRONOS who showed an inadequate efficacy response to oral CsA or were intolerant to oral CsA or patients who did not receive prior oral CsA treatment because CsA was contra-indicated or otherwise medically inadvisable.

Therefore, TA534 was a key source of evidence for the adult systemic-exposed NMA.

Data for upadacitinib was extracted from the registration studies (Measure UP 1, Measure UP 2 and AD UP) for a subgroup of patients previously exposed to CsA, which enables comparison vs dupilumab in the systemic-exposed population.

The NMA was expanded to include Heads UP when data became available to synthesise evidence for the adult systemic-exposed population for the EASI 50 and EASI 75 end-points within the monotherapy network. However, inconsistency was observed in the NMA with Heads UP results, limiting the reliability of these estimates. The results of the NMA with Heads Up and the inconsistency plots are presented in Appendix D (Section D.2.1.6.2.1.2 and Section D.2.1.6.2.2.2) for completeness. In order to ensure the most robust results are used in the CEA, scenario analyses on those end-points were performed using outputs from the NMA excluding Heads UP and from unadjusted data from Heads UP.

Data on CsA-exposed patients extracted from the upadacitinib studies does not fully align with the sub-population used in TA534 (CAFE-like population) since patients with a contra-indication to CsA were not identified in the upadacitinib data. However, UK experts felt that this was an appropriate approach since contra-indication to CsA would not affect response as it is not a treatment effect modifier[1].

The CAFÉ trial reported EASI 75 data for a subgroup of CsA-exposed patients which aligns with the CsA-exposed definition from the upadacitinib trials. However, the subgroup of CAFÉ + CHRONOS-CAFÉ-like was used in the NMA to inform efficacy data for dupilumab in combination. Using CAFÉ + CHRONOS-CAFÉ-like allows the use of all available data and ensures consistency with other comparisons (monotherapy network and alternative outcomes).

The selected approach is conservative, since the EASI 75 response rates reported for the two subgroups indicated that dupilumab performed better in the CsA-exposed and contra-indicated subgroup (62.6%) than in the CsA-exposed subgroup (58.0%).

B.2.9.4.1.2 Adolescent

Analyses in the adolescent population were not presented in TA534 as the initial marketing authorisation for dupilumab was for adults. Only one trial, AD ADOL[59] was identified evaluating dupilumab monotherapy in adolescents with moderate to severe AD. However, data on the composite end-point EASI 50 + DLQI ≥4 was not presented in AD ADOL.

Furthermore, the children's version of the DLQI questionnaire (CDLQI) usually replaces the DLQI in younger patients (<15 years old). DLQI and CDLQI scores should not be combined[61] and no mapping algorithm from CDLQI to DLQI was identified. Therefore, a comparison of upadacitinib vs dupilumab using the composite

outcome of EASI 50 + DLQI ≥4 was not feasible; instead, single EASI scores (EASI 50 and EASI 75) were considered in the NMA.

Data for dupilumab was extracted from the AD ADOL phase III trial which evaluated dupilumab vs placebo in monotherapy in adolescents (12-17 years) inadequately controlled by topical medications or for whom topical therapy was inappropriate[59].

Data for upadacitinib was extracted from the monotherapy registration studies (Measure UP 1, Measure UP 2) which included a pre-specified adolescent subgroup. It is anticipated that upadacitinib will be licensed at the 15 mg dose for adolescents, therefore the NMA compares dupilumab vs upadacitinib 15 mg monotherapy.

The feasibility of performing indirect comparisons in a subgroup of adolescent systemic-exposed populations was assessed. An abstract presented data for the subset of adolescent patients with a history of inadequate response or intolerance to CsA in AD ADOL[60]. Unfortunately, the sample size was very small (n=11 for dupilumab and n=14 for placebo) which would underpower the statistical analysis, therefore this study was not selected for the NMA. Similarly, no evidence was identified evaluating CsA or systemic therapies in a population of adolescents with moderate to severe AD.

B.2.9.4.1.3 Study selection summary

A summary of the trials included in the adult systemic-exposed and adolescent NMA and the availability of included end-points are shown below in Table 26.

For more detail please see Appendix D.1.2.

Table 26: Contribution of included RCTs to outcomes evaluated in the NMA

Study	Active treatment arm(s)	Data source adult systemic-exposed	Data source adolescent	Adolescent patients included	All patients received TCS	All observed dataset			Primary dataset		
						EASI 50+ DLQI≥4	EASI 50	EASI 75	EASI 50+ DLQI≥4	EASI 50	EASI 75
Upadacitinib vs placebo											
Measure UP 1	UPA_15_mg	Post-hoc analysis	Pre-specified analysis	X		X	X	X	X	X	X
Measure UP 1	UPA_30_mg			X		X	X	X	X	X	X
Measure UP 2	UPA_15_mg			X		X	X	X	X	X	X
Measure UP 2	UPA_30_mg			X		X	X	X	X	X	X
AD UP	UPA_15_mg_TCS			X	X	X	X	X	X	X	X
AD UP	UPA_30_mg_TCS			X	X	X	X	X	X	X	X
Dupilumab vs placebo											
CAFÉ	DUP_Q2W_TCS	Clinical paper	N/A		X		X	X		X	X
CHRONOS- CAFÉ-like	DUP_Q2W_TCS	Post-hoc analysis in TA534*	N/A		X		X	X		X	X
CAFÉ+CHRONOS CAFÉ-like	DUP_Q2W_TCS	Post-hoc analysis in TA534	N/A		X	X			X		
SOLO CAFÉ-like	DUP_Q2W					X	X	X	X	X	X
AD ADOL	DUP_Q2W	N/A	Clinical paper	X				X		X	X
Upadacitinib vs dupilumab											
Heads UP	UPA_30_mg	Post-hoc analysis	N/A				X	X		X	X
Heads UP	DUP_Q2W		N/A				X	X		X	X

DLQI: Dermatology Life Quality Index, DUP: Dupilumab, EASI: Eczema Area and Severity Index, N/A: Not Applicable, NMA: Network Meta-Analysis, Q2W: Every 2 weeks, RCTs: Randomised Controlled Trial, TCS: Topical Corticosteroids UPA: Upadacitinib

*Derived by subtracting CAFÉ individual study results from pooled CAFÉ+CHRONOS CAFÉ-like population results reported in TA534

B.2.9.4.2 Networks included in the NMA

B.2.9.4.2.1 Adult systemic-exposed

For the systemic-exposed adult population, four networks were conducted for each outcome (EASI 50 + DLQI≥4, EASI 75 and EASI 50).

1. All observed/combination therapy: All included RCTs for combination therapy with TCS using all observed data regardless of rescue medication use to determine response – this data is used in the base case CEA for the end-point EASI 50 + DLQI≥4.

2. All observed/monotherapy: All included RCTs for monotherapy using all observed data regardless of rescue medication use to determine response.

3. Primary/combination therapy: All included RCTs for combination therapy with TCS where patients requiring rescue medication are considered non-responders.

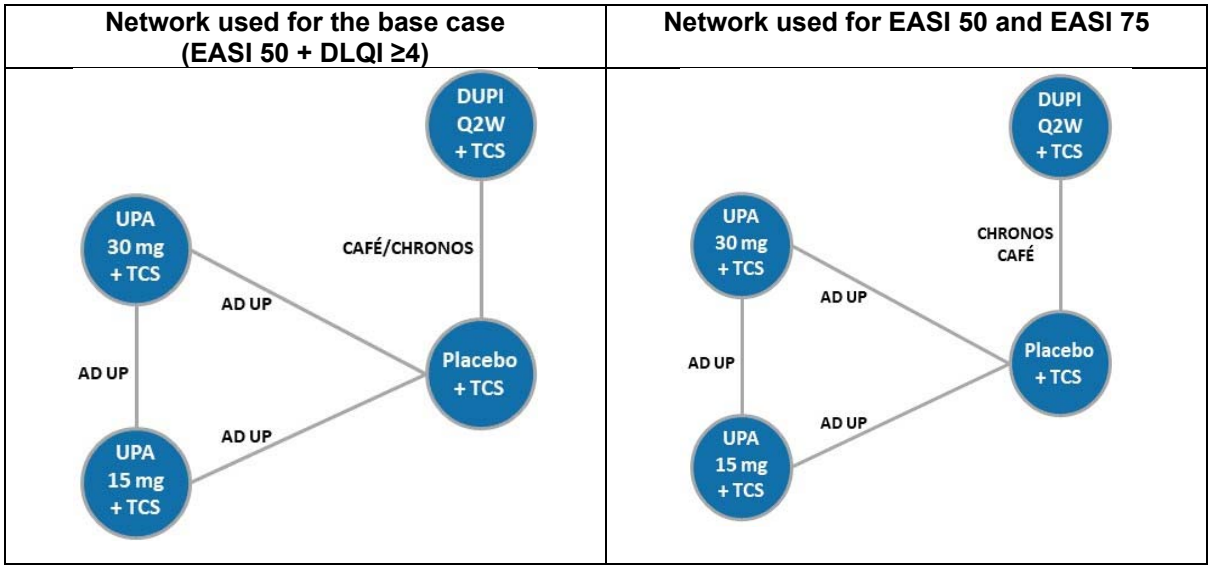
4. Primary/monotherapy: All included RCTs for monotherapy where patients requiring rescue medication are considered non-responders.

This section includes the results for the all observed combination population, since this data was used in the base case CEA. Data for the all observed monotherapy population and the primary dataset are shown in Appendix D.2.1.

NMA were also carried out using Heads UP to synthesise evidence for the adult systemic-exposed population for the EASI 50 and EASI 75 end-points. Use of Heads UP is limited for the base case CEA since the study only included upadacitinib 30 mg as monotherapy in adults and did not collect data on the DLQI end-point which is part of the response definition in the economic model. However, inconsistency was observed when incorporating data from Heads UP in the NMA. Therefore, in order to ensure the most robust results, scenario analyses on these end-points were performed using outputs from the NMA excluding Heads UP and from unadjusted data from Heads UP.

Network diagrams for the adult systemic-exposed NMA are shown below in Figure 26 (combination therapy including base case) and Figure 27 (monotherapy)

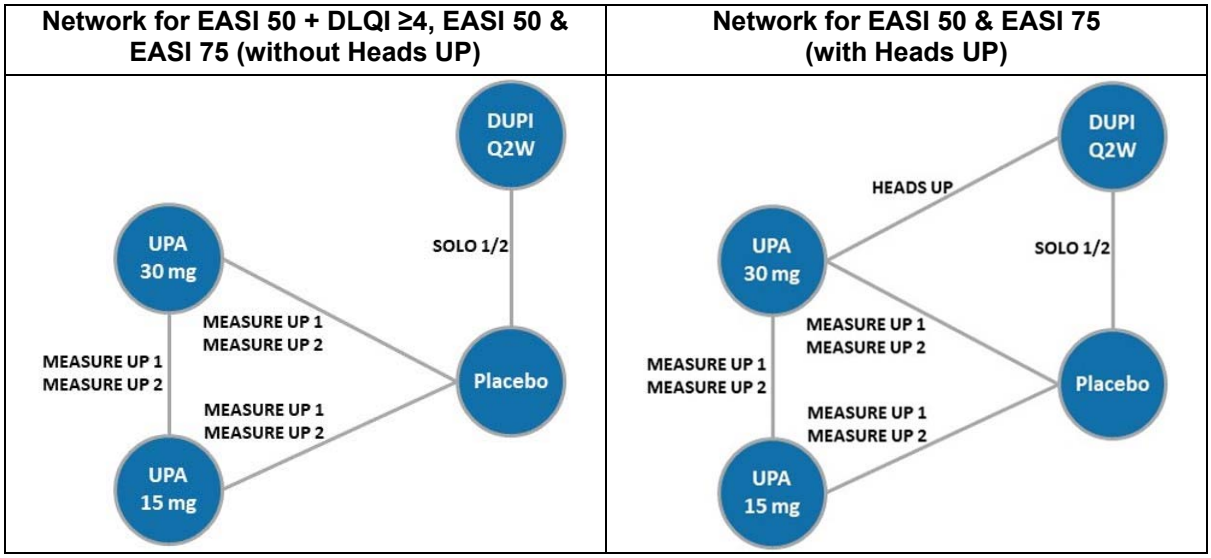
Figure 26: Adult systemic-exposed NMA – network plot for EASI 50 + DLQI ≥4, EASI 50 and EASI 75 for combination therapy with TCS (all observed/primary analysis)



DLQI: Dermatology Life Quality Index, DUPI: Dupilumab, EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks, TCS: Topical Corticosteroids, UPA: Upadacitinib

Pooled results for CAFÉ+CHRONOS CAFÉ-like reported in TA534 were split into two separate studies (CAFÉ and CHRONOS CAFÉ-like) where possible (depending on data availability) by subtracting numbers reported for the CAFÉ trials only from the pooled results. As a result, the number of responders for EASI 50 and EASI 75 for the primary and all observed analyses pooled for CAFÉ+CHRONOS CAFÉ-like could be separated into two studies. However, pooled results for the composite EASI-50 + DLQI ≥ 4 could not be separated as results were not reported for CAFÉ or CHRONOS CAFÉ-like separately.

Figure 27: Adult systemic-exposed NMA – network plots for EASI 50 + DLQI ≥4, EASI 50 and EASI 75 for monotherapy (all observed/primary analysis)



DLQI: Dermatology Life Quality Index, DUPI: Dupilumab, EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks, UPA: Upadacitinib

For all end-points in the monotherapy NMA, results for SOLO 1 and SOLO 2 are reported pooled across both studies and will therefore be considered as a single study.

B.2.9.4.2.2 Adolescents

For the adolescent population, two networks were conducted. Data in the all observed dataset was only available for EASI 75 and both EASI 75 and EASI 50 were reported in the primary dataset, all as monotherapy only. The anticipated dose of upadacitinib in adolescents is 15 mg.

1. All observed/monotherapy: All included RCTs for monotherapy using all observed dataset regardless of rescue medication use to determine response – this data is used in the base case.

2. Primary/combination therapy: All included RCTs where patients who respond and receive rescue medication are considered non-responders.

Figure 28: Adolescent NMA – network plot for EASI 50 and EASI 75 for monotherapy (all observed/primary analysis)

DUPI: Dupilumab, Q2W: Every 2 Weeks, UPA: Upadacitinib

B.2.9.4.3 Results

The main results of the Bayesian all observed analyses are detailed below for each of the outcomes of interest. These results in *red italics* reflect the data used in the base case.

The FE models were the preferred models in all analyses. RE models were not preferred due to wide credible intervals (CrI) which did not agree with RCT results (in terms of aligning with CI) and/or the posterior distribution of the between-study heterogeneity did not appear sufficiently updated from the uniform (0,5) prior. This is likely to have been driven by the low number of studies per treatment in the networks, with some networks only having one study per treatment, leading to insufficient data to sensibly estimate between-study heterogeneity.

Relative treatment effects are presented as median odds ratios (ORs) and associated 95% CrI and were organised in a league table, so that the comparative OR of any two therapies could be referenced.

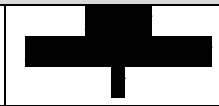
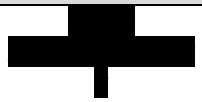
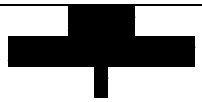
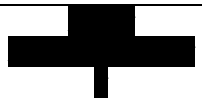
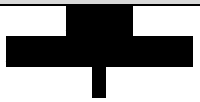
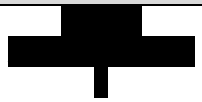
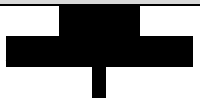
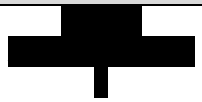
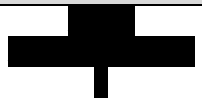
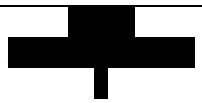
In addition, the chance for each intervention of being ranked as first, second, third, fourth, and so on was presented using the Surface Under the Cumulative RAnking (SUCRA) curve statistic for each treatment where SUCRA is 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst[66].

Appendix D.2.1 provides further details of the all observed analysis, together with results for the primary analysis.

B.2.9.4.3.1 Adult systemic-exposed: combination therapy network

The results below indicate that upadacitinib 30 mg in combination with [redacted]

Table 27: Adult systemic-exposed network – OR and 95% CrI for pairwise comparisons (FE) (All observed, combination network)

	Placebo + TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS	Dupilumab 300 mg Q2W + TCS
EASI 50 + DLQI ≥4				
Placebo + TCS				
Upadacitinib 15 mg + TCS				
Upadacitinib 30 mg + TCS				
Dupilumab 300 mg Q2W + TCS				
EASI 75				
Placebo +TCS				
Upadacitinib 15 mg + TCS				
Upadacitinib 30 mg + TCS				
Dupilumab 300 mg Q2W + TCS				
EASI 50				
Placebo +TCS				
Upadacitinib 15 mg +TCS				
Upadacitinib 30 mg +TCS				
Dupilumab 300 mg Q2W + TCS				

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks, TCS: Topical Corticosteroids

Table 28: Adult systemic-exposed network – SUCRA ranking (FE) (All observed, combination network)

	EASI 50 + DLQI ≥4	EASI 75	EASI 50
Placebo			
Upadacitinib 15 mg			
Upadacitinib 30 mg			
Dupilumab 300 mg Q2W			

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks

B.2.9.4.3.2 Adolescent network

The results below indicate that upadacitinib 15 mg monotherapy is the most efficacious treatment based on SUCRA.

Table 29: Adolescent network – OR and 95% CrI for pairwise comparisons (FE) (All observed, monotherapy network)

EASI 75	Placebo	Upadacitinib 15 mg	Dupilumab 300 mg Q2W
Placebo		[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]		[redacted]
Dupilumab 300 mg Q2W	[redacted]	[redacted]	

EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks

Table 30: Adolescent network – SUCRA ranking (FE) (All observed, monotherapy network)

	EASI 75
Placebo	[redacted]
Upadacitinib 15 mg	[redacted]
Dupilumab 300 mg Q2W	[redacted]

EASI: Eczema Area and Severity Index, Q2W: Every 2 Weeks

B.2.9.4.4 Heterogeneity

Potential sources of heterogeneity across the included RCTs were identified:

1. Imputation methods for missing outcomes data
2. Baseline characteristics identified a priori from published clinical research to be potential treatment effect modifiers
3. Baseline (placebo) risks

B.2.9.4.4.1 Imputation methods

For the primary analysis, all dupilumab studies used NRI for missing data at week 16. In addition, the upadacitinib studies handled missing values due to COVID-19 using NRI incorporating multiple imputation (NRI-C) and this data was presented in Section B.2.6.

However, missing data due to COVID-19 could be due to logistical issues (e.g. AD patients unable to attend the hospital due to it being overwhelmed with COVID-19 caseload) or due to patients having COVID-19 and being unable to attend follow-up visits. This was observed for a limited number of visits and is not expected to have a significant impact on results.

The reporting of sample sizes for analysis was different between the dupilumab trial publications and TA534 for DLQI and EASI 50 + DLQI ≥4 end-points. TA534 reported the complete sample at randomisation for EASI 50 + DLQI ≥4 while the trial publications reported a subset when presenting the DLQI results.

We believe the reported subset for the DLQI end-point in the primary publications were those patients with baseline DLQI measures ≥4 only (i.e., patients with DLQI <4 at baseline were excluded because the DLQI response threshold of a reduction of 4 points or more could not be met). Substantially more patients randomised to the placebo arm were excluded in the published trials but included in the TA534 analysis. Indeed, when comparing total sample size reported in the CAFÉ publication and TA534, 12% of patients were excluded in the placebo arm vs <1% in the dupilumab arm in the CAFÉ trial. This means that placebo EASI-50 + DLQI ≥4 rate may be lower in the TA534 analysis than it would be in an analysis using data directly from the trials, which in turn biases upward the dupilumab treatment effect (by artificially depressing the placebo response rate) in TA534.

B.2.9.4.4.2 Baseline characteristics

The following baseline characteristics were identified *a priori* from published clinical research[67-69] as potential treatment effect modifiers:

- Age
- Gender
- Duration of disease
- Baseline severity (i.e., baseline EASI, baseline IGA, baseline WP-NRS, baseline DLQI)

Tables listing the baseline characteristics are listed in Appendix D.2.1. Baseline patient characteristic plots were used to indicate heterogeneity.

Patient age was similar in trials used for adult systemic-exposed combination therapy network, however, there were modest differences in age across the trials in adult systemic-exposed patients receiving monotherapy and in adolescents. It was noted that 95% CIs of patient age by trial arm calculated from reported standard deviations (SDs) all overlap, suggesting that differences in patient age are not significant.

Trials within the adult systemic-exposed networks generally contained more men than women, with both adult networks having an overall average of approximately 65% male patients. The adolescent network contained a more even gender split, with the network having an overall average of 49% male patients. Modest heterogeneity was observed between trials with respect to patient gender within the adult systemic-exposed monotherapy and adolescent network while trials were

generally less heterogeneous within the adult systemic exposed combination therapy network.

Modest differences were also observed in disease duration between trials within the adult systemic-exposed monotherapy network, while disease duration was generally similar between trials within the adult systemic-therapy combination therapy and adolescent networks.

Severity at baseline in respect to EASI, IGA, WP-NRS, and DLQI/CDLQI scores were similar across trials within all networks.

In summary, there appeared to be minimal cross-study heterogeneity with respect to baseline patient characteristics in the networks and it was not considered necessary to adjust for these characteristics in the analysis.

B.2.9.4.4.3 Baseline (placebo) risk

Placebo response rates of each outcome were assessed across the included RCTs.

GLMM with the logit transformation were fitted using the R function *metaprop ()* from R package meta[70,71]. Data for binary outcomes from the included RCTs, GLMM estimates, I^2 statistics and p-values for the Wald-type test of heterogeneity are presented in Table 31. An I^2 statistic of >50% was considered indicative of heterogeneity[72].

The base case data for adult systemic-exposed has some evidence of heterogeneity, however the adolescent base case has no evidence of heterogeneity.

For those end-points with evidence of heterogeneity, we attempted to estimate baseline risk adjusted models. However, these baseline risk adjusted models either did not converge per the Potential Scale Reduction Factor (PSRF) <1.05 criteria (potentially due to the small number of studies in the networks) and/or the baseline adjustment regression term (B) was not found to be significant. Furthermore, CI for baseline placebo risks overlapped in all instances. We therefore do not consider this heterogeneity to be overly problematic.

Data in *red italics* represents the base case.

Table 31: Assessment of placebo response rate heterogeneity (adult systemic-exposed and adolescent)

Network	End-point	Response rate	ln (odds)	SE ln (odds)	I^2 statistic	Heterogeneity p-value
Adult systemic-exposed						
All observed, monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All observed, combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary, monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary, combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescent						
All observed, monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary, monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, SE: Standard Error.

B.2.9.5 Adult systemic-eligible NMA

B.2.9.5.1 Studies identified in the SLR

The initial SLR did not identify any RCTs to allow connectivity between upadacitinib and CsA in the network for this population. A subsequent SLR, which considered non-comparative and observational studies was carried out to inform this NMA, see Appendix D.1.2. This SLR led to the identification of a paper published by Ariëns *et al*. in 2019[73], which indirectly compared dupilumab vs CsA using EASI 50 and EASI 75 end-points.

Ariëns used patient-level data from the phase III dupilumab study CHRONOS and data from patients receiving CsA as part of their treatment at the Department of Dermatology and Allergology, University Medical Center (UMC) Utrecht (Netherlands).

Concomitant use of TCS was permitted for patients treated with CsA and required for the CHRONOS study which evaluated dupilumab in combination with TCS, therefore the AD UP trial was selected as the source of efficacy for upadacitinib.

No data was collected on the use of rescue medication within the UMC Registry meaning that no censoring was applied for responders experiencing flares. This corresponds to the all observed dataset definition used in the adult systemic-exposed and adolescent NMAs. To ensure consistency, the all observed dataset was sourced from AD UP for upadacitinib[47] and from TA534 for dupilumab (since the CHRONOS publication[74] only reported the primary dataset).

The dataset presented for CsA in Ariëns included patients both naïve and previously exposed to systemic therapies, therefore the overall trial populations were selected from AD UP and CHRONOS to ensure consistency.

Ariëns performed a logistic regression analysis to assess the efficacy outcomes for each end-point. The dependent variables were EASI 50 and EASI 75 and were reported as binary variables (achieved or not achieved) and the focal regressor was a treatment indicator for CsA vs dupilumab use.

Covariates considered in the logistic regression were age, gender, EASI score and thymus and activation-regulated chemokine (TARC) level (where available) and adjusted-weighting was carried out according to these baseline data. Patients with missing baseline TARC levels or EASI scores were excluded from the analysis.

Coefficients from the adjusted regression models were then used to estimate the mean predicted rate of responders under each treatment scenario (dupilumab vs CsA) for the CHRONOS and UMC Utrecht populations separately. This enabled the prediction of responder rates for dupilumab and CsA within each of the study populations.

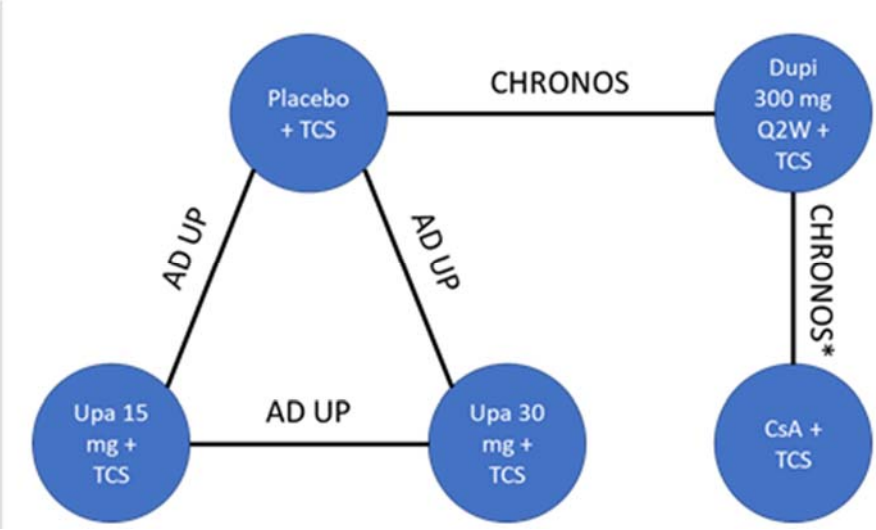
For this NMA, in order to form a network of evidence with a common comparator we have selected the estimates of CsA efficacy within the CHRONOS population from Ariëns et al. The CsA efficacy estimated within the CHRONOS study could then be considered as a hypothetical additional arm of the CHRONOS trial, allowing an NMA of upadacitinib vs CsA to be carried out.

B.2.9.5.2 Networks included in the NMA

An NMA was carried out to provide comparative data for upadacitinib vs CsA in the adult systemic-eligible population.

The network plot of included studies is shown in Figure 29 below.

Figure 29: Network plot of all included studies for adult systemic-eligible network (all observed analysis)



CsA: Ciclosporin, Dupi: Dupilumab, Q2W: Every 2 Weeks, TCS: Topical Corticosteroids, Upa: Upadacitinib
*For this NMA, we assumed that CsA can be considered as an additional treatment arm of CHRONOS trial using the CsA efficacy estimated within CHRONOS population reported in Ariëns *et al*. 2019

B.2.9.5.3 Results

The main results of the Bayesian all observed analyses are detailed below for each of the outcomes of interest. These results in *red italics* reflect the data used in the base case.

Both models (FE and RE models) indicated an appropriate model fit. The FE and RE models yielded similar deviance information criteria (DIC) and residual deviance although they were marginally smaller for the FE. Both models converged and their leverage plots suggested that the models are not problematic. The DIC suggested that there is little to choose between the two models and the FE model was preferred since it is easier to interpret.

Appendix D provides further details of the all observed analysis.

EASI 75 was selected as the base case in the CEA for the adult systemic-eligible population, results are shown in *red italics* in [redacted]

Table 32

For the chosen analysis (FE model), the results suggested that systemic-eligible adult patients, [redacted]

[redacted]

[redacted]

Table 32: Adult systemic-eligible network – OR and 95% CrI for pairwise comparisons (FE) (All observed, combination network)

	Placebo + TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS	CsA + TCS	Dupilumab 300 mg Q2W + TCS
EASI 50					
Placebo + TCS		[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + TCS	[redacted]		[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]		[redacted]	[redacted]
CsA + TCS	[redacted]	[redacted]	[redacted]		[redacted]
Dupilumab 300 mg Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]	
EASI 75					
Placebo +TCS		[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg + TCS	[redacted]		[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]		[redacted]	[redacted]
CsA + TCS	[redacted]	[redacted]	[redacted]		[redacted]
Dupilumab 300 mg Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]	

CsA: Ciclosporin, EASI: Eczema Area and Severity Index, Q2W: Every 2 weeks, TCS: Topical corticosteroids

Table 33: Adult systemic-eligible network – SUCRA ranking (FE) (All observed, combination network)

	EASI 50	*EASI 75*
Placebo +TCS	[redacted]	[redacted]
Upadacitinib 15 mg + TCS	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]
CsA + TCS	[redacted]	[redacted]
Dupilumab 300 mg Q2W + TCS	[redacted]	[redacted]

CsA: Ciclosporin, EASI: Eczema Area and Severity Index, Q2W: Every 2 weeks, TCS: Topical corticosteroids

B.2.9.5.4 Heterogeneity

B.2.9.5.4.1 Baseline characteristics

The baseline characteristics exhibit significant heterogeneity – with differences seen in

- Duration of AD (24-25 years for upadacitinib, 30 years for dupilumab and no data for CsA)
- Baseline EASI score (29-30 for upadacitinib, 34 for dupilumab and 19 for CsA)
- % of patients previously exposed to systemic therapy (57%-60% for upadacitinib, 41% for dupilumab and 30% for CsA).

B.2.9.5.4.2 Baseline (placebo) risk

Assessment of placebo rate heterogeneity was carried out using the same methods as the adult systemic-exposed NMA.

The results of the assessment of the placebo response rate for EASI 50 and EASI 75 endpoints are reported in Table 34 below. Placebo baseline responses were obtained only from AD UP and CHRONOS trials as the Ariëns *et al*. 2019 does not include placebo.

Table 34: Assessment of placebo response rate heterogeneity (adult systemic-eligible)

Network	End-point	Response rate	ln (odds)	SE ln (odds)	I^2 statistic	Heterogeneity p-value
All observed, combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EASI: Eczema Area and Severity Index, SE: Standard error.

The assessment of placebo rate heterogeneity indicates that there is no heterogeneity across the placebo-effect studies included in the network NMA with I^2 < 50% for both end-points. This suggests that the AD UP and CHRONOS studies included in the NMA are similar in terms of parameters that are potential treatment effect modifiers.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

The NMAs do not capture a number of additional benefits associated with upadacitinib treatment, such as rapid onset of action, demonstrated by improvement in itch, skin pain and sleep within 1 week of upadacitinib initiation.

These end-points are not reflected in the NMAs, due to a lack of comparative data in the dupilumab trials and for the subgroups of interest, however they are key to fully understand treatment benefits.

B.2.9.6.1.1 Adult systemic-exposed

A difference in denominator between DLQI in the dupilumab publication and composite end-point in TA534 may have led to an overestimation of the relative effect of dupilumab vs placebo in TA534. This may also impact the NMA output in favour of dupilumab as detailed in B.2.9.4.4.1.

Data on CsA-exposed patients extracted from the upadacitinib studies does not fully align with the sub-population used in TA534 (CAFÉ-like population) since patients with a contra-indication to CsA were not identified in the upadacitinib data. However, UK experts felt that this was an appropriate approach since contra-indication to CsA would not affect response as it is not considered a treatment effect modifier[1].

B.2.9.6.1.2 Adolescent

We were unable to carry out an NMA for the systemic-exposed adolescent population, due to a lack of data in systemic-exposed individuals. One identified abstract reported data from the AD ADOL trial for adolescent patients with moderate to severe AD and with an inadequate response to CsA however, the sample size was very small (n=11 for dupilumab)[60].

It was considered infeasible to perform an NMA on this subgroup, instead an analysis in the overall trial population (adolescent population of moderate to severe AD inadequately controlled by topical therapy) was considered. It was noted that statistical tests of interaction were found to be non-significant in the upadacitinib trial results between CsA-exposed and CsA-naïve adolescent population.

This approach was discussed with UK clinical experts who suggested that results from the overall trial population could be extrapolated to adolescents previously exposed to CsA since differences in efficacy would not be expected between the two groups. UK clinical experts also confirmed that they would be comfortable using upadacitinib in systemic-exposed adolescent patients based on the efficacy data from the adult population.

B.2.9.6.1.3 Adult systemic-eligible

The main limitation of this analysis is that the Ariëns study is an ITC[73]. The patient populations in the Ariëns study were obtained from different sources: the dupilumab data from the phase III RCT (CHRONOS) and the CsA data from records of patients receiving treatment with CsA at the Department of Dermatology and Allergology at UMC. Although logistic regression including achievement of EASI 50 and EASI 75, gender, baseline EASI, and baseline TARC level was carried out, this cannot replace randomisation in an RCT, since it only accounts for the known covariates.

Discrepancy was observed across the studies in terms of baseline characteristics, including those that were considered as treatment effect modifiers. For instance, the proportion of patients previously exposed to systemic therapy, duration of AD and baseline EASI differs across the studies, introducing an additional source of bias.

However, assessment of placebo response rate heterogeneity indicated that there is no heterogeneity across the studies included in the NMA with I^2 <50% for both end-points, suggesting that the studies included in the NMA are similar in terms of potential treatment effect modifying factors.

B.2.10. Adverse reactions

Upadacitinib was well tolerated in the three registration studies (Measure UP 1, Measure UP 2 and AD UP)[45-47].

The safety profile of upadacitinib in Heads UP, which compared upadacitinib 30 mg vs dupilumab (both as monotherapy), was consistent with that seen in the three registration studies.

B.2.10.1 Discontinuations

Upadacitinib resulted in consistently low rates of discontinuation due to treatment-emergent AE (TEAE) in all three registration studies vs placebo during the 16-week double-blind period, see Table 35.

- Measure UP 1: in the overall population discontinuation rates were lower with upadacitinib than with placebo, no adolescents discontinued treatment.
- Measure UP 2: in the overall population discontinuation rates were lower with upadacitinib than with placebo, in the adolescent population, none of the patients in the upadacitinib 30 mg population discontinued treatment.
- AD-UP: in the overall population discontinuation rates were lower with upadacitinib than with placebo, in the adolescent population, none of the patients in the upadacitinib 30 mg population discontinued treatment.

Table 35: TEAE leading to discontinuation in the double-blind period[45-47]

	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	Upadacitinib 15 mg vs placebo		Upadacitinib 30 mg vs placebo	
				Absolute risk (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)	Relative risk (95% CI)
Measure UP 1							
Overall population	N=281 12 (4.3%)	N=281 4 (1.4%)	N=285 11 (3.9%)	0.03 (0.00, 0.06)	0.33 (0.11, 1.02)	0.00 (-0.03, 0.04)	0.90 (0.41, 2.01)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Measure UP 2							
Overall population	N=278 12 (4.3%)	N=276 11 (4.0%)	N=272 7 (2.5%)	0 (-0.03, 0.037)	0.92 (0.414, 2.057)	[redacted]	0.6 (0.238, 1.492)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo +TCS	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg +TCS	Upadacitinib 15 mg + TCS vs placebo + TCS		Upadacitinib 30 mg + TCS vs placebo + TCS	
AD UP							
Overall population	N=303 7 (2.3%)	N=300 4 (1.3%)	N=297 4 (1.3%)	0.01 (-0.01, 0.03)	0.58 (0.17,1.95)	0.01 (-0.01, 0.03)	0.58 (0.17, 1.97)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

CI: Confidence intervals, TCS: Topical Corticosteroids.

B.2.10.2 Treatment emergent adverse events

For the three registration studies, TEAE are listed below for each study for the overall population (Table 36, Table 37 and Table 38) and in Appendix B (Section B.3.1) for the adolescent population.

The tables list the following

- Any TEAE
- Any serious AE (SAE)
- Severe TEAE
- Any TEAE with reasonable possibility of being related to study drug
- TEAE occurring in ≥5% of patients in any arm during the 16-week double-blind period
- Any TEAE leading to death

The tables show that:

- There were no deaths resulting from TEAE.
- No new safety signals were observed in the overall population compared with the known safety profile of upadacitinib.
- TEAE were slightly increased in the upadacitinib arms vs placebo, with a dose dependent effect.
- There were no TEAE occurring in ≥5% of patients in any arm during the 16-week double-blind period in Measure UP 2. Acne, upper respiratory tract infection and nasopharyngitis were the most frequently reported TEAE occurring in ≥5% of patients, both in the overall population and the adolescent population in Measure UP 1 and AD UP.
- No venous thromboembolism (VTE) or major adverse cardiovascular events (MACE) were seen in the upadacitinib treatment arms.
- Most (~75%) cases of acne were mild, some were moderate, and there was one severe case of acne in Measure UP 1 in the 30 mg arm.
- Adolescents reported a similar pattern of TEAE to the overall population, please see Appendix B, Section B.3.1.

In Heads UP, the comparative study vs dupilumab, a similar picture was seen.

- There was one death resulting from TEAE. A patient who died from fatal bronchopneumonia secondary to beta hemolytic streptococcal infection, influenza, pneumonia, methicillin-resistant staphylococcal infection. [redacted]
- No new safety signals were observed in the overall population compared with the known safety profile of upadacitinib.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

For details, please see Table 39 and Table 40.

Table 36: Measure UP 1 (overall population) – TEAE occurring in ≥5% of patients in any arm during the double-blind period[45]

	Placebo (n=281)	Upadacitinib 15 mg (n=281)	Upadacitinib 30 mg (n=285)	Upadacitinib 15 mg vs placebo		Upadacitinib 30 mg vs placebo	
				Absolute risk (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)	Relative risk (95% CI)
Any TEAE	166 (59.1%)	176 (62.6%)	209 (73.3%)	-0.04 (-0.12, 0.05)	1.06 (0.93, 1.21)	-0.14 (-0.22, -0.07)	1.24 (1.1, 1.4)
Any SAE	8 (2.8%)	6 (2.1%)	8 (2.8%)	0.01 (-0.02, 0.03)	0.75 (0.26, 2.13)	0 (-0.03, 0.03)	0.99 (0.38, 2.59)
Any severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE with reasonable possibility of being related to study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to death	0	0	0				
TEAE occurring in ≥5% of patients in any arm during the double-blind period							
Acne	6 (2.1%)	19 (6.8%)	49 (17.2%)	-0.05 (-0.08, -0.01)	3.17 (1.28, 7.81)	-0.15 (-0.2, -0.1)	8.05 (3.51, 18.5)
Upper respiratory tract infection	20 (7.1%)	25 (8.9%)	38 (13.3%)	-0.02 (-0.06, 0.03)	1.25 (0.71, 2.2)	-0.06 (-0.11, -0.01)	1.87 (1.12, 3.14)
Nasopharyngitis	16 (5.7%)	22 (7.8%)	33 (11.6%)	-0.02 (-0.06, 0.02)	1.38 (0.74, 2.56)	-0.06 (-0.1, -0.01)	2.03 (1.15, 3.61)
Headache	12 (4.3%)	14 (5.0%)	19 (6.7%)	-0.01 (-0.04, 0.03)	1.17 (0.55, 2.48)	-0.02 (-0.06, 0.01)	1.56 (0.77, 3.16)
Blood CPK increased	7 (2.5%)	16 (5.7%)	16 (5.6%)	-0.03 (-0.06, 0)	2.29 (0.96, 5.47)	-0.03 (-0.06, 0)	2.25 (0.94, 5.39)
Atopic dermatitis	26 (9.3%)	9 (3.2%)	4 (1.4%)	0.06 (0.02, 0.1)	0.35 (0.17, 0.73)	0.08 (0.04, 0.12)	0.15 (0.05, 0.43)

CI: Confidence Interval, CPK: Creatine Phosphokinase, TEAE: Treatment Emergent Adverse Event, SAE: Serious Adverse Event.

Table 37: Measure UP 2 (overall population) – TEAE occurring in ≥5% of patients in any arm during the double-blind period[46]

	Placebo (n=278)	Upadacitinib 15 mg (n=276)	Upadacitinib 30 mg (n=282)	Upadacitinib 15 mg vs placebo		Upadacitinib 30 mg vs placebo	
				Absolute risk (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)	Relative risk (95% CI)
Any TEAE	146 (52.5%)	166 (60.1%)	173 (61.3%)	-0.08 (-0.16, 0.01)	1.15 (0.99, 1.33)	-0.11 (-0.19, -0.03)	1.21 (1.05, 1.4)
Any SAE	8 (2.9%)	5 (1.8%)	7 (2.5%)	0.01 (-0.01, 0.04)	0.63 (0.21, 1.9)	0 (-0.02, 0.03)	0.89 (0.33, 2.43)
Any severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE with reasonable possibility of being related to study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to death	0	0	0				

CI: Confidence Interval, TEAE: Treatment Emergent Adverse Event, SAE: Serious Adverse Event

Table 38: AD UP (overall population) – TEAE occurring in ≥5% of patients in any arm during the double-blind period[47]

	Placebo +TCS (n=303)	Upadacitinib 15 mg + TCS (n=300)	Upadacitinib 30 mg +TCS (n=297)	Upadacitinib 15 mg + TCS vs placebo		Upadacitinib 30 mg + TCS vs placebo	
				Absolute risk (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)	Relative risk (95% CI)
Any TEAE	190 (62.7%)	200 (66.7%)	215 (72.4%)	-0.04 (-0.12, 0.04)	1.06 (0.94, 1.2)	-0.1 (-0.17, -0.02)	1.15 (1.03, 1.29)
Any SAE	9 (3.0%)	7 (2.3%)	4 (1.3%)	0.01 (-0.02, 0.03)	0.79 (0.3, 2.08)	0.02 (-0.01, 0.04)	0.45 (0.14, 1.46)
Any severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE with reasonable possibility of being related to study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE leading to death	0	0	0	0 (0, 0)		0 (0, 0)	
TEAE occurring in ≥5% of patients in any arm during the double-blind period							
Nasopharyngitis	34 (11.2%)	37 (12.3%)	40 (13.5%)	-0.01 (-0.06, 0.04)	1.1 (0.71, 1.7)	-0.02 (-0.08, 0.03)	1.2 (0.78, 1.84)
Acne	6 (2.0%)	30 (10.0%)	41 (13.8%)	-0.08 (-0.12, -0.04)	5.05 (2.13, 11.96)	-0.12 (-0.16, -0.08)	6.97 (3, 16.17)
Upper respiratory tract infection	22 (7.3%)	21 (7.0%)	23 (7.7%)	0 (-0.04, 0.04)	0.96 (0.54, 1.72)	0 (-0.05, 0.04)	1.07 (0.61, 1.87)
Oral herpes	5 (1.7%)	10 (3.3%)	23 (7.7%)	-0.02 (-0.04, 0.01)	2.02 (0.7, 5.84)	-0.06 (-0.09, -0.03)	4.69 (1.81, 12.18)
Blood CPK increased	7 (2.3%)	13 (4.3%)	18 (6.1%)	-0.02 (-0.05, 0.01)	1.88 (0.76, 4.64)	-0.04 (-0.07, -0.01)	2.62 (1.11, 6.19)
Headache	15 (5.0%)	15 (5.0%)	14 (4.7%)	0 (-0.04, 0.03)	1.01 (0.5, 2.03)	0 (-0.03, 0.04)	0.95 (0.47, 1.94)
Dermatitis atopic	20 (6.6%)	11 (3.7%)	2 (0.7%)	0.03 (-0.01, 0.06)	0.56 (0.27, 1.14)	0.06 (0.03, 0.09)	0.1 (0.02, 0.43)

CI: Confidence Interval, CPK: Creatine Phosphokinase, TCS: Topical Corticosteroids, TEAE: Treatment Emergent Adverse Event, SAE: Serious Adverse Event

Table 39: Heads UP – TEAE occurring in ≥5% of patients in any arm during the double-blind period[49]

	Dupilumab 300 mg (n=344) n (%)	Upadacitinib 30 mg (n=348) n (%)	Upadacitinib 30 mg vs dupilumab	
			Absolute risk (95% CI)	Relative risk (95% CI)
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
AE with reasonable possibility of being drug related	[redacted]	[redacted]	[redacted]	[redacted]
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to death	[redacted]	[redacted]	[redacted]	
TEAE occurring in ≥5% of patients in any arm during the double-blind period				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE: Adverse Event, CI: Confidence Interval, SAE: Serious Adverse Event, TEAE: Treatment Emergent Adverse Event

Table 40: Heads UP – AE of special interest in any arm during the double-blind period[49]

	Dupilumab 300 mg (n=344) n (%)	Upadacitinib 30 mg (n=348) n (%)	Upadacitinib 30 mg vs dupilumab	
			Absolute risk (95% CI)	Relative risk (95% CI)
Serious infections	2 (0.6%)	4 (1.1%)	-0.01 (-0.02, 0.01)	1.98 (0.36, 10.72)
Opportunistic infection excluding TB and herpes zoster	[redacted]	[redacted]	[redacted]	
Herpes zoster	[redacted]	[redacted]	[redacted]	[redacted]
Active tuberculosis	[redacted]	[redacted]	[redacted]	[redacted]
Any malignancy	[redacted]	[redacted]	[redacted]	[redacted]
NMSC	1 (0.3%)	0	0 (0, 0.01)	
Malignancy other than NMSC	[redacted]	[redacted]	[redacted]	
Lymphoma	[redacted]	[redacted]	[redacted]	
Hepatic disorder	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated gastrointestinal perforations	[redacted]	[redacted]	[redacted]	
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	[redacted]	
CPK elevation	[redacted]	[redacted]	[redacted]	[redacted]
Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]

Adjudicated MACE	[redacted]	[redacted]	[redacted]	
Adjudicated venous thromboembolic events (fatal and non-fatal)	0	0	0 (0, 0)	

AE: Adverse Event, CI: Confidence Intervals, CPK: Creatine Phosphokinase, MACE: Major Adverse Cardiac Events, NMSC: Non-Melanoma Skin Cancer, TB: Tuberculosis

B.2.10.3 Drug-related adverse events

Drug-related AE occurring in ≥2% of patients in any arm during the double-blind period are listed in Appendix B, Section B.3.2.

The most frequently reported drug-related AE was acne in all three studies, with [redacted] and [redacted] of patients in the upadacitinib 15 mg arm and [redacted] and [redacted] of patients in the upadacitinib 30 mg arm of Measure UP 1, Measure UP 2 and AD UP respectively.

Early data for Heads UP provides information on patients with TEAE with a reasonable possibility of being related to study drug, please see Appendix B, Section B.3.2 for tabulation of data.

The most common TEAE with a reasonable possibility of being related to study drug with upadacitinib were [redacted]

The most common TEAE with a reasonable possibility of being related to study drug with dupilumab were [redacted]

B.2.11. Ongoing studies

All four pivotal studies are ongoing, please see publication plan (Table 5). No other studies are planned.

B.2.12. Innovation

Upadacitinib is an oral QD selective and reversible JAK inhibitor, engineered to have greater potency for JAK1 vs JAK2, JAK3 and TYK2, thereby targeting multiple cytokines involved in the pathogenesis of AD through inhibition of shared signalling pathways.

Upadacitinib's innovation lies not only with its mode of action, but also with its clinical profile in terms of an extremely rapid onset of action and magnitude of response, making upadacitinib a step change in the management of patients with moderate to severe AD. Importantly, it also provides patients with an oral treatment option.

Furthermore, efficacy is consistent regardless of whether upadacitinib is used as monotherapy or in combination with TCS. This represents a potential transformation in the management of AD and subsequent patient care, since existing treatments require concomitant TCS in order to achieve optimum efficacy. This is not the case with upadacitinib, which provides rapid and effective symptomatic relief from AD regardless of whether concomitant TCS are used.

Indeed, upadacitinib showed rapid clinical improvement in a phase II dose finding study and these positive early results meant that upadacitinib was the first oral agent for AD granted breakthrough therapy designation by the US Food and Drug Administration for development in AD[50].

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Findings from the clinical evidence

Three placebo-controlled registration phase III studies, Measure UP 1, Measure UP 2 and AD UP provide consistent and robust evidence to support the use of upadacitinib in people with moderate to severe AD, with significant improvements in all aspects of AD[45-47]. Significant improvements were seen across all age groups.

A head to head study demonstrates that upadacitinib 30 mg provides superior efficacy to dupilumab, the standard of care in systemic-exposed patients. Significantly more patients achieved the primary end-point of EASI 75 by 16 weeks with upadacitinib 30 mg vs dupilumab (71.1% vs 61.1%, p=0.006). Onset of action was significantly quicker with upadacitinib than with dupilumab[49].

[redacted][49].

An extremely rapid onset of action and magnitude of response are characteristic features of upadacitinib.

- Upadacitinib has a rapid onset of action with a clinically meaningful improvement in itch as early as 1 day after starting treatment.
- Patients see 75% skin clearance (achieve EASI 75) as early as week 1 of treatment and 90% clearance (achieve EASI 90) as early as week 2.
- Upadacitinib significantly improves AD symptoms and clears or almost clears the skin in up to 62% of patients by week 16, [redacted]

The symptomatic relief provided by upadacitinib results in significant and rapid improvements in sleep, mental health and QOL.

The early clinical impact is sustained over 16 weeks, [redacted][45-47]. Up to [redacted] of patients receiving upadacitinib remained flare free for the duration of treatment vs [redacted] of patients receiving placebo[45].

Upadacitinib provides rapid and effective symptomatic relief from AD regardless of whether concomitant TCS are used. This is a step change in the management of AD, since existing treatments require concomitant TCS in order to achieve optimum efficacy.

Upadacitinib in combination with TCS reduces the need for steroids, whilst maintaining skin clearance. In the 16-week double-blind period of AD UP, upadacitinib-treated patients experienced more steroid-free days while maintaining a 75% reduction in EASI vs placebo (mean of 34 days with upadacitinib 15 mg, 47 days with upadacitinib 30 mg vs 8 days with placebo, $p<0.001$)[47].

To date, all three placebo-controlled studies have follow-up data for 1 year of treatment, although not in the full study population. [redacted]

Upadacitinib 30 mg showed numerically higher results than upadacitinib 15 mg for all end-points, although the studies were not powered to compare this.

Initial 16-week data from the placebo-controlled registration phase III studies, reveals that AE were generally mild to moderate, with acne, upper respiratory tract infection and nasopharyngitis being the most common AE. Serious AE occurred in 1.3%-2.8% of patients depending on the study and the dose[45-47].

Safety was consistent across adults and adolescents in the placebo-controlled registration phase III studies[45-47]. The safety profile for upadacitinib meant that patients were able to continue treatment with upadacitinib, discontinuation due to AE was low, ranging from 1.3% to 3.9% depending on the study and the dose[45-47].

The head to head study, Heads UP, showed a similar safety profile to the phase III registration studies[49].

NMA were carried out to synthesize evidence for upadacitinib vs dupilumab in the adult-systemic exposed population and the adolescent population and for

upadacitinib vs CsA in the systemic-eligible population. The NMA produced remarkably consistent results across all scenarios, demonstrating that [redacted]

B.2.13.2 Strengths and limitations

Upadacitinib is supported by three large placebo-controlled studies, a fourth study, Heads UP, which compares upadacitinib with dupilumab, has recently reported top-line results. Heads UP is a phase III study in 692 people with moderate to severe AD. The primary end-point is at week 16 (superiority of upadacitinib vs dupilumab in achievement of EASI 75), with a 12 week follow-up period[48].

To date 16-week and some early 52-week data is available for the three placebo-controlled studies (Measure UP 1, Measure UP 2 and AD UP). The studies all follow the same design with a 16-week double-blind period, followed by a 120-week blinded extension. Therefore, by the end of the studies, long-term data will be available for up to 2 years and 8 months.

Upadacitinib has been shown in clinical practice to be an efficacious and well tolerated in patients with RA with an inadequate response to conventional DMARDs and biologic DMARDs[75]. Furthermore, upadacitinib has been studied in >10,500 patients providing additional evidence regarding safety and efficacy.

B.2.13.2.1 Internal validity

The three randomised placebo-controlled registration studies show consistent, significant benefit across all end-points. Benefit with upadacitinib is seen across all subgroups, with the 30 mg dose having a numerically larger effect than the 15 mg dose. The end-points used in the studies are well accepted and validated for use in people with AD, particularly the co-primary end-points of achievement of EASI 75 and IGA score of 0/1 with a clinically meaningful reduction (at least two grade reductions from baseline). Indeed, end-points used in the upadacitinib studies were also studied in the pivotal studies for dupilumab.

A fourth study, head to head of upadacitinib 30 mg vs dupilumab (Heads UP) provides further evidence of benefit in skin clearance and relief of pruritus with upadacitinib. Indeed, patients receiving upadacitinib 30 mg achieved significantly improved and more rapid skin clearance and relief of pruritus vs dupilumab[49].

B.2.13.2.2 External validity

An HTA Advisory Board was held to inform the approach to this submission and ensure the submission reflects clinical practice in the UK [1]. Eight UK experts

attended the Advisory Board and included consultant dermatologists (n=4), a paediatric consultant dermatologist, a clinical dermatology specialist research nurse, a professor of health economics and a professor of health economic methodology[1].

Participants were asked whether they felt the inclusion criteria for the clinical study programme reflected patients with moderate to severe disease in UK clinical practice. The clinicians confirmed the generalisability of the clinical trial programme for upadacitinib to UK clinical practice. They noted that EASI score is preferred for Health Technology Assessment (HTA), but that IGA score is often seen as a more practical and useful measurement of assessment of severity in clinical practice.

Participants also reviewed patient baseline demographics for the clinical trial programme for upadacitinib, looking specifically at Measure UP 1. Overall, the clinicians did not suggest any significant differences or concerns in trial baseline characteristics and their generalisability when compared to the treated UK AD population.

A medical Advisory Board was held, engaging with six UK experts to inform the submission[62].

The submission was also reviewed by three UK clinical experts, which includes two Consultant Dermatologists and one Paediatric Consultant Dermatologist.

B.2.13.3 Burden of disease

AD does not have an impact on life expectancy, although as already discussed it does have a considerable negative impact on QOL and daily life.

AD does not meet the end of life criteria.

B.3 Cost effectiveness

A *de novo* cost-utility analysis was undertaken based on a combined decision tree and Markov model, following the precedent set by the appraisal of dupilumab (TA534).

- A response-based model included four health states: maintenance treatment, BSC-responder, BSC non-responder and death. Costs and benefits were discounted at a rate of 3.5% and a lifetime-equivalent time horizon was used (100 years).
- Three populations are considered as the base cases, in line with the anticipated positioning of upadacitinib in the clinical pathway for moderate to severe AD: adult systemic-exposed, adolescent systemic exposed and adult systemic eligible.
- Response in the model was defined as the composite outcome of EASI 50 + DLQI ≥4 in the adult systemic-exposed population and EASI 75 in the adolescent systemic-eligible and adult systemic-eligible populations. Efficacy rates estimated within an all observed dataset (where patients are considered as responders regardless of rescue medication use) were selected as the base case.
- Utilities values were estimated within the relevant dataset for each population and response threshold.
- Costs and healthcare resource use were captured in the analysis for treatment costs and concomitant medication, administration, monitoring, resource use associated with response or non-response and AE management.

Base case analysis

- In the adult systemic-exposed population, upadacitinib 15 mg and 30 mg are cost-effective. Both doses are dominant vs dupilumab and incremental cost effectiveness ratios (ICER) vs BSC are £9,961/Quality adjusted life year (QALY) and £25,069/QALY for upadacitinib 15 mg and upadacitinib 30 mg, respectively.
- In a scenario using direct evidence from Heads UP, upadacitinib 30 mg monotherapy is dominant vs dupilumab.
- In the adolescent population, upadacitinib 15 mg is cost-effective vs both dupilumab and BSC. Upadacitinib is dominant vs dupilumab and the ICER is £10,173/QALY vs BSC.

- In the adult systemic-eligible population, upadacitinib is cost-effective vs CsA at the 15 mg dose (ICER of £12,929/QALY) and is marginally over the £30,000 threshold (£31,979/QALY) at the 30 mg dose, driven by the increased incremental cost of upadacitinib vs CsA.

B.3.1. Published cost-effectiveness studies

Appendix G describes and compares the methods and results of any published CEA available for the technology and/or the comparator technologies.

An SLR was undertaken to identify published economic evaluations and HTA appraisals to address the decision problem and inform the structure of the economic model. The searches were conducted in July 2020 and updated in October 2020 to identify studies assessing the cost-effectiveness of interventions for patients with moderate to severe AD. The SLR identified two publications reporting CEA, summarised in Table 41. Full details of the search are provided in Appendix G, as well as detailed inclusion/exclusion criteria for the review.

Table 41: Summary list of published UK-based cost-effectiveness studies

TA534, NICE 2018 [2,58]	
Year	2018
Summary of model	CUA conducted to estimate the cost-effectiveness of dupilumab for moderate to severe AD vs BSC in adult patients who have received systemic treatment (defined as systemic-experienced as per CAFÉ trial population [inadequate response or contra-indicated to CsA], and named CAFÉ-like) 1-year decision tree followed by a 4-state Markov model (health states are annual cycles) *Comparators* Dupilumab monotherapy vs BSC Dupilumab combination therapy (+TCS) vs BSC + TCS *Health states* *One year decision tree with 16 and 52 weeks response assessment nodes* Long term Markov model with four health states: Maintenance treatment (dupilumab) BSC responder BSC non-responder Death *Scenario analysis* 1. Dupilumab vs BSC in full licensed population (patients suitable for systemic therapy) 2. Dupilumab vs CsA in licensed population (patients suitable for systemic therapy)
Patient population (average age in years)	38.1 years
QALYs (intervention, comparator)	Data redacted
Costs (currency) (intervention, comparator)	Data redacted

ICER (per QALY gained)	Base case: patients who have failed systemic treatment (systemic-exposed) Dupilumab vs BSC – Monotherapy: £24,703/QALY, Combination therapy: £28,874/QALY Scenario: patients eligible for systemic treatment Dupilumab vs BSC – Monotherapy: £26,729/QALY, Combination therapy: £25,188/QALY Dupilumab vs CsA – Monotherapy: £28,092/QALY, Combination therapy: £25,638/QALY
Scottish Medicines Consortium (SMC) medicines advice on dupilumab[76]	
Year	2018
Summary of model	As per TA534
Patient population	As per TA534
QALYs (intervention, comparator)	Incremental (dupilumab vs BSC) – Monotherapy: 1.41, Combination therapy: 1.81
Costs (currency) (intervention, comparator)	With PAS discount Incremental (dupilumab vs BSC) – Monotherapy: £41,532, Combination therapy: £63,911
ICER (per QALY gained)	With PAS discount Incremental (dupilumab vs BSC) – Monotherapy: £29,504/QALY, Combination therapy: £35,351/QALY

AD: Atopic Dermatitis, BSC: Best Supportive Care, CsA: Ciclosporin, CUA: Cost-utility Analysis, ICER: Incremental Cost-effectiveness Ratio; PAS: Patient Access Scheme, QALY: Quality-Adjusted Life Year, SMC: Scottish Medicines Consortium, TCS: Topical Corticosteroids

B.3.2. Economic analysis

A *de novo* economic model was developed to compare upadacitinib vs relevant comparators from the UK NHS and PSS perspective for the treatment of moderate to severe AD. The model developed was consistent with that used for the NICE TA submission for dupilumab (TA534)[2,58,77]. Adaptations were made where necessary to incorporate the modelling of upadacitinib therapy and additional populations.

B.3.2.1 Patient population

The economic evaluation presented in this submission aligns with the decision problem described in Section B.1.1. As detailed in Section B.1.1, the anticipated marketing authorisation for upadacitinib is the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

The following populations were considered in the economic modelling:

- **Adult systemic-exposed**: defined as adult patients who have received treatment with at least one conventional systemic therapy and had an inadequate response or these treatments were not suitable. This sub-population aligns to the population that NICE recommend dupilumab is used in, making it appropriate for the comparison of upadacitinib vs dupilumab. We have used CsA exposure as a

proxy for systemic treatment since it is the only licensed treatment for AD and to ensure comparability with the dupilumab CAFÉ-like population.

- **Adolescent systemic-eligible**: defined as adolescent patients aged 12-17 years, eligible for conventional systemic treatment and may or may not have received prior conventional systemic treatment(s). This population matches the expected marketing authorisation. The limited data available for evidence synthesis in this population means it was not feasible to separate out systemic-exposed patients.

- **Adult systemic-eligible**: defined as adult patients eligible for conventional systemic treatment. This population includes patients who have yet to receive systemic treatment as well as those who have already received treatment with conventional systemic treatment(s) and had an inadequate response or were unsuitable for treatment. This population matches the expected marketing authorisation.

As described in Section B.2.3, the upadacitinib trials enrolled patients who had moderate to severe AD defined as EASI ≥16, IGA ≥3 and baseline weekly average of daily WP-NRS ≥4, with or without prior exposure to systemic therapies.

- Monotherapy trials: Measure UP 1 and Measure UP 2 compare upadacitinib 15 mg and 30 mg with placebo[45,46] and Heads UP compares upadacitinib 30 mg with dupilumab 300 mg[49].
- Combination trial: AD UP compares upadacitinib 15 mg and 30 mg with placebo with concurrent TCS[47].

B.3.2.1.1 Adult systemic-exposed population

The positioning of the systemic-exposed population aligns with the base case economic analysis in TA534[58,77].

The CAFÉ-like population reported in TA534 was defined as patients exhibiting an inadequate response or intolerant to oral CsA or patients for whom CsA was contra-indicated.

To align with the CAFÉ-like populations, which were used as a proxy for the systemic-exposed population in TA534, data was extracted from a pre-specified subgroup of the upadacitinib studies to provide efficacy information on subsets of CsA-exposed patients.

As described in Section B.2.6.6.2.1, data on contra-indications to CsA was not collected in the upadacitinib trials, leading to a difference in the definition of the CsA-exposed subgroup between the upadacitinib trials and the CAFÉ-like population.

This difference is not expected to impact on efficacy outcomes according to UK clinical experts[1] and both subgroups (Dupilumab CAFÉ-like and Upadacitinib CsA-exposed) are referred to as adult systemic-exposed. Furthermore, efficacy data presented in the CAFÉ trial for both subgroups separately ('CsA-exposed and 'contra-indicated' and 'CsA-exposed only') suggest that dupilumab shows higher response rates in the CsA-exposed and contra-indicated subgroup, therefore this difference, if significant, would favour dupilumab in this analysis.

B.3.2.1.2 Adolescent systemic-eligible population

In the adolescent analysis, data from patients aged 12-17 in Measure UP 1 and Measure UP 2 was extracted to ensure comparability with the dupilumab AD ADOL monotherapy study[59].

In the adolescent population of the upadacitinib clinical trials between 33% and 49% of patients had previous exposure to systemic treatments (Measure UP 1: 41/124, 33%; Measure UP 2: 51/104, 49% and AD UP: 57/126, 45%).

However, as described in B.2.6.6.2.2 the feasibility of comparing upadacitinib in subgroups of adolescent systemic-exposed patients was limited by data availability for comparators. Only one study was identified which reported dupilumab efficacy data for a small subgroup (n=11) of adolescents with prior systemic exposure[60]. No studies were retrieved evaluating CsA in adolescents with moderate to severe AD

Furthermore, CsA is not licensed in patients aged under 16 years, therefore, prior exposure to CsA in adolescents aged 12-16 years would be outside the product licence.

In order to use all the available evidence, upadacitinib was compared with dupilumab in the overall adolescent population, regardless of their prior exposure to systemic treatments.

The anticipated licensed dose for upadacitinib in the adolescent population is 15 mg QD.

No data was available evaluating dupilumab in combination therapy in the adolescent population, therefore, the model considers dupilumab and upadacitinib 15 mg as monotherapy in this population. Nonetheless, clinical opinion is that the cost-effectiveness of combination therapy demonstrated in systemic-exposed adults would be reliable evidence to justify the use of upadacitinib with concomitant TCS in adolescents as age was not seen to be a treatment effect modifier in the upadacitinib clinical trials.

B.3.2.1.3 Adult systemic-eligible population

The ITT population from the AD UP trial[47] was used to derive comparative data vs CsA for the systemic-eligible population using the results of the NMA described in Section B.2.9.5.

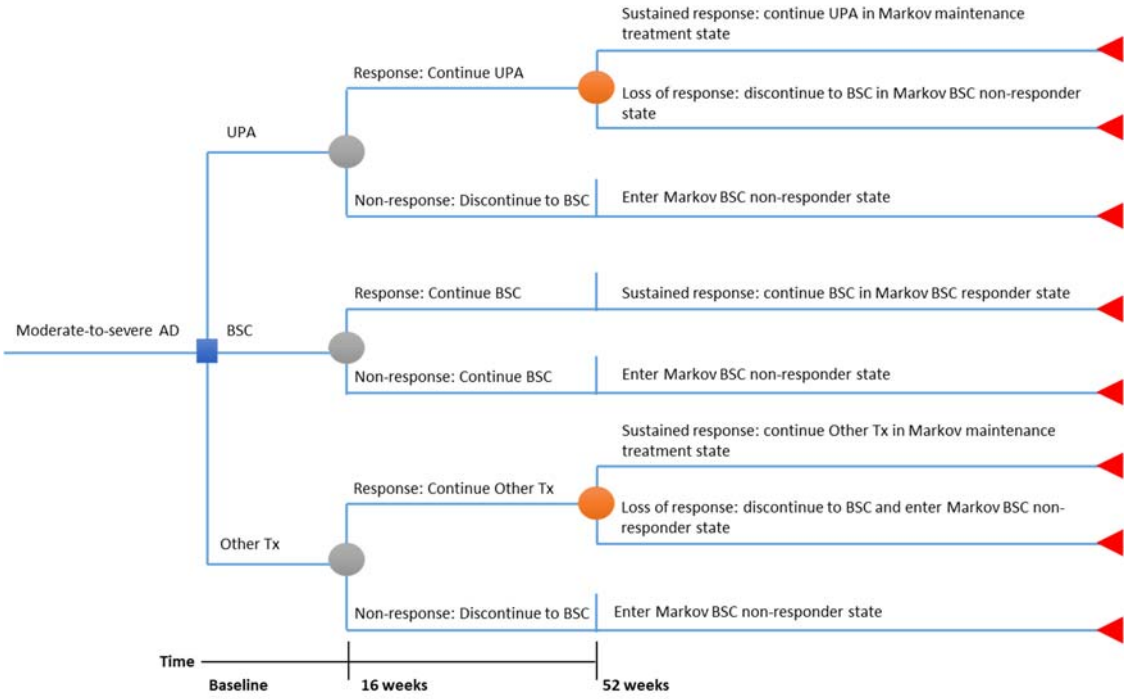
B.3.2.2 Model structure

The de novo cost-effectiveness model was developed in Microsoft Excel 2016® using Visual Basic for Applications (VBA) functionality. The analysis used a combined decision tree and Markov model structure and follows the precedent set by TA534.

The model used a UK NHS and PSS perspective with the results expressed as ICERs (£/QALY) and Incremental Net Monetary Benefit (INMB) (£).

The 1-year decision tree was designed to capture short-term treatment decisions and initial responses to treatment at 16 and 52 weeks. The Markov model reflects the long-term course of AD with treatment response health states starting from Year 2. The Markov cycles are 1-year long, over a lifetime horizon defined as patients reaching 100 years. Figure 30 illustrates the decision tree and Figure 31 the long-term Markov model.

Figure 30: Decision tree model structure



AD: Atopic Dermatitis, BSC: Best Supportive Care, Tx: Treatment, UPA: Upadacitinib

All patients enter the model and receive upadacitinib (±TCS), BSC (±TCS) or comparator treatment which could be dupilumab (±TCS) or CsA +TCS.

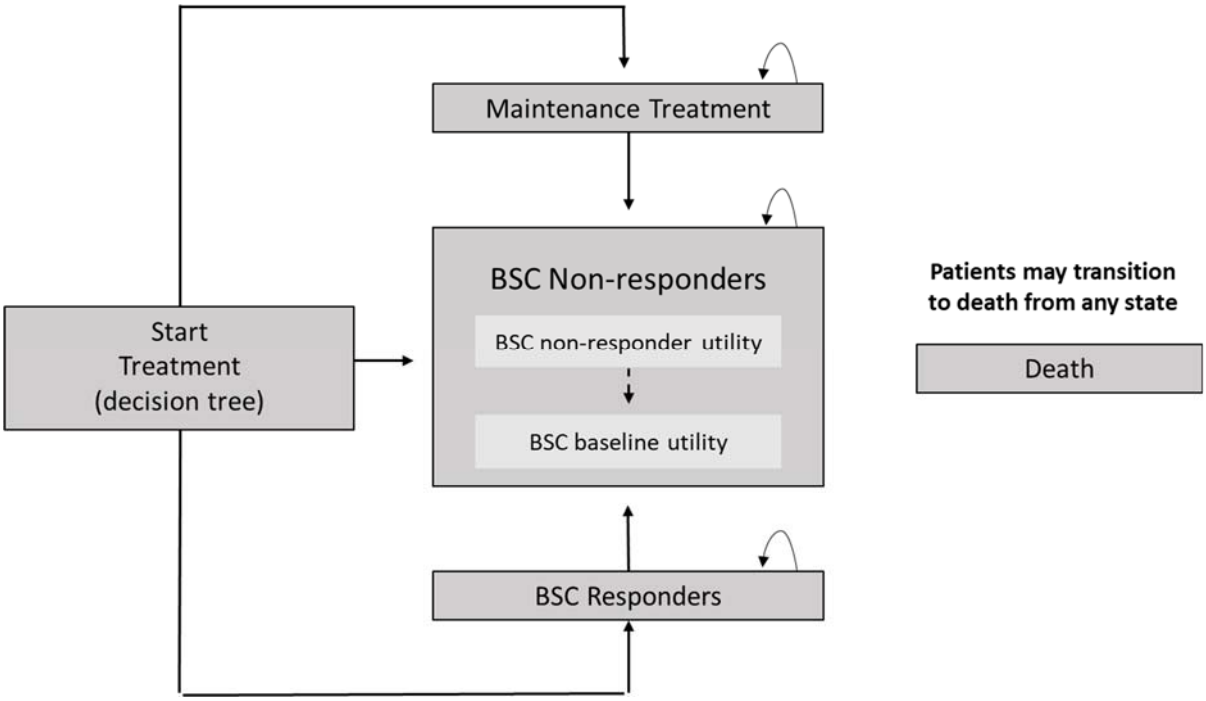
Response to treatment is assessed at 16 weeks, non-responders on active treatment discontinue to BSC, while responders continue with the same treatment for the remainder of the year.

Response is determined by a composite measure of EASI 50 + DLQI ≥4 or EASI 75, depending on the population assessed, please see Section B.3.3.2 for further detail.

At week 52, a second decision node assesses response to therapy which determines the state in which patients enter the Markov model. Costs and QOL associated with each treatment state are captured in the Markov model.

- If response is maintained on upadacitinib or active treatment at 52 weeks, patients enter the maintenance treatment state in the Markov model where they accrue the costs and utilities associated with the selected response level.
- Patients who lose response to treatment or discontinue treatment for other reasons (including AEs, patient or physician preference) transition to the BSC non-responder health state.
- If response is maintained on BSC, patients enter the BSC responder health state.
- If there is a lack of response to BSC, patients enter BSC non-responder health state.

Figure 31: Long-term Markov model



Notes: Transitions to death may occur from any treatment-related state. Arrows to death are omitted from this diagram for simplicity.
BSC: Best Supportive Care

This modelling approach, based on relative change in response from baseline, aligns with the NICE submission for dupilumab (TA534)[58] as well as the original model developed for the first submission to NICE in psoriasis[78] which has been adapted in a range of technology assessments[79-81]. UK clinical experts[1] supported this approach.

Table 42: Features of the economic analysis

Feature	Chosen values	Justification
Time horizon	Lifetime	Adopted to capture all relevant costs and health-related utilities per NICE reference case[82] and aligned with TA534[2,58,77]
Model structure	Decision tree and Markov model	The model structure allows for treatment decisions and maintenance of response over an extended time horizon. It captures impact on HRQOL and cost profile as per TA534[2,58,77].
Cycle length	Decision tree: Week 16 and week 52 Markov model: Annual	Aligned with TA534[2,58,77]
Half-cycle correction	Decision tree: None Markov model: None	In TA534, a half-cycle correction for efficacy measured at week 16 is applied at Week 8 in the decision tree, [2,58,77]. Upadacitinib clinical trial data suggests that many patients exhibit significant response earlier than the week 16 assessment timepoint. Therefore, the

		timepoint for efficacy application in the model was week 8 for upadacitinib. The peak response of dupilumab was observed at week 16 in Heads UP which was therefore selected as the timepoint of efficacy application for dupilumab in the economic model. Response to BSC and CsA was also implemented at week 16.
Treatment waning effect?	Waning applied in the Markov model until Year 10. Probability of sustained QOL benefit BSC: 75% in year 2, 50% in year 3, 25% in year 4 and 0% from year 5 onwards Dupilumab: 98% in year 2, 95% in year 3, 93% in year 4, 92% in year 5 and approx. 1% decrement from year 5 until year 10 Upadacitinib: similar waning assumption as dupilumab CsA: equivalent to BSC	BSC: Waning for BSC was estimated from TA534 which used a panel of clinicians to derive waning estimates. Scenario analysis explore alternative waning distributions Upadacitinib and dupilumab: Given the lack of long-term evidence to assess differences in waning effect between upadacitinib and dupilumab, the same waning rates were applied to both treatments as described in TA534. Year 1-5 from TA534 and an assumption was made for years 6-10. Given that CsA is only given for 1 year and our model does not include subsequent treatment sequencing, we have made an assumption that BSC waning applies when patients discontinue CsA after 1 year.
Non-responders to active treatment revert to BSC until death	Transition to BSC non-responders	Simplifying assumption in the model aligned with TA534[2,58,77]
Source of utilities	Patient level EQ-5D data from upadacitinib pooled phase III trials (Measure UP 1, Measure UP 2, AD UP) were used to generate values by EASI levels and for the subgroups considered EQ-5D data from each individual study can be found in Table 18 (Measure UP 1), Appendix (Section B.2.1) and Table 19 (AD UP) Patient level DLQI data from upadacitinib pooled phase III trials (Measure UP 1, Measure UP 2, AD UP) was used to generate the composite end-point for the base case for the adult systemic-exposed population	Aligned with TA534[2,58,77] Adoption of EQ-5D data is consistent with the NICE reference case[82] Use of DLQI as part of the composite end-point for the adult systemic-exposed population is aligned with TA534[2,58,77]
Disutility associated with treatment of AD flares or AEs are already accounted for in the EQ-5D data from upadacitinib trials	The model does not capture treatment-specific utilities No disutilities for AEs and flares are considered in the model	To avoid double counting given the use of trial-based utilities and data collection frequency. Aligned with TA534[2,58,77]
Source of costs	NHS reference costs, BNF, Drug Tariff, published literature	Aligned with TA534 [2,58,77] Consistent with the NICE reference case[82]
Health effects measured by	QALYs	NICE reference case[82]
Discount rate for benefits and costs	3.5% annually	NICE reference case[82]

Perspective	NHS	NICE reference case[82]
Mortality	General population mortality with no adjustment	Aligned with TA534 base case[2,58,77]

AD: Atopic Dermatitis; AE: Adverse Event, BNF: British National Formulary, BSC: Best Supportive Care, EASI: Eczema Area and Severity Index, EQ-5D: European Quality of Life-5 Dimensions, QOL: Quality of Life, QALY: Quality-adjusted Life Year

B.3.2.3 Intervention technology and comparators

The model compares upadacitinib with active treatment or BSC.

- For adult systemic-experienced patients the comparators are dupilumab and BSC.
- For adolescent systemic-eligible patients the comparators are dupilumab and BSC.
- For adult systemic-eligible patients the comparator is CsA.

Upadacitinib is available as two oral QD doses in adults: 15 mg and 30 mg, either of which can be used as monotherapy (as per Measure UP 1, Measure UP 2 and Heads UP trials) or in combination with TCS (as per AD UP trial). The anticipated licensed dose for upadacitinib in the adolescent population is 15 mg QD.

Treatment with dupilumab was modelled in alignment with TA534[58,77]. Dupilumab is given SC, as an initial loading dose of 600 mg, followed by 300 mg given Q2W.

BSC was defined as a combination of emollients, low-to-mid potency TCS and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs) phototherapy and psychological support. This reflects UK clinical practice[83] and is in line with the definition of BSC in TA534[58,77].

Treatment with CsA was modelled as per clinical advice at 3 mg/kg daily for weeks 1-16 followed by 5 mg/kg daily for the remainder of the year[84]. Treatment with CsA was limited to 1 year. This differs from TA534[58,77] which used a dose of 5 mg/kg daily week 1 to 6 and 3 mg/kg daily week 6 to 52. This was derived from a study comparing mycophenolate sodium vs CsA in patients with long-term severe AD[85], which was used in TA534 to derive comparative data vs dupilumab. A similar dose regimen was observed in a Dutch patient registry (Ariëns, 2019)[73], in which the median dose at baseline was 4.8 mg/kg, falling to 3.3mg/kg at week 12-16. However, we believe that dosing information (3 mg/kg daily rising to 5 mg/kg daily) received from our clinical experts is more robust and reflects current UK practice.

Table 43: Intervention technology and comparators

Treatment	Mode of administration	Dosage	Rationale
Upadacitinib 15 mg	Oral	15 mg QD	Measure UP 1, Measure UP 2[45,46]
Upadacitinib 30 mg	Oral	30 mg QD	Measure UP 1, Measure UP 2[45,46]
Upadacitinib 15 mg + TCS	Oral/topical	15 mg QD + TCS	AD UP[47]
Upadacitinib 30 mg + TCS	Oral/topical	30 mg QD + TCS	AD UP[47] Heads UP[49]
Dupilumab	SC	300 mg Q2W, after a 600 mg loading dose on Day 0	SOLO 1, SOLO 2[54] TA534[58]
Dupilumab + TCS	SC/topical	300 mg Q2W, after a 600 mg loading dose on Day 0 + TCS	CAFÉ[65] CHRONOS[74] TA534[58]
BSC	TCS, TCI, phototherapy, psychological support		Clinical opinion[83] TA534[58]
CsA	3 mg/kg daily week 1 to 16 and 5 mg/kg daily week 16 to 52		Clinical opinion[84]

BSC: Best Supportive Care, CsA: Cyclosporin, Q2W: Every 2 Weeks, QD: Once Daily, SC: Subcutaneous, TCI: Topical Calcineurin Inhibitor, TCS: Topical Corticosteroids.

B.3.3. Clinical parameters and variables

B.3.3.1 Model baseline patient characteristics

Baseline characteristics used in the model are shown below for each of the base case populations: adult systemic-exposed, adolescent systemic-eligible and adult systemic-eligible. For the adult systemic-exposed and the adolescent systemic-eligible populations data is based on a pooled analysis of patients enrolled in Measure UP 1, Measure UP 2 and AD UP. Baseline characteristics are comparable in the monotherapy and combination trials for upadacitinib and therefore the model uses baseline characteristic specific to each subgroup rather than to regimen.

For the adult systemic-eligible population, baseline characteristics are taken from the AD UP study, see Table 9.

Table 44: Baseline characteristics in adult systemic-exposed population

Parameter	Base
Number of patients	476
Age, years, mean (SD)	34.61 (12.85)
Gender (male), n (%)	321 (67.44%)
Weight, kg, mean (SD)	75.92 (18.24)
Baseline worst pruritus, mean score (SD), primary	7.32 (1.53)
Baseline worst pruritus, mean score (SD), all observed	7.29 (1.52)
EQ-5D utility, mean (SD), primary	0.530 (0.28)
EQ-5D utility, mean (SD), all observed	0.532 (0.28)

EQ-5D: European Quality of Life-5 Dimensions, SD: Standard Deviation

Table 45: Baseline characteristics in adolescent systemic-eligible population

Parameter	Base
Number of patients	344
Age, years, mean (SD)	15.54 (1.73)
Gender (male), n (%)	172 (50%)
Weight, kg, mean (SD)	63.06 (16.14)
Baseline worst pruritus, mean score (SD), primary	7.06 (1.78)
Baseline worst pruritus, mean score (SD), all observed	7.01 (1.80)
EQ-5D utility, mean (SD), primary	0.605 (0.28)
EQ-5D utility, mean (SD), all observed	0.596 (0.28)

EQ-5D: European Quality of Life-5 Dimensions, SD: Standard Deviation

Table 46: Baseline characteristics in adult systemic-eligible population

Parameter	Base
Number of patients	785
Age, years, mean (SD)	36.8 (14.13)
Gender (male), n (%)	484 (61.7%)
Weight, kg, mean (SD)	77.22 (19.2)
Baseline worst pruritus, mean score (SD), all observed	7.240 (1.63)
EQ-5D utility, mean (SD), all observed	0.66 (0.26)

EQ-5D: European Quality of Life-5 Dimensions, SD: Standard Deviation

B.3.3.2 Efficacy response model inputs

B.3.3.2.1 Dataset

As discussed in Section B.3.6, the base case analyses use data from the 'all observed' population dataset, in which responders were defined as all patients responding to treatment, regardless of whether they received rescue medication. UK clinical experts[1] supported this approach and reinforced that flares in AD should not define non-response.

Primary data sets were explored in scenario analyses, where available.

B.3.3.2.2 Response definition

The composite outcome of EASI 50 + DLQI ≥4 was selected as the base case response definition in the economic analysis in TA534[58]. This outcome was considered appropriate by the ERG and Committee[86] and aligns with the dupilumab stopping rule. Post hoc data was sourced from the upadacitinib clinical study programme for upadacitinib and from the manufacturer's submission for dupilumab (TA534)[58] in order to generate efficacy estimates via an NMA, see Section B.2.9.4.2.1.

This approach was supported by UK clinical experts[1], who confirmed they commonly use a combination of several outcomes when assessing response including EASI and DLQI scores and suggested that EASI 50 + DLQI ≥4 is a suitable composite outcome.

Therefore, where feasible, the composite end-point of EASI 50 + DLQI≥ 4 was the preferred response definition in the model. However, this is not a primary end-point in clinical trials and limited data was available outside of the scope of TA534. Thus, no evidence reporting the composite end-point for the comparators in the adult and adolescent systemic-eligible populations was identified. Instead, EASI 75 was chosen as it was one of the primary end-points in the upadacitinib trials and aligned with clinical opinion. Scenario analyses consider the single end-points in the systemic-exposed population to enable comparison with the composite end-point.

B.3.3.2.3 Choice of tool to measure response

The efficacy response criteria define which patients continue on treatment or discontinue treatment and move to the non-responder group. The response criteria for each base case are as follows and explained in detail in Section B.2.6.6.

- Adult systemic-exposed: EASI 50 + DLQI ≥4
- Adolescent systemic-eligible: EASI 75

- Adult systemic-eligible: EASI 75

Table 47 illustrates the base cases and scenario analyses, the base cases are in *red italics.*

Table 47: Base cases and scenario analyses, base case in red italics

Base case	Response criteria by data source		Dose		Mono/Combo	
	All observed	**Primary**	**15 mg**	**30 mg**	**Mono**	**Combo**
Adult systemic-exposed	*EASI 50 + DLQI ≥4*	EASI 50 +DLQI ≥4	✓	✓	(✓)	✓
	EASI 50	EASI 50	(✓)	(✓)	(✓)	(✓)
	EASI 75	EASI 75	(✓)	(✓)	(✓)	(✓)
Adolescent systemic-eligible	*EASI 75*	EASI 50	✓		✓	
		EASI 75	(✓)		(✓)	
Adult systemic-eligible	EASI 50		(✓)	(✓)		(✓)
	EASI 75		✓	✓		✓

COMBO: Combination Therapy, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, MONO: Monotherapy

✓base case, (✓) data presented as a scenario.

B.3.3.2.4 Week 16 treatment efficacy

In the adult population, the Heads UP study evaluates upadacitinib 30 mg monotherapy vs dupilumab monotherapy[49]. However, this study did not collect data on the DLQI score limiting the feasibility of the composite end-point and did not evaluate treatments in combination with TCS.

Therefore, the proportion of patients achieving response at week 16 was determined from the NMAs described in Section B.2.9, see Table 48 and Table 49.

Data from Heads UP was explored in scenario analyses using all observed efficacy data at 16 weeks, see Table 50.

Table 48: Response at week 16 (combination therapy) NMA, red italic numbers are base case

Treatment	Percentage of patients achieving EASI response (mean [95% CrI])		
	EASI 50 + DLQI ≥4	EASI 50	EASI 75
Adult systemic-exposed (all observed)			
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]
Dupilumab + TCS	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Adult systemic-exposed (primary)			
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]
Dupilumab + TCS	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Adult systemic-eligible (all observed)			
Upadacitinib 15 mg + TCS	N/A	[redacted]	[redacted]
Upadacitinib 30 mg + TCS	N/A	[redacted]	[redacted]
CsA + TCS	N/A	[redacted]	[redacted]
BSC	N/A	[redacted]	[redacted]

BSC: Best Supportive Care, CrI: Credible Interval, CsA: Ciclosporin, DLQI: Dermatology Life Quality Index, EASI : Eczema Area and Severity Index, N/A: Not Applicable, TCS: Topical Corticosteroid

Table 49: Response at week 16 (monotherapy) NMA, red italic numbers are base case

Treatment	Percentage of patients achieving EASI response (mean [95% CrI])		
	EASI 50 + DLQI ≥4	EASI 50	EASI 75
Adult systemic-exposed (all observed)			
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Adult systemic-exposed (primary)			
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]
Adolescent systemic-eligible (all observed)			
Upadacitinib 15 mg	N/A	N/A	[redacted]
Dupilumab	N/A	N/A	[redacted]
BSC	N/A	N/A	[redacted]
Adolescent systemic-eligible (primary)			
Upadacitinib 15 mg	N/A	[redacted]	[redacted]
Dupilumab	N/A	[redacted]	[redacted]
BSC	N/A	[redacted]	[redacted]

BSC: Best Supportive Care, CrI: Credible Interval, CsA: Ciclosporin, DLQI: Dermatology Life Quality Index, EASI : Eczema Area and Severity Index, N/A: Not Applicable

Table 50: Response at week 16 in Heads UP, all observed data

Treatment	Percentage of patients achieving EASI response (mean)	
	EASI 50	EASI 75
Adult systemic-eligible (all observed)		
Upadacitinib 30 mg	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]

EASI :Eczema Area and Severity Index

B.3.3.2.5 Timepoint for efficacy application

The decision tree component of the economic model includes two response assessment timepoints: one at week 16 and one at week 52.

The upadacitinib clinical trial data suggests that many patients exhibit significant response earlier than the week 16 assessment timepoint, see Figure 8 to Figure 10. Onset of action with upadacitinib is rapid and patients achieve EASI 75 as early as

week 1[45-47]. Therefore, the timepoint for efficacy application in the model was applied at week 8 for upadacitinib.

Similarly, the peak response of dupilumab was observed at week 16 in Heads UP which was therefore selected as the timepoint of efficacy application for dupilumab in the economic model. Response to BSC and CsA was also implemented at week 16.

A conservative approach assuming that response occurred at 16 weeks with all treatments is explored in a scenario analysis.

B.3.3.2.6 Week 52 sustained response

Given that 52-week data is not yet available for all study participants within the upadacitinib trials, data from dupilumab trials was used to calculate the probability of sustained response from week 16 to week 52 per level of response and applied to upadacitinib week 16 data. Conditional probabilities of response at 52 weeks on week 16 for EASI 50 + DLQI ≥4, EASI 50 and EASI 75 were calculated as the ratio of the proportion of responders at week 52 by the proportion of responders at week 16, using the CAFÉ+CHRONOS-CAFÉ like data for the combination analyses and from SOLO-CAFÉ-like for the monotherapy analyses reported in TA534.

Data is available for this approach for the adult systemic-exposed population; however, this data is not available for the adult and adolescent systemic-eligible populations. Therefore, for these systemic-eligible populations the adult systemic-exposed conditional probabilities have been applied.

In the absence of 52-week data for CsA, the probability of sustained response for CsA was derived from the mean probabilities of sustained response of dupilumab and BSC and applied to CsA week 16 response rates. This is a conservative approach, given that real world data suggest that around 70% of patients discontinue treatment with CsA due to ineffectiveness by the end of year 1[87].

Table 51: Probability of response at 52 weeks conditional on response at 16 weeks

Treatment	EASI 50 + DLQI ≥4	EASI 50	EASI 75	Reference
Upadacitinib or dupilumab	93.9%	94.5%	82.1%	TA534[58]
CsA	85.3%	87.9%	76.3%	Assumption (mean of upadacitinib/dupilumab and BSC)
BSC	76.7%	81.3%	70.6%	TA534[58]

BSC: Best Supportive Care, CsA: Ciclosporin, DLIQ: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index

B.3.3.3 Annual discontinuation rate

The annual probability of discontinuation represents the annual rate at which patients discontinue their AD treatment due to lack of long-term efficacy, AEs, patient or physician preference.

Discontinuation rates contribute to the rate of patient progression from maintenance treatment health state to BSC non-responder health state each year in the Markov model.

Given that complete 52-week data from the upadacitinib trials are not yet available, annual discontinuation rates have been adopted from the NICE TA534 dupilumab appraisal. Data from the dupilumab open label extension (OLE) has been used, since it provides the longest period over which discontinuation is measured in the clinical evidence. This was tested as a scenario analysis in the dupilumab revised submission.

An annual discontinuation rate was applied for all comparators and all end-points of 6.3% for monotherapy using data from SOLO-CONTINUE[58] and 6.4% for combination therapy[77] which represents the discontinuation rate from treatment at week 52 in the dupilumab OLE.

This limitation is not specific to AD and a similar solution has been applied to Single Technology Appraisal (STA) submissions in plaque psoriasis[81] and accepted by the ERG and Committee.

B.3.3.4 Adverse events

AEs considered in the model are based on those reported in the upadacitinib and dupilumab clinical trials with an incidence of >5%. Data for the incidence of AE for upadacitinib have been derived from Measure UP 1, Measure UP 2 and AD UP, while those for dupilumab were derived from TA534 and the clinical trial programme. Headache and oral herpes were identified as AEs, however, have not been included in the AE modelling since clinical advice suggested that patients with headache or oral herpes would self-medicate with over the counter medication, resulting in zero cost to the NHS.

For those AE with an incidence of >5% for one active treatment and 0% on the alternative active treatment, the placebo rate was used rather than 0% to ensure clinical validity.

AE data for upadacitinib is available at 16 weeks. For dupilumab, one study – CHRONOS – provided data at both 16 and 52 weeks. The increment in incidence of

AE in CHRONOS from 16 weeks to 52 weeks was ascertained and found to be approximately 178% and 161% across all AE for BSC and dupilumab respectively.

This increment was applied to individual upadacitinib AE incidence rates at 16 weeks to estimate incidence at 52 weeks. AEs were captured throughout follow-up, with costs incurred applied at each cycle.

Unlike dupilumab, upadacitinib is an oral treatment and therefore does not cause injection site reactions. Rates of injection site reaction for dupilumab are applied annually as per the revised submission for TA534[77].

Given the limited treatment duration with CsA (1 year) the economic model does not consider AE for CsA. This assumption is in line with TA534 and is likely to be conservative since patients on systemic treatments experience AE as described in Section B.1.3.4.1. Furthermore, clinical advice suggests that patients experiencing AE with CsA would cease treatment.

Data for the BSC arm are based on a weighted average of the respective placebo arms of upadacitinib and dupilumab clinical studies. For the NMA, comparison is made within each network. Thus, BSC AE rates used in the model are based on placebo for monotherapy and placebo + TCS for combination therapy.

Sensitivity analyses varying the AE rates are included to assess their impact on the model results.

Table 52: Annual AE rates used in the model (monotherapy)

Adverse event	Upadacitinib 15 mg	Upadacitinib 30 mg	Dupilumab
Adult systemic-exposed and systemic-eligible			
Injection site reaction	[redacted]	[redacted]	17.68%
Allergic conjunctivitis	[redacted]	[redacted]	4.84%
Infectious conjunctivitis	[redacted]	[redacted]	6.94%
Adolescents systemic-eligible			
Injection site reaction	[redacted]	[redacted]	13.73%
Conjunctivitis	[redacted]	[redacted]	15.82%
Skin infections	[redacted]	[redacted]	17.76%
Upper respiratory tract infection	[redacted]	[redacted]	19.70%
Acne	[redacted]	[redacted]	1.11%

Table 53: AE rates used in the model (combination therapy)

Adverse event	Upadacitinib 15 mg + TCS	Upadacitinib 30 mg + TCS	Dupilumab + TCS (systemic-exposed only)	CsA + TCS (systemic-eligible only)
Adult systemic-exposed and systemic-eligible				
Injection site reaction	[redacted]	[redacted]	14.50%	N/A
Allergic conjunctivitis	[redacted]	[redacted]	13.60%	N/A
Infectious conjunctivitis	[redacted]	[redacted]	13.60%	N/A

CsA: Ciclosporin, N/A: Not Applicable, TCS: Topical Corticosteroid

Table 54: AE rates used in the model (BSC)

Adverse event	Placebo	Placebo + TCS	BSC
Adults			
Injection site reaction	[redacted]	[redacted]	0.00%
Allergic conjunctivitis	[redacted]	[redacted]	3.78%
Infectious conjunctivitis	[redacted]	[redacted]	3.21%
Adolescents			
Injection site reaction	[redacted]	N/A	0.00%
Conjunctivitis	[redacted]	N/A	4.42%
Skin infections	[redacted]	N/A	18.80%
Upper respiratory tract infection	[redacted]	N/A	20.96%
Acne	[redacted]	N/A	1.11%

BSC: Best Supportive Care, N/A: Not Applicable, TCS: Topical Corticosteroid

B.3.3.5 Mortality

Death is the absorbing state in the model and patients may transition to death from any health state. An equal probability of death from each state in the model has been assumed, since AD does not impact on mortality.

Annual rates of transition to the death state are based on background mortality, determined by age and gender specific all-cause mortality rate estimates, extracted from UK National Life Tables[88].

B.3.4. Measurement and valuation of health effects

As discussed in Section B.1.3.2, AD has a profound impact on QOL. Moderate to severe AD is associated with worse QOL outcomes than many common chronic illnesses, including heart disease and diabetes in adults[14]. In adolescents, the impact of AD on QOL is comparable to asthma or cystic fibrosis[25].

According to the NICE reference case[82], QALYs are the preferred health outcome measure for CEA. These should be provided as utility values derived from validated generic, preference-based measures of HRQOL.

B.3.4.1 HRQOL data from clinical trials

The EQ-5D-5L questionnaire was used to collect HRQOL data in the upadacitinib clinical trial programme (Measure UP 1, Measure UP 2 and AD UP[45-47]). EQ-5D was measured at baseline, week 4, week 16, week 32, week 52 and every 24 weeks after the week 52 visit.

These data were used to derive health state utility data. Using HRQOL data from this source allows us to derive utilities for each of the subgroups and response levels.

In accordance with the NICE position statement, updated in October 2019[89], on the EQ-5D-5L valuation set, patient responses to the EQ-5D-5L questionnaire were mapped onto the UK European Quality of Life-5 Dimensions 3 Levels (EQ-5D-3L) value set using the crosswalk developed by van Hout *et al*. (2012)[90].

Regression models were used to account for the correlation among repeated measures for the same individual. The dependent variable of each model was the observed EQ-5D-5L index score at the 16-week visit.

Utility weights were estimated based on the dataset selected ('all observed' in base case and 'primary' for scenario analyses).

The regression model best-fit to predict utility was determined by selecting covariates using the Furnival-Wilson leaps-and-bound algorithm[91] and a backward selection approach. Covariates included in the selection process, in addition to response level, included: gender, baseline EASI level, patient age group (adult or adolescent), patient age, baseline utility, TCI/TCS intolerance and whether the patient was considered to have severe AD at baseline, as reported in Table 55.

All subset variables were selected using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). The model was selected using the covariates which minimise AIC and BIC. Covariate selection for adolescents is not altered since the population is small and BIC coincides with the covariate selection for the adult populations.

Table 55: Health utility model goodness-of-fit statistics (all observed analysis)

Additional covariate (added to model sequentially unless otherwise noted)	EASI 50 + DLQI ≥4		EASI 50			EASI 75		
Covariate	**AIC**	**BIC**	**Covariate**	**AIC**	**BIC**	**Covariate**	**AIC**	**BIC**
Adult systemic-exposed								
Baseline utility	**-396.49**	**-384.37**	Baseline utility	**-359.35**	**-347.19**	Baseline utility	**-376.77**	**-364.62**
Female	-395.95	-379.79	Female	-358.31	-342.10	Female	-376.33	-360.12
Baseline EASI	-394.88	-374.68	Baseline EASI	-356.86	-336.60	Age	-374.97	-354.70
Age	-393.74	-369.50	Age	-355.20	-330.88	Baseline EASI	-373.04	-348.73
Baseline AD severity	-391.93	-363.65	Baseline AD severity	-353.28	-324.91	Baseline AD severity	-371.09	-342.73
TCI/TCS intolerance	-390.04	-357.72	TCI/TCS intolerance	-351.33	-318.91	TCI/TCS intolerance	-369.10	-336.68
Adult	-390.04	-357.72	Adult	-351.33	-318.91	Adult	-369.10	-336.68
Adolescent systemic-eligible								
Baseline utility	-72.91	**-64.15**	Baseline utility	-157.41	**-146.27**	Baseline utility	-166.14	**-154.99**
Baseline EASI	**-74.01**	-62.33	Baseline EASI	-158.38	-143.52	Age	-167.65	-152.79
TCI/TCS intolerance	-72.40	-57.80	Baseline AD severity	-160.39	-141.82	Baseline AD severity & Baseline EASI (no Age)	-169.72	-151.15
Age	-70.53	-53.01	Age	**-160.77**	-138.49	Age added back in	**-171.38**	-149.10
Baseline AD severity	-68.54	-48.10	TCI/TCS intolerance	-159.09	-133.10	TCI/TCS intolerance	-170.29	-144.29
Female	-66.55	-43.19	Female	-157.10	-127.39	Female	-168.41	-138.70
Adult	-66.55	-43.19	Adult	-157.10	-127.39	Adult	-168.41	-138.70
Adult systemic-eligible								
Baseline utility	**-1498.43**	**-1481.69**	Baseline utility	**-1393.22**	**-1376.42**	Baseline utility	**-1429.45**	**-1412.66**
TCI/TCS intolerance	-1497.02	-1474.70	Female	-1391.36	-1368.97	Baseline AD severity	-1427.70	-1405.31
Baseline AD severity	-1495.23	-1467.32	Baseline AD severity & Baseline EASI (no Female)	-1389.41	-1361.42	Baseline EASI	-1425.89	-1397.90
Age	-1493.36	-1459.87	Female added back in	-1387.54	-1353.95	Female	-1423.94	-1390.34

Female	-1491.38	-1452.31	Age	-1385.56	-1346.37	TCI/TCS intolerance	-1421.97	-1382.78
Baseline EASI	-1489.39	-1444.75	TCI/TCS intolerance	-1383.56	-1338.77	Age	-1419.98	-1375.20
Adult	-1489.39	-1444.75	Adult	-1383.56	-1338.77	Adult	-1419.98	-1375.20

AD: Atopic Dermatitis, AIC: Akaike's Information Criterion, BIC: Bayesian Information Criterion, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, TCI: Topical Calcineurin Inhibitor, TCS: Topical Corticosteroid

Table 56: Health utility model goodness-of-fit statistics (primary analysis)

Additional covariate (added to model sequentially unless otherwise noted)	**EASI 50 + DLQI ≥4**		**EASI 50**			**EASI 75**		
Covariate	**AIC**	**BIC**	**Covariate**	**AIC**	**BIC**	**Covariate**	**AIC**	**BIC**
Adult systemic-exposed								
Baseline utility	**-353.48**	**-342.02**	Baseline utility	**-317.14**	**-305.63**	Baseline utility	**-334.20**	**-322.68**
Baseline EASI	-352.41	-337.12	Baseline EASI	-315.66	-300.31	Female	-332.96	-317.60
Female	-351.12	-332.01	Female	-314.09	-294.90	Baseline EASI	-331.50	-312.31
Age	-349.35	-326.41	Age	-312.18	-289.15	Age	-329.74	-306.72
Baseline AD severity	-347.38	-320.62	Baseline AD severity	-310.21	-283.34	TCI/TCS intolerance	-327.77	-300.91
TCI/TCS intolerance	-345.40	-314.81	TCI/TCS intolerance	-308.21	-277.51	Baseline AD severity	-325.80	-295.10
Adult	-345.40	-314.81	Adult	-308.21	-277.51	Adult	-325.80	-295.10
Adolescent systemic-eligible								
Baseline utility	**-68.54**	**-60.38**	Baseline utility	-129.99	**119.35**	Baseline utility	-136.12	**-125.49**
Baseline EASI	-67.79	-56.91	Baseline EASI	**-130.65**	-116.47	Baseline EASI	-138.07	-123.89
Age	-65.97	-52.38	Age	-130.62	-112.89	Age	**-138.26**	-120.53
TCI/TCS intolerance	-64.09	-47.78	Baseline AD severity	-129.46	-108.19	Baseline AD severity	-137.19	-115.92
Female	-62.16	-43.13	Female	-127.60	-102.78	Female	-135.62	-110.81
Baseline AD severity	-60.20	-38.45	TCI/TCS intolerance	-125.64	-97.28	TCI/TCS intolerance	-133.93	-105.57
Adult	-60.20	-38.45	Adult	-125.64	-97.28	Adult	-133.93	-105.57
Adult systemic-eligible								
Baseline utility	**-1374.48**	**-1358.26**	Baseline utility	**-1287.38**	**-1271.10**	Baseline utility	**-1327.86**	**-1311.58**
Female	-1372.80	-1351.17	Female	-1286.10	-1264.38	Baseline AD severity	-1326.43	-1304.72
Age	-1370.94	-1343.91	TCI/TCS intolerance	-1284.53	-1257.39	Baseline EASI	-1324.93	-1297.79
Baseline EASI	-1369.01	-1336.56	Age	-1282.65	-1250.08	Age	-1323.01	-1290.44

Baseline AD severity	-1367.02	-1329.17	Severe & Baseline EASI (No Age)	-1280.79	-1242.80	TCI/TCS intolerance	-1321.08	-1283.08
TCI/TCS intolerance	-1365.02	-1321.77	Age added back in	-1278.91	-1235.49	Female	-1319.15	-1275.72
Adult	-1365.02	-1321.77	Adult	-1278.91	-1235.49	Adult	-1319.15	-1275.72

AD: Atopic Dermatitis, AIC: Akaike's Information Criterion, BIC: Bayesian Information Criterion, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, TCI: Topical Calcineurin Inhibitor, TCS: Topical Corticosteroid

Table 57: Health utility model covariates for all observed analysis

Response	Covariates	Coefficient	SE	p value
Adult systemic-exposed				
EASI 50 + DLQI ≥4 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50 + DLQI ≥4	[redacted]	[redacted]	[redacted]
EASI 50 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50	[redacted]	[redacted]	[redacted]
EASI 75 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 75	[redacted]	[redacted]	[redacted]
Adolescent systemic-eligible				
EASI 75 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 75	[redacted]	[redacted]	[redacted]
Adult systemic-eligible				
EASI 50 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50	[redacted]	[redacted]	[redacted]
EASI 75 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 75	[redacted]	[redacted]	[redacted]

DLQI: Dermatology Life Quality Index, EASI: Eczema Area Severity Index, SE: Standard Error

Table 58: Health utility model covariates for primary analysis

Response	Covariates	Coefficient	SE	p value
Adult systemic-exposed				
EASI 50 + DLQI ≥4 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50 + DLQI ≥4	[redacted]	[redacted]	[redacted]
EASI 50 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50	[redacted]	[redacted]	[redacted]
EASI 75 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 75	[redacted]	[redacted]	[redacted]
Adolescent systemic-eligible				
EASI 50 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 50	[redacted]	[redacted]	[redacted]
EASI 75 response	Intercept	[redacted]	[redacted]	[redacted]
	Baseline utility	[redacted]	[redacted]	[redacted]
	EASI 75	[redacted]	[redacted]	[redacted]

DLQI: Dermatology Life Quality Index, EASI: Eczema Area Severity Index, SE: Standard Error

B.3.4.2 Utility state values used in the base case

Using the coefficients presented in Table 57 and Table 58 and the baseline patient characteristics, utility values for all health states corresponding treatment response or non-response were estimated using the regression model below. Results are presented in

Table 59 and Table 60.

$$Health\ state\ utility = \boldsymbol{Intercept} + \mathbf{0.2261} \times \boldsymbol{Baseline\ Utility} - \mathbf{0.0016} \times \boldsymbol{male} - \mathbf{0.00003} \times \boldsymbol{age} + \boldsymbol{level\ of\ response}$$

Table 59: Summary of utility values used in the model base case for all observed

	Parameter	Utility value: mean (SE)
Adult systemic-exposed		
Overall	Baseline, mean (SD)	[redacted]
	Overall week 16, mean (SD)	[redacted]
Responders	EASI 50 + DLQI ≥4, mean (SD)	[redacted]
	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Non-responders	EASI 50 + DLQI ≥4, mean (SD)	[redacted]
	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Adolescent systemic-eligible		
Overall	Baseline, mean (SD)	[redacted]
	Overall week 16, mean (SD)	[redacted]
Responders	EASI 75, mean (SD)	[redacted]
Non-responders	EASI 75, mean (SD)	[redacted]
Adult systemic-eligible		
Overall	Baseline, mean (SD)	[redacted]
	Overall week 16, mean (SD)	[redacted]
Responders	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Non-responders	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, SD: Standard deviation, SE: Standard error

Table 60: Summary of utility values used for primary analysis

	Parameter	Utility value: mean (standard error)
Adult systemic-exposed		
Overall	Baseline, mean (SD)	[redacted]
	Overall week 16, mean (SD)	[redacted]
Responders	EASI 50 + DLQI ≥4, mean (SD)	[redacted]
	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Non-responders	EASI 50 + DLQI ≥4, mean (SD)	[redacted]
	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Adolescent systemic-eligible		
Overall	Baseline, mean (SD)	[redacted]
	Overall week 16, mean (SD)	[redacted]
Responders	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]
Non-responders	EASI 50, mean (SD)	[redacted]
	EASI 75, mean (SD)	[redacted]

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, SD: Standard deviation, SE: Standard error

The utility values for each health state have been multiplied by the proportion of patients in each of the health states, to derive the total QALYs per health state in a year, and the accrued QALYs over a lifetime, coupled with discounting at an annual factor of 3.5% after year 1.

Table 61: Application of utility values in the economic model

Timepoint	Rule for utility value applied
From week 0 to initial response	Baseline utility
From initial response to week 16 decision node	Week 16 utility
From week 16 to week 52	EASI 50 + DLQI ≥4 EASI 50 EASI 75 Non-responders
Markov (Year 2+)	As for weeks 16-52

DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index

B.3.4.2.1 Utility adjustments based on age

In the base cases, overall decline in HRQOL due to age in both adults and adolescents is included in derivation of health state utility. The utility values were adjusted using the baseline age and proportion of males as informed by the Company evidence submission for Upadacitinib for treating moderate to severe atopic dermatitis in people aged 12 and over [ID3733]

quadratic relationship between age and utility depicted by Ara and Brazier (2010)[92]. The regression model (below) was based on EQ-5D data from the Health Survey for England in 2003 and 2006:

$$U_{base}(age, gender) = 0.9508566 + 0.0212126 * Male - 0.0002587 * Age - 0.0000332 * Age^2$$

B.3.4.3 Change in utility over time due to waning effect

With a lifetime horizon, it is important to model the effectiveness of treatments beyond trial duration. Therefore, in the model, change in utility over time is attributed to a waning of treatment effect.

B.3.4.3.1 Impact of the placebo-effect

Placebo-controlled clinical trials are considered the gold-standard of clinical evidence but, increasingly in AD, high responses are often observed in the placebo arm. To investigate this placebo treatment effect, the International Eczema Council (IEC) published a position statement to guide future placebo controlled clinical trials in AD[93]. Increased visits and monitoring as part of a clinical trial setting and better education about skin care are thought to play a role in high placebo responses observed in trials and HRQOL recorded for patients receiving placebo (proxy for BSC). The regimen offered as part of BSC are usually topical treatments for which adherence plays a key role in treatment effect. Outside of a clinical trial setting it is expected that adherence would be reduced, meaning that the high HRQOL and efficacy benefits observed during the trial with placebo would not be sustained over the long-term.

Clinical experts consulted to support this submission confirmed the findings from the IEC study[1]. In addition, they explained that waning of efficacy and HRQOL benefits over time is commonly seen with placebo but is less likely to be observed with active treatments. Indeed, when receiving an active therapy, reduced adherence to background treatment would have a negligible impact on observed efficacy rates and HRQOL, since almost all improved efficacy results from the active treatment effect, whereas efficacy and HRQOL benefits in the BSC arm rely on adherence to background medications.

B.3.4.3.2 Waning

The model applies waning in the BSC responder and non-responder states over a 5-year period. For the maintenance treatment state waning is assumed to apply for a period of 10 years, following which only discontinuation rates are applied. The method for waning in this submission was sourced from the ERG review of the revised dupilumab submission[77].

In the BSC arm, waning implies that all patients (regardless of response) return to their baseline state, i.e., non-responder cost profile and baseline utility.

For active treatments, waning acts as discontinuation, patients move to BSC non-responder health state and first incur the utility of BSC non-responders then gradually return to the baseline utility following BSC non-responders waning rates.

Waning rates for dupilumab and BSC were sourced from TA534, which used input from an expert panel to validate the waning rates.

Secondary loss of response due to the development of neutralising anti-drug antibodies is well documented in the literature with biologics and it was pointed out at an Advisory Board meeting that upadacitinib is a small molecule and patients are highly unlikely to develop resistance to treatment. In contrast, dupilumab is a monoclonal antibody and patients may develop resistance to treatment, due to the emergence of anti-drug antibodies[1]. The higher response rates observed with upadacitinib, together with advantages arising from the mechanism of action could lead to a more sustainable response[1]. However, in the absence of longer-term evidence, a conservative approach of applying similar waning rates for upadacitinib and dupilumab was selected.

An annual probability of waning of 1% applied from years 6-10 is based on the difference in cumulative proportion of patients losing QOL benefit between year 4 and year 5. The year 10 cut-off point reflects uncertainty in predicting the risk of response loss over an extended period of time.

Given that CsA is only given for 1 year and our model does not include subsequent treatment sequencing, we have made the assumption that CsA waning is equivalent to BSC waning. This represent the loss of benefits following CsA withdrawal and assumes that patients are maintained on background medications following a course of CsA. However, in clinical practice patients may receive alternative systemic therapies as subsequent treatment.

Scenario analyses will be carried out to explore alternative probability of sustained response for the BSC/CsA arms.

- Scenario 1: Waning in the BSC/CsA arm using curve fit estimator of maintenance of response Year 2: 18.2%; Year 3:10.3%; Year 4: 6.2%, Year 5: 3.7% and Year 6-10: 0.0%.

- Scenario 2: Waning in the BSC/CsA arm using annual waning rate of 57% (probability of sustained QOL benefit Year 2: 43.0%; Year 3: 18.49%, Year 4:

7.95%; Year 5: 3.42%; Year 6: 1.47%; Year 7: 0.63%; Year 8: 0.27%; Year 9: 0.12%, Year 10: 0.05%).

Table 62 details the cumulative proportion of patients losing response for BSC, upadacitinib, dupilumab and BSC up to year 10 of the model, after response is assumed to stabilise.

Table 62: Probability of sustained QOL benefit

Year	Upadacitinib and dupilumab without and with TCS		BSC and CsA without and with TCS	
	Base case	Reference	Base case	Reference
Year 2	98.0%	Table 1, (revised base case), TA534[77,94949494949494]	75%	Table 1, (revised base case), TA534[77,94]
Year 3	95.0%		50%	
Year 4	93.0%		25%	
Year 5	92.0%		0%	
Year 6	91.0%	Calculation aligned with ERG critique of the new economic evidence submitted by Sanofi Genzyme in response to the ACD[77]	0%	
Year 7	90.0%		0%	
Year 8	89.0%		0%	
Year 9	88.0%		0%	
Year 10	87.0%		0%	
Year 11+	N/A	Assumption	N/A	

ACD: Appraisal Consultation Document, BSC: Best Supportive Care, CsA: Ciclosporin, ERG: Evidence Review Group, N/A: Not Applicable, TCS: Topical Corticosteroids

B.3.4.4 Disutility associated with AE

Disutility due to AE was not included in the model since AE observed with upadacitinib and dupilumab are generally mild in severity. Therefore, a significant detriment in QOL is not expected with AE. Furthermore, the frequency of utility collection in the upadacitinib clinical trials is sufficient to capture any potential decrements related to AE and no treatment specific utilities are applied in the model.

This approach was consistent with previous appraisals in AD[58].

B.3.5. Cost and healthcare resource use identification, measurement and valuation

The costs and healthcare resource use included in the model were as follows:

- Drug acquisition, administration and monitoring
- Concomitant and background medication
- AD-related healthcare resource use

Company evidence submission for Upadacitinib for treating moderate to severe atopic dermatitis in people aged 12 and over [ID3733]

- Management of AEs and flares

Identification and valuation of resource use has been undertaken using an NHS perspective, reflecting annual utilisation rates and costs for direct medical resources involved in AD treatment and specific medication administered. Assumptions were validated with UK clinicians.

B.3.5.1 Identification of studies

A systematic search for published cost and healthcare resource identification, measurement and valuation data in moderate to severe AD was run alongside the searches for economic evaluation and HRQOL data. As reported in Appendix D and Appendix I, the original search was carried out in July 2020, and an update was performed in October 2020.

B.3.5.2 Intervention and comparators' drug acquisition costs

B.3.5.2.1 Active treatment costs

Drug acquisition costs were calculated in the model as a function of unit drug costs and dosing schedules for the included treatments. Dosing schedules are based on clinical trial protocols for upadacitinib[45-47], the BNF[32] for dupilumab and on UK clinical expert opinion for CsA[83,84].

For weight-based dosing of CsA, baseline patient weight was calculated as the baseline weight reported in adults in the AD UP study of 76.88 kg. Treatment with CsA was modelled as per clinical advice at 3 mg/kg daily for weeks 1-16 followed by 5 mg/kg daily for a total of 1 year[84].

Unit costs are based on the NHS indicative prices published by the Drug Tariff (for generic products) and BNF[32] (for branded products) for each medication, whichever is lower.

Drug acquisition costs per annual cycle are derived as a function of drug unit price and quantity administered as per the dosing schedules for each treatment regimen, described in Table 63.

Table 63: Drug acquisition costs and dosage

Drug	Dosing	Unit cost	Cost with PAS discount	Mean cost Year 1	Mean cost Year 2+	Source
Upadacitinib 15 mg	15 mg QD	£28.77 per tablet (day)	[redacted]	List: £10,508.24 PAS: [redacted]	List: £10,508.24 PAS: [redacted]	BNF[32]
Upadacitinib 30 mg	30 mg QD	[redacted] per tablet (day)	[redacted]	List: [redacted] PAS: [redacted]	List: [redacted] PAS: [redacted]	Confidential company information
Dupilumab	600 mg loading dose, followed by 300 mg Q2W	£632.45 per injection	Unknown	£17,076.02	£16,444.70	BNF[32]
CsA	3 mg/kg daily for weeks 1-12 followed by 5 mg/kg daily	£5.24 per day	None	£1,913.91	0	BNF[32]

BNF: British National Formulary, CsA: Ciclosporin, PAS: Patient Access Scheme, Q2W: Every 2 Weeks, QD: Once Daily

B.3.5.2.2 Drug administration costs

The mode of treatment administration impacts on drug administration costs. We have assumed zero administration cost for topical (TCS) and orally administered treatments (upadacitinib, CsA).

Dupilumab is administered via SC injection and requires a one-off 30-minute instruction in self-administration by a qualified nurse. This is estimated at £56.50, as the cost of 30 minutes patient contact with a Band 6, hospital-based Nurse Specialist/team leader (£113/hour), from the Unit Costs of Health and Social Care[95].

B.3.5.2.3 Monitoring costs

Patients receiving active AD treatments require routine monitoring of absolute neutrophil count, absolute lymphocyte count, haemoglobin, hepatic transaminases and lipid levels. Therefore, the cost of a FBC is included in the model.

For responders and non-responders an annual rate of four FBC tests is considered clinically appropriate, based on guidance from UK clinical advisors[1]. A unit cost of £3 cost for FBC has been extracted from 2018/19 HES data[96], National schedule of reference costs: the main schedule, Currency Code: DAPS05],(Haematology).

Although each test would also require a Practice Nurse/GP visit to schedule the phlebotomy, GP visits are already included in direct costs and we wished to avoid double counting of GP visits. Therefore, cost of scheduling the phlebotomy has not been included.

The annual cost of monitoring for upadacitinib and dupilumab is therefore, £12 per person.

CsA requires careful monitoring for potentially severe side-effects including nephrotoxicity[3]. The monitoring requirements are a considerable burden: dermatological and physical examination, including blood pressure and renal function measurement is required at least twice prior to starting treatment for AD and blood lipids should be measured before treatment and after the first month of treatment. Serum creatinine must be measured Q2W for the first 3 months of treatment and monthly thereafter. Regular monitoring of blood pressure, renal function, FBC and liver function is recommended[32].

Advice from a clinical expert suggests that increased monitoring (FBC and blood pressure) is carried out every other week for 8 weeks following treatment initiation, every other week for 4 weeks on dose change and then every 3 months when the dose is stable.

The dose schedule for CsA is 3 mg/kg for the first 16 weeks, increased to 5 mg/kg for the following 36 weeks to complete 1 year of treatment. This results in four monitoring visits for weeks 1-8, followed by one visit for weeks 9-15, two visits for weeks 16-20 weeks and two visits for weeks 21-52. This results in nine FBC and blood pressure tests for the year of treatment. Monitoring is generally performed in dermatology services, although may be managed in Primary Care to limit patients' travel[84]. The estimated cost associated with this is £27 (£3x9) for FBC and nine visits to the dermatology nurse. It is assumed that 50% of the dermatology visits would be routine visits and captured in direct costs. Therefore, the total cost is £27 + (£48.50 x 4.5 = £218.25) = £245.25.

B.3.5.2.4 Concomitant medications

Background treatment costs are derived from the estimated annual use rates and unit costs of routinely prescribed products for managing the symptoms of AD.

Resource use items explored in the model include TCS, emollients, bathing products, coupled with phototherapy and psychological support for patients receiving BSC, as per TA534 and validated by an AbbVie-organised Advisory Board[1].

In the model, responders to active treatment have a reduction in their concomitant medication. However, responders to BSC do not have a reduction in concomitant medication, since patients on BSC receive the treatments making up concomitant medication as standard.

To determine the brands of each class of concomitant medications used in clinical practice, the approach of TA534 was followed. TA534 used the Prescription Cost

Analysis to determine the most frequently prescribed agents in each class and validated the findings with UK clinical experts at an Advisory Board. Advice was sought at an AbbVie-organised Advisory Board to assess whether the agents listed in TA534 were still reflective of UK practice. Changes were made where appropriate[83].

Similar doses were applied to adults and adolescents following clinical advice[1].

B.3.5.2.4.1 TCS

The base case analyses in this submission assume that patients will receive concurrent TCS in both adult populations. For adolescents, comparative data is only available for monotherapy, therefore concomitant therapy has not been considered in the adolescent analyses.

Clinical experts advised that Mometasone ointment, Hydrocortisone, Eumovate and Betnovate are the most commonly used TCS in England[83] and are therefore used to estimate the resource use of TCS in the model.

Weekly TCS use for all treatment arms was based on covering 47.9% BSA, which was the skin involvement at baseline in the upadacitinib studies.

The BNF[32] recommends that 500 mg of product from a tube with a standard 5 mm diameter nozzle is sufficient to cover an area twice the size of a flat adult handprint (palm and fingers). One handprint has been calculated to be 0.87% of the area of an adult[97], which gives an estimate of 13.8 g per application, 96.6 g per week, assuming QD application.

For responders to dupilumab, a weekly amount of TCS was estimated at 49.26 g, based on a 49.4% decline in TCS use between week 16 and baseline observed in the dupilumab studies[58]. The same reduction was applied to upadacitinib and CsA. However, responders to BSC do not have a reduction in their TCS, since TCS are a key element of BSC, as outlined above.

Costs are taken from the Drug Tariff[98]. The unit cost for TCS is used to compute a weekly cost of £8.43 for non-responders and £4.16 for responders, as presented in Table 64.

Table 64: TCS costs used in the economic model

TCS	g/tube	£/tube	£/g	g/day	Non-responder and BSC responder		Responder	
					g/week	£/week	g/week	£/week
Mometasone 1% ointment	100	£10.57	£0.11	13.76	96.35	£10.18	47.60	£5.03
Hydrocortisone 1% cream	50	£5.20	£0.10			£10.02		£4.95
Eumovate Eczema and Dermatitis 0.05% cream	100	£6.12	£0.061			£5.90		£2.91
Betnovate - Clobetasol 0.05% ointment	100	£7.9	£0.08			£7.61		£3.76
Weekly cost						£8.43		£4.16
Annual cost						£483.36		£216.32

BSC: Best Supportive Care, TCS: Topical Corticosteroid

B.3.5.2.4.2 TCI

Protopic 0.1% ointment (tacrolimus) is used to model TCI resource use, following guidance from clinical experts in the TA534 submission[58] and supported by AbbVie's clinical advisors[83].

TCIs are considered more appropriate for facial involvement than steroid treatments. Tacrolimus is applied thinly, twice weekly, with an interval of 2–3 days between applications. TCI are recommended by the BNF for short-term treatment of flares and prevention of flares in patients with moderate to severe AD[32].

As per TA534[58], a weekly estimate of 1.75 g was adopted for non-responders and TCI is assumed to be stopped in responders. Both assumptions were validated by AbbVie's clinical advisors[83].

Costs are taken from the Drug Tariff[98].

Table 65: TCI costs used in the economic model

TCI	g/tube	£/tube	£/g	Non-responder and BSC responder		Responder	
				g/week	£/week	g/week	£/week
Tacrolimus 0.1% ointment	60	£42.44	£0.71	1.75	£1.24	0	£0
Weekly cost				£1.24		£0	
Annual cost				£64.48		£0	

BSC: Best Supportive Care, TCI: Topical Calcineurin Inhibitor

B.3.5.2.4.3 Bathing products

Bathing products were modelled at BD application rates, with quantities per application reflecting the user guidelines for each product.

For responders, QD application rate was assumed, following a 50% reduction in use rates recommended by the TA534 and following expert advice. The use of background medication is key to achieve a response on BSC, therefore we did not consider a reduction of the use of bathing products for BSC responders.

Costs were obtained from the BNF[32], since they were not available in the Drug Tariff[98]. The average cost of all the products has been computed and multiplied with weekly rates, to derive an annual cost of £171.60 for non-responders and £85.80 for responders.

Table 66: Bathing product costs used in the model

Bathing products	Pack size	£/pack	Non-responder/BSC responder		Responder
			Amount/week	£/week	£/week assuming 50% reduction
QV 85.09% bath oil (Crawford Healthcare Ltd)	500 ml	£4.79	Assume 1 pack per week	£4.79	£2.40
Dermol 200 Shower Emollient	200 ml	£3.55	Assumed 1 pack per week	£3.55	£1.78
Dermol 600 Bath Emollient	600 ml	£7.55	210ml (30 ml per bath)	£2.64	£1.32
Oilatum Bath Formulation	500ml	£7.94	140 ml (20 ml per bath)	£2.22	£1.11
Average cost per week				£3.30	£1.65

BSC: Best Supportive Care

B.3.5.2.4.4 Emollient products

Clinical advisors confirmed that the weekly rate of 250 to 500 g was plausible therefore similarly to TA534, the model assumed a use of 500 g/week[58].

For patients who respond to active treatment, it was assumed that there would be a 50% reduction in the use of emollients as per clinical experts cited in TA534[58]. Similarly, to bathing products, no reduction in emollient use has been assumed for patients who respond BSC since background medication is key to sustain response.

Costs were obtained from the BNF[32], since they were not available in the Drug Tariff.

Table 67: List of emollients products used in the economic model.

Emollient product	Pack size	£/pack	Number of packs per week: Non-responder	Non-responder/ BSC responder	Responder (50% reduction)
				£/pack	£/week
Hydramol ointment (Alliance Pharmaceuticals Ltd)	1,000 g	£8.20	0.5	£4.10	£2.05
Epaderm ointment (Molnlycke Health Care Ltd	1,000 g	£12.25	0.5	£6.13	£3.06
Diprobase cream	500 g	£5.99	1	£5.99	£3.00
Cetraben ointment (Thornton & Ross Ltd)	450 g	£5.39	1	£5.39	£2.70
50/50 white soft paraffin	500 g	£4.57	1	£4.57	£2.29
Average cost per week				£5.24	£2.62

BSC: Best Supportive Care

B.3.5.2.5 Treatment for flares

In the model, the use of rescue medication is considered as a proxy to determine the frequency of flares. Patients experiencing flares are usually offered rescue medication with TCS or systemic steroids. This definition of flare is consistent with the definition used in TA534[58] and has been validated by clinical experts[83].

TA534 reported rates of flare from the CHRONOS study at week 52. Given that only 16-week data are available for upadacitinib, use of rescue medication for dupilumab at week 16 was sourced from the CAFÉ publication (4.9%) for combination therapy and SOLO 1 & 2 for monotherapy (17.9%). Rates of rescue medication use for upadacitinib were sourced from Measure UP 1, Measure UP 2 and AD UP.

In the absence of data for CsA, we have assumed a 15% decrement in flares from the rates applied to the BSC arm.

Table 68: Rates of flare (defined as use of rescue medication)

Agent	Rate	Source	Time point
BSC	[redacted]	Mean AD UP and CAFÉ + CHRONOS	16 weeks
Upadacitinib			
15 mg + TCS	[redacted]	AD UP	16 weeks
30 mg + TCS	[redacted]	AD UP	16 weeks
15 mg	[redacted]	Mean Measure UP 1 and Measure UP 2	16 weeks
30 mg	[redacted]	Mean Measure UP 1 and Measure UP 2	16 weeks
Dupilumab			
Dupilumab + TCS	4.91%	CAFÉ	16 weeks
Dupilumab	17.94%	SOLO 1 & 2	16 weeks
CsA	18.04%	Assuming a 15% decrement in flare from BSC	16 weeks

BSC: Best Supportive Care, CsA: Ciclosporin, TCS: Topical Corticosteroid

The cost of flare was estimated by reviewing the class of agents used as rescue therapy in the upadacitinib clinical studies (Measure UP 1, Measure UP 2 and AD UP). [redacted]. Biologic therapy and TCI were excluded since the Advisory Board did not recommend their use for the treatment of flares in the UK. Phototherapy was also excluded as only one patient across the whole clinical trial programme received phototherapy for flare. The ratio of TCS to systemic steroids was 79:21 in the upadacitinib clinical trial programme.

Treatment costs were based on the most commonly used products for the treatment of flares as described in TA534[58] and validated by UK experts at the AbbVie Advisory Board[1].

Table 27: Cost of medications to treat flares

Treatment	Duration	Dose per week (g)	Cost	Packs per week	cost for 4 weeks
TCS					
Bethmetasone valerate 0.1%	2-4 weeks	96.6 g	£3.85/100g	1.00	£15.40
Cutivate 0.05%	2-4 weeks	96.6 g	£4.24/30 g	3.00	£50.88
Dermovate 0.05%	2-4 weeks	96.6 g	£7.90/100 g	1.00	£31.60
				Mean	**£32.63**
Systemic steroids					
Prednisolone 5 mg	2-4 weeks	245 g (49 tablets)	£3.65/28 tablets	1.75	**£25.55**
Average cost to treat one episode of flare					
79% TCS and 21% systemic steroids					**£31.17**

TCS: Topical Corticosteroids

B.3.5.2.6 Best supportive care

Treatment costs for BSC was based on the use of TCS, TCI, emollient products, phototherapy and psychotherapy, with frequency of use subject to the response rate. Estimates for the components of BSC were validated by clinical experts[1,83].

For phototherapy, a unit cost of £94 was extracted from the HES 2018/19 data[96], focusing on out-patient procedures of phototherapy/photo chemotherapy corresponding to dermatology services (currency code JC47Z). The annual rate of 22 procedures per person was extracted from TA534 appraisal committee papers[77].

Annual cost of psychology treatment was derived from the £155 cost per patient, receiving other mental health specialist services, (currency code MHSTOTHA**)** HES 2018/19 data[96], and the annual rate of 0.07 extracted from TA534 appraisal committee papers[77].

Table 69: Costs of best supportive care

Treatment	Annual rates			Unit cost		Annual cost		
	Non-responders	Responders Year 1	Responders Year 2+			Non-responders	Responders Year 1	Responders Year 2+
Phototherapy	0.06	0.00	0.00	£2,074.34		£124.46	£0	£0
Psychology	0.07	0.00	0.00	£154.85		£10.13	£0	£0
Treatment of flares	0.212	0.212	0.212	£31.17		£6.61	£6.61	£6.61
Total costs						£141.20	£6.61	£6.61
Medication				Weekly cost		Annual cost		
				Non- responders	Responders	Non-responders	Responders	
TCS concomitant medication costs				£8.43	£4.16	£438.27	£438.27	
TCI				£1.24	£0	£64.48	£0	

TCI: Topical Calcineurin Inhibitor, TCS: Topical Corticosteroids

B.3.5.3 Health-state unit costs and resource use

Direct medical resource use rates for responders and non-responders were modelled using clinical expert guidance sought by Sanofi for TA534[58] and validated by UK clinical experts. Costs for CsA are equivalent to those for responders to upadacitinib and dupilumab since the additional monitoring costs (£238.50) are already accounted for.

Unit costs for each resource were derived from HES 2018/19[96].

Visits to the GP and dermatology nurse were costed at £39.30 and £48.50 respectively, as per 2019 Unit Costs of Health and Social Care Professionals[95].

A dermatology out-patient visit was costed at £117.13[96], derived from HES data as a weighted average of attendances (currency codes: WF01A, WF01B, WF01C, WF01D, WF02A, WF02B and WF02C) and unit costs of dermatology and allergy clinics.

A hospitalisation unit cost of £1,257.00[96] was derived as a weighted average cost of non-elective hospital stays for skin disorders (currency codes: JD07E, JD07F, JD07G, JD07H, JD07J, JD07K).

A mean cost of £378.92 per day case was derived from finished consultant episodes for skin disorders corresponding to day cases (currency codes: JD07E, JD07F, JD07G, JD07H, JD07J, JD07K).

A £162.81 mean cost for emergency admissions[96], reflects a weighted average of NHS emergency attendance and average unit costs, corresponding to service descriptions Type 01 admitted and Type 01 non-admitted and currency code Category 2 Investigation with Category 2 Treatment (currency codes: VB07Z, VB08Z, VB09Z, VB11Z).

Table 70 details the direct medical costs used in the model, using resource rates from TA534[58].

Table 70: Direct medical costs used in the model

Resources used	Annual rates			Unit cost	Annual cost		
	Non-responders	Responders Year 1	Responders Year 2+		Non-responders	Responders Year 1	Responders Year 2+
A&E attendance (total patient visits/year)	0.09	0.02	0.02	£162.81	£14.65	£3.26	£3.26
Day case	0.21	0	0	£378.92	£79.57	£0	£0
Hospital admissions (total patient visits/year)	0.12	0.02	0.02	£1,256.94	£150.83	£25.14	£25.14
OP visits to dermatologist (total patient visits/year)	6.09	4	2	£117.13	£713.32	£468.52	£234.26
OP visits to dermatology nurse (total patient visits/year)	0.55	0.42	0.42	£48.50	£26.68	£20.37	£20.37
Visits to the GP (total patient visits/year)	12.8	2	2	£39.30	£503.04	£78.60	£78.60
Total annual costs					£1,488.09	£585.89	£361.63

A&E: Accident and Emergency, OP: Out-patient

B.3.5.4 Adverse event costs

Resource use due to AE was modelled based on AE seen with each treatment and corresponding incidence rates as discussed in Table 52 to Table 54. The estimated treatment resources to manage each AE was based on guidance from clinical experts[84].

Treatment of injection site reactions, allergic and infectious conjunctivitis, acne, skin infection and upper respiratory tract infection require GP visits at a cost of £39.30/GP visit[95].

Our clinical advisor suggested that allergic conjunctivitis might also be treated by a nurse, dermatologist or ophthalmologist. Acne and skin infections might also be treated during routine dermatologist visits. In order to simplify cost inputs we have assumed that allergic conjunctivitis, acne and skin infections are treated by a GP (see Table 71).

Expert advice recommended that infectious conjunctivitis is treated with a course of chloramphenicol eye drops at £4.25 per 10 ml pack, acne is treated with a monthly course of oral lymecycline at £8.10 or topical clindamycin at £8.66 per month and skin infection treated with fusidic acid cream at £6.16 per month.

Costs for treatments have been extracted from the December 2020 NHS Drug Tariff[98].

Table 71: AE costs

Adverse event	Annual costs (£)	Detail
Injection site reaction	£39.30	GP visit (no prescription)
Allergic conjunctivitis	£39.30	GP visit (no prescription)
Infectious conjunctivitis	£44.75	GP visit + chloramphenicol eye drops
Acne	£103.74	2 x GP visits + 3 months topical clindamycin (£8.66 per month) or oral lymecycline (£8.10/month)
Skin infection	£45.46	GP visit + fusidic acid 30 g 2% cream
Upper respiratory tract infection	£39.30	GP visit (no prescription)

Unit costs associated with each AE are multiplied by the proportion of patients experiencing the event to estimate the annual treatment-specific AE costs.

Use of CsA is restricted to 1-year in the model thus, CsA-related AE and related costs were not included. Furthermore, clinical opinion suggested that patients who experienced AE on CsA would cease treatment.

B.3.5.5 Miscellaneous unit costs and resource use

No other costs are considered.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

Please see Appendix L for details of the inputs for each base case.

B.3.6.2 Assumptions

Many of the assumptions in the economic modelling follow previous appraisals (TA534) and were accepted by the ERG and by the Committee at the time of the dupilumab appraisal and have been discussed and validated with UK clinical experts.

Assumptions around probability of sustained response, discontinuation rates and waning were necessary since 52-week data for upadacitinib is not yet available.

Table 72: Assumptions in the economic modelling

Assumption	Rationale
CsA exposure is used as a proxy for systemic treatment	CsA is the only licensed systemic treatment for AD in the UK, all other systemics are used outside their licence. It should be noted that CsA is only licensed from age 16. In TA534, the evidence available for dupilumab was based on the CAFÉ trial and CAFÉ-like population from other dupilumab trials, which was defined according to previous exposure or contra-indication to CsA.
Non-responders to active treatment revert to BSC until death	Simplifying assumption in the model aligned with TA534[2,58,77]
Conditional probability of response at 52 weeks sourced from CHRONOS and applied to week 16 data (see Table 51)	Simplifying assumption, as the upadacitinib clinical studies have not yet reported 52-week data. We have used the dupilumab 52-week conditional probability of response (94.4% as monotherapy and 94.5% as combination therapy) for upadacitinib.
The annual probability of discontinuation as per TA534	Simplifying assumption, as the upadacitinib clinical studies have not yet reported 52-week data. We have used the same discontinuation rate for all comparators (6.3% for monotherapy and 6.4% for combination therapy).
Waning assumptions for BSC and upadacitinib as per TA534 (see Table 62)	Simplifying assumption, due to the absence of published longer term evidence. TA534 reported waning rates for dupilumab and BSC. We have used equivalent waning rates for dupilumab and upadacitinib and for BSC and CsA.
Waning assumptions for CsA	Simplifying assumption, maintaining the CsA efficacy observed at 52 weeks once CsA is withdrawn would be inappropriate, given that the costs and effect of subsequent therapy are not included. BSC waning was applied assuming that following CsA patients still receive concomitant therapy which is comparable to BSC.
Management of flare for CsA	In the absence of data, flare rates for CsA have been estimated by applying a 15% decrement to the rate of flare observed with BSC.
Concomitant medications	Concomitant medication use was validated by clinical experts[1,83].

Monitoring costs	Monitoring costs were taken from TA534 and validated by a General Practitioner and clinical experts[84].
AE costs	AE costs were estimated by a General Practitioner and validated by clinical experts[84].

AD: Atopic Dermatitis, AE: Adverse Events, BSC: Best Supportive Care, CsA: Ciclosporin

B.3.7. Base case results

B.3.7.1 Overview

ICER and NMB were used as summary statistics. NMB is calculated as (benefit x cost-effectiveness threshold) –cost. This scales health outcomes and use of resources to costs, allowing comparisons to be made without ratios (such as in ICERs). A cost-effectiveness threshold of £30,000 was used. INMB measures the difference in NMB between alternative interventions, a positive INMB indicates that the intervention is cost-effective compared with the alternative at the given cost-effectiveness threshold[99].

Results described below reflect the PAS price for upadacitinib and the list price for all comparators (dupilumab and CsA).

In the adult systemic-exposed population, upadacitinib 15 mg and 30 mg are cost-effective. Both doses are dominant vs dupilumab and ICER vs BSC are £9,961/ QALY and £25,069/QALY for upadacitinib 15 mg and upadacitinib 30 mg, respectively.

In the adolescent population, upadacitinib 15 mg is cost-effective vs both dupilumab and BSC. Upadacitinib is dominant vs dupilumab and the ICER is £10,173/QALY vs BSC.

In the adult systemic-eligible population, upadacitinib is cost-effective vs CsA at the 15 mg dose (ICER of £12,929/QALY) and is marginally over the £30,000 threshold (£31,979/QALY) at the 30 mg dose, driven by the increased incremental drug cost of upadacitinib vs CsA.

The probabilistic sensitivity analysis (PSA) reveals that for all base cases, upadacitinib remains well below the cost-effectiveness threshold with the exception of upadacitinib 30 mg vs CsA in the adult systemic-eligible population, where the ICER is marginally above the threshold. All ICERs vs dupilumab are dominant, ICERs vs BSC range from £9,468/QALY to £23,880/QALY and ICERs vs CsA are £13,057/QALY for upadacitinib 15 mg and £32,309/QALY for upadacitinib 30 mg.

For all base cases the key areas of uncertainty are efficacy response at 16 and 52 weeks, sustained response at 52 weeks and direct medical costs for non-responders.

For the adult systemic-exposed population, upadacitinib remains cost-effective in all explored scenario analyses. Positive INMB are seen for all scenarios tested (use of alternative time horizons, discount rates, response timepoints, primary dataset, response definitions, waning projections, base case using monotherapy and direct evidence from Heads UP vs dupilumab).

ICERs are dominant or below the £30,000 threshold, except for the scenario using response observed at 16 weeks as an alternative timepoint. For upadacitinib 15 mg vs dupilumab, the ICER lies in the SW quadrant, although the difference in QALYs is negligible [redacted]. Upadacitinib 30 mg is dominant vs dupilumab in this scenario.

In the scenario using direct evidence from Heads UP, upadacitinib 30 mg monotherapy is dominant vs dupilumab.

For the adolescent population, upadacitinib 15 mg remains cost-effective in all scenarios (dominant or below the £30,000 threshold). The direction of the results differ in one scenario, using the primary data set and EASI 50 response definition, where upadacitinib lies in the SW quadrant for upadacitinib 15 mg vs dupilumab (QALY difference [redacted]). Nonetheless, upadacitinib remains cost-savings with positive INMB.

For the adult systemic-eligible population, upadacitinib 15 mg remains cost-effective in all scenarios. The upadacitinib 30 mg dose is marginally above £30,000/QALY in most scenarios, but is cost-effective when testing alternative waning projections for CsA.

B.3.7.2 Presentation of results

Given that upadacitinib is available in two doses and can be used as monotherapy or in combination with TCS there are numerous results tables.

Results in the dossier presented below reflect the three base case populations (see Table 47), with additional information in Appendix L.

- Adult systemic-exposed: combination therapy, EASI 50 + DLQI ≥4
- Adolescent systemic-eligible: monotherapy, EASI 75
- Adult systemic-eligible: combination therapy, EASI 75

Results are shown for the PAS price for upadacitinib vs the list price for all comparators (dupilumab, BSC and CsA).

Table 73 displays a summary of base case cost-effectiveness results.

Base case and scenario results using the upadacitinib list price are included in Appendix L.

Disaggregated results are presented in Appendix J.

Table 73: Summary of base case results (all observed), PAS price

Response criteria	Upadacitinib dose	Mono/combo	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£)	INMB (£ using WTP/QALY of £30,000)	Table
Adult systemic-exposed								
EASI 50 + DLQI ≥4	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Table 74
EASI 50 + DLQI ≥4	15 mg	Combo	BSC	[redacted]	[redacted]	£9,961	[redacted]	Table 74
EASI 50 + DLQI ≥4	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Table 75
EASI 50 + DLQI ≥4	30 mg	Combo	BSC	[redacted]	[redacted]	£25,069	[redacted]	Table 75
Adolescent systemic-eligible								
EASI 75	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Table 76
EASI 75	15 mg	Mono	BSC	[redacted]	[redacted]	£10,173	[redacted]	Table 76
Adult systemic-eligible								
EASI 75	15 mg	Combo	CsA	[redacted]	[redacted]	£12,929	[redacted]	Table 77
EASI 75	30 mg	Combo	CsA	[redacted]	[redacted]	£31,979	[redacted]	Table 78

BSC: Best Supportive Care, COMBO: Combination Therapy, CsA: Ciclosporin, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, MONO: Monotherapy, QALYs: Quality-adjusted life years, WTP: Willingness to Pay

B.3.7.3 Adult systemic-exposed

Results of the base case analyses for upadacitinib 15 mg and 30 mg are presented in Table 74 and Table 75.

Table 74: Adult systemic-exposed – base case results, upadacitinib 15 mg combination therapy, all observed, PAS price

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Upadacitinib 15 mg vs dupilumab (combination therapy)						
Upadacitinib 15 mg	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Upadacitinib 15 mg vs BSC (combination therapy)						
Upadacitinib 15 mg	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£9,961	[redacted]

BSC: Best Supportive Care, ICER: incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-Adjusted Life Years, WTP: Willingness to Pay

Table 75: Adult systemic-exposed – base case results, upadacitinib 30 mg combination therapy, all observed, PAS price

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Upadacitinib 30 mg vs dupilumab (combination therapy)						
Upadacitinib 30 mg	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Upadacitinib 30 mg vs BSC (combination therapy)						
Upadacitinib 30 mg	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£25,069	[redacted]

BSC: Best Supportive Care, ICER: Incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

B.3.7.4 Adolescent systemic-eligible

Results of the base case analyses for upadacitinib 15 mg are presented in Table 76.

Table 76: Adolescent systemic-eligible – base case results, upadacitinib 15 mg monotherapy, all observed, PAS price

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Upadacitinib 15 mg vs dupilumab (monotherapy)						
Upadacitinib 15 mg	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Upadacitinib 15 mg vs BSC (monotherapy)						
Upadacitinib 15 mg	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	£10,173	[redacted]

BSC: Best Supportive Care, ICER: Incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

B.3.7.5 Adult systemic-eligible

Results of the base case analyses for upadacitinib 15 mg and 30 mg are presented in Table 77 and Table 78.

Table 77: Adult systemic-eligible – base case results, upadacitinib 15 mg combination therapy, all observed, PAS price

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Upadacitinib 15 mg vs CsA (combination therapy)						
Upadacitinib 15 mg	[redacted]	[redacted]				
CsA	[redacted]	[redacted]	[redacted]	[redacted]	£12,929	[redacted]

BSC: Best Supportive Care, ICER: Incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

Table 78: Adult systemic-eligible – base case results, upadacitinib 30 mg combination therapy, all observed, PAS price

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Upadacitinib 30 mg vs CsA (combination therapy)						
Upadacitinib 30 mg	[redacted]	[redacted]				
CsA	[redacted]	[redacted]	[redacted]	[redacted]	£31,979	[redacted]

BSC: Best Supportive Care, ICER: Incremental Cost-effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

B.3.8. Sensitivity analyses

Probabilistic (PSA) and deterministic sensitivity analysis (DSA) assess the impact of key variables on the model outcomes.

B.3.8.1 Probabilistic sensitivity analysis

PSA were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 1,000 simulations to calculate the uncertainty in costs and outcomes. In cases where uncertainty data was not available for an input, variability (i.e. SE) of 10% of the mean values was assumed.

Parameters varied in the PSA are shown in Appendix L, Section L.1 and listed below:

- Baseline patient characteristics (age, % male, worst pruritus)
- Health utility (baseline, week 16, responders and non-responders)
- Direct medical costs (responders and non-responders)
- Costs associated with AE
- Efficacy (week 16, sustained response at week 52)
- Treatment discontinuation
- TCS concomitant medication costs (responders and non-responders)

Convergence Diagnosis and Output Analysis (CODA) samples were used for efficacy to reflect uncertainty over the NMA results in the base cases. However, given the number of plausible scenarios and to optimise model performance an alternative approach of using beta distribution for the NMA output has been used for all other scenarios.

A normal distribution is used for baseline age, whereas a log-normal distribution is used for relative effects parameters. Those include the overall week 16 utility which is dependent on baseline utility, together with week 52 sustained response, which is in turn linked to week 16 efficacy response.

The proportion of male, baseline utility and annual rate of discontinuation were all assumed to have a beta distribution. Health utilities in the model are varied using the Cholesky decomposition, since it is necessary to account for covariance between the coefficients of the health utility regression[100]. The parameters generated from the

Cholesky decomposition were varied using a normal distribution. Costs were varied using a gamma distribution.

Table 79: Mean PSA base case results (PAS price)

Response criteria	Upadacitinib dose	Mono/combo	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)	Figure
Adult systemic-exposed								
EASI 50 + DLQI ≥4	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Figure 32
EASI 50 + DLQI ≥4	15 mg	Combo	BSC	[redacted]	[redacted]	£9,468	[redacted]	Figure 33
EASI 50 + DLQI ≥4	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Figure 34
EASI 50 + DLQI ≥4	30 mg	Combo	BSC	[redacted]	[redacted]	£23,880	[redacted]	Figure 35
Adolescent systemic-eligible								
EASI 75	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]	Figure 36
EASI 75	15 mg	Mono	BSC	[redacted]	[redacted]	£9,831	[redacted]	Figure 37
Adult systemic-eligible								
EASI 75	15 mg	Combo	CsA	[redacted]	[redacted]	£13,057	[redacted]	Figure 38
EASI 75	30 mg	Combo	CsA	[redacted]	[redacted]	£32,309	[redacted]	Figure 39

BSC: Best Supportive Care, CsA: Ciclosporin, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-Effectiveness Ratio, INMB: Incremental Net Monetary Benefit, QALYs: Quality-Adjusted Life Years, WTP: Willingness To Pay

B.3.8.1.1 PSA results: adult systemic-exposed (PAS price)

Figure 32: Adult systemic-exposed – cost-effectiveness acceptability curves and scatter plots, upadacitinib 15 mg combination therapy vs dupilumab, all observed, PAS price

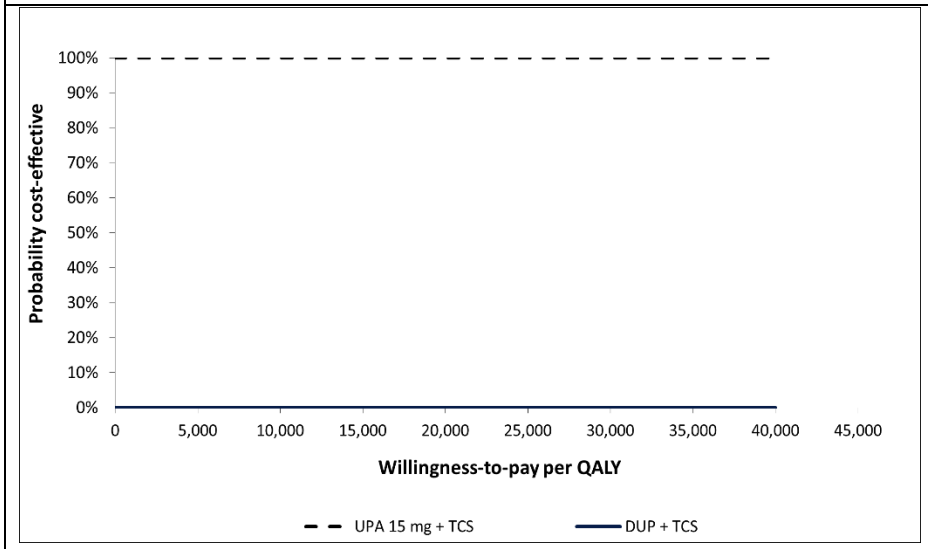
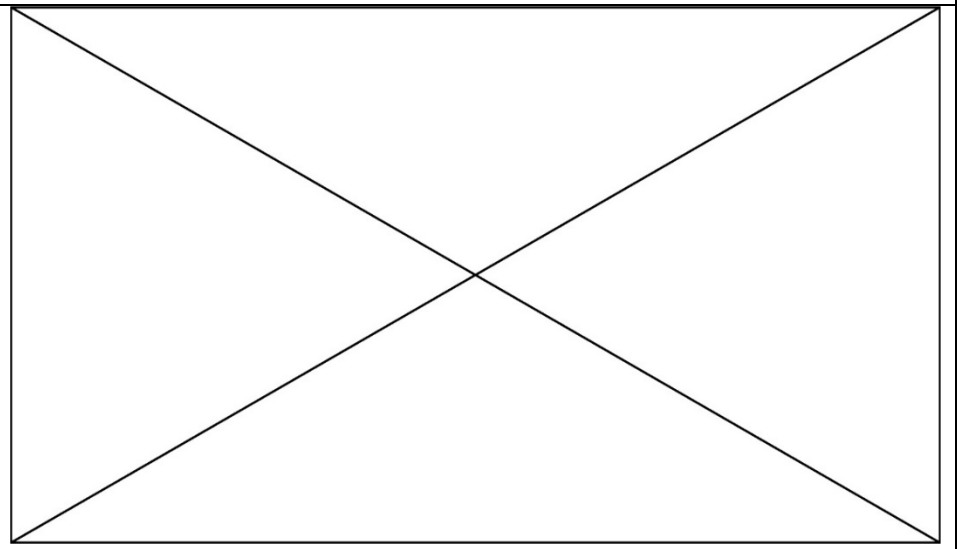
Cost-effectiveness acceptability curve (upadacitinib 15 mg)	Scatter plot (upadacitinib 15 mg)
	

Figure 33: Adult systemic-exposed – cost-effectiveness acceptability curves and scatter plots, upadacitinib 15 mg combination therapy vs BSC, all observed, PAS price

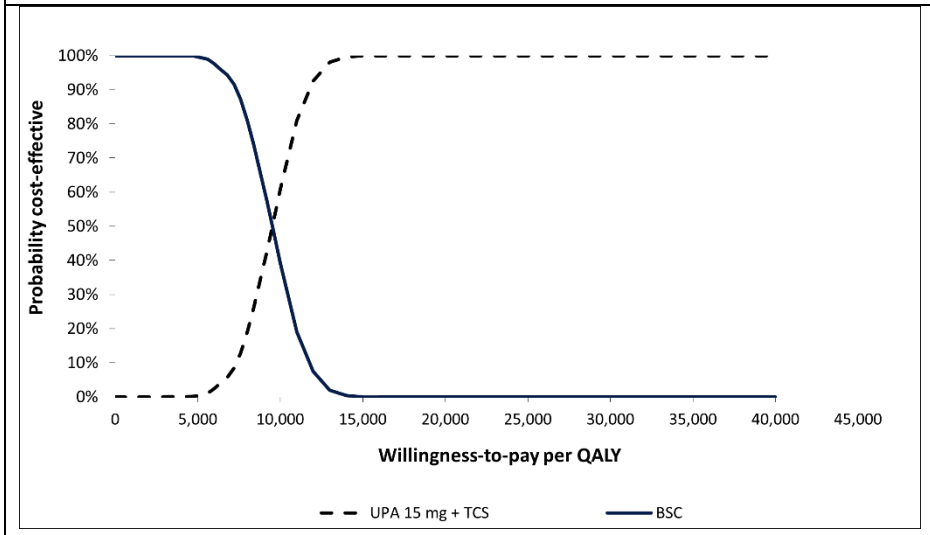
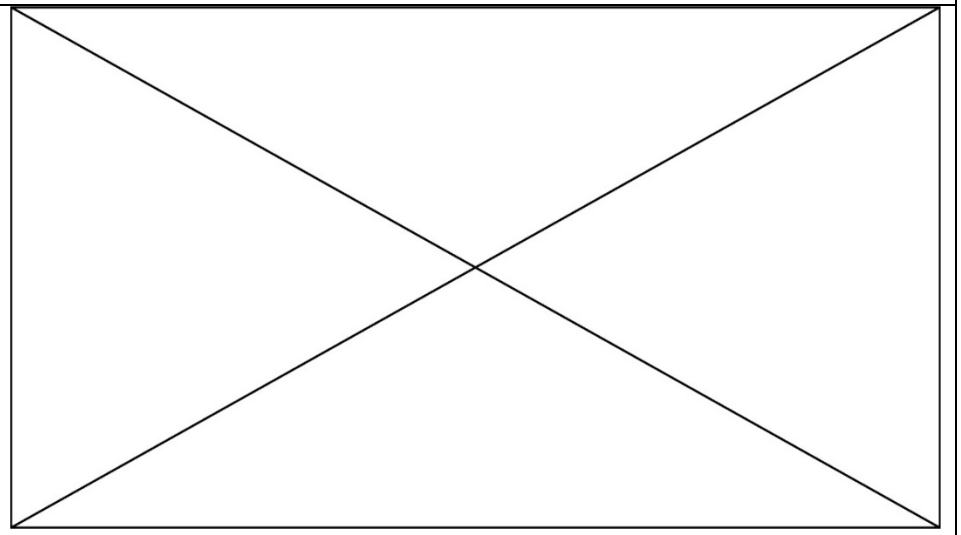
Cost-effectiveness acceptability curve (upadacitinib 15 mg)	Scatter plot (upadacitinib 15 mg)
	

Figure 34: Adult systemic-exposed – cost-effectiveness acceptability curves and scatter plots, upadacitinib 30 mg combination therapy vs dupilumab, all observed, PAS price

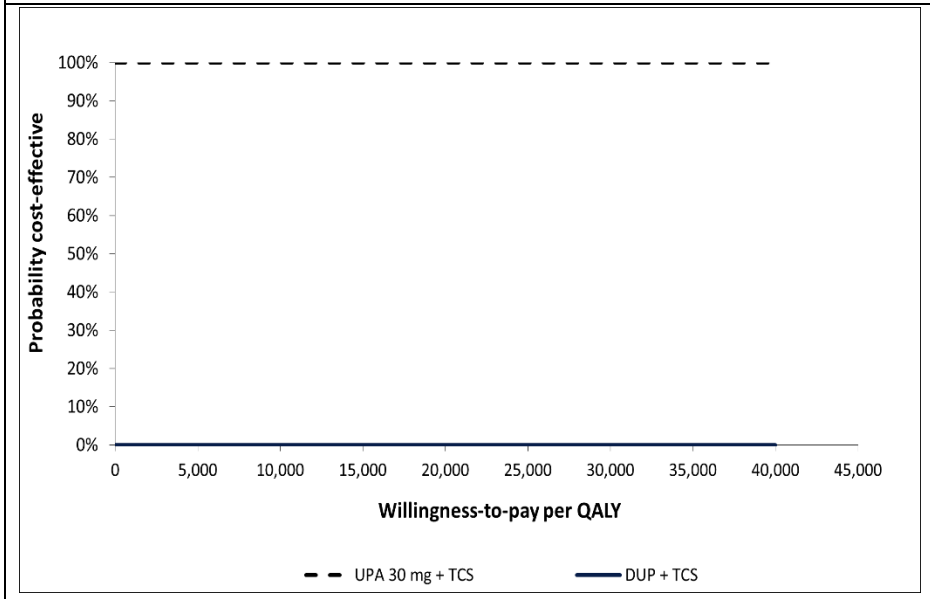
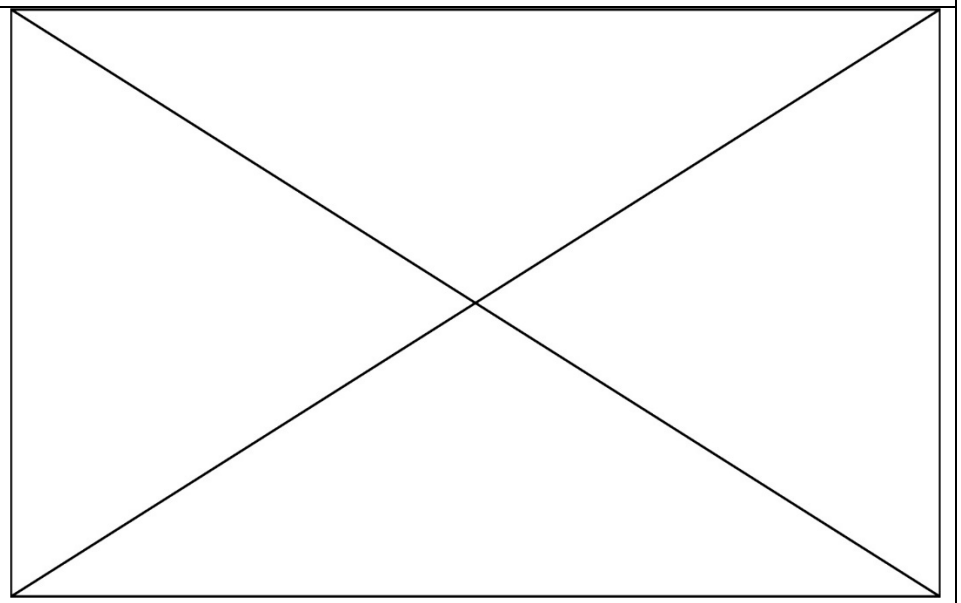
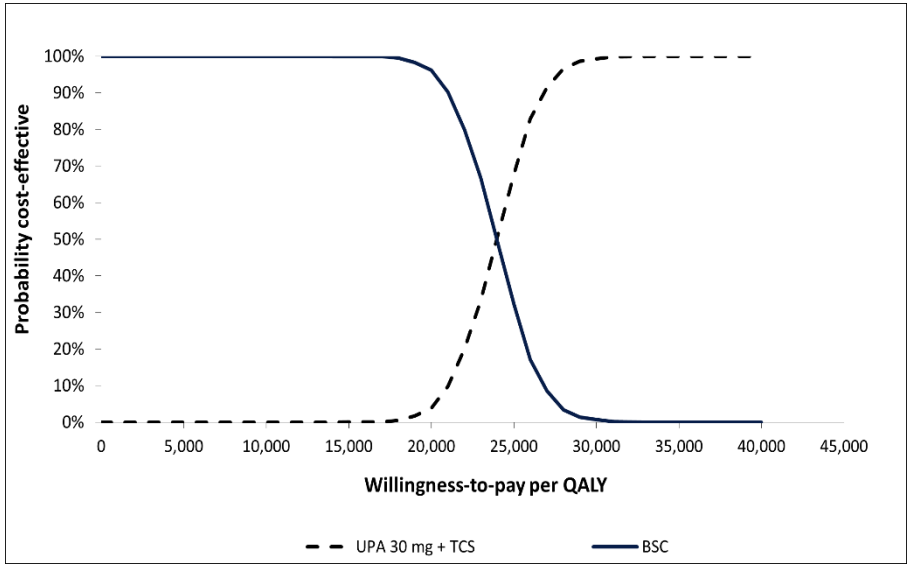
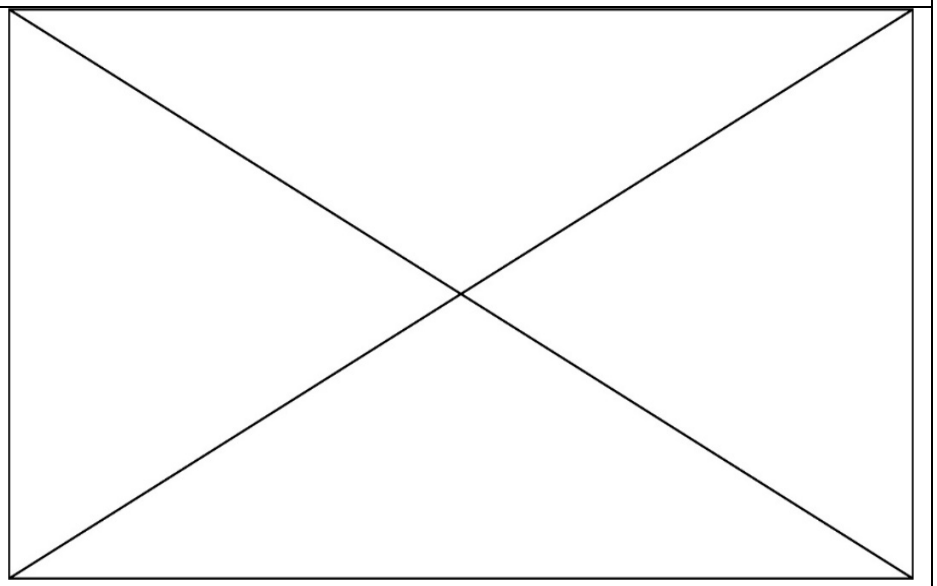
Cost-effectiveness acceptability curve (upadacitinib 30 mg)	Scatter plot (upadacitinib 30 mg)
	

Figure 35: Adult systemic-exposed – cost-effectiveness acceptability curves and scatter plots, upadacitinib 30 mg combination therapy vs BSC, all observed, PAS price

Cost-effectiveness acceptability curve (upadacitinib 30 mg)	Scatter plot (upadacitinib 30 mg)
	

B.3.8.1.2 PSA results: adolescent systemic-eligible (PAS price)

Figure 36: Adolescent systemic-eligible – cost-effectiveness acceptability curves and scatter plots, upadacitinib 15 mg monotherapy vs dupilumab, all observed, PAS price

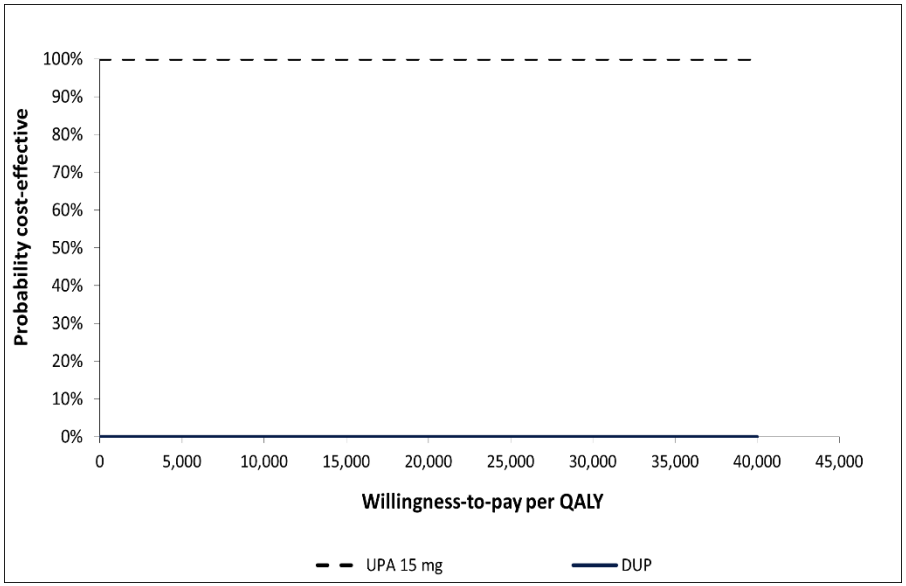
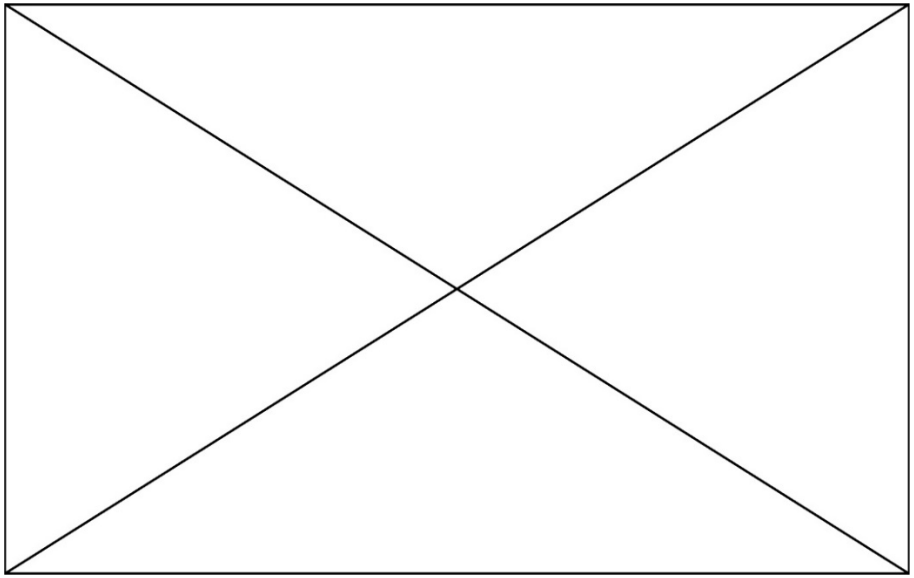
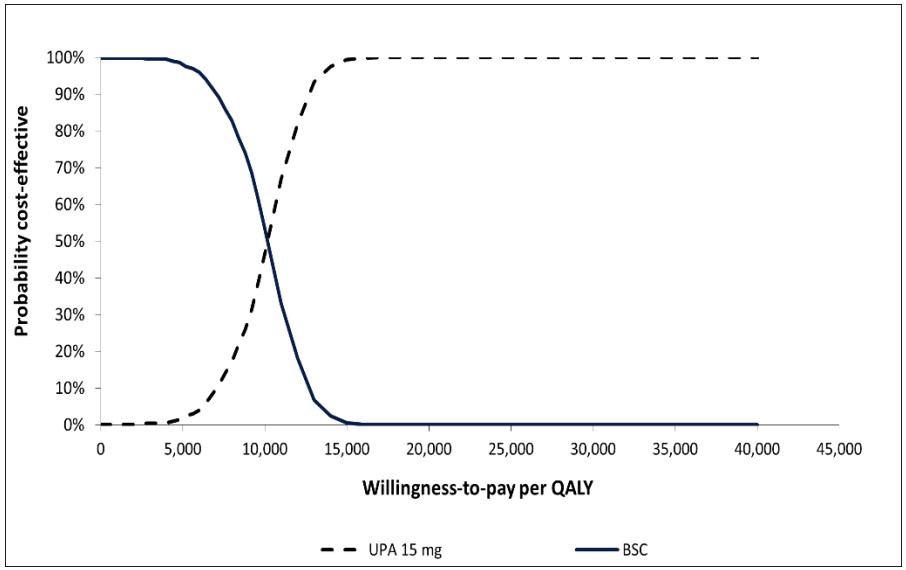
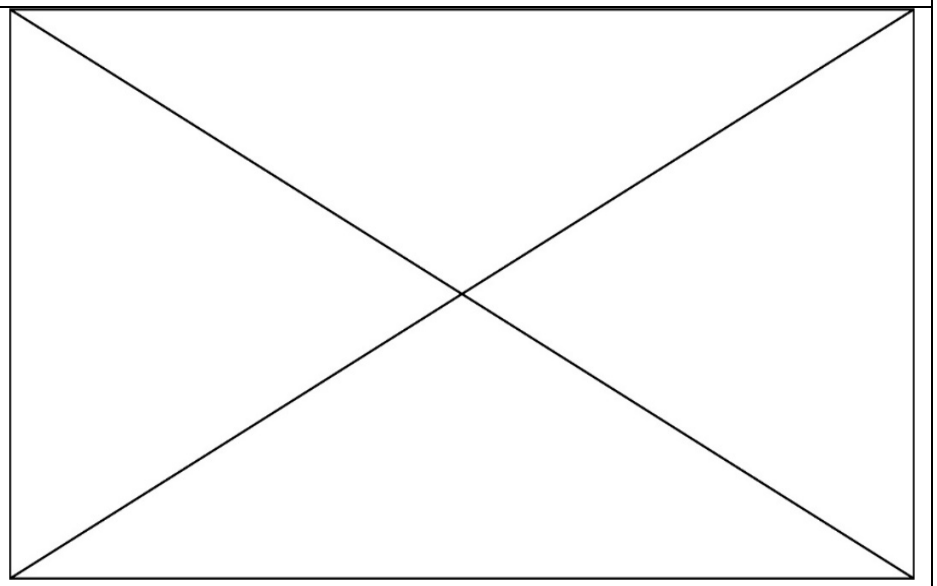
Cost-effectiveness acceptability curve (upadacitinib 15 mg)	Scatter plot (upadacitinib 15 mg)
	

Figure 37: Adolescent systemic-eligible – cost-effectiveness acceptability curves and scatter plots, upadacitinib 15 mg monotherapy vs BSC, all observed, PAS price

Cost-effectiveness acceptability curve (upadacitinib 15 mg)	Scatter plot (upadacitinib 15 mg)
	

B.3.8.1.3 PSA results: adult systemic-eligible (PAS price)

Figure 38: Adult systemic-eligible – cost-effectiveness acceptability curves and scatter plots, upadacitinib 15 mg combination therapy, all observed, PAS price

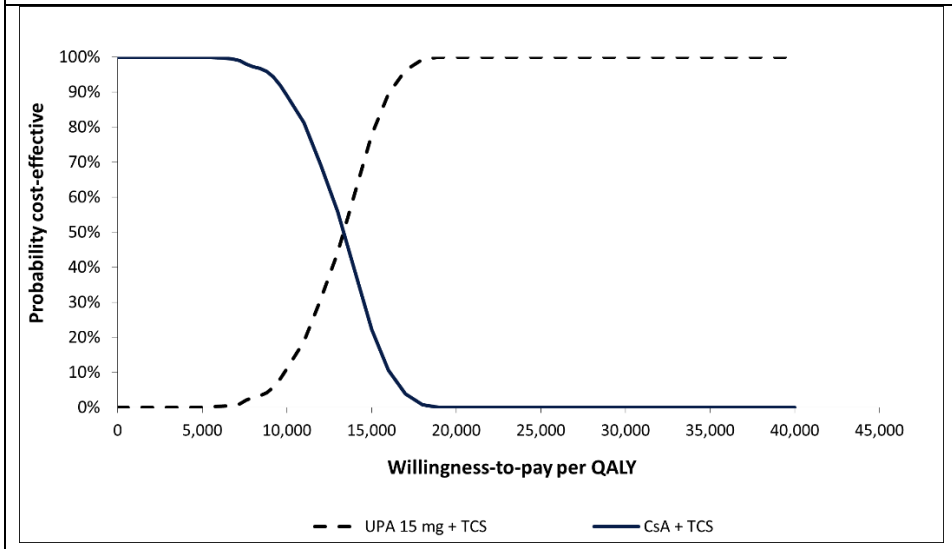
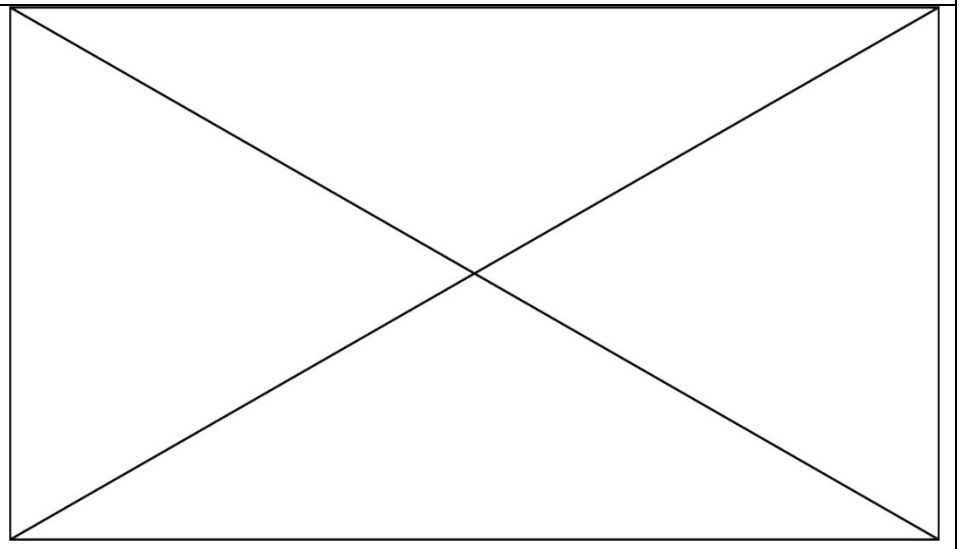
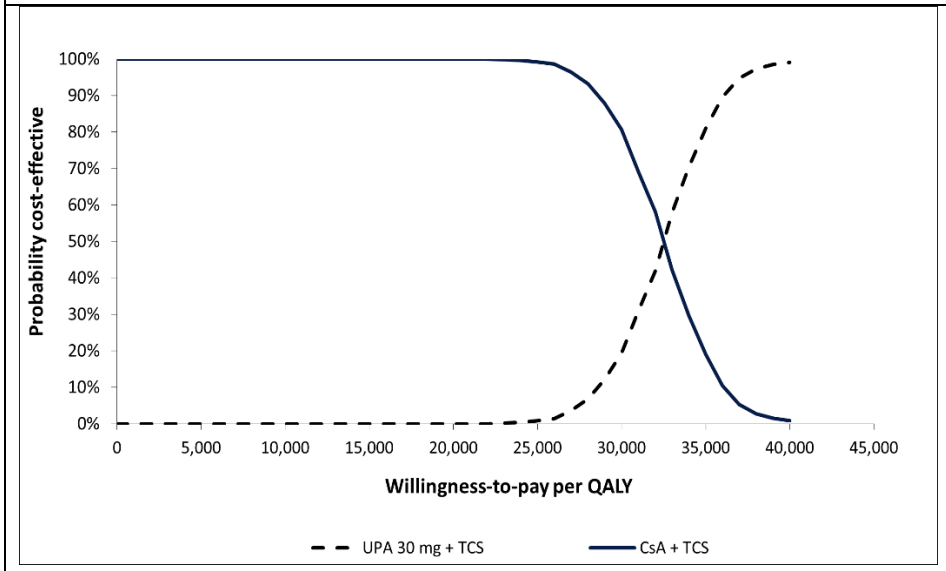
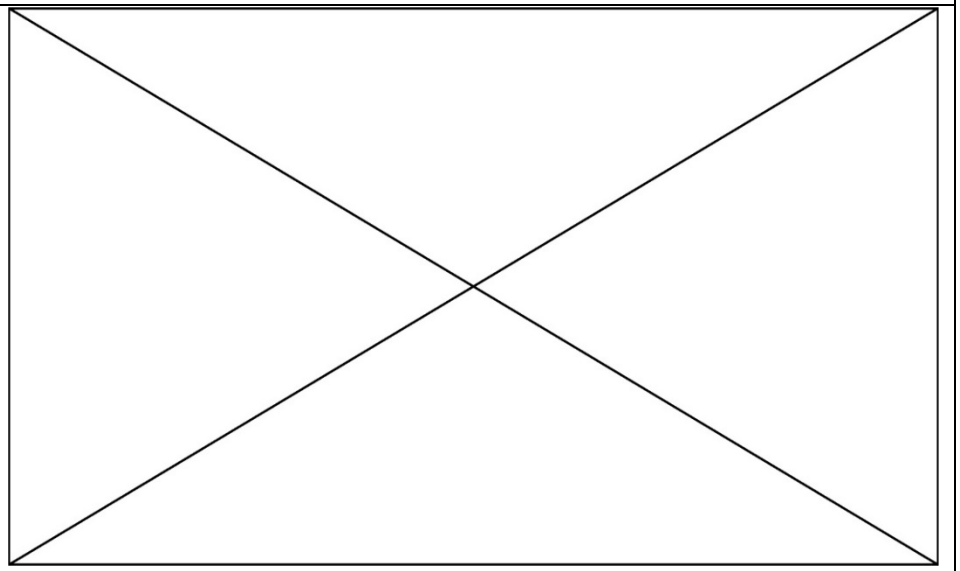
Cost-effectiveness acceptability curve (upadacitinib 15 mg)	Scatter plot (upadacitinib 15 mg)
	

Figure 39: Adult systemic-eligible – cost-effectiveness acceptability curves and scatter plots, upadacitinib 30 mg combination therapy, all observed, PAS price

Cost-effectiveness acceptability curve (upadacitinib 30 mg)	Scatter plot (upadacitinib 30 mg)
	

B.3.8.2 Deterministic sensitivity analyses

To assess the robustness of the model results, one-way sensitivity analyses (OWSA) were conducted in which each model input or assumption was varied one at a time. Values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the CIs reported in Appendix L, Section L.3.

Tornado diagrams illustrate the impact on base case model results for pairwise comparisons of upadacitinib vs relevant comparators in each population considered. To account for the analyses that resulted in negative ICERs, the tornado diagrams were instead presented using NMB, at a WTP threshold of £30,000.

Parameters varied in the DSA are listed below:

- Baseline patient characteristics (age, % male, worst pruritus)
- Health utility (baseline, week 16, responders and non-responders)
- Direct medical costs (responders and non-responders)
- Costs associated with AE
- Efficacy (week 16, sustained response at week 52)
- Overall AE rates
- Treatment utility
- TCS concomitant medication costs (responders and non-responders)

Baseline characteristics, health utilities and AE rates are varied individually for each comparator by ±1.96 SE around the base case value. Efficacy response at week 16 for each comparator is varied using the 95% CrI estimated by the NMA. Response levels (EASI 50 + DLQI ≥4, EASI 50, EASI 75) are varied simultaneously. Drug acquisition costs do not vary and all other cost items are varied ±50%. For direct medical costs and other treatment-related costs, variation by response level is introduced in the DSA to circumvent the base case assumption of no differentiation in cost by response level.

B.3.8.2.1 DSA results: adult systemic-exposed (PAS price)

Figure 40: Net monetary benefit – adult systemic-exposed, upadacitinib vs dupilumab combination therapy, all observed, PAS price

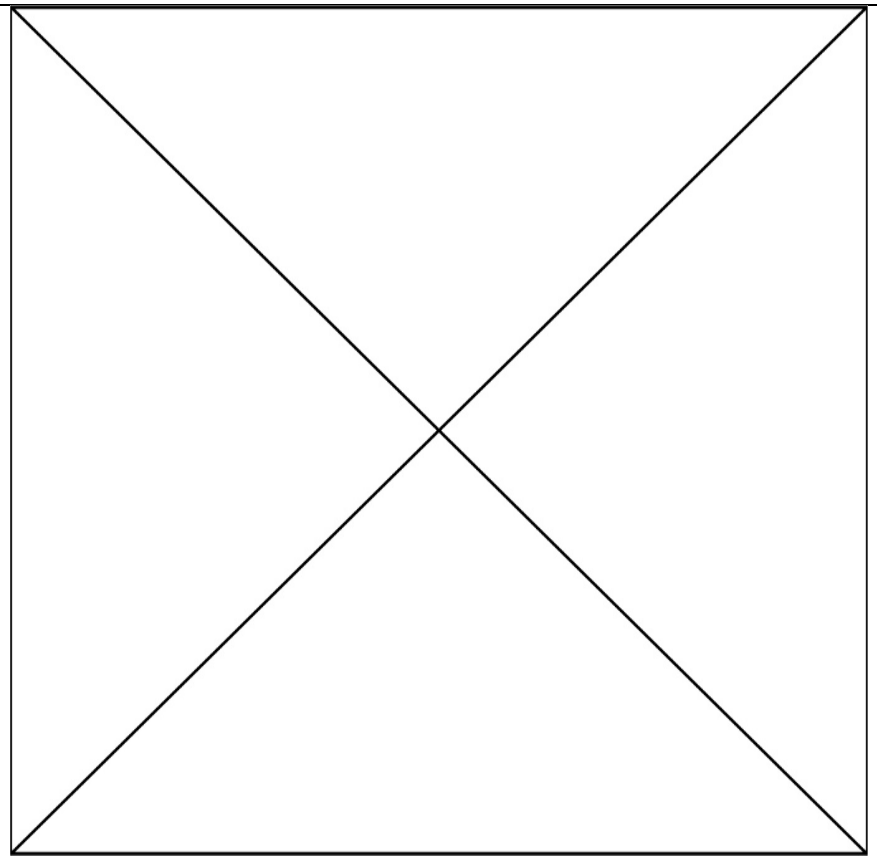
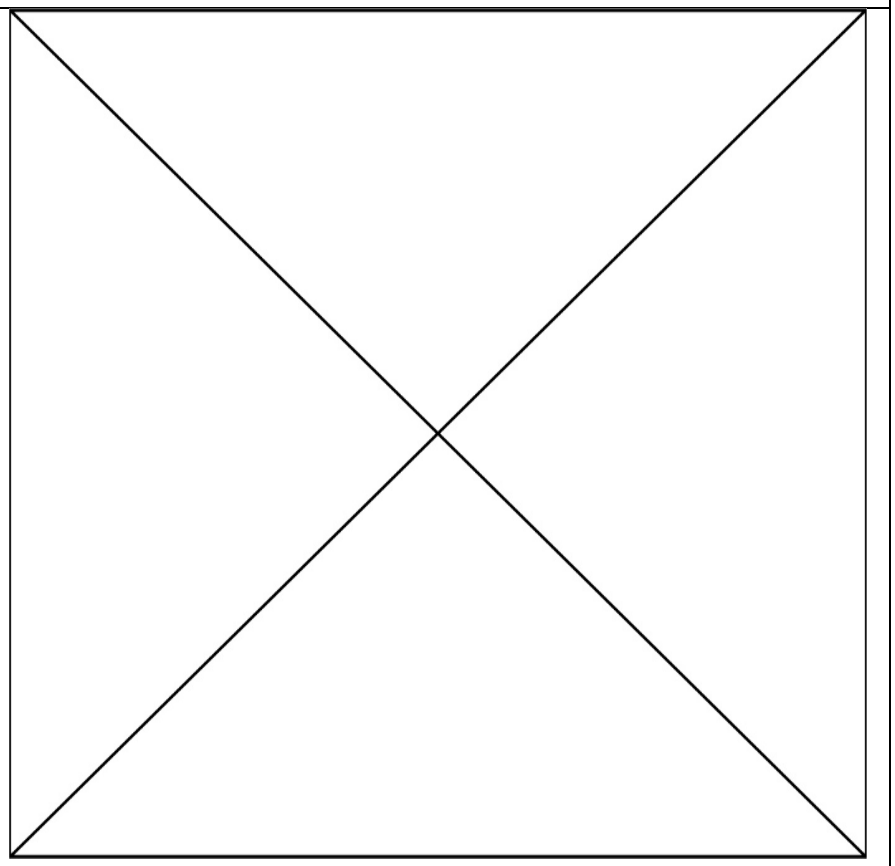
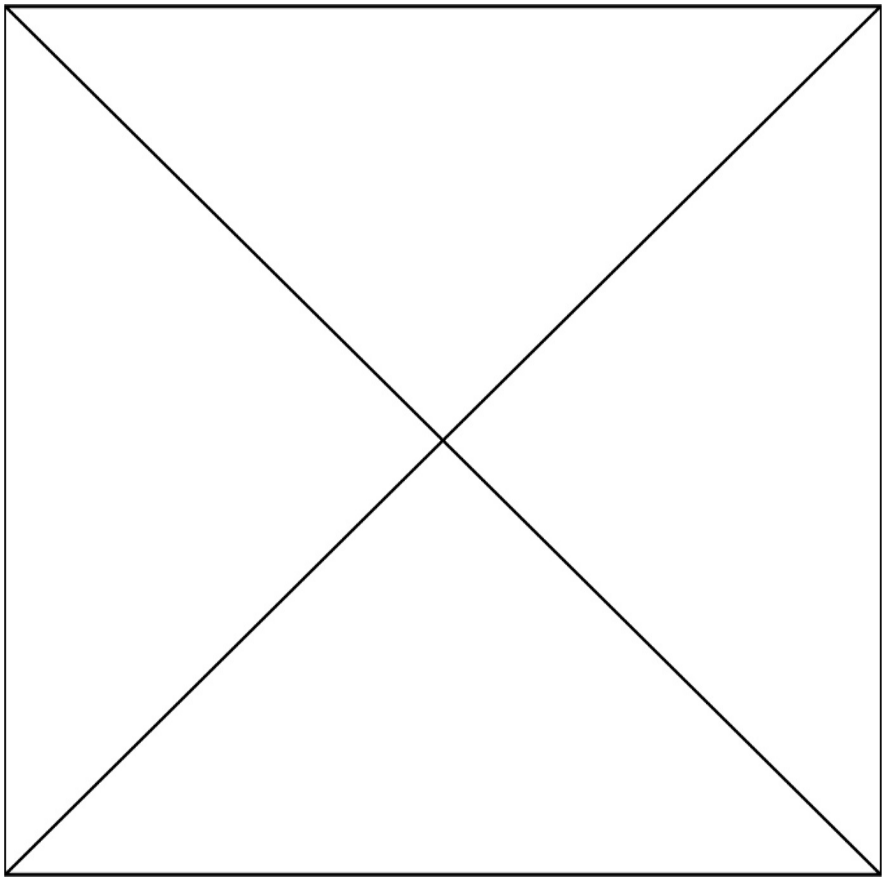
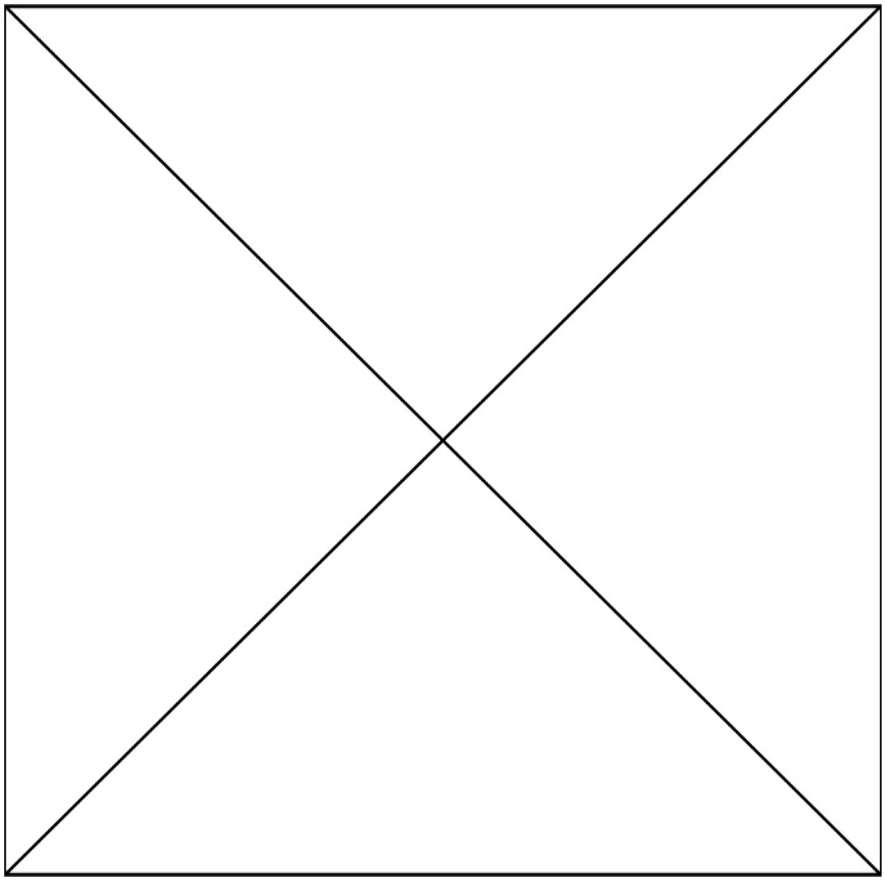
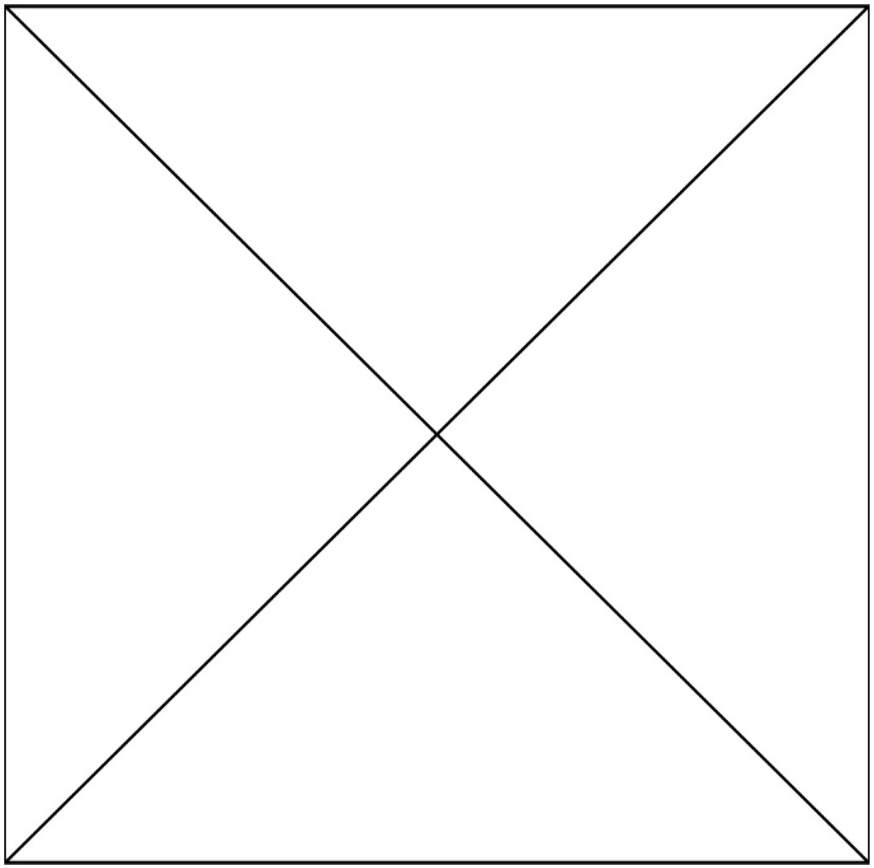
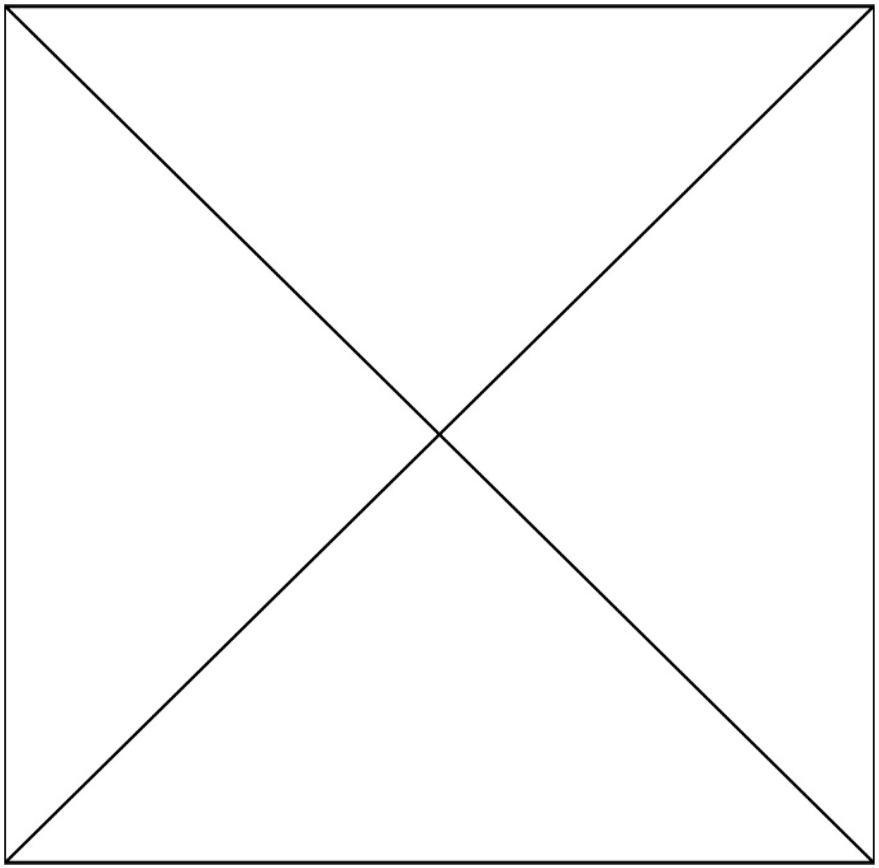
Upadacitinib 15 mg (base case: [redacted])	Upadacitinib 30 mg (base case: [redacted])
	

Figure 41: Net monetary benefit – adult systemic-exposed, upadacitinib vs BSC combination therapy, all observed, PAS price

Upadacitinib 15 mg (base case: [redacted])	Upadacitinib 30 mg (base case: [redacted])
	

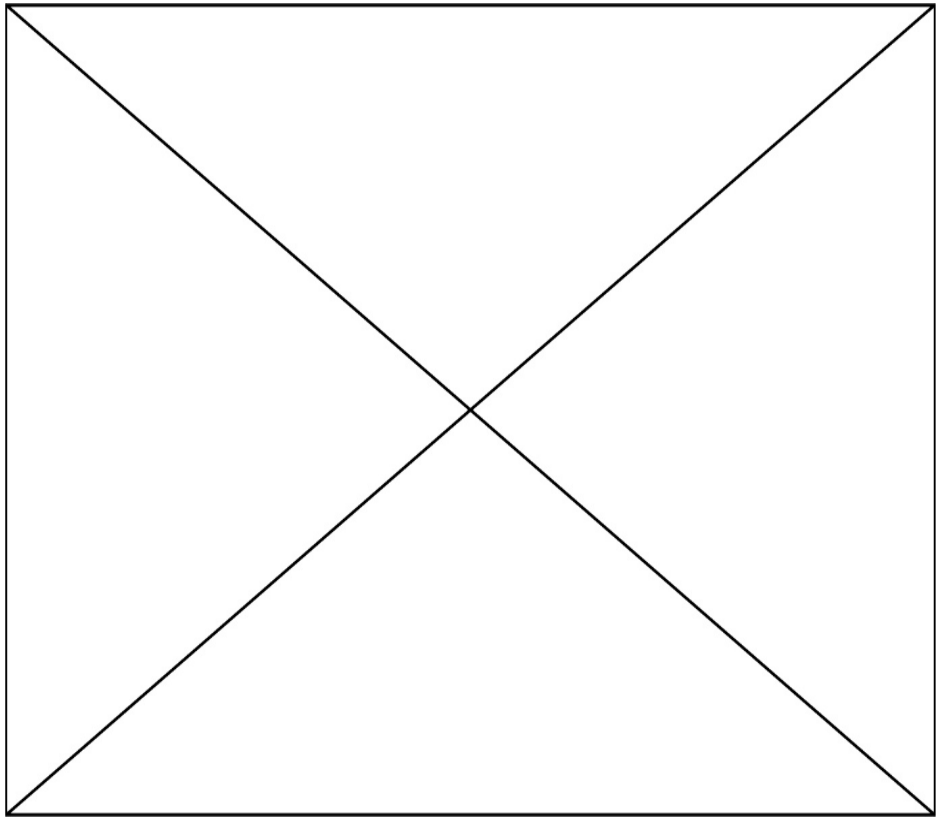
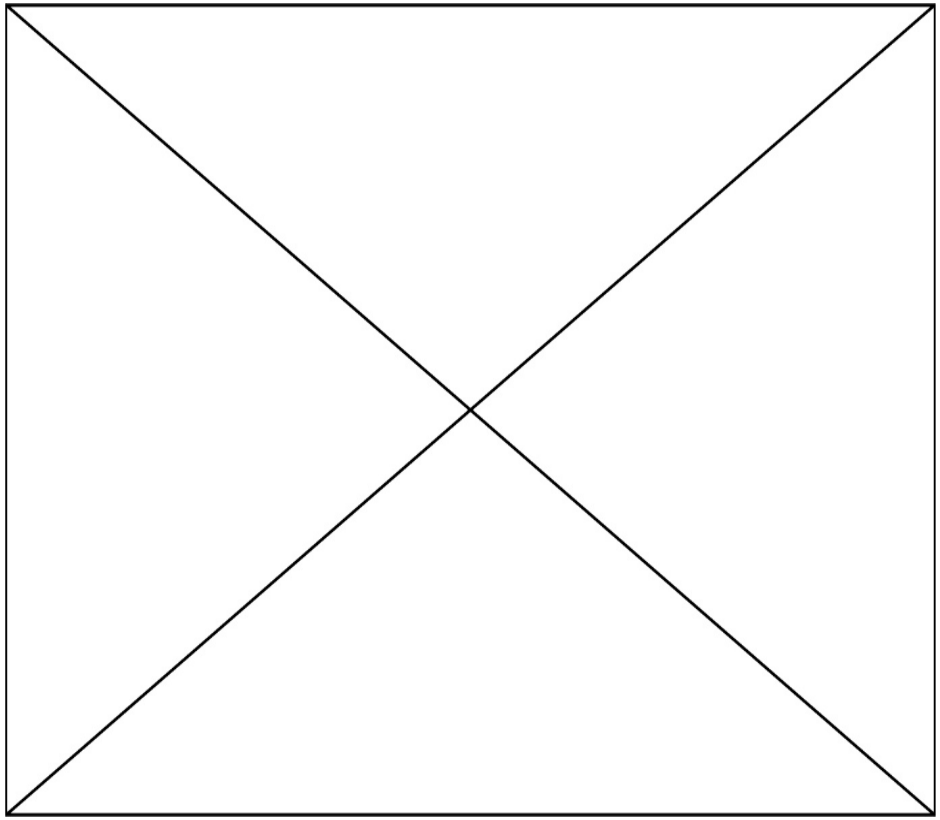
B.3.8.2.2 DSA results: adolescent systemic-eligible (PAS price)

Figure 42: Net monetary benefit – adolescent systemic-eligible, upadacitinib monotherapy, all observed, PAS price

Upadacitinib 15 mg vs dupilumab (base case: [redacted])	Upadacitinib 15 mg vs BSC (base case: [redacted])
	

B.3.8.2.3 DSA results: adult systemic-eligible (PAS price)

Figure 43: Net monetary benefit – adult systemic-eligible, upadacitinib combination therapy, all observed vs CsA, PAS price

Upadacitinib 15 mg (base case: [redacted])	Upadacitinib 30 mg (base case: [redacted])
	

B.3.9. Scenario analyses

In the scenario analyses, certain model assumption and efficacy inputs were varied while holding the other parameters at base-case values. Inputs varied in the scenario analyses are shown in Table 80 with results shown in Table 81 to Table 83.

Table 80: Scenario analyses, input variables

Base case equivalent	Scenario detail	Brief rationale	Adult systemic-exposed	Adolescent systemic-eligible	Adult systemic-eligible
Time horizon: 100 years (lifetime)	Time horizon: 15 years	Alternative time horizons	✓	✓	✓
	Time horizon: 30 years		✓	✓	✓
Discount rate: 3.5%	Annual discount rate for costs 0%; QALYs 0%	Alternative time discounting assumptions	✓	✓	✓
	Annual discount rate for costs 6.0%; QALYs 6.0%		✓	✓	✓
Alternative response timepoint	Response observed at week 16 for all treatments and BSC	Alternative response assessment assumptions	✓	✓	✓
			✓	✓	✓
Analyses using the all observed dataset	Alternative approach to censoring rescue medication	Alternative assumption on treatment discontinuation for flare using the primary dataset	✓	✓	N/A
Alternative all exposed response definitions	EASI 50 or EASI 75 used to define response	Alternative response definitions	✓ EASI 50, EASI 75	✓ EASI 50	✓ EASI 50
Scenario using direct evidence from Heads UP for upadacitinib 30 mg vs dupilumab (monotherapy)	EASI 50 at 16 weeks All observed dataset 92.0% vs 89.3%	Direct efficacy data based on Heads UP, 30 mg dose as monotherapy Scenario only vs dupilumab as head to head evidence	✓ Mono 30 mg only	N/A as 30 mg dose only and adolescent dose is 15 mg	N/A as no mono data for this population
	EASI 75 at 16 weeks All observed dataset		✓ Mono 30 mg only	N/A as 30 mg dose only and	N/A as no mono data for this population

	86.0% vs 67.9%			adolescent dose is 15 mg	
Base case using monotherapy for systemic-exposed	EASI 50 + DLQI ≥4, all observed	Alternative dosing	✓	N/A	N/A
Alternative waning estimates	Scenario 1: Waning in the BSC arm using curve fit estimator of maintenance of response 18.2%, 10.3%, 6.2% and 3.7%, 0% response in years 6-10	Note only vs BSC as waning equivalent for upadacitinib and dupilumab	✓	✓	N/A
	Scenario 2: Waning in the BSC arm using annual rate of 57% (loss QOL year 2: 57%, year 3: 81.5%, year 4: 92%, year 5: 96.6%, year 6: 98.5%, year 7: 99.4%, year 8: 99.7% year 9: 99.9% and year 10; 99.9%)	Note only vs BSC as waning equivalent for upadacitinib and dupilumab	✓	✓	N/A

BSC: Best Supportive Care, CsA: Ciclosporin, DQLI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, N/A: Not Applicable, MONO: Monotherapy, QALYs: Quality-adjusted Life Years

Table 81: Summary of scenario analyses for adult systemic-exposed population, PAS price

Response criteria	Upadacitinib dose	Mono/combo	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB (£ using WTP/QALY of £30,000)
Time horizon							
15 years	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£10,410	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£25,895	[redacted]
30 years	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£9,997	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£25,116	[redacted]
Discount rate							
Annual discount rate for costs 0%; QALYs 0%	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£9,420	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£24,067	[redacted]
Annual discount rate for costs 6.0%; QALYs 6.0%	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£10,392	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£25,888	[redacted]

Alternative response timepoint							
Response observed at week 16 for all treatments and BSC	15 mg	Combo	Dupilumab	[redacted]	[redacted]	£3,101,397*	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£10,271	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£25,602	[redacted]
Analyses using the primary dataset							
EASI 50 + DLQI ≥4	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£9,398	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£23,962	[redacted]
EASI 50	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£10,285	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£26,119	[redacted]
EASI 75	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£9,426	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£23,926	[redacted]
Alternative response definition: systemic-exposed							
EASI 50	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Combo	BSC	[redacted]	[redacted]	£10,920	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£27,458	[redacted]
EASI 75	15 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]

	15 mg	Combo	BSC	[redacted]	[redacted]	£9,754	[redacted]
	30 mg	Combo	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£24,604	[redacted]
Alternative response definition: systemic-exposed including data from Heads UP							
EASI 50 at 16 weeks All observed dataset 92.0% vs 89.3%	30 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
EASI 75 at 16 weeks All observed dataset 86.0% vs 67.9%	30 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
Base case using monotherapy (EASI 50 + DLQI ≥4, all observed)							
EASI 50 + DLQI ≥4	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£9,197	[redacted]
	30 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	30 mg	Mono	BSC	[redacted]	[redacted]	£24,429	[redacted]
Alternative waning scenarios							
Scenario 1: 18.2%, 10.3%, 6.2%, 3.7% thereafter	15 mg	Combo	BSC	[redacted]	[redacted]	£9,327	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£23,945	[redacted]
Scenario 2: Waning in the BSC arm using annual rate of 57%	15 mg	Combo	BSC	[redacted]	[redacted]	£9,514	[redacted]
	30 mg	Combo	BSC	[redacted]	[redacted]	£24,276	[redacted]

BSC: Best Supportive Care, COMBO: Combination Therapy, DLQI: Dermatology Life Quality Index, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-Effectiveness Ratio, INMB: Incremental Net Monetary Benefit, MONO: Monotherapy, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

*This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold. Positive INMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

Table 82: Summary of scenario analyses for adolescent systemic-eligible population, PAS price

Response criteria	Upadacitinib dose	Mono/combo	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£)	INMB (£ using WTP/QALY of £30,000)
Time horizon							
15 years	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£10,590	[redacted]
30 years	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£10,218	[redacted]
Discount rate							
Annual discount rate for costs 0%; QALYs 0%	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£9,684	[redacted]
Annual discount rate for costs 6.0%; QALYs 6.0%	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£10,568	[redacted]
Alternative response timepoint							
Response observed at week 16 for all treatments and BSC	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£10,495	[redacted]
Analyses using the primary dataset							
EASI 50	15 mg	Mono	Dupilumab	[redacted]	[redacted]	£501,844*	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£11,572	[redacted]
EASI 75	15 mg	Mono	Dupilumab	[redacted]	[redacted]	Dominant	[redacted]
	15 mg	Mono	BSC	[redacted]	[redacted]	£10,376	[redacted]
Alternative waning scenarios							
Scenario 1: Waning in the BSC arm using curve fit estimator of maintenance of	15 mg	Mono	BSC	[redacted]	[redacted]	£9,810	[redacted]

response 18.2%, 10.3%, 6.2% and 3.7%							
Scenario 2: Waning in the BSC arm using annual rate of 57%	15 mg	Mono	BSC	[redacted]	[redacted]	£9,919	[redacted]

BSC: Best Supportive Care, COMBO: Combination Therapy, CsA: Ciclosporin, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-Effectiveness Ratio, INMB: Incremental Net Monetary Benefit, MONO: Monotherapy, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

*This is a South West Quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold. Positive INMB values imply that the intervention is a cost-effective use of NHS resources at the given willingness-to-pay threshold.

Table 83: Summary of scenario analyses for adult systemic-eligible population, PAS price

Response criteria	Upadacitinib dose	Mono/combo	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£)	INMB (£ using WTP/QALY of £30,000)
Time horizon							
15 years	15 mg	Combo	CsA	[redacted]	[redacted]	£14,194	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£34,490	[redacted]
30 years	15 mg	Combo	CsA	[redacted]	[redacted]	£13,056	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£32,215	[redacted]
Discount rate							
Annual discount rate for costs 0%; QALYs 0%	15 mg	Combo	CsA	[redacted]	[redacted]	£11,714	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£29,500	[redacted]
Annual discount rate for costs 6.0%; QALYs 6.0%	15 mg	Combo	CsA	[redacted]	[redacted]	£13,866	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£33,904	[redacted]
Alternative response timepoint							
Response observed at week 16 for all treatments and BSC	15 mg	Combo	CsA	[redacted]	[redacted]	£13,486	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£32,957	[redacted]
Alternative response definition: all exposed							
EASI 75	15 mg	Combo	CsA	[redacted]	[redacted]	£13,783	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£34,584	[redacted]
Alternative waning scenario							
Assuming equivalent waning for BSA and CsA using Scenario 2: Waning in the BSC arm using annual rate of 57%	15 mg	Combo	CsA	[redacted]	[redacted]	£11,030	[redacted]
	30 mg	Combo	CsA	[redacted]	[redacted]	£28,646	[redacted]

BSC: Best Supportive Care, COMBO: Combination Therapy, CsA: Ciclosporin, EASI: Eczema Area and Severity Index, ICER: Incremental Cost-Effectiveness Ratio, INMB: Incremental Net Monetary Benefit, MONO: Monotherapy, QALYs: Quality-adjusted Life Years, WTP: Willingness to Pay

B.3.10. Subgroup analysis

No further subgroup analyses were conducted as part of this economic evaluation. All relevant subgroups have been considered in the three base case populations and alternatives explored in scenario analyses.

B.3.11. Validation of cost-effectiveness analysis

B.3.11.1 Technical and internal validation

The model aligns with the International Society for Pharmacoeconomic and Outcomes Research (ISPOR), Society for Medical Decision Making (SMDM) best practices and NICE guidance for HTAs[82,101,102] and with the previously submitted economic model for dupilumab in moderate to severe AD (TA534).

Prior to submission, the cost-effectiveness model underwent quality control checks. In these processes, an economist not involved in the model build reviewed the model for coding errors, inconsistencies and the plausibility of inputs; this was carried out as a thorough sheet-by-sheet check. The model was also subject to review against a the AdViSHE checklist[103] of known modelling errors and questioning of assumptions, including:

- Extreme value testing
- Logical relationship testing (for example, if intervention drug acquisition costs increase, do total intervention costs increase accordingly? Does the ICER increase accordingly?)
- Consistency checks (for example, is an input parameter value cost in one cell consistently reflected elsewhere?)

For technical validity, model structure and parameters were reviewed by two experienced independent modellers, who each checked the software and cleaned it for potential programming errors.

Internal validation involved comparing the model's predictions with the data used, in addition to conducting different routine tests, which yielded the expected results.

Cross validity checks were also planned against the results presented in the most recent appraisal in moderate to severe AD, TA534 (dupilumab). However, in TA534 all results were redacted, preventing a comparison being made.

B.3.11.2 External validation

Ideally, external validation is conducted by comparing the clinical predictions from the model with those in clinical literature. However, published real-world studies following EASI or other outcomes of interest in this patient population are not available. Long-term observational studies have not been carried out for upadacitinib; therefore, external validity of real-world clinical effectiveness is difficult to assess.

AbbVie held an Advisory Board to inform their approach to the economic modelling in this submission to ensure that the modelling reflected UK clinical practice[1]. Eight UK experts attended the Advisory Board and included consultant dermatologists (n=4), a paediatric consultant dermatologist, a clinical dermatology specialist research nurse, a professor of health economics and a professor of health economic methodology[1]. Ad hoc advice was also sought where required. The advisors supported the modelling approach and provided advice on response end-points, definition and management of flares, discontinuation rates, utility, waning, resource use and costs[83].

We sought specific advice on the treatments used in BSC, cost associated with flares, commonly used treatments for management of flare, frequencies of resource use with active therapy and with BSC from the Advisory Board.

Advice on management of AE was sought from an ex-General Practitioner and validated by a Consultant Dermatologist[84].

B.3.12. Interpretation and conclusions of economic evidence

Upadacitinib is cost-effective in all three populations assessed in the base case, see Table 73: Summary of base case results (all observed), PAS price.

PSA and DSA indicate that the results are robust and that upadacitinib remains cost-effective when key areas of uncertainty are investigated.

Scenario analyses exploring the use of alternative time horizons, discount rates, response timepoints, dataset (primary), response definitions, waning scenarios, base case using monotherapy and direct evidence from Heads UP vs dupilumab demonstrated the robustness of the conclusions. In the adult systemic-eligible population, upadacitinib 30 mg is marginally over the £30,000 threshold in several scenarios, driven by the increased incremental cost of upadacitinib vs CsA.

In the adult systemic-exposed population scenarios using direct evidence from the Heads UP trial demonstrated that upadacitinib 30 mg monotherapy was dominant vs dupilumab and cost-effective vs BSC.

In summary, the results of the CEA support the use of both doses of upadacitinib in monotherapy or combination therapy in patients with moderate to severe AD (aged >12 years) who are eligible for, or who have been previously exposed to, conventional systemic therapy.

B.3.12.1 Strengths

The approach taken in this submission model has a number of important strengths.

Firstly, the model has been developed in line with the most recent NICE TA (TA534) in moderate to severe AD, taking into account ERG and Committee feedback was validated by UK experts in the field.

Extensive sensitivity and scenario analyses were performed to test alternative approaches where possible and to validate the robustness of the model results. The analyses provided are consistent with the NICE reference case and the decision problem at hand (see Table 1).

This is the first CEA performed in a population of adolescents with moderate to severe AD. The cost-effectiveness of upadacitinib 15 was demonstrated using robust evidence from subsets of adolescents patients within the upadacitinib registration trials.

Response definitions used in the CEA were accepted by clinical experts as a valid response assessment criteria. Where feasible, the percentage of participants achieving EASI 50 and DLQI ≥4 was used to define response, since it aligns with current clinical practice in the UK. Alternatively, the EASI-75 was selected since it reflects one of the main primary end-points used in clinical trials in AD.

Finally, the efficacy, safety and health state utility values in the model were informed by a large evidence base of phase III trials allowing reliable comparisons of upadacitinib vs relevant comparators in the populations of interest. Direct evidence from the Heads UP trial was used to assess the cost-effectiveness of upadacitinib 30 mg vs dupilumab in the adult systemic-exposed population. This key source of evidence confirmed the conclusions drawn from the base case analysis that upadacitinib 30 mg is dominant versus dupilumab.

B.3.12.2 Limitations

There is a paucity of randomised clinical evidence of CsA in moderate to severe AD thus, comparisons in the systemic eligible population had to rely on an indirect treatment comparison of RCTs and real world evidence. Some differences in population characteristics and study design were noted between the sources considered in this analysis. Nonetheless, this is considered to be the most robust

indirect comparison that has been performed to date in this population since it uses end-points relevant for UK clinical practice. Therefore, this provides the most reliable estimate of the cost-effectiveness of upadacitinib versus CsA in systemic-eligible patients.

Data limitations restricted the feasibility of subgroup analyses or treatment regimen comparisons in the adult and adolescent populations eligible for systemic therapies. Nonetheless, we would expect that the demonstration of upadacitinib cost-effectiveness vs dupilumab and CsA in the adult subgroup analyses could be extrapolated to the adolescent population. Indeed, clinical experts confirmed their willingness to use treatments in adolescent patients that have proven clinical efficacy, safety and cost-effectiveness in adult patients. Furthermore, due to the high efficacy of upadacitinib monotherapy, the direction of the cost-effectiveness results is expected to remain identical irrespective of TCS use.

Given the limited clinical evidence beyond 1-year, assumptions were required to estimate projections of treatment and BSC waning over time. Exploration of these assumptions through scenario analyses did not affect the conclusions of the analyses.

Finally, CsA was selected as a proxy for conventional systemic therapy in the systemic-eligible adult population, however, other agents (methotrexate, mycophenolate mofetil, azathioprine) are also used in clinical practice in the UK. This approach was previously accepted by NICE and aligns with the systemic-exposed definition in TA534 enabling a fair comparison with the dupilumab evidence.

Although the selected outcomes are considered to be the most clinically relevant to UK practice, they may not entirely capture the benefits associated with higher efficacy response that is, a higher QOL and lower costs. Therefore, these analyses may not reflect the full benefits associated with upadacitinib which has demonstrated high response rates for EASI 90 and EASI 100 end-points and improvement of worst pruritus NRS score.

Despite these limitations, the analyses presented in this appraisal take a pragmatic approach and demonstrate the cost-effectiveness of upadacitinib in both systemic-exposed and systemic-eligible populations.

B.3.12.3 Conclusions

Moderate to severe AD is a chronic condition with a considerable impact on physical and mental health. The symptoms of AD are challenging to manage, in particular the often intractable itch, which is the hallmark of disease. Many patients have poor symptom control, therefore, there is a need for new treatment options to manage AD

over a patient's lifetime. Upadacitinib offers an efficacious, fast-acting, well tolerated oral treatment option, which may be given as monotherapy or in combination with TCS.

It is clear from the clinical community that health care professionals would value the option to use upadacitinib in systemic-exposed patients or as an alternative to systemic-therapies reducing the burden of side effects and monitoring and improving patients' QOL.

Overall, the results demonstrate that upadacitinib is a cost-effective option for use in the NHS in all three populations considered and provides an effective alternative treatment option with the potential to address the unmet need for patients with moderate the severe AD.

B.4 List of appendices

Appendix B Additional clinical data
B.1 Special warnings and precautions for use
B.2 Additional efficacy results
B.3 Additional safety results
Appendix C Summary of product characteristics (SmPC) and European public assessment report (EPAR)
C.1 SmPC
C.2 EPAR
Appendix D Identification, selection and synthesis of clinical evidence
D.1 Identification and selection of relevant studies
D.2 Network meta-analyses: supplementary information
D.3 Participant flow in the relevant RCT
D.4 Quality assessment for each trial
Appendix E Subgroup analysis
E.1 Measure UP 1
E.2 Measure UP 2
E.3 AD UP
E.4 Heads UP 1
Appendix F Adverse reactions
Appendix G Published cost-effectiveness studies
G.1 Search strategy
G.2 Study selection
G.3 Results: cost effectiveness evaluations
G.4 Quality assessment
Appendix H Health-related quality-of-life studies
H.1 Search strategy and study selection
H.2 Results: HRQOL studies
Appendix I Cost and healthcare resource identification, measurement and valuation
I.1 Search strategy and study selection
I.2 Results: cost and healthcare resource identification, measurement and valuation studies
I.3 Advice from UK clinicians
Appendix J Clinical outcomes and disaggregated results from the model
J.1 Clinical outcomes from the model
J.2 Disaggregated results of the base case incremental cost-effectiveness analysis
Appendix K Checklist of confidential information
Appendix L Additional information from the economic modelling
L.1 Summary of base case analysis inputs
L.2 Deterministic sensitivity analysis inputs
L.3 List price results from the economic model
Appendix M References

B.5 References

1. Abbvie Ltd. Report for Virtual Advisory Board for Atopic Dermatitis held 30 September 2020. 2020.
2. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis. Available at www.nice.org.uk/guidance/ta534. 2018.
3. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol* 2018; **32**(6): 850-78.
4. National Institute for Health and Care Excellence. Alitretinoin for the treatment of severe chronic hand eczema. Available at www.nice.org.uk/guidance/ta177, 2009.
5. AbbVie Ltd. Summary of Product Characteristics: RINVOQ 15 mg prolonged-release tablets and RINVOQ 30 mg prolonged-release tablets (proposed), 2021.
6. Leung DY, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J Allergy Clin Immunol* 2014; **134**(4): 769-79.
7. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *The Lancet* 2020; **396**(10247): 345-60.
8. Rodrigues MA, Torres T. The Changing Landscape of Atopic Dermatitis - Focusing on JAK Inhibitors. *Eur Ann Allergy Clin Immunol* 2020; **52**(1): 45-8.
9. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**(10023): 1109-22.
10. National Eczema Society. Atopic eczema. Available at https://eczema.org/information-and-advice/types-of-eczema/atopic-eczema/, 2020.
11. Ameen M, Rabe A, Blanthorn-Hazell S, Millward R. The Prevalence and Clinical Profile of Atopic Dermatitis (AD) in England- A Population Based Linked Cohort Study Using Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) (abstract). *Value Health* 2020; **23**.
12. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy* 2018; **73**(6): 1284-93.
13. Ameen M, Rabe AR, Blanthorn-Hazell S, Millward R. The prevalence and clinical profile of atopic dermatitis (AD) in England: a population-based linked cohort study using Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). Available at https://europe2020-ispor.ipostersessions.com/Default.aspx?s=52-2B-C2-4C-A5-6E-1B-12-22-9D-EC-02-09-AE-06-9A. ISPOR Europe 202. Virtual 2020.
14. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol* 2018; **121**(3): 340-7.
15. Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. *J Am Acad Dermatol* 2019; **81**(1): 187-95.
16. Leo Pharma and National Eczema Society. Eczema unmasked: revealing the true impact of life with eczema 2020.
17. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. *Protein Sci* 2018; **27**(12): 1984-2009.

18. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol* 2018; **32**(5): 657-82.
19. Newsom M, Bashyam AM, Balogh EA, Feldman SR, Strowd LC. New and Emerging Systemic Treatments for Atopic Dermatitis. *Drugs* 2020; **80**(11): 1041-52.
20. Simpson EL, Bieber T, Eckert L, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol* 2016; **74**(3): 491-8.
21. Narala S, Hata TR. Adult Atopic Dermatitis with Comorbid Atopic Disease is Associated with Increased Risk of Infections: A Population-Based Cross-Sectional Study. *Dermatol Ther (Heidelb)* 2017; **7**(1): 111-21.
22. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. *J Invest Dermatol* 2019; **139**(3): 583-90.
23. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy* 2010; **65**(12): 1506-24.
24. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013; **131**(2): 428-33.
25. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; **155**(1): 145-51.
26. Ameen M, Rabe A, Blanthorn-Hazell S, Unal G, Alamgir G, Millward R. Healthcare Resource Utilization of Atopic Dermatitis Patients in England: A Population-Based Linked Cohort Study using Clinical Practice Research Datalink and Hospital Episode Statistics (poster). European Academy of Dermatology and Venereology (EADV) Congress Virtual; 2020.
27. Brown SJ. Atopic eczema. *Clin Med (Lond)* 2016; **16**(1): 66-9.
28. Primary Care Dermatology Society. Eczema - atopic eczema, 2019.
29. National Institute for Health and Care Excellence. Frequency of application of topical corticosteroids for atopic eczema (TA 81). Available at www.nice.org.uk/guidance/ta81, 2004.
30. National Institute for Health and Care Excellence. Tacrolimus and pimecrolimus for atopic eczema. Available at www.nice.org.uk/guidance/ta82, 2004.
31. Pereyra-Rodriguez JJ, Domínguez-Cruz J, Ruiz-Villaverde R, et al. Drug survival of systemic and biological treatments for moderate-to-severe atopic dermatitis in adults: a multicentre retrospective observational study. *Br J Dermatol* 2020.
32. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available at https://bnf.nice.org.uk/; 2021.
33. NHS England. Early Access to Medicines Scheme – Dupilumab in the treatment of adolescent patients ≥12 to <18 years of age with severe atopic dermatitis who have responded inadequately to at least one systemic therapy or where the available systemic therapies are not recommended or are not tolerated, 2019.

34. Patel NU, D'Ambra V, Feldman SR. Increasing Adherence with Topical Agents for Atopic Dermatitis. *Am J Clin Dermatol* 2017; **18**(3): 323-32.
35. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol* 2000; **142**(5): 931-6.
36. Retzler J, Smith A, Reaney M, Rout R, Hudson R. Process utilities for topical treatment in atopic dermatitis. *Quality of Life Research* 2019; **28**(9): 2373-81.
37. Villeneuve S, Gadkari A, Blackburn S, et al. Disease Severity and Control in Adults with a History of Moderate to Severe Atopic Dermatitis: Results from a Large Patient-Physician Survey in the United Kingdom, Germany, and France. 2016.
38. Nakahara T, Fujita H, Arima K, Taguchi Y, Motoyama S, Furue M. Treatment satisfaction in atopic dermatitis relates to patient-reported severity: A cross-sectional study. *Allergy* 2019; **74**(6): 1179-81.
39. Boeri M, Sutphin J, Hauber B, Cappelleri JC, Romero W, Di Bonaventura M. Quantifying patient preferences for systemic atopic dermatitis treatments using a discrete-choice experiment. *J Dermatolog Treat* 2020: 1-10.
40. McLenon J, Rogers MAM. The fear of needles: A systematic review and meta-analysis. *J Adv Nurs* 2019; **75**(1): 30-42.
41. Beck LA, Thaci D, Deleuran M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol* 2020; **21**(4): 567–77.
42. Horton E, Benson A, Povall A, Laws P. RF03 Ocular side-effects of dupilumab for the treatment of atopic dermatitis: real-world data from a U.K. cohort. *British Journal of Dermatology* 2020; **183** 15.
43. Hendricks AJ, Lio PA, Shi VY. Management Recommendations for Dupilumab Partial and Non-durable Responders in Atopic Dermatitis. *Am J Clin Dermatol* 2019; **20**(4): 565-9.
44. National Eczema Society. Eczema: an information pack for schools 2016.
45. AbbVie Inc. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis Week 16 Clinical Study Report (Upadacitinib/Protocol M16-045) Measure UP 1, 2020.
46. AbbVie Inc. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis Week 16 Clinical Study Report Upadacitinib/Protocol M18-891 (Measure UP2). 2020.
47. AbbVie Inc. A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis Week 16 Clinical Study Report R&D/20/0650 Upadacitinib/Protocol M18-891 (AD UP), 2020.
48. AbbVie Inc. Protocol for Study M16-046–Heads Up, Atopic Dermatitis: Evaluation of Upadacitinib in Adult Subjects withModerate to Severe Atopic Dermatitis, 2020.
49. AbbVie Inc. Topline Results Upadacitinib Study M16-046 (Phase 3b) Intended Indication: Atopic Dermatitis 2020.
50. Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology* 2020; **145**(3): 877-84.

51. Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Safety and Efficacy of Upadacitinib Monotherapy in Adolescents and Adults with Moderate-to-severe Atopic Dermatitis: Results From 2 Pivotal, Phase 3, Randomized, Double-blinded, Placebo-controlled Studies (Measure Up 1 and Measure Up 2) (Conference presentation). European Academy of Dermatology and Venereology; 2020; Virtual
52. Reich A, Teixeira H, De Bruin-Weller M, et al. Safety and Efficacy of Upadacitinib in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: Results From the Pivotal Phase 3, Randomized, Double-Blind, Placebo-Controlled AD Up Study (Abstract). Revolutionizing Atopic Dermatitis 2020 December 2020; Virtual
53. Reich A, Teixeira H, De Bruin-Weller M, et al. Safety and Efficacy of Upadacitinib in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: Results From the Pivotal Phase 3, Randomized, Double-Blind, Placebo-Controlled AD Up Study (Poster 321). Revolutionizing Atopic Dermatitis 2020 December 2020; Virtual
54. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med* 2016; **375**(24): 2335-48.
55. Canadian Agency for Drugs and Technologies in Health. Clinical Review Report Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD). Appendix 5 Validity of Outcomes Measures. 2018.
56. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**(1): 27-33.
57. Howells L, Ratib S, Chalmers JR, Bradshaw L, Thomas KS. How should minimally important change scores for the Patient-Oriented Eczema Measure be interpreted? A validation using varied methods. *Br J Dermatol* 2018; **178**(5): 1135-42.
58. Sanofi Genzyme. Single technology appraisal Dupilumab for treating adults with moderate-to-severe atopic dermatitis [ID1048] Document B Company evidence submission. 2018.
59. Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol* 2019; **156**(1): 44-56.
60. Paller AS, Simpson EL, de Bruin-Weller M, et al. Dupilumab in adolescents with moderate-to-severe atopic dermatitis and a history of inadequate response, or intolerance to cyclosporine: subgroup analysis from a pivotal 16-week trial. *J Invest Dermatol* 2019; **139**(Suppl 5): S106.
61. Finlay AY, Basra MK. DLQI and CDLQI scores should not be combined. *Br J Dermatol* 2012; **167**(2): 453-4.
62. AbbVie Ltd. Medical Affairs Atopic Dermatitis Advisory Board Meeting 4 November 2020, meeting report. 2020.
63. Dias S. NICE TSD2 A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. *NICE Doc* 2011.
64. Dias S. NICE TSD4 Evidence Synthesis for Decision Making 4: Inconsistency in Networks of Evidence Based on Randomized Controlled Trials. . *NICE Doc* 2011.
65. de Bruin-Weller M, Thaçi D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate

response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol* 2018; **178**(5): 1083-101.
66. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64**(2): 163-71.
67. Chou JS, LeBovidge J, Timmons K, Elverson W, Morrill J, Schneider LC. Predictors of clinical success in a multidisciplinary model of atopic dermatitis treatment. *Allergy Asthma Proc* 2011; **32**(5): 377-83.
68. Bosma AL, de Wijs LEM, Hof MH, et al. Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: Results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. *J Am Acad Dermatol* 2020; **83**(5): 1375-84.
69. Bosma AL, Spuls PI, Garcia-Doval I, et al. TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for a European safety study of dupilumab and other systemic therapies in patients with atopic eczema. *Br J Dermatol* 2020; **182**(6): 1423-9.
70. Schwarzer G. meta: an R package for meta-analysis. . *R News* 2007; **7**(3): 40-5.
71. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods* 2019; **10**(3): 476-83.
72. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ. Cochrane Handbook for Systematic Reviews of Interventions. Available at https://training.cochrane.org/handbook. Chichester, UK: John Wiley & Sons; 2019.
73. Ariëns LFM, Gadkari A, van Os-Medendorp H, et al. Dupilumab Versus Cyclosporine for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults: Indirect Comparison Using the Eczema Area and Severity Index. *Acta Derm Venereol* 2019; **99**(10): 851-7.
74. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**(10086): 2287-303.
75. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. *Arthritis Rheumatol* 2019; **71**(11): 1788-800.
76. Scottish Medicines Consortium (SMC). Medicines advice: Dupilumab (Dupixent). NHS Scotland. 2018.
77. National Institute for Health and Care Excellence. Single Technology Appraisal - Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048] - Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD). Committee Papers 2 June 2018.
78. Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006; **10**(46): 1-233, i-iv.

79. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis. *NICE technology appraisal guidance (TA350)* 2017.
80. National Institute for Health and Care Excellence. Ixekizumab for treating moderate to severe plaque psoriasis. *NICE technology appraisal guidance 442 (TA442)* 2017.
81. National Institute for Health and Care Excellence. Tildrakizumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance [TA575]. London: National Institute for Health and Care Excellence; 2019.
82. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. Process and methods [PMG9]. 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword#.
83. AbbVie Ltd. Atopic Dermatitis Health Technology Assessment Advisory Board: Responses to Pre-Meeting Questionnaire, 2020.
84. AbbVie Ltd. Meeting with Andrew Pink, dermatologist, 2021.
85. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; **64**(6): 1074-84.
86. National Institute for Health and Care Excellence. Single Technology Appraisal - Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048] Committee Papers. . 2018.
87. van der Schaft J, Politiek K, van den Reek J, et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015; **172**(6): 1621-7.
88. Office for National Statistics. National life tables, UK : 2017 to 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables (accessed November 9, 2020.
89. National Institute for Health and Care Excellence. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf, 2019.
90. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**(5): 708-15.
91. Furnival GM, Wilson RW. Regressions by Leaps and Bounds. *Technometrics* 1974; **16**(4): 499-511.
92. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**(5): 509-18.
93. Leshem YA, Bissonnette R, Paul C, et al. Optimization of placebo use in clinical trials with systemic treatments for atopic dermatitis: an International Eczema Council survey-based position statement. *J Eur Acad Dermatol Venereol* 2019; **33**(5): 807-15.
94. NICE. Final Appraisal Document: Dupilumab for treating moderate to severe atopic dermatitis. London, UK: National Institute for Health and Care Excellence, 2018.

95. Curtis L, Burns A. Unit Costs of Health and Social Care 2020, Personal Social Services Research Unit, University of Kent, Canterbury. https://kar.kent.ac.uk/84818/1/Unit_Costs_of_Health_and_Social_Care_2020.pdf. 2020.
96. NHS Digital. Hospital Admitted Patient Care Activity 2018-19. Available at https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19. 2020.
97. Rhodes J, Clay C, Phillips M. The surface area of the hand and the palm for estimating percentage of total body surface area: results of a meta-analysis. *Br J Dermatol* 2013; **169**(1): 76-84.
98. NHS Business Services Authority. December Drug Tariff Part VIIIA. 2020.
99. Messori A, Trippoli S. The results of a pharmacoeconomic study: incremental cost-effectiveness ratio versus net monetary benefit. *Heart* 2017; **103**(21): 1746.
100. Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation: Oxford University Press; 2006.
101. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health* 2012; **15**(6): 835-42.
102. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health* 2003; **6**(1): 9-17.
103. Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. *Pharmacoeconomics* 2016; **34**(4): 349-61.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tralokinumab for treating moderate-to-severe atopic dermatitis [ID3960]

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID3960 - Tralokinumab AD - Document B [redacted]	2.0	No	14 October 2021

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables

Figures

Abbreviations

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
AS	as observed
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
CAD	Canadian dollar
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	cost-effectiveness acceptability curve
CrI	credible interval
CSA	ciclosporin A
CSR	clinical study report
DCI	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
DUP	dupilumab
EASI	Eczema Area and Severity Index
EE	economic evaluation
EQ-5D	5-dimension EuroQol questionnaire
EQ-5D-3L	3-level, 5-dimension EuroQol questionnaire
EQ-5D-5L	5-level, 5-dimension EuroQol questionnaire
ERG	evidence review group
FE	fixed-effects
g	grams
GBP	Great British Pound
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HCLI	higher limit of confidence interval

HCRU	health-related cost and resource use
HOME	Harmonising Outcome Measures for Eczema
HPTC	high-potency topical corticosteroid
HRQoL	health-related quality of life
IC&ER	Institute for Clinical and Economic Review
ICER	incremental cost-effectiveness ratio
IGA	Investigator Global Assessment
IL	interleukin
IMP	investigational medicinal product
INMB	incremental net monetary benefit
IQR	interquartile range
IR	inadequate control with, or intolerance or contraindications to
ITC	indirect treatment comparison
ITT	intention to treat
LLCI	lower limit of confidence interval
LY	life year
MAR	missing at random
mg	milligrams
MI	multiple imputation
MedDRA	Medical Dictionary for Regulatory Activities
MIMS	Monthly Index of Medical Specialties
MMRM	mixed model with repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
NRI	non-responder imputation
NRS	numeric rating scale
OWSA	one-way sensitivity analysis
PAS	Patient Access Scheme
PDE4	phosphodiesterase 4
PO-SCORAD	Patient-Oriented SCORAD

POEM	Patient-Oriented Eczema Measure
PROM	patient-reported outcome measure
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	psoralen–ultraviolet A
PYE	patient-years of exposure
PYFU	patient-years of follow-up
RCGP	Royal College of General Practitioners
RCT	randomised controlled trial
RE	random-effects
RM	rescue medication
RMM	repeated measurements model
RSC	Research and Surveillance Centre
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCORAD	Scoring Atopic Dermatitis
SF-6D	6-dimension short-form health index
SF-12	12-item short-form health survey
QD	once daily
QW	every week
Q2W	every 2 weeks
Q4W	every 4 weeks
QALY	quality-adjusted life year
QoL	quality of life
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
SE	standard error
SoC	standard of care
SOC	system organ class
TA	technology appraisal

TCS	topical corticosteroids
TCI	topical calcineurin inhibitor
TEAE	treatment-emergent adverse event
TRA	tralokinumab
URTI	upper respiratory tract infection
UVB	ultraviolet B
VTE	venous thromboembolism

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation: use as monotherapy or in combination with topical corticosteroids or topical calcineurin inhibitors in adults with moderate-to-severe atopic dermatitis that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated. The proposed position in the treatment pathway is narrower than the marketing authorisation because this position optimises the cost effectiveness of tralokinumab and is in line with the positioning and use of baricitinib and of dupilumab, the only currently available biologic therapy for the management of moderate-to-severe atopic dermatitis.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe atopic dermatitis and who are candidates for systemic therapy	Adults with moderate-to-severe atopic dermatitis that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated	This position optimises the cost effectiveness of tralokinumab and is in line with the positioning of baricitinib and of dupilumab, the only currently available biologic therapy for the management of moderate-to-severe atopic dermatitis
Intervention	Tralokinumab	Tralokinumab as monotherapy or in combination with topical corticosteroids	
Comparator(s)	• Phototherapy including with ultraviolet (UVB) radiation or PUVA • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) • Oral corticosteroids • Alitretinoin (in people with atopic dermatitis affecting the hands) • Dupilumab • Baricitinib • Best supportive care	• Dupilumab • Best supportive care	RCT data for baricitinib were not available for the EASI 50 & ΔDLQI ≥ 4 combined endpoint used in the base-case economic analysis. However, baricitinib was included in a scenario analysis. The lack of comparable data for baricitinib was raised at the checkpoint meeting, and NICE were informed of the approach we have taken Trial data for other comparators did not connect to evidence network via a common comparator

Outcomes	• Measures of disease severity • Measures of symptom control • Disease free period/maintenance of remission • Time to relapse/prevention of relapse • Adverse effects of treatment • Health-related quality of life	Clinical outcomes supported by evidence from the ECZTRA trial programme are reported addressing all the points raised in the scope. Outcomes used in the economic modelling are: • Measures of symptom control according to relative EASI scores (reduction in absolute score) • Adverse effects of treatment • Health-related quality of life	As per final NICE scope
Subgroups to be considered	If the evidence allows: • People with atopic dermatitis affecting the hands • People for whom systemic therapies have been inadequately effective, not tolerated or contraindicated • Skin colour subgroups	• People for whom CSA has been inadequately effective, not tolerated or contraindicated • People for whom systemic therapies have been inadequately effective, not tolerated or contraindicated	No evidence is available for the subgroup of people with atopic dermatitis that affects the hands, or for skin colour subgroups

CSA, cyclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, 5-dimension EuroQol questionnaire; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; Patient-Oriented Eczema Measure; PUVA, psoralen–ultraviolet A; UVB, ultraviolet B.

B.1.2 Description of the technology being appraised

Appendix C includes the summary of product characteristics; the European public assessment report is not yet available.

Table 2 Technology being appraised

UK approved name and brand name	Tralokinumab (Adtralza®)
Mechanism of action	Tralokinumab is a first-in-class fully human immunoglobulin G4 (IgG4) monoclonal antibody which specifically binds with high affinity to circulating IL-13, a key primary cytokine that causes the signs and symptoms of moderate-to-severe AD
Marketing authorisation/CE mark status	Marketing Authorisation (MA) from the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) was obtained on the 17 June 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Tralokinumab is indicated for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy
Method of administration and dosage	• The recommended dose of tralokinumab for adult patients is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as subcutaneous injection. • At prescriber's discretion, every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. • Tralokinumab can be administered with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.
Additional tests or investigations	• Not required
List price and average cost of a course of treatment	• £1,070 per pack of four 150 mg pre-filled syringes, which covers two 2-weekly or two 4-weekly doses • Annual cost of treatment (list price): year 1, £14,445; subsequent years, £13,910 (Q2W) or £6,955 (Q4W) [a] • Annual cost of treatment (PAS price): year 1, [redacted]; subsequent years, [redacted] (Q2W) or [redacted] (Q4W) [a]
Patient access scheme (PAS) (if applicable)	Tralokinumab is subject to a confidential simple PAS. The tralokinumab PAS price is [redacted] per dose ([redacted] per pack of four 150 mg pre-filled syringes)

[a] Maintenance therapy dosing frequency is expected to be based on criteria outlined in the label.
AD, atopic dermatitis; PAS, Patient Access Scheme; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Clinical features

Atopic dermatitis (AD), the most common form of eczema, is a chronic, heterogeneous, relapsing–remitting, inflammatory skin condition [1, 2]. AD (also called atopic eczema) most frequently presents initially during early infancy and childhood, but can occur at any age [3, 4].

AD is characterised by a red blotchy rash, dry, itchy and inflamed skin, which can ooze and weep, accompanied by intense pruritus [5, 6], and has a fluctuating pattern of remission and flare [7, 8]. During periods of remission, despite an absence of visible signs of inflammation, the underlying inflammation of the skin can still be present [9].

AD lesions and itch mostly affect the flexural surfaces of the body; AD is often found on the neck, eyelids, forehead, face, wrists, feet and hands [1]. However, all regions of the body can be affected, and AD is clinically heterogeneous, particularly in adults [10, 11].

Epidemiology

AD affects around 1 in 12 adults in the UK [12], although estimates vary due to the fluctuating nature of the condition. In an international epidemiological study (n = 10 001 UK adults aged 18–65 years), the point prevalence of AD in the UK was 2.5% for both men and women [13]. Prevalence was highest among people aged 25–34 years (4.3%), and lowest among those aged 55–65 years (1.4%). The prevalence of AD over the previous 12 months, defined according to UK Working Party criteria modified for self-diagnosis of AD (described in the classification sub-section below), was 6.7% [13].

In the NICE resource impact report for dupilumab in the treatment of moderate-to-severe AD (TA534), it was estimated that 7% of the people who need treatment for AD have moderate-to-severe disease, corresponding to approximately 53 000 adults in 2018 [14]. Of these, 27% were estimated to be eligible to receive a systemic treatment rather than a topical therapy [14]. For half of patients, non-biological systemic treatments will not adequately control their AD [14, 15], resulting in approximately 7500 uncontrolled patients eligible for biological therapy [14].

Impact on health and health-related quality of life

Patients with moderate-to-severe AD can suffer from intense pruritus, as well as skin lesions, dry skin, skin pain, erythema, oedema, lichenification, oozing and crusting [6]. The pruritus associated with AD can be particularly debilitating, worsening in line with disease severity and affecting patients' health-related quality of life (HRQoL) and sleep [16-18]. In a recent German study, 96.0% of patients (n = 1678) ranked being free of itch as a quite important or very important therapeutic goal [19]. A 2017 systematic literature review found that in surveys a substantial proportion (33% to 87%) of adults with AD reported difficulty

falling asleep, frequent awakenings, a shorter overall duration of sleep or sleep fragmentation [20].

The impact of AD on adult mental health is considerable [16, 21, 22]. An analysis of baseline data from a phase 2b clinical trial found that of 349 patients with moderate-to-severe AD, 10.0% had clinically significant depression (Hospital Anxiety and Depression Scale [HADS] depression score ≥ 11) and 17.6% had clinically significant anxiety (HADS anxiety score ≥ 11) [16]. A European survey of dermatology outpatients (n = 162 patients with AD) reported similar proportions of patients to have depression and anxiety: 10.1% and 17.6%, respectively, based on HADS subscale scores ≥ 11 [21]. In this study, 15.0% of patients with AD reported suicidal ideation [21].

The impact of AD on mental health appears to increase with disease severity. A multinational survey (n = 1467) found that HADS depression scores ≥ 11 were reported by 6.2%, 11.7% and 29.9% of participants with mild, moderate and severe AD, respectively; the corresponding proportions for anxiety were 11.0%, 23.0% and 40.3% [18]. Similarly, a Japanese survey (n = 6748) found that suicidal ideation was reported by 0.21%, 6.0% and 19.6% of patients with mild, moderate and severe AD, respectively [23].

Overall, moderate-to-severe AD has a substantial impact on HRQoL. A recent systematic literature review found 5-dimension EuroQol questionnaire (EQ-5D) scores to be 0.77–0.80 for patients with moderate AD, and 0.61–0.76 for those with severe AD [24]. The reduction in HRQoL due to moderate-to-severe AD may therefore be comparable to that seen in psoriasis (0.52–0.90), representing a significant burden to patients [24].

Impact on patients' lives

AD can have a substantial impact on patients' lives, as demonstrated in a recent survey of UK adults with eczema, 39% of whom had AD, conducted by the National Eczema Society and LEO Pharma [25]. Of the 530 respondents, 67% reported experiencing skin so sore that it bleeds, while 63% said that eczema had negatively affected their physical functioning and 61% had difficulty sleeping. A total of 74% reported that eczema negatively impacted their mental health, 85% felt embarrassed and 66% said they were lonely or socially isolated as a result of their eczema. More than half of respondents (61%) said that eczema had negatively affected their social life. One in five adult participants (18%) said they had struggled to find someone attracted to them, and 1 in 10 (11%) described relationships having ended because of their eczema, while 59% said that eczema negatively affected their sexual intimacy. Nearly half of adult respondents (49%) said eczema had affected their ability to do paid work; some reported having lost a job (9%); some thought they had been overlooked for promotion (13%); and some said they had lost wages (8%); all specifically because of eczema [25].

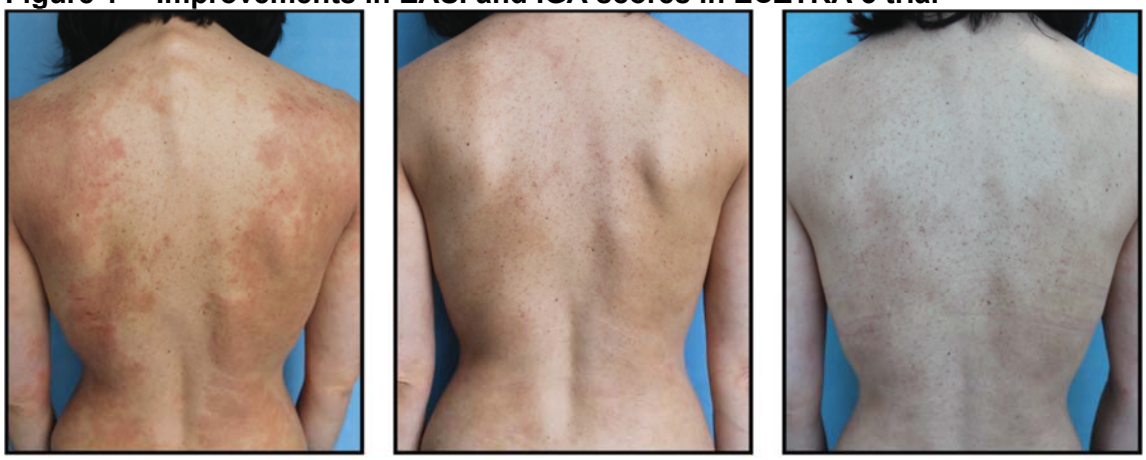
Classification

The most widely used criteria for AD diagnosis were developed by Hanifin and Rajka and include four major (pruritus; dermatitis affecting flexural surfaces; chronic or relapsing dermatitis; and personal or family history of cutaneous or respiratory allergy) and 23 minor criteria. To be diagnosed with AD, patients should demonstrate at least three major and three minor criteria [26].

The widely used UK Working Party criteria aim to simplify the diagnosis of AD and require the presence of an itchy area of skin within the previous year and three or more of the following: onset before 2 years of age; history of involvement of skin folds; generalised dry skin; presence of other atopic diseases; and visible flexural eczema [27].

In a clinical trial setting, AD severity is mostly assessed by one of the following scales: Eczema Area and Severity Index (EASI); Investigator Global Assessment (IGA); and Scoring Atopic Dermatitis (SCORAD) index [28]. These scales aim to classify AD as mild, moderate or severe based on pre-defined cut-offs (see section B.2.3.1.6, Table 6 for more details). Responses to treatment in clinical trials are typically measured as the proportions of patients achieving a 75% reduction in EASI or an IGA score of 0 (clear) or 1 (almost clear) (e.g. Figure 1). In clinical practice, physicians make a global assessment of AD severity based on appearance, location and extent of lesions, as well as response to previous treatment. A combined endpoint of a 50% reduction in EASI and an improvement in Dermatology Life Quality Index (DLQI) score of at least 4 points is widely used in clinical practice, in order to include HRQoL in treatment decisions [29].

Figure 1 Improvements in EASI and IGA scores in ECZTRA 3 trial



EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numeric rating scale.
Source: Silverberg *et al.* 2020a [30].

Inflammatory pathway in atopic dermatitis

The immune dysregulation in AD is predominantly driven by mediators of the type II inflammatory response, the signature cytokines of which are interleukin (IL)-4 and IL-13, which are produced by Th2 lymphocytes [31, 32]. Both IL-13 and IL-4 cytokines are upregulated in lesional and non-lesional skin, suggesting that both cytokines can contribute

to AD pathogenesis [33-35]. However, while IL-13 and IL-4 share receptors and biological activity, IL-4 appears to have a primary role in central aspects of the type II inflammatory response (acting for example in the lymph nodes and in the regulation of humoral immunity) [36]. By contrast, IL-13 seems to have a more prominent role in the periphery, including the skin [32]. Accordingly, IL-13 appears to be one of the primary cytokines that cause the signs and symptoms of moderate-to-severe AD [32, 35].

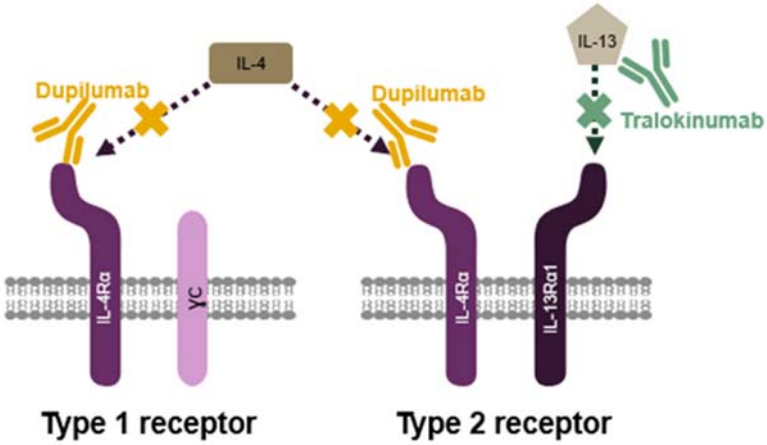
Increased levels of IL-13 and associated chemokine mRNA and serum levels correlate with increased severity of AD [37], while reductions in IL-13 concentrations are associated with treatment response and improved clinical outcomes [33]. IL-13 acts on keratinocytes by stimulating immune cell recruitment, leading to further inflammation, as well as reducing the expression of skin barrier proteins, antimicrobial peptides and lipids [32]. Together, these activities contribute to skin barrier disruption and lead to an increased susceptibility to infection by microorganisms [32, 38].

B.1.3.2 Tralokinumab mechanism of action

Tralokinumab is a first-in-class fully human immunoglobulin G4 (IgG4) monoclonal antibody [39]. Tralokinumab specifically binds with high affinity to circulating IL-13 at an epitope that overlaps the binding site of the IL-13R receptors [32, 39]. This prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2, inhibiting IL-13–mediated downstream signalling [32, 40].

Tralokinumab has a mechanism of action different from those of dupilumab, the only other monoclonal antibody approved in AD, and of the small-molecule therapy baricitinib (Figure 2). Whereas tralokinumab acts specifically on IL-13, dupilumab binds to the IL-4Rα receptor 2 subunit, thereby preventing both IL-4– and IL-13–mediated signalling [32, 38]. Baricitinib is an inhibitor of the Janus-associated kinase (JAK) 1 and 2 signalling pathway, which mediates cellular responses to a wide range of cytokines, such as IL-2, IL-7, IL-3, IL-5, IL-9, IL-15 and IL-21, as well as IL-4 and IL-13 [41-43].

Figure 2 Differences in Tralokinumab and Dupilumab Mechanisms of Action



Adapted from Bieber T. *et al.* [32].

B.1.3.3 Clinical pathway of care for atopic dermatitis

Management of AD in adults normally uses a stepwise approach, starting with emollients and progressing through mild topical anti-inflammatory therapy to high-potency topical therapy, phototherapy and in some cases to systemic immunosuppressive therapy. Topical anti-inflammatory therapy currently includes the use of topical corticosteroids (TCS) and topical calcineurin inhibitor (TCIs, e.g. tacrolimus, pimecrolimus), as well as the topical phosphodiesterase 4 (PDE4) inhibitor crisaborole (which is not recommended by NICE) [44]. Topical therapy is used in patients with mild-to-moderate AD and as concomitant treatment for more severe disease [44].

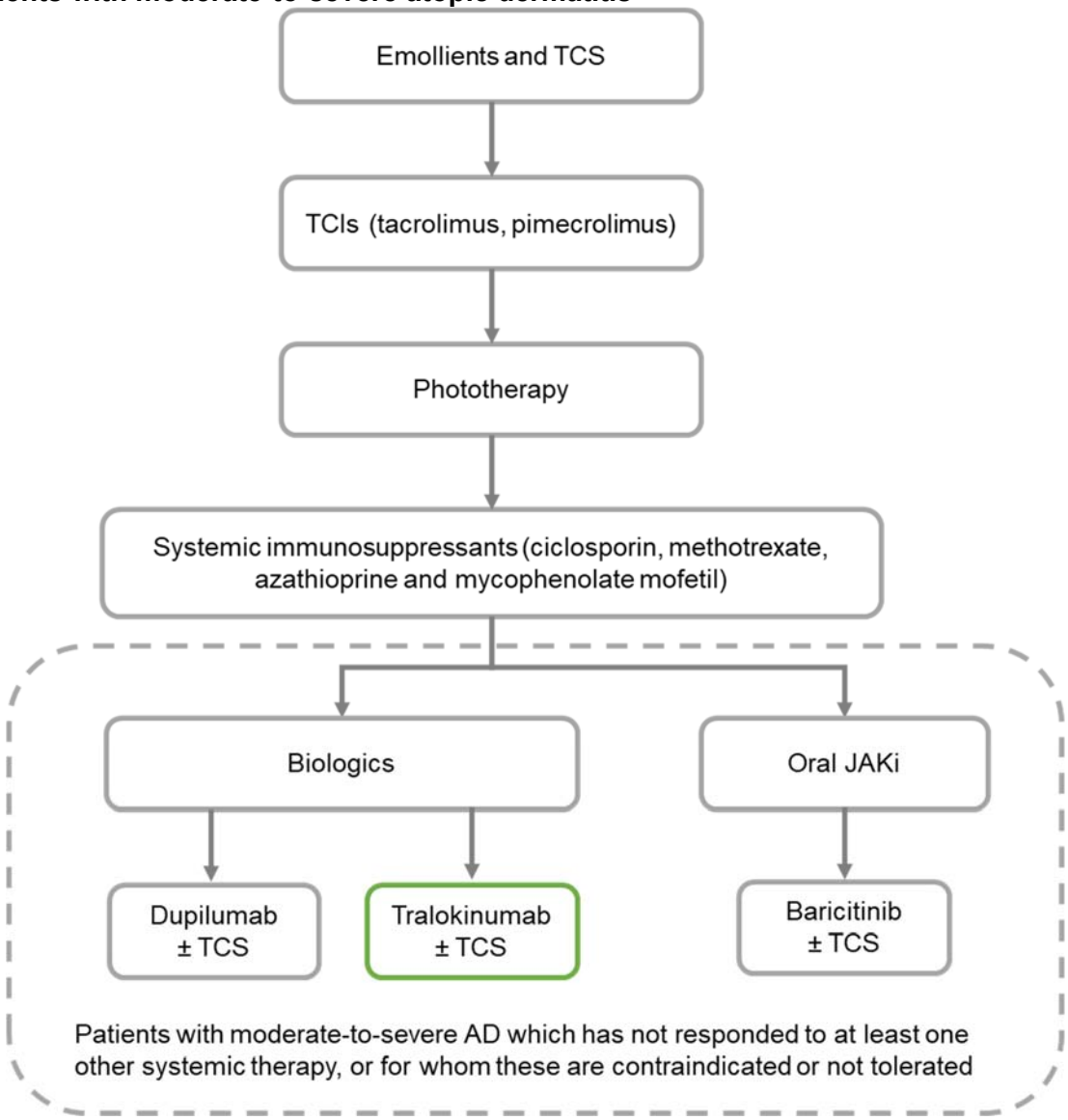
People with moderate-to-severe AD not responding to topical treatments may be referred to secondary care and treated with stronger oral medications such as oral corticosteroids or systemic immunosuppressants (CSA, methotrexate, azathioprine and mycophenolate mofetil) [45]. In addition, phototherapy and photochemotherapy (psoralen–ultraviolet A; PUVA) can be used to manage chronic severe AD [45].

Both dupilumab and baricitinib are recommended by NICE as an option for treating moderate-to-severe AD in adults, if the disease has not responded to at least one other systemic therapy, such as CSA, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated (TA534 and TA681) [29, 46]. Unlike other chronic inflammatory skin conditions such as psoriasis, there is currently only one biological treatment – dupilumab – available in AD. There is a need for more biological options to improve patients' choice of therapy for the long-term management of their condition and increase the likelihood of achieving disease control for all patients with moderate-to-severe AD [37].

B.1.3.4 Proposed positioning of tralokinumab in the treatment pathway

Patients with moderate-to-severe AD, and especially patients with AD that is inadequately controlled with current therapies, require effective and well-tolerated treatment options suitable for long term-use. Tralokinumab should be considered as a novel biological treatment option at the same place in the treatment algorithm as dupilumab and the oral JAK inhibitor baricitinib, offering an additional treatment choice and an alternative targeted treatment option for adult patients who have moderate-to-severe AD which has not responded to at least one other systemic therapy, or for whom these are contraindicated or not tolerated (Figure 3), a population for which there remains a considerable unmet need in the UK. The proposed position in the treatment pathway is narrower than the marketing authorisation and is in line with the positioning and use of the biologic dupilumab. The heterogeneity of the disease means that it is particularly important to have an additional targeted therapy with a different mechanism of action, to enable physicians to better address patients' individual needs. The targeted patient population is the one considered relevant to the National Health Service (NHS): it is anticipated that clinicians will use tralokinumab after considering a systemic immunosuppressant.

Figure 3 Proposed position of tralokinumab within the treatment pathway for patients with moderate-to-severe atopic dermatitis



JAKi, Janus kinase inhibitor; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids.

B.1.4 Equality considerations

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Summary

Clinical trial evidence

- The efficacy and safety of tralokinumab for the treatment of moderate-to-severe AD has been investigated in four phase 3 RCTs: as monotherapy (ECZTRA 1 and ECZTRA 2) or combination therapy with TCS (ECZTRA 3) for all patients who are candidates for systemic therapy; and as combination therapy with TCS for patients who do not have adequate control with, or have intolerance or contraindications to, CSA (ECZTRA 7)

Efficacy

- The primary endpoints of the ECZTRA RCTs were the proportion of patients achieving an IGA 0/1 response (ECZTRA 1–3) or an EASI 75 response (all RCTs) at week 16
- In all four trials, tralokinumab Q2W (± TCS) was associated with a statistically significant increase in the proportion of patients achieving the primary endpoints, compared with placebo (± TCS)
- In ECZTRA 3, most patients receiving maintenance therapy with tralokinumab Q2W or Q4W plus TCS retained their week 16 responses after a further 16 weeks (EASI 75: Q2W, 92.5%; Q4W, 90.8%)
- In the pooled ECZTRA 1 and ECZTRA 2 population, significantly more patients treated with tralokinumab Q2W or Q4W retained week 16 responses to week 52, compared with those receiving placebo (EASI 75: Q2W, [redacted]; Q4W, [redacted] placebo, [redacted])
- Results for clinical efficacy endpoints were generally similar in analyses of subgroups of patients who had inadequate control with, or intolerance or contraindications either to CSA ('ECZTRA 7-like') or to any systemic therapy
- In all four RCTs, tralokinumab was consistently associated with statistically significant improvements in the key symptoms of pruritus and sleep disturbance, in HRQoL, measured with the POEM and DLQI instruments, and in EQ-5D-3L index scores

Safety

- Overall, the results of the safety analyses show that tralokinumab Q2W is generally well tolerated
- In all four RCTs, the incidence of SAEs during randomised treatment was lower with tralokinumab than with placebo
- Discontinuation due to AEs was rare, affecting a maximum of 3.3% of patients in any tralokinumab-treated group
- The safety network meta-analysis (NMA) suggests that AEs of interest are expected to occur at similar or lower frequencies with tralokinumab, compared with dupilumab

Network meta-analysis

- In the absence of head-to-head RCT data comparing tralokinumab, dupilumab and baricitinib, an NMA was performed
- There was considerable heterogeneity and uncertainty in the analysis, with important differences in study design and considerable variation in placebo response rates for which adjustment could not be performed for the endpoint used in the economic model – EASI 50 & ΔDLQI ≥ 4. For this endpoint, only tralokinumab and dupilumab could be compared, as there were no relevant data for baricitinib

Innovation

- Tralokinumab has a novel mechanism of action that is both different from, and more targeted than, those of dupilumab and baricitinib, providing clinicians and patients with an alternative choice of targeted therapy for the treatment of moderate-to-severe AD
- Tralokinumab has additional benefits that may not be captured in the economic model, including improvements in pruritus and sleep; no monitoring requirements; reductions in skin infections; potential for Q4W maintenance therapy; and reductions in TCS use.

B.2.1 Identification and selection of relevant studies

Identification and selection of relevant clinical evidence is described in Appendix D. In brief, searches of relevant publication databases and grey literature sites were conducted on 16 February 2021. Eligible studies were limited to randomised controlled trials (RCTs) of systemic immunosuppressant treatments, phototherapy or biologics for the treatment of moderate-to-severe AD in adults. The SLR identified 81 sources of evidence for 32 different clinical trials where active treatment was of at least 12 weeks duration. Of these, 19 trials provided evidence for the network meta-analysis (NMA) described in section B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

The evidence in this submission is based on four phase 3 trials:

- ECZTRA 7 (NCT03761537) is a randomised, double-blind, placebo-controlled phase 3 study of tralokinumab in combination with TCS, in patients with severe AD who do not have adequate control with, or have intolerance or contraindications to, CSA.
- ECZTRA 3 (NCT03363854) is a randomised, double-blind, placebo-controlled, pivotal phase 3 study evaluating the efficacy and safety of tralokinumab in combination with TCS in adult patients with moderate-to-severe AD who are candidates for systemic therapy.
- ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) are two identical randomised, double-blind, placebo-controlled, pivotal phase 3 studies evaluating the efficacy and safety of tralokinumab as monotherapy in adult patients with moderate-to-severe AD who are candidates for systemic therapy.

The ECZTRA 7 trial provides evidence for tralokinumab combination therapy in the decision problem population. Further evidence for combination therapy in the decision problem population is provided by *post hoc* subgroup analyses of ECZTRA 3 (section B.2.7). In addition, evidence for tralokinumab monotherapy in an 'ECZTRA 7-like' population – patients who do not have adequate control with, or have contraindications to, CSA – is provided by *post hoc* subgroup analyses of the ECZTRA 1 and ECZTRA 2 trials (Figure 4).

The main sources of data from ECZTRA 7 are the clinical study report (CSR) and data tables [47-50], and a statistical appendix [51]. The main sources of data from ECZTRA 1, ECZTRA 2 and ECZTRA 3 are the primary study publications [30, 52], with further data derived from CSRs [53-55] and additional statistical analyses [56-58]. Subgroup data are derived from statistical appendices [59-62]. The data cut-off dates for the primary analyses were 30 October 2020 (ECZTRA 7), 18 July 2019 (ECZTRA 1), 14 August 2019 (ECZTRA 2) and 27 June 2019 (ECZTRA 3) [47, 53-55].

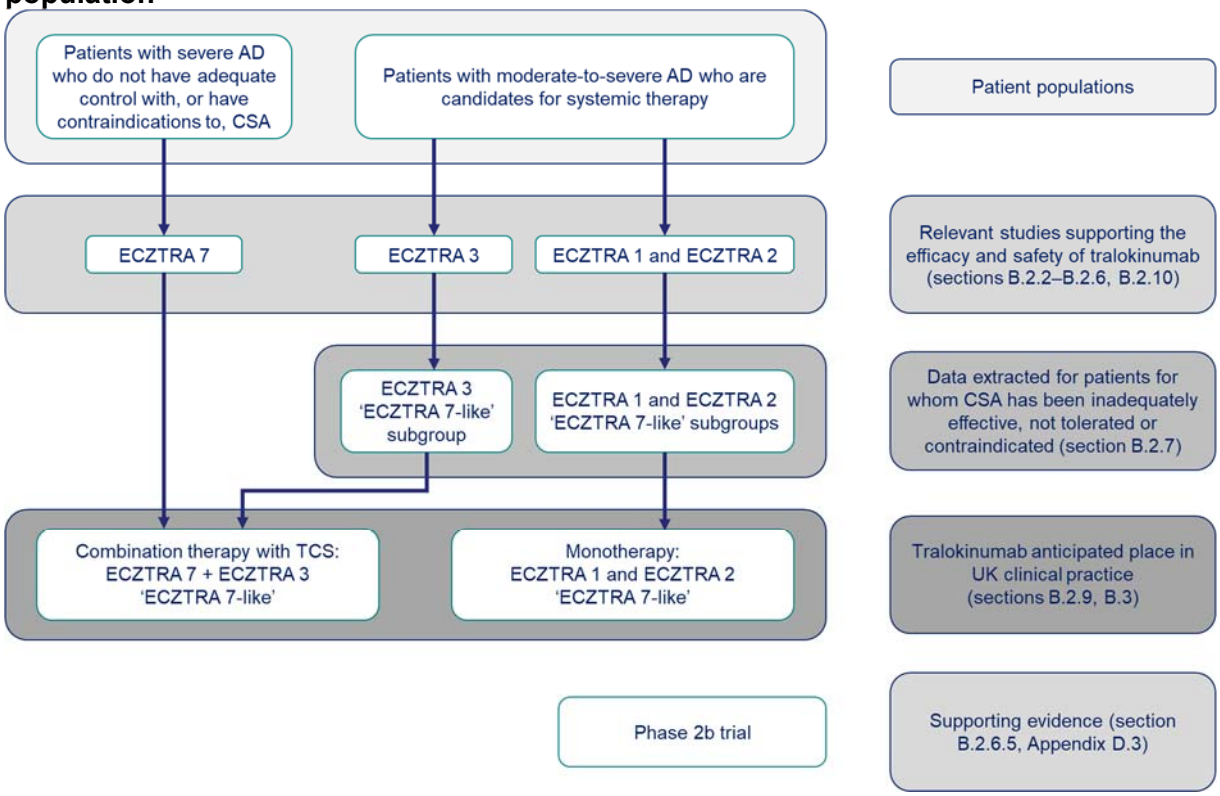
Additional evidence from a phase 2b study of tralokinumab versus placebo (NCT02347176) and from a phase 2 vaccine response trial (ECZTRA 5; NCT03562377) was also identified in the systematic review [33, 63]. Because data are available from four phase 3 trials, the phase 2 results are summarised in section B.2.6.5 and Appendix D.3, but are not described in detail in this submission. For completeness, they are included in the pooled safety

analysis described in section B.2.10.2, with the phase 2b efficacy trial also included in the NMA described in section B.2.9.

Clinical outcomes in the economic model (section B.3) are based on a comprehensive NMA of evidence from clinical trials including ECZTRA 7 and subgroup data from ECZTRA 1, ECZTRA 2 and ECZTRA 3 (section B.2.9). There was considerable heterogeneity and uncertainty in the analysis, with important differences in study design and considerable variation in placebo response rates for which adjustment could not be performed for the endpoint used in the economic model base case – the proportion of patients achieving the combined endpoint of a 50% reduction in EASI (EASI 50) plus an improvement in Dermatology Life Quality Index (DLQI) of ≥ 4 points (EASI 50 & ΔDLQI ≥ 4). Other endpoints included in the NMA and economic model are the proportion of patients achieving a 75% reduction in EASI (EASI 75) and the proportion of patients achieving EASI 50. Utility values in the model also incorporate data from reductions in pruritus in the clinical trials.

Patients in the phase 3 trials were eligible to transfer to a long-term, open-label extension study (ECZTEND; NCT03587805) [64, 65]. Although this study is not expected to be completed within 12 months of this submission, the results of an interim analysis are summarised in section B.2.6.5 and Appendix D.3.

Figure 4 Summary of main ECZTRA trial evidence with respect to decision problem population



Numbers indicate sections in this submission in which relevant data are presented.
AD, atopic dermatitis; CSA, ciclosporin A; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA; TCS, topical corticosteroids.

Table 3 Clinical effectiveness evidence

Study	ECZTRA 7 (NCT03761537)				ECZTRA 3 (NCT03363854)				ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885)			
Study design	Multicentre, randomised, double-blind, placebo-controlled trial with a single 26-week treatment period				Multicentre, randomised, double-blind, placebo-controlled, trial with a 16-week initial treatment period and a 16-week maintenance treatment				Multicentre, randomised, double-blind, placebo-controlled, trials with a 16-week initial treatment period and a 36-week maintenance treatment			
Population	Adults aged ≥ 18 years with AD involvement of ≥ 10% BSA, an EASI of ≥ 20, an IGA score of ≥ 3 and a Worst Daily Pruritus NRS score of ≥ 4 who had a recent (within 1 year) history of inadequate response to treatment with topical medications and an inadequate response or intolerance to CSA, or for whom CSA was contraindicated				Adults aged ≥ 18 years with AD involvement of ≥ 10% BSA, an EASI of ≥ 16, an IGA score of ≥ 3 and a Worst Daily Pruritus NRS score of ≥ 4 who had a recent (within 1 year) history of inadequate response to treatment with topical medications				Adults aged ≥ 18 years with AD involvement of ≥ 10% BSA, an EASI of ≥ 16, an IGA score of ≥ 3 and a Worst Daily Pruritus NRS score of ≥ 4 who had a recent (within 1 year) history of inadequate response to treatment with topical medications			
Intervention(s)	Tralokinumab 600 mg followed by 300 mg Q2W plus mometasone furoate 0.1% cream as needed				Tralokinumab 600 mg followed by 300 mg Q2W induction therapy, then Q2W or Q4W maintenance therapy; plus mometasone furoate 0.1% cream as needed				Tralokinumab 600 mg followed by 300 mg Q2W induction therapy, then Q2W or Q4W maintenance therapy			
Comparator(s)	Placebo plus mometasone furoate 0.1% cream as needed				Placebo plus mometasone furoate 0.1% cream as needed				Placebo			
Supports application for marketing authorisation	Yes		**No**	✓	**Yes**	✓	No		**Yes**	✓	No	
Used in the economic model	**Yes**	✓	No		**Yes**	✓	No		**Yes**	✓	No	

Study	ECZTRA 7 (NCT03761537)	ECZTRA 3 (NCT03363854)	ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885)
Rationale for use/non-use in the model	The ECZTRA 7 trial provides evidence for tralokinumab combination therapy in the decision problem population	ECZTRA 3 provides evidence for the efficacy and safety of tralokinumab combination therapy; subgroup data provide additional evidence in 'ECZTRA 7-like' patients who do not have adequate control with, or have contraindications to, CSA	ECZTRA 1 and ECZTRA 2 provide evidence for the efficacy and safety of tralokinumab monotherapy; subgroup data provide additional evidence in 'ECZTRA 7-like' patients who do not have adequate control with, or have contraindications to, CSA
Reported outcomes specified in the decision problem	• Measures of disease severity: **EASI 50, EASI 75**, EASI 90, IGA 0/1 • Measures of symptom control: SCORAD, **pruritus NRS**, sleep NRS, POEM • Adverse effects of treatment: AEs, SAEs, **AESIs** • Health-related quality of life: DLQI, **EQ-5D-3L**	• Measures of disease severity: **EASI 50, EASI 75**, EASI 90, IGA 0/1 • Measures of symptom control: SCORAD, **pruritus NRS**, sleep NRS, POEM • Adverse effects of treatment: AEs, SAEs, **AESIs** • Health-related quality of life: DLQI, **EQ-5D-3L**, HADS	• Measures of disease severity: **EASI 50, EASI 75**, EASI 90, IGA 0/1 • Measures of symptom control: SCORAD, **pruritus NRS**, sleep NRS, POEM • Adverse effects of treatment: AEs, SAEs, **AESIs** • Health-related quality of life: DLQI, **EQ-5D-3L**, HADS
All other reported outcomes	• TCS use • Rescue medication use • Combined endpoint: **EASI 50 & ΔDLQI ≥ 4**	• **TCS use** • Rescue medication use • Combined endpoint: **EASI 50 & ΔDLQI ≥ 4**	• TCS use • Rescue medication use • Combined endpoint: **EASI 50 & ΔDLQI ≥ 4**

Outcomes in **bold** are incorporated into the economic model.
AD, atopic dermatitis; AE, adverse event; AESI, adverse event of special interest; BSA, body surface area; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; IGA, Investigator Global Assessment; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Methodology

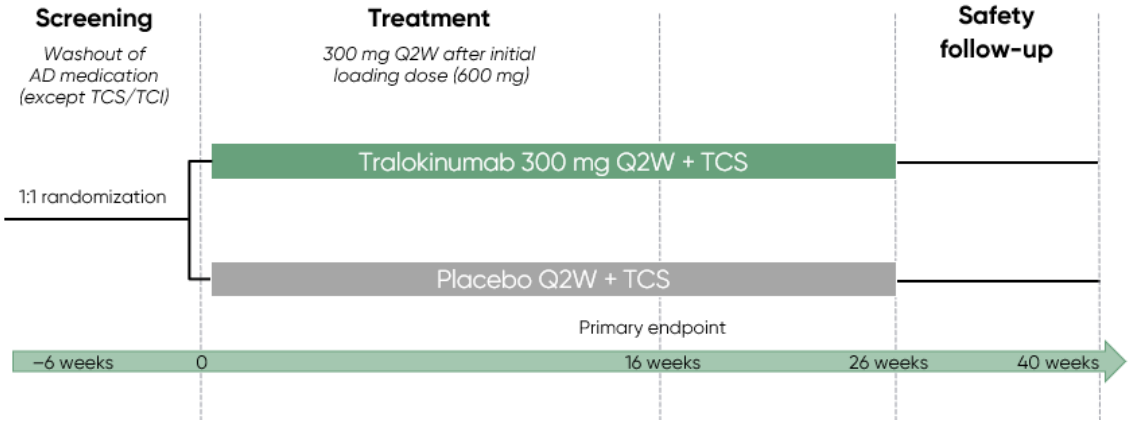
B.2.3.1.1 Study design and interventions

ECZTRA 7

ECZTRA 7 was a multicentre, randomised, double-blind, placebo-controlled trial in patients with severe AD (Figure 5) [47]. The objective was to demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating severe AD in patients who do not have adequate control with, or have contraindications to, CSA [47].

ECZTRA 7 was conducted over a single 26-week treatment period (Figure 5) [47]. Patients in ECZTRA 7 were randomised 1:1 to tralokinumab or placebo. Following an initial dose of 600 mg, tralokinumab was administered at a dose of 300 mg every 2 weeks (Q2W) [47].

Figure 5 Study design – ECZTRA 7



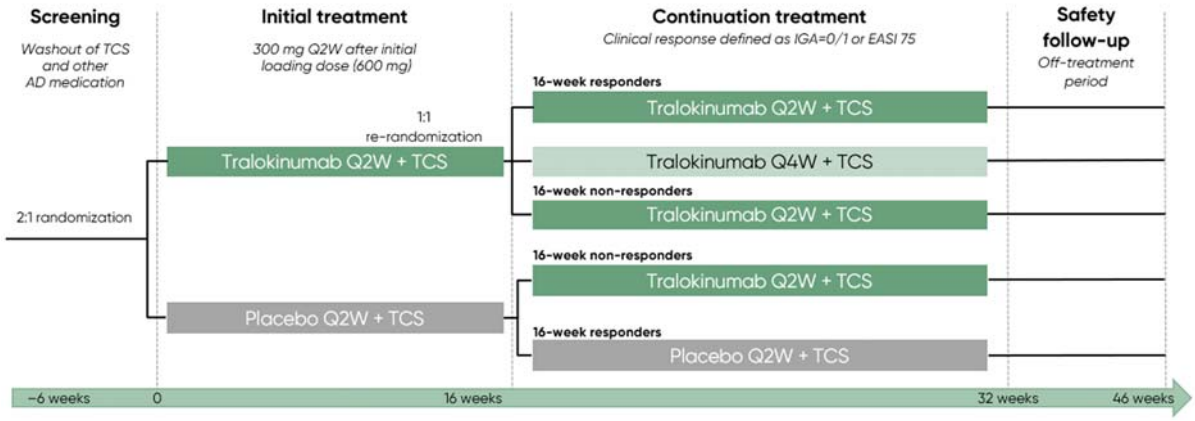
AD, atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; Q2W, every 2 weeks.

ECZTRA 3

ECZTRA 3 was a multicentre, randomised, double-blind, placebo-controlled trial in patients with moderate-to-severe AD (Figure 6) [30]. The objective was to evaluate the efficacy and safety of tralokinumab versus placebo, both in combination with TCS.

Patients were randomly assigned in a 2:1 ratio to receive tralokinumab (a 600 mg loading dose followed by 300 mg Q2W) or placebo, both in combination with TCS [30]. After a 16-week initial treatment period, patients in the tralokinumab arm who achieved EASI 75 or an IGA score of 0 or 1 (IGA 0/1) were re-randomised 1:1 to receive tralokinumab 300 mg Q2W or every 4 weeks (Q4W), both plus TCS. Patients in the placebo plus TCS arm who achieved EASI 75 or IGA 0/1 continued to receive placebo plus TCS. Patients in both initial arms who did not achieve EASI 75 or IGA 0/1 were assigned to receive tralokinumab Q2W plus TCS [30].

Figure 6 Study design – ECZTRA 3

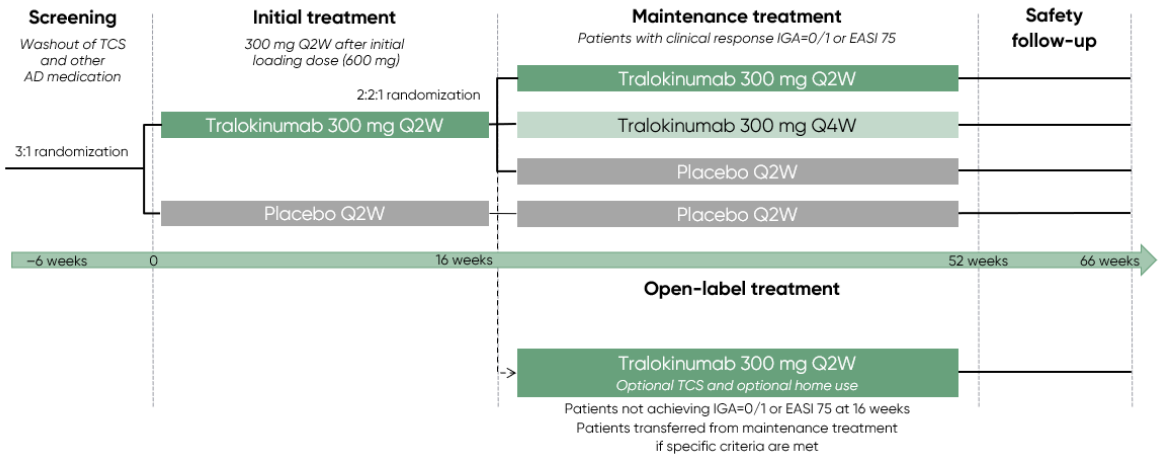


AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

ECZTRA 1, ECZTRA 2

ECZTRA 1 and ECZTRA 2 were identically-designed multicentre, randomised, double-blind, placebo-controlled trials in patients with moderate-to-severe AD (Figure 7) [52]. The objective was to demonstrate the efficacy and safety of tralokinumab monotherapy for patients with moderate-to-severe AD who are candidates for systemic therapies.

Figure 7 Study design – ECZTRA 1 and ECZTRA 2



AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

Patients were randomly assigned in a 3:1 ratio to receive tralokinumab (a 600 mg loading dose followed by 300 mg Q2W) or placebo [52]. After a 16-week initial treatment period, patients in the tralokinumab arm who achieved EASI 75 or IGA 0/1 were re-randomised 2:2:1 to receive tralokinumab 300 mg Q2W or Q4W, or placebo. Patients in the placebo arm who achieved EASI 75 or IGA 0/1 continued to receive placebo. The remaining patients received open-label tralokinumab Q2W and had the option of adding TCS [52].

B.2.3.1.2 Washout, emollient, TCS and rescue therapy

Prior to randomisation, AD treatments were washed out for 6 weeks for tanning beds or phototherapy, 4 weeks for systemic treatments and 2 weeks for topical therapies [30, 47, 52]. In ECZTRA 7 only, TCS use was allowed up to randomisation [47].

Patients in ECZTRA 7 and ECZTRA 3 were provided with mometasone furoate 0.1% cream at each visit and instructed to treat areas with active lesions once daily as needed until control was achieved.

In all four trials, patients were instructed to use an emollient twice daily throughout the study period [30, 47, 52]. Rescue treatment, if medically necessary, could be provided at the discretion of the investigator [30, 47, 52]. Patients receiving topical rescue treatment (with a TCS of higher potency than mometasone furoate 0.1% cream in ECZTRA 3 and ECZTRA 7) continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued the study drug, but could resume at least five half-lives after the last rescue treatment dose [30, 47, 52]. Use of biological rescue treatment was not permitted in ECZTRA 7, which was conducted after the approval of dupilumab [47]. There was no penalty for early rescue medication use, and patients could continue in the trials even if they required rescue therapy during the first 2 weeks.

B.2.3.1.3 Randomisation and blinding

Patients were randomised centrally using an interactive response system, with stratification as shown in Table 4 [47].

Table 4 Stratification in ECZTRA trials

	ECZTRA 7	ECZTRA 3	ECZTRA 1 and ECZTRA 2
Baseline	Prior CSA use, country (Germany, yes or no) and baseline disease severity (IGA 3 or 4)	Region (North America and Europe) and baseline disease severity (IGA 3 or 4)	Region (ECZTRA 1: North America, Japan and Europe; ECZTRA 2: North America, Europe, Australia and Korea) and baseline disease severity (IGA 3 or 4)
Week 16	–	Region and IGA response at week 16 (IGA 0/1 or IGA > 1)	

CSA, ciclosporin A; IGA, Investigator Global Assessment. Source: ECZTRA trial CSRs [47, 53-55]; Wollenberg *et al.* 2020 [52]; Silverberg *et al.* 2020a [30].

Patients, investigators and staff involved in treatment, clinical evaluation or monitoring were unaware of the treatment received by each patient [30, 47, 52]. Because tralokinumab and placebo were visually distinct and not matched for viscosity, study medication was handled and administered by an unblinded healthcare professional (HCP) at each study site; these HCPs were not involved in the management of patients and did not perform any assessments. The tralokinumab 300 mg Q4W regimen was administered as alternating 2-weekly administrations of tralokinumab and placebo [30, 47, 52].

B.2.3.1.4 Eligibility criteria

Inclusion and exclusion criteria are summarised in Table 5 and listed in full in Appendix D, Table 139 [30, 47, 52]. Patients were required to have EASI of ≥ 12 at screening and ≥ 16 at baseline (ECZTRA 7, ≥ 20 at screening and baseline) [30, 47, 52]

In ECZTRA 7 patients were required either: to be naïve to CSA and not a candidate for CSA treatment due to medical contraindications, use of prohibited concomitant medications or

increased susceptibility to CSA-induced renal- or liver damage, or increased risk of infection; or to have prior exposure to CSA, and to have experienced intolerance or unacceptable toxicity, inadequate response or a requirement for CSA at > 5 mg/kg/day or for > 1 year.

Table 5 Inclusion and exclusion criteria in ECZTRA trials

Inclusion criteria
• Adults with a diagnosis of AD as defined by the Hanifin and Rajka (1980) [26] criteria for ≥ 1 year • Recent history of inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable (e.g. due to important side effects or safety risks) **[ECZTRA 1 and ECZTRA 2 only]** • AD involvement of ≥ 10% BSA at screening and baseline • IGA score ≥ 3 at screening and at baseline • EASI ≥ 12 at screening and ≥ 16 at baseline **[ECZTRA 7, ≥ 20 at screening and baseline]** • Worst daily pruritus NRS average score of ≥ 4 during the week prior to baseline
Exclusion criteria
• Concurrent enrolment in another clinical trial or previous randomisation in tralokinumab trials • Patients for whom use of TCS was medically inadvisable in the opinion of the investigator **[ECZTRA 3 and ECZTRA 7 only]** • Use of AD treatments prior to randomisation: o Tanning beds or phototherapy within 6 weeks o Systemic immunosuppressive/immunomodulating drugs, corticosteroids or three of more bleach baths per week within 4 weeks o TCS, TCIs or PDE4 inhibitors within 2 weeks • Receipt of any biologic agent, including dupilumab, prior to randomisation: o Cell-depleting agents including rituximab within 6 months, or until lymphocyte count returns to normal, whichever was longer o Other biologics within 3 months or 5 half-lives, whichever was longer • Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation • Receipt of blood products within 4 weeks prior to screening • Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalisation • Known or suspected allergy or reaction to any component of the IMP formulation • History of any active skin infection within 1 week prior to randomisation

AD, atopic dermatitis; BSA, body surface area; IGA, Investigator Global Assessment; IMP, investigational medicinal product; NRS, numeric rating scale; PDE4, phosphodiesterase 4; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor. Sources: Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52]; ECZTRA 7 CSR [47].

B.2.3.1.5 Settings and locations

ECZTRA 7 was conducted at 68 sites in Europe, including six sites in the UK [66]. ECZTRA 1 was conducted at 124 sites in North America, Japan and Europe [52]. ECZTRA 2 was conducted at 108 sites in North America, Australia, Korea and Europe, including 13 sites in the UK [52]. ECZTRA 3 was conducted at 64 sites in North America and Europe, including seven sites in the UK [30].

B.2.3.1.6 Outcome measures

Outcome definitions, which were consistent across the ECZTRA trials, are summarised in Table 6. EASI, IGA and SCORAD were assessed every 2 weeks throughout the studies [30, 47, 52]. Worst pruritus NRS and eczema-related sleep NRS data, and use of topical treatment in ECZTRA 3, were collected using daily electronic diaries. For patient-reported outcome measures, assessments were carried out at varying intervals (Table 7) [47, 53-55].

Table 6 Outcome measures used in the ECZTRA trials

Outcome	Definition
Efficacy	
EASI	EASI is an investigator-assessed, validated measure of objective AD signs [67, 68]. Scores range from 0 to 72, with higher scores indicating more severe AD. A 6.6-point change is considered to be clinically meaningful [28]
EASI 50, EASI 75, EASI 90	Patients achieving 75% improvement in EASI compared with baseline are defined as EASI 75 responders. Other EASI thresholds reported in this submission are EASI 50 (≥ 50% improvement) and EASI 90 (≥ 90% improvement)
IGA	The IGA is a static, investigator-reported assessment instrument used to rate the severity of the subject's global AD [69]. The IGA is based on a 5-point scale ranging from 0 (clear) to 4 (severe) with distinct, morphological descriptors for each category
SCORAD	SCORAD is a validated composite score which includes the intensity and extent of clinical signs of AD and the severity of AD symptoms [67]. SCORAD scores range from 0 to 103, with higher scores indicating more severe AD. An 8.2-point change is considered to be clinically meaningful [70]
Patient-reported outcomes	
Worst daily pruritus NRS	The worst daily pruritus NRS is a self-reported measure designed to assess the worst pruritus experienced over the previous 24 hours on a scale of 0 (no itch) to 10 (worst itch imaginable), assessed using weekly averages. A 4-point reduction in worst daily pruritus NRS is considered to be a clinically meaningful change
Eczema-related sleep NRS	The eczema-related sleep NRS is a self-reported measure designed to assess how much patients' eczema interfered with their sleep the previous night on a scale of 0 (did not interfere) to 10 (completely interfered), assessed using weekly averages
POEM	POEM is a 7-item tool for assessing patient-reported severity of AD that is used in clinical practice and clinical trials to assess AD symptoms and sleep interference [71]. POEM items assess the frequency of dryness, itch, flaking, cracking, sleep disturbance, bleeding, and weeping/oozing because of eczema during the past week. Response options are 0 (no days), 1 (1–2 days), 2 (3–4 days), 3 (5–6 days), and 4 (every day), and scores range from 0 to 28 [71, 72]
TCS use	The quantity of TCS used and the number of days on which patients used TCS [ECZTRA 3 and ECZTRA 7]
DLQI	The DLQI is a skin disease-specific instrument that has been validated for use in patients with AD [73, 74]. The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL. Scores range from 0 to 30, with higher scores indicating worse HRQoL [73]. A 4-point improvement from baseline is defined as a clinically meaningful change [75]
HADS	HADS is a 14-item questionnaire assessing seven anxiety items and seven depression items. Each item is scored 0–3, for a total score of 0–21 for each of the anxiety and depression scales [76]. For each scale, severity groups are categorised as 'normal' (score 0–7), 'mild' (8–10), 'moderate' (11–14) and 'severe' (15–21)
EQ-5D	The EQ-5D is a standardised instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire is used to calculate a utility score based on a descriptive profile, or 'health state'. Data in the ECZTRA trials were collected using the 5-level version (EQ-5D-5L) and cross-walked using the van Hout *et al.* 2012 mapping function [77] to obtain index scores for the 3-level version (EQ-5D-3L), which are reported in this submission
Combined endpoint	
EASI 50 & ΔDLQI ≥ 4	A 50% improvement in EASI plus a ≥ 4-point improvement in DLQI is used in clinical practice and NICE guidance as a routine stopping rule [46]

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, 5-dimension EuroQol questionnaire; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

Table 7 Schedule of PROM completion in ECZTRA trials

PROM	ECZTRA 7	ECZTRA 3	ECZTRA 1 and ECZTRA 2
DLQI and POEM	[redacted]	Weeks 0, 2, 4, 6, 8, 12, 16, 20, 28, 32	Weeks 0, 2, 4, 6, 8, 12, 16, 20, Q8W to week 52
EQ-5D-3L and HADS	[redacted]	Weeks 0, 4, 8, 12, 16, 20, 28, 32	Weeks 0, 4, 8, 12, 16, 20, Q8W to week 52

DLQI, Dermatology Life Quality Index; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; HADS, Hospital Anxiety and Depression Scale; POEM, Patient-Oriented Eczema Measure; PROM, patient-reported outcome measure; Q8W, every 8 weeks. Source: ECZTRA 7 protocol [47]; ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54]; ECZTRA 3 CSR [55]; Wollenberg *et al.* 2020 [52]; Silverberg *et al.* 2020a [30].

B.2.3.1.7 Study endpoints

Primary, secondary and maintenance endpoints in the ECZTRA trials are summarised in Table 8 [30, 47, 52]. The proportion of patients achieving EASI 75 at week 16 was a primary endpoint in all trials [30, 47, 52].

Table 8 Primary and secondary endpoints in ECZTRA trials

Type of Endpoint	ECZTRA 7	ECZTRA 3	ECZTRA 1 and ECZTRA 2
Initial treatment period			
Primary	EASI 75 at week 16		
	–	IGA 0/1 at week 16	
Secondary	IGA 0/1 at week 16	–	
	≥ 4-point reduction in Worst Daily Pruritis NRS at week 16		
	Change in SCORAD at week 16		
	Change in DLQI at week 16		
Maintenance/continuation period			
Maintenance	EASI 75 at week 26 IGA 0/1 at week 26 ≥ 4-point reduction in Worst Daily Pruritis NRS at week 26 Change in SCORAD at week 26 Change in DLQI at week 26	EASI 75 at week 32 IGA 0/1 at week 32	EASI 75 at week 52 IGA 0/1 at week 52

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numeric rating scale; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids. Sources: ECZTRA 7 protocol [47]; Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52].

B.2.3.2 Baseline characteristics

Demographics and baseline characteristics of patients included in the four ECZTRA studies are shown in Table 10. In all four studies, baseline characteristics were balanced across the treatment groups [30, 47, 48, 52]. A substantial proportion of patients had previously used systemic treatments (prior systemic steroid use ranged from 58.5% to [redacted] across randomised groups).

B.2.3.3 Comparative summary of trial methodology

Table 9 Comparative summary of trial methodology

Trial number (acronym)	ECZTRA 7 (NCT03761537) [47]	ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) [52]	ECZTRA 3 (NCT03363854) [30]
Location	68 sites in Europe (6 in UK)	ECZTRA 1: 124 sites in North America, Japan and Europe. ECZTRA 2: 108 sites in North America, Australia, Korea and Europe (13 in UK)	64 sites in North America and Europe (7 in UK)
Trial design	Multicentre, randomised, double-blind, placebo-controlled trial in patients with severe AD: single 26-week treatment period	Multicentre, randomised, double-blind, placebo-controlled trials: 16-week initial treatment period followed by re-randomisation of responders and a 36-week maintenance/open-label treatment period	Multicentre, randomised, double-blind, placebo-controlled trial: 16-week initial treatment period followed by re-randomisation of responders and a 16-week continuation treatment period
Eligibility criteria for participants	Adults with AD, involvement of ≥ 10% BSA, IGA 3 or 4, worst daily pruritis NRS score ≥ 4 and a recent history of inadequate response to treatment with topical medications		
	EASI at screening and baseline of ≥ 20; must not be a candidate for CSA due to contraindication, intolerance or inadequate response	EASI ≥ 12 at screening and ≥ 16 at baseline	
Settings and locations where the data were collected	Data were collected during scheduled visits to study centres, or in daily electronic diaries completed by patients		
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	1:1 ratio of tralokinumab (600 mg loading dose followed by 300 mg Q2W; n = [redacted]) or placebo (n = [redacted]) in combination with use of mometasone furoate 0.1% cream daily until control was achieved.	*Initial treatment* 3:1 ratio of tralokinumab (600 mg loading dose followed by 300 mg Q2W; n = 603, 593 in ECZTRA 1 and ECZTRA 2, respectively) or placebo (n = 199, 201) *Maintenance treatment* Patients in the tralokinumab arm with EASI 75 or IGA 0/1 were re-randomised 2:2:1 to tralokinumab 300 mg Q2W (n = 68, 91), tralokinumab 300 mg Q4W	*Initial treatment* 2:1 ratio of tralokinumab (600 mg loading dose followed by 300 mg Q2W; n = 252) or placebo (n = 126) in combination with use of mometasone furoate 0.1% cream daily until control was achieved *Continuation treatment* Patients in the tralokinumab arm with EASI 75 or IGA 0/1 were re-randomised 1:1 to tralokinumab 300 mg Q2W (n = 69)

Trial number (acronym)	ECZTRA 7 (NCT03761537) [47]	ECZTRA 1 (NCT03131648) and ECZTRA 2 (NCT03160885) [52]	ECZTRA 3 (NCT03363854) [30]
		(n = 76, 89) or placebo (n = 35, 46) Patients in the placebo arm with EASI 75 or IGA 0/1 continued to receive placebo ([redacted]) *Open-label treatment* Patients without EASI 75 or IGA 0/1 received tralokinumab 300 mg Q2W (n = 356, 325)	or tralokinumab 300 mg Q4W (n = 16) Patients in the tralokinumab arm without EASI 75 or IGA 0/1 received tralokinumab 300 mg Q2W (n = 95) Patients in the placebo arm with EASI 75 or IGA 0/1 continued on placebo ([redacted]) Patients in the placebo arm without EASI 75 or IGA 0/1 received tralokinumab 300 mg Q2W ([redacted]X) All continuation treatment included mometasone furoate 0.1% cream
	Rescue treatment, if medically necessary, could be provided at the discretion of the investigator. Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last dose of systemic rescue treatment		
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of patients with EASI 75 at week 16	• Proportion of patients with EASI 75 at week 16 • Proportion of patients with IGA 0/1 at week 16	
Other outcomes used in the economic model	• EASI 50 at week 16 and during maintenance treatment • EASI 75 during maintenance treatment • Combined endpoint: EASI 50 & ΔDLQI ≥ 4 at week 16 and during maintenance treatment • EQ-5D-3L at week 16 • Reduction in Worst Daily Pruritis NRS at week 16		
Pre-planned subgroups	• None	• No pre-planned subgroups are included • Data from a *post hoc* analysis of patients who do not have adequate control with, or have contraindications to, CSA are presented in section B.2.7 and used in the economic model	

Outcomes in **bold** are incorporated into the economic model.
AD, atopic dermatitis; BSA, body surface area; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks.
Sources: Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52]; ECZTRA 1 and ECZTRA 2 CSRs [53, 54]; ECZTRA 7 baseline characteristics tables [48]

Table 10 Characteristics of participants in the studies across treatment groups – ECZTRA trials

	ECZTRA 7		ECZTRA 3		ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W plus TCS (N = 140)	Placebo plus TCS (N = 137)	Tralokinumab Q2W plus TCS (N = 253)	Placebo plus TCS (N = 127)	Tralokinumab Q2W (N = 603)	Placebo (N = 199)	Tralokinumab Q2W (N = 593)	Placebo (N = 201)
Median age (IQR)	[redacted]	[redacted]	37.0 (28.0–52.0)	34.0 (24.0–50.0)	37·0 (27·0–48·0)	37·0 (26·0–49·0)	34·0 (25·0–48·0)	30·0 (23·0–46·0)
Male sex, n (%)	[redacted]	[redacted]	125 (49.4)	84 (66.1)	351 (58.2)	123 (61.8)	359 (60.5)	114 (56.7%)
Race, n (%)	[redacted]	[redacted]						
White	[redacted]	[redacted]	203 (80.2)	85 (66.9)	426 (70.6)	138 (69.3)	374 (63.1)	123 (61.2)
Black	[redacted]	[redacted]	23 (9.1)	12 (9.4)	41 (6.8)	18 (9.0)	43 (7.3)	17 (8.5)
Asian	[redacted]	[redacted]	17 (6.7)	24 (18.9)	120 (19.9)	40 (20.1)	154 (26.0)	52 (25.9)
Other/missing	[redacted]	[redacted]	10 (4.0)	6 (4.7)	16 (2.6)	3 (1.5)	22 (3.7)	9 (4.5)
Median duration of AD, years (IQR)	[redacted]	[redacted]	27.0 (17.0–39.0)	26.0 (18.0–39.0) [a]	27.0 (19.0–38.0)	28.0 (18.0–41.0)	25.5 (17.0–39.0)	25.0 (18.0–36.0)
Median BSA involvement with AD, % (IQR)	[redacted]	[redacted]	41.0 (30.0–63.0)	40.0 (26.0–74.0)	50.0 (33.0–70.0)	52.5 (31.0–77.0)	50.0 (31.0–74.0)	50.0 (31.0–74.0)
Severe disease (IGA score of 4), n (%)	[redacted]	[redacted]	116 (45.8)	60 (47.2)	305 (50.6%)	102 (51.3%)	286 (48.2%)	101 (50.2%)
Median EASI (IQR)	[redacted]	[redacted]	24.7 (18.4–35.9) [a]	26.5 (19.9–39.3) [a]	28.2 (21.3–40.0)	30.3 (22.0–41.5)	28.2 (19.8–40.8)	29.6 (20.6–41.4)
Median SCORAD (IQR)	[redacted]	[redacted]	66.2 (57.6–76.3) [a]	67.9 (59.4–79.0) [a]	69.2 (61.5–79.1)	70.8 (63.8–81.0)	69.5 (60.5–79.1)	69.9 (61.9–79.1)
Median weekly average worst daily pruritus NRS score (IQR)	[redacted]	[redacted]	8.0 (6.6–8.7) [b]	8.0 (7.0–9.0) [a]	7.9 (6.7–8.9)	7.9 (6.9–8.7)	8.0 (7.0–9.0)	8.1 (7.1–9.0)
Median DLQI (IQR)	[redacted]	[redacted]	18.0 (12.0–23.0) [c]	18.0 (12.0–23.0) [b]	17.0 (12.0–22.0)	16.0 (13.0–22.0)	18.0 (13.0–23.0)	18.0 (12.5–24.0)
Median weekly average eczema-related sleep interference NRS score (IQR)	[redacted]	[redacted]	[redacted]	[redacted]	7.1 (5.7–8.4)	7.0 (5.7–8.0)	7.4 (6.2–8.7)	7.9 (6.4–8.6)
Median total POEM score (IQR)	[redacted]	[redacted]	23.0 (20.0–26.0) [c]	24.0 (20.0–27.0) [c]	24.0 (20.0–27.0)	24.0 (20.0–27.0)	24.0 (20.0–27.0)	24.0 (20.0–27.5)

	ECZTRA 7		ECZTRA 3		ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W plus TCS (N = 140)	Placebo plus TCS (N = 137)	Tralokinumab Q2W plus TCS (N = 253)	Placebo plus TCS (N = 127)	Tralokinumab Q2W (N = 603)	Placebo (N = 199)	Tralokinumab Q2W (N = 593)	Placebo (N = 201)
Previous AD treatment, N (%)								
Any previous treatment	[redacted]	[redacted]	253 (100)	127 (100)	598 (99.2)	197 (99.0)	591 (99.7)	201 (100.0)
TCS	[redacted]	[redacted]	251 (99.2)	122 (96.1)	591 (98.0)	195 (98.0)	584 (98.5)	200 (99.5)
Systemic steroids	[redacted]	[redacted]	148 (58.5)	86 (67.7)	357 (59.2)	119 (59.8)	410 (69.1)	125 (62.2)
TCI	[redacted]	[redacted]	[redacted]	[redacted]	298 (49.4)	103 (51.8)	271 (45.7)	98 (48.8)
CSA	[redacted]	[redacted]	75 (29.6)	43 (33.9)	227 (37.6)	65 (32.7)	204 (34.4)	65 (32.3)
Methotrexate	[redacted]	[redacted]	29 (11.5)	30 (23.6)	77 (12.8)	26 (13.1)	127 (21.4)	38 (18.9)
Azathioprine	[redacted]	[redacted]	13 (5.1)	12 (9.4)	39 (6.5)	7 (3.5)	72 (12.1)	25 (12.4)
Mycophenolate	[redacted]	[redacted]	7 (2.8)	5 (3.9)	27 (4.5)	9 (4.5)	37 (6.2)	14 (7.0)
Other immunosuppressant	[redacted]	[redacted]	6 (2.4)	0	29 (4.8)	11 (5.5)	31 (5.2)	10 (5.0)
Phototherapy	[redacted]	[redacted]	122 (48.2)	53 (41.7)	291 (48.3)	95 (47.7)	258 (43.5)	89 (44.3)
Biologics	[redacted]	[redacted]	14 (5.5)	10 (7.9)	–	–	–	–
Antibiotics	[redacted]	[redacted]	107 (42.3)	45 (35.4)	–	–	–	–
Wet wraps	[redacted]	[redacted]	35 (13.8)	15 (11.8)	–	–	–	–

[a] Data were missing for one patient. [b] Data were missing for two patients. [c] Data were missing for three patients. [d] Data were missing for five patients.
AD, atopic dermatitis; BSA, body surface area; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numeric rating scale; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor.
Sources: Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52]; ECZTRA 3 CSR [55]; ECZTRA 7 CSR [47]; ECZTRA 7 baseline characteristics tables [48]; ECZTRA 7 efficacy tables [49].

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Sample size calculation and testing procedure

Sample size calculations are summarised in Table 11.

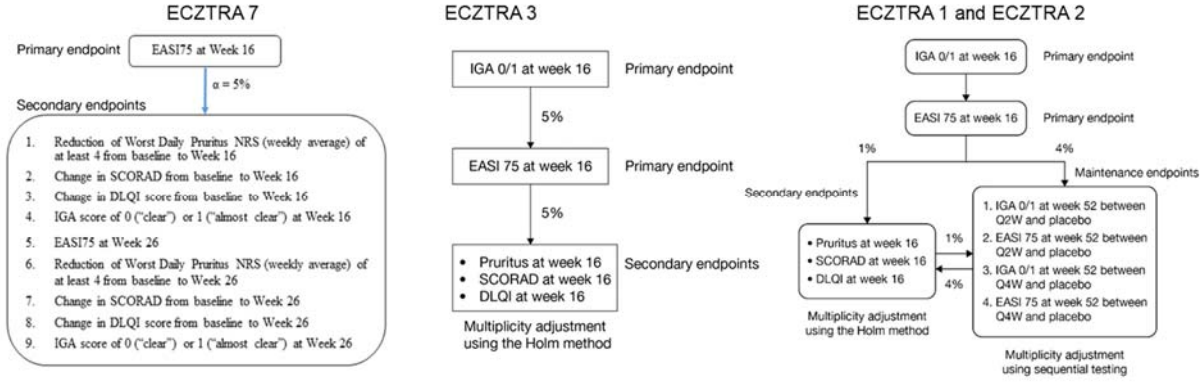
Table 11 Sample size calculations in the ECZTRA trials

Trial	Sample size	Power [a]
ECZTRA 7	250 patients	99% power for detecting a treatment difference for the primary endpoint, assuming 40%/15% response rates for the two arms 80% power for detecting a treatment difference for the pruritus endpoint, assuming 30%/15% response rates for the two arms
ECZTRA 3	369 patients	> 99% power for detecting a treatment difference for the primary endpoints, assuming 40%/15% EASI 75 and 30%/15% IGA 0/1 response rates for the two arms
ECZTRA 1 and ECZTRA 2	780 patients	

[a] Assuming 5% significance level.
EASI, Eczema Area and Severity Index score; IGA, Investigator Global Assessment.
Sources: ECZTRA 7 CSR [47]; Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52].

To control the overall type 1 error rate at a 5% significance level, a prespecified testing hierarchy was used [30, 47, 52]. Primary and secondary endpoints were evaluated hierarchically in the order shown in Figure 8. The hypothesis relating to a specific endpoint could not be rejected unless all hypotheses relating to endpoints earlier in the hierarchy were also rejected at the 5% significance level. In ECZTRA 1 and ECZTRA 2, week 16 secondary endpoints and week 52 maintenance endpoints were tested simultaneously (using the Bonferroni–Holm method), at the 1% and 4% level, respectively. If all hypotheses in either of these groups were rejected, hypotheses in the other group could be evaluated at the 5% significance level [52].

Figure 8 Statistical testing hierarchy



Pruritus: reduction of weekly average of worst daily pruritus NRS from baseline to week 16.
SCORAD: change in SCORAD from baseline to week 16.
DLQI: change in DLQI from baseline to week 16.
α, statistical significance level; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index score; IGA, Investigator Global Assessment; NRS, numeric rating scale; SCORAD, SCOring Atopic Dermatitis.
Source: ECZTRA 7 CSR [47]; Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52].

B.2.4.2 Analysis populations

Efficacy analyses were conducted using the full analysis set, which included all patients randomised to treatment [30, 47, 52].

B.2.4.3 Estimand framework and imputation methodology

The design of the phase 3 ECZTRA studies allows for two intercurrent events that would influence estimates of treatment effects: initiation of rescue treatment, and the permanent discontinuation of investigational product.

To address the possibility of these events, analysis of efficacy endpoints was conducted using three different estimands (Table 12) [30, 47, 52]:

- Composite – treatment difference achieved without rescue medication.
- Hypothetical – treatment difference achieved among patients who did not use rescue medication and did not discontinue treatment.
- Treatment policy sensitivity analysis – treatment difference achieved ignoring use of rescue medication and treatment discontinuation.

Because of disruption caused by the SARS-CoV-2 pandemic, some assessments were missed for some patients in ECZTRA 7. An alternative estimand was explored in that trial to explore the impact of the missing assessments [47]. The trial results using the modified estimand –summarised in Appendix D.3.1, Table 140 – were similar to the main analysis.

Table 12 Overview of the estimand framework and imputation method for week 16 analyses in ECZTRA trials

Estimand type	Estimand	Primary analysis aspects		Relevance/ rationale
		Intercurrent events	Missing data	
Composite	Treatment difference achieved without RM, regardless of treatment discontinuation	Patients who received RM were considered non-responders. Data retrieved at week 16 after permanently discontinued IMP were included	Missing data were imputed as non-response for binary endpoints, while for continuous endpoints MI assuming MAR within arms was used	Reflects a treatment effect attributable to the randomised treatment where initiation of rescue medication reflects lack of response
Hypothetical	Treatment difference if all patients adhered in the sense that they did not discontinue IMP permanently and RM was not available	Data collected after initiation of RM or permanent discontinuation of IMP were not included [a]	Missing data imputed using MI assuming MAR within arms for binary endpoints, RMM analysis for continuous endpoints	Reflects a treatment effect in a situation where intercurrent events would not occur
Treatment policy sensitivity analysis	Treatment difference regardless of RM and treatment discontinuation	Intercurrent events are irrelevant, all data were used as observed	Missing data were imputed as non-responses [b]	Reflects a treatment effect regardless of what additional rescue was actually received which may mimic the real-life clinical setting

[a] For the hypothetical estimand in ECZTRA 7, data collected after a prolonged interruption of IMP due to the SARS-CoV-2 pandemic were not included.
[b] Note, this is different from the pre-specified analysis in which MI assuming MAR was used [47, 53-55].
IMP, investigational medicinal product; MAR, missing at random; MI, multiple imputation; RM, rescue medication; RMM, repeated measurements model; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Source: ECZTRA 7 CSR [47]; Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52].

Primary and secondary endpoints (see section B.2.3.1.7) were assessed using the composite estimand, with the exception of changes in SCORAD and DLQI from baseline to weeks 16 and 26, which were assessed using the hypothetical estimand. This submission focuses on the results of a primary analysis for the primary estimand ('composite' or 'hypothetical' depending on the type of endpoint; 'composite' for binary endpoints and 'hypothetical' for continuous endpoints). Key endpoint results for the 'treatment policy sensitivity analysis' estimand, which attempts to mimic treatment effects in the real-life clinical setting as closely as possible in RCT conditions, are summarised in section B.2.6.1.

The difference in response rates between treatment groups was analysed using the Cochran–Mantel–Haenszel test, stratified as for randomisation (see Table 4) for single imputation analyses or using combined inference from multiple Mantel–Haenszel risk differences and associated standard errors using Rubin's rule for multiple imputation analyses [30, 47, 52]. Stratification in ECZTRA 7 was by prior CSA use and baseline IGA [47].

B.2.4.4 Participant flow

Full details of patient disposition in the phase 3 studies are shown in Appendix D, Figure 41, Figure 42 and Figure 43.

ECZTRA 7

In ECZTRA 7, [redacted] patients were randomised and [redacted] completed 26 weeks of treatment [48].

ECZTRA 3

In ECZTRA 3, 380 patients were randomised and 355 completed 16 weeks of treatment. Of the 233 patients randomly assigned to continuation treatment with tralokinumab, 141 of whom achieved EASI 75 or IGA 0/1 at week 16, 220 completed the 16-week continuation phase [30].

ECZTRA 1 and ECZTRA 2

In ECZTRA 1, 802 patients were randomised and 729 completed the initial treatment phase. In the tralokinumab arm, 185 patients achieved EASI 75 or IGA 0/1 at week 16, and were re-randomised to maintenance therapy, with 118 completing the 36-week maintenance phase [52].

In ECZTRA 2, 794 patients were randomly assigned and 737 completed the initial treatment phase. 227 patients treated with tralokinumab achieved EASI 75 or IGA 0/1 at week 16, and were re-randomised to maintenance therapy, with 117 completing the 36-week maintenance phase [52].

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A summary of the quality assessment for the ECZTRA trials is shown in Table 13, with a detailed description of the quality assessment presented in Appendix D, Table 142.

Table 13 Quality assessment results for ECZTRA trials

Trial number (acronym)	ECZTRA 7	ECZTRA 3	ECZTRA 1 and ECZTRA 2
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Sources: ECZTRA 7 CSR [47]; Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52].

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Summary of key efficacy endpoint results

ECZTRA 7

Results for key efficacy endpoints in ECZTRA 7 are summarised in Table 14. The trial met its primary endpoint, with significantly more patients receiving tralokinumab Q2W in combination with TCS (as needed) having an EASI 75 response at week 16, compared with the placebo plus TCS (as needed) group ([redacted]) [49]. This difference was maintained at week 26 ([redacted]) [49]. Similarly, patients treated with tralokinumab Q2W plus TCS were more likely than those receiving placebo plus TCS to achieve IGA 0/1, EASI 50 and EASI 90 at week 16 and week 26 [49].

[redacted]

Key endpoint results calculated using the treatment policy sensitivity analysis estimand (Table 14) and the Covid-19 modified composite estimand (Appendix D.3.1, Table 140) were generally similar to the primary composite estimand results (Table 14).

ECZTRA 3

Results for key efficacy endpoints in ECZTRA 3 are summarised in Table 15. The trial met its primary endpoint. Significantly more patients treated with tralokinumab Q2W in combination with TCS (as needed) had IGA 0/1 and EASI 75 responses at week 16,

compared with the placebo plus TCS (as needed) group (38.9% vs 26.2% and 56.0% vs 35.7%, respectively) [30]. Among tralokinumab-treated patients with EASI 75 responses at week 16, 92.5% and 90.8% of patients re-randomised to tralokinumab Q2W or Q4W plus TCS, respectively, retained these responses at week 32; for sustained IGA 0/1 responses, the corresponding proportions were 89.6% and 77.6% (Table 17) [30]. More than half ([redacted]) of tralokinumab-treated patients in ECZTRA 3 who achieved EASI 50 but not EASI 75 at week 16 (EASI 50–74) achieved EASI 75 at week 24 and maintained this response to week 32 (Table 23) [56].

In addition, patients treated with 16 weeks of tralokinumab Q2W plus TCS were significantly more likely than the corresponding placebo plus TCS groups to have an improvement of ≥ 4 points in worst daily pruritis NRS score (Table 16) and to achieve the combined endpoint of EASI 50 & ΔDLQI ≥ 4 (Table 15). Tralokinumab-treated patients also had significantly greater mean improvements in SCORAD and DLQI, compared with placebo (Table 16).

Key endpoint results calculated using the treatment policy sensitivity analysis estimand were generally similar to the primary, composite estimand results (Table 15).

ECZTRA 1 and ECZTRA 2

Results for key efficacy endpoints in ECZTRA 1 and ECZTRA 2 are summarised in Table 15. Both trials met their primary endpoints, with significantly greater efficacy observed at week 16 with tralokinumab Q2W than with placebo [30, 52]. The proportion of patients with IGA 0/1 at 16 weeks was significantly higher with tralokinumab Q2W than with placebo (ECZTRA 1, 15.8% vs 7.1%; ECZTRA 2, 22.2% vs 10.9%) [52]. Similarly, significantly more patients receiving tralokinumab Q2W had EASI 75 responses at week 16, compared with the placebo group (ECZTRA 1, 25.0% vs 12.7%; ECZTRA 2, 33.2% vs 11.4%) [52]. Among patients achieving IGA 0/1 or EASI 75 responses to tralokinumab Q2W at week 16, more than half retained these responses at week 52 when re-randomised to tralokinumab Q2W (Table 17) [52]. Week 52 responses were consistently higher for tralokinumab Q2W and Q4W, compared with placebo, but this difference was statistically significant only for tralokinumab Q2W in the ECZTRA 2 trial [52]. More than half (53.2%) of tralokinumab-treated patients who had EASI 50–74 at week 16 achieved EASI 75 during maintenance therapy with tralokinumab Q2W and optional TCS (Table 32) [78].

In both trials, patients treated with 16 weeks of tralokinumab Q2W were significantly more likely than the corresponding placebo groups to have an improvement of ≥ 4 points in worst daily pruritis NRS score, and had significantly greater mean improvements in SCORAD and DLQI (Table 16). In addition, significantly more patients treated with tralokinumab achieved the combined endpoint of EASI 50 & ΔDLQI ≥ 4, compared with the placebo groups (Table 15).

Key endpoint results calculated using the treatment policy sensitivity analysis estimand were generally similar to the primary, composite estimand results (Table 15).

Table 14 Key outcomes at week 16 and week 26 in ECZTRA 7 (multiple estimands)

Outcome	Week 16		Week 26	
	Tralokinumab Q2W plus TCS (N = 138)	Placebo plus TCS (N = 137)	Tralokinumab Q2W plus TCS (N = 138)	Placebo plus TCS (N = 137)
Composite estimand				
IGA 0/1, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 75, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 50, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 90, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 50 and DLQI improvement ≥ 4, n/N (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
≥ 4-point reduction in DLQI, n/N (%) Difference (95% CI) and *p* value vs placebo plus TCS				
≥ 4-point reduction in worst daily pruritis NRS, n/N (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
Treatment policy sensitivity analysis estimand				
IGA 0/1, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 75, n (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
EASI 50, n (%) Difference (95% CI) and p value vs placebo plus TCS [a]				
EASI 50 and DLQI improvement ≥ 4, n/N (%) Difference (95% CI) and *p* value vs placebo plus TCS [a]				
Hypothetical estimand				
Adjusted mean change in SCORAD (SD) Difference (95% CI) and *p* value vs placebo plus TCS				
Adjusted mean change in DLQI (SD) Difference (95% CI) and *p* value vs placebo plus TCS				

[a] stratified by prior CSA use and baseline IGA. [b] Data are missing for 1 patient. [c] Data are missing for 3 patients. Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders. Treatment policy sensitivity analysis estimand: treatment difference regardless of permanent discontinuation of IMP or initiation of rescue medication; missing data imputed as non-responders. Hypothetical estimand: data collected after permanent discontinuation of IMP, initiation of rescue medication or prolonged interruption of IMP due to the SARS-CoV-2 pandemic were not included; missing data imputed. CI, confidence interval; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IMP, investigational medicinal product; Q2W, every 2 weeks; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCS, topical corticosteroids. Sources: ECZTRA 7 efficacy tables [49]; statistical appendix, 9 April 2021 [51].

Table 15 Key outcomes at week 16 in ECZTRA 3, ECZTRA 1 and ECZTRA 2 (multiple estimands)

Outcome	ECZTRA 3		ECZTRA 1		ECZTRA 2		ECZTRA 1 + 2 pooled	
	Tralokinumab Q2W plus TCS (N = 252)	Placebo plus TCS (N = 126)	Tralokinumab Q2W (N = 601)	Placebo (N = 197)	Tralokinumab Q2W (N = 591)	Placebo (N = 201)	Tralokinumab Q2W (N = 1192)	Placebo (N = 398)
Composite estimand								
IGA 0/1, n (%)	98 (38.9)	33 (26.2)	95 (15.8)	14 (7.1)	131 (22.2)	22 (10.9)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	12.4 (2.9–21.9) *p* = 0.015		8·6 (4·1–13·1) *p* = 0·002		11.1 (5.8–16.4) *p* < 0.001			
EASI 75, n (%)	141 (56.0)	45 (35.7)	150 (25.0)	25 (12.7)	196 (33.2)	23 (11.4)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	20.2 (9.8–30.6) *p* < 0.001		12.1 (6.5–17.7) *p* < 0.001		21.6 (15.8–27.3) *p* < 0.001			
EASI 50, n (%)	200 (79.4)	73 (57.9)	250 (41.6)	42 (21.3)	295 (49.9)	41 (20.4)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	21.3 (11.3–31.3) *p* < 0.001		20.1 (13.3–26.8) *p* < 0.001		29.3 (22.5–36.1) *p* < 0.001			
EASI 90, n (%)	83 (32.9)	27 (21.4)	87 (14.5)	8 (4.1)	108 (18.3)	11 (5.5)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	11.4 (2.1–20.7) *p* = 0.022		10.3 (6.4–14.1) *p* < 0.001		12.7 (8.4–17.0) *p* < 0.001			
EASI 50 and DLQI improvement ≥ 4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
Treatment policy sensitivity analysis estimand								
IGA 0/1, n (%)	98 (38.9)	33 (26.2)	115 (19.1)	16 (8.1)	142 (24.0)	25 (12.4)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	12.4 (2.9–21.9) *p* < 0.015		10.9 (6.1–15.7) *p* < 0.001		11.4 (5.8–17.0) *p* < 0.001			
EASI 75, n (%)	141 (56.0)	45 (35.7)	201 (33.4)	34.5 (17.3)	224 (37.9)	38.5 (19.2)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	20.2 (9.8–30.6) *p* < 0.001		16.0 (9.6–22.4) *p* < 0.001		21.3 (14.9–27.7) *p* < 0.001			
EASI 50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and p value vs comparator								
EASI 50 and DLQI improvement ≥ 4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Treatment policy sensitivity analysis estimand: treatment difference regardless of permanent discontinuation of IMP or initiation of rescue medication; missing data imputed as non-responders.

CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IMP, investigational medicinal product; Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52]; statistical appendix, 9 April 2021 [51].

Table 16 SCORAD and key patient-reported outcomes at week 16 in ECZTRA 3, ECZTRA 1 and ECZTRA 2 (multiple estimands) [a]

Outcome	ECZTRA 3		ECZTRA 1		ECZTRA 2		ECZTRA 1 + 2 pooled	
	Tralokinumab Q2W plus TCS (N = 253)	Placebo (N = 127)	Tralokinumab Q2W (N = 601)	Placebo (N = 197)	Tralokinumab Q2W (N = 591)	Placebo (N = 201)	Tralokinumab Q2W (N = 1192)	Placebo (N = 398)
Composite estimand								
≥ 4-point reduction in worst daily pruritis NRS, n/N (%)	113/249 (45.4)	43/126 (34.1)	119/594 (20.0)	20/194 (10.3)	144/575 (25.0)	19/200 (9.5)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	11.3 (0.9–21.6) *p* = 0.037		9.7 (4.4–15.0) *p* = 0.002		15.6 (10.3–20.9) *p* < 0.001		[redacted]	
≥ 4-point reduction in DLQI, n/N (%)	207/248 (83.5%)	81/123 (65.9)	258/578 (44.6)	60/190 (31.6)	325/577 (56.3)	54/198 (27.3)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	17.6 (8.0–27.1) *p* < 0.001		13.0 (5.4–20.5) *p* = 0.001		28.9 (21.4–36.3) *p* < 0.001		[redacted]	
Hypothetical estimand								
Adjusted mean change in SCORAD (SD)	−37.7 (1.25)	−26.8 (1.80)	−25.2 (0.94)	−14.7 (1.80)	−28.1 (0.92)	−14.0 (1.79)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	−10.9 (−15.2, −6.6) *p* < 0.001		−10.4 (−14.4, −6.5) *p* < 0.001		−14.0 (−18.0, −10.1) *p* < 0.001		[redacted]	
Adjusted mean change in DLQI (SD)	−11.7 (0.39)	−8.8 (0.56)	−7.1 (0.31)	−5.0 (0.59)	−8.8 (0.30)	−4.9 (0.60)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	−2.9 (−4.3, −1.6) *p* < 0.001		−2.1 (−3.4, −0.8) *p* = 0.002		−3.9 (−5.2, −2.6) *p* < 0.001		[redacted]	

[a] Hypothetical estimand for SCORAD and DLQI; composite estimand for pruritus NRS and ≥ 4-point reduction in DLQI.
Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed.
CI, confidence interval; DLQI, Dermatology Life Quality Index; IMP, investigational medicinal product; NRS, numeric rating scale; SCORAD, Scoring Atopic Dermatitis; Q2W, every 2 weeks; TCS, topical corticosteroids. Sources: Silverberg *et al.* 2020a [30]; Wollenberg *et al.* 2020 [52]; monotherapy pool statistical appendix [56].

Table 17 Clinical responses at weeks 24 and 32/52 among tralokinumab-treated patients with EASI 75 or IGA 0/1 at week 16 in ECZTRA 3, ECZTRA 1 and ECZTRA 2 (composite estimand)

Outcome	ECZTRA 3		ECZTRA 1			ECZTRA 2			ECZTRA 1 + 2 pooled		
	Q2W plus TCS to Q2W plus TCS	Q2W plus TCS to Q4W plus TCS	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16 IGA response, N	48	49	39	36	19	54	49	28	[redacted]	[redacted]	[redacted]
Week 24 IGA 0/1, n (%) [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32 IGA 0/1, n (%)	43 (89.6)	38 (77.6)	–	–	–	–	–	–	–	–	–
Week 52 IGA 0/1, n (%)	–	–	20 (51.3)	14 (38.9)	9 (47.4)	32 (59.3)	22 (44.9)	7 (25.0)	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	–	–	6.0 (−21.8, 33.7) *p* = 0.68	−9.5 (−37.1, 18.0) *p* = 0.50		34.1 (13.4–54.9) *p* = 0.004	19.9 (−1.2, 40.9) *p* = 0.84		[redacted]	[redacted]	
Week 16 EASI 75 response, N	67	65	47	57	30	77	74	42	[redacted]	[redacted]	[redacted]
Week 24 EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32 EASI 75, n (%) [a]	62 (92.5)	59 (90.8)	–	–	–	–	–	–	–	–	–
Week 52 EASI 75, n (%)	–	–	28 (59.6)	28 (49.1)	10 (33.3)	43 (55.8)	38 (51.4)	9 (21.4)	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	–	–	21.2 (−0.2, 42.6) *p* = 0.056	11.7 (−8.7, 32.0) *p* = 0.27		33.7 (17.3–50.0) *p* < 0.001	30.0 (13.7–46.4) *p* = 0.001		[redacted]	[redacted]	

[a] No statistical analysis was performed for week 24 data or for ECZTRA 3.
Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: Wollenberg *et al.* 2020 [52]; Silverberg *et al.* 2020a [30]; ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54]; ECZTRA 3 CSR [47]; monotherapy pool statistical appendix [56].

B.2.6.2 ECZTRA 7

B.2.6.2.1 Statistical significance of key primary and secondary endpoints

In ECZTRA 7, the primary endpoint showed statistically significantly greater efficacy with tralokinumab Q2W in combination with TCS than with placebo plus TCS (Table 18) [49]. [redacted]

Table 18 Statistical significance of comparisons between tralokinumab and placebo in ECZTRA 7 (Composite/hypothetical estimand)

Endpoint	*p* value (nominal *p* value)
Primary endpoint	
EASI 75 at week 16	[redacted]
Secondary endpoints	
≥ 4-point improvement in worst daily pruritis NRS at week 16	[redacted]
Change in SCORAD at week 16	[redacted]
Change in DLQI at week 16	[redacted]
IGA 0/1 at week 16	[redacted]
EASI 75 at week 26	[redacted]
≥ 4-point improvement in worst daily pruritis NRS at week 26	[redacted]
Change in SCORAD at week 26	[redacted]
Change in DLQI at week 26	[redacted]
IGA 0/1 at week 26	[redacted]

Nominal *p* values are shown for comparisons not formally tested due to being lower in the statistical testing hierarchy than a non-significant comparison.
DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numeric rating scale; NT, not formally tested; SCORAD, Scoring Atopic Dermatitis.
Sources: ECZTRA 7 efficacy tables [49]; statistical appendix, 9 April 2021 [51].

B.2.6.2.2 Clinical results

B.2.6.2.2.1 EASI responses

Significantly more patients achieved EASI 75 with tralokinumab plus TCS than with placebo plus TCS

The proportion of patients with an EASI 75 response at week 16 was the primary endpoint of ECZTRA 7 [47]. At week 16, [redacted] of patients in the tralokinumab Q2W plus TCS group achieved EASI 75, compared with [redacted] in the placebo plus TCS group (difference, [redacted]; Table 14; Figure 9) [51].

A similar difference between groups was seen at week 26 ([redacted]; Table 14; Figure 9) [51].

Patients treated with tralokinumab plus TCS were more likely to achieve EASI 50 than those receiving placebo plus TCS

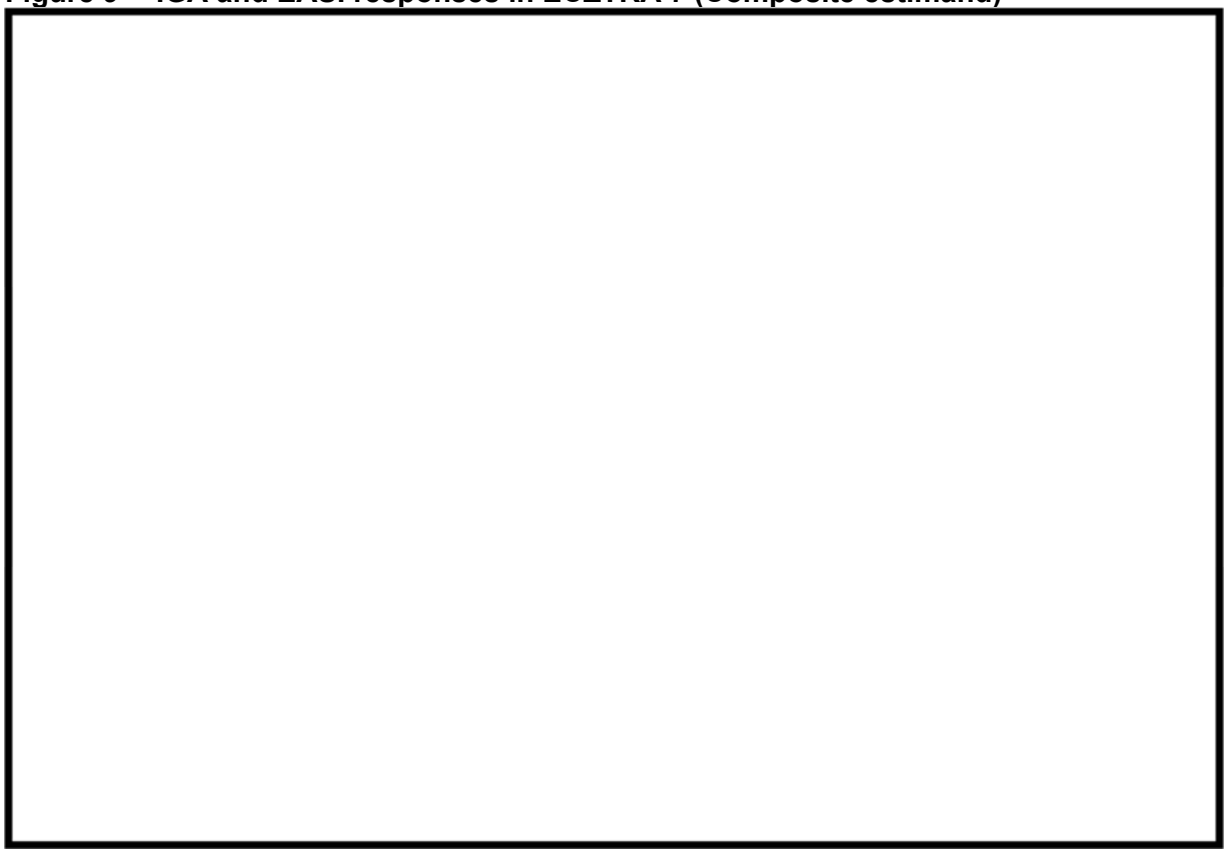
At week 16, [redacted] of patients in the tralokinumab Q2W plus TCS group had an EASI 50 response, compared with [redacted] in the placebo plus TCS group (difference, [redacted]; Table 14; Figure 9) [51].

At week 26, the proportion of patients with an EASI 50 response was significantly higher in the tralokinumab Q2W plus TCS combination therapy group than in the placebo plus TCS group ([redacted] vs [redacted]; difference, [redacted]; Table 14; Figure 9) [51].

Significantly more patients achieved EASI 90 with tralokinumab plus TCS than with placebo plus TCS

In ECZTRA 7, the proportion of patients with an EASI 90 response at week 16 was significantly higher in the tralokinumab Q2W plus TCS combination therapy group than in the placebo plus TCS group ([redacted] vs [redacted] difference, [redacted]; Table 14; Figure 9) [51]. A similar difference between groups was seen at week 26 ([redacted]; Table 14; Figure 9) [51].

Figure 9 IGA and EASI responses in ECZTRA 7 (Composite estimand)



* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.
Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: Statistical appendix, 9 April 2021 [51]. Data in this figure are academic-in-confidence.

B.2.6.2.2.2 IGA response

Significantly more patients achieved IGA 0/1 with tralokinumab plus TCS than with placebo plus TCS

Significantly more patients had an IGA 0/1 response (clear [0] or almost clear [1]; IGA 0/1) at week 16 in the tralokinumab Q2W plus TCS group than in the placebo plus TCS group ([redacted] vs [redacted]; difference, [redacted]; Table 14; Figure 9) [51].

Similarly, at week 26, [redacted] of patients in the tralokinumab Q2W plus TCS group had an IGA 0/1 response, compared with [redacted] in the placebo plus TCS group (difference, [redacted]; Table 14; Figure 9) [51].

B.2.6.2.2.3 SCORAD

Patients treated with tralokinumab plus TCS had significantly greater reductions in SCORAD score, compared with those receiving placebo plus TCS

In ECZTRA 7, use of tralokinumab Q2W plus TCS was associated with an adjusted mean change (standard deviation [SD]) in SCORAD score of [redacted] at week 16, compared with [redacted] among patients receiving placebo ([redacted]; Table 14) [49]. A similar difference between groups was seen at week 26 (Table 14) [49].

B.2.6.2.2.4 Combined endpoint – EASI 50 plus DLQI improvement

EASI 50 plus a DLQI improvement of ≥ 4 points was more common among patients treated with tralokinumab plus TCS, compared with placebo plus TCS

In ECZTRA 7, [redacted] of patients in the tralokinumab Q2W group achieved the combined endpoint of EASI 50 & ΔDLQI ≥ 4 at week 16, compared with [redacted] in the placebo group (difference, [redacted]; Table 14) [51]. At week 26, the difference between groups was [redacted]) [51].

B.2.6.2.3 Rescue medication and TCS use

B.2.6.2.3.1 Use of rescue medication

Fewer patients treated with tralokinumab plus TCS used rescue medication, compared with those receiving placebo plus TCS

During the 26-week treatment period, fewer patients in ECZTRA 7 who were treated with tralokinumab Q2W plus TCS used rescue medication, compared with those receiving placebo plus TCS (Table 19) [48]. The majority of rescue medication use was TCS. In the tralokinumab Q2W plus TCS arm, few patients used rescue medication, and none received systemic immunosuppressants [48].

Table 19 Rescue medication use during 26-week treatment period in ECZTRA 7

Type of rescue medication, n (%)	Tralokinumab Q2W plus TCS (N = 140)			Placebo plus TCS (N = 137)		
Any rescue medication		[redacted]			[redacted]	
Topical corticosteroids		[redacted]			[redacted]	
Systemic corticosteroids		[redacted]			[redacted]	
Systemic immunosuppressants		[redacted]			[redacted]	

Q2W, every 2 weeks; TCS, topical corticosteroids. Source: ECZTRA 7 baseline characteristics tables [48].

B.2.6.2.3.2 TCS use

In ECZTRA 7, mean TCS use was lower among patients treated with tralokinumab Q2W than among those receiving placebo (Figure 10) [49]. In addition, from week 4 onward, patients in the tralokinumab Q2W group had a significantly higher mean number of days per week on which they did not use topical treatments (Figure 10); this difference was maintained throughout the treatment period [49].

Figure 10 Mean TCS use (left) and mean days per week without TCS use (right) in ECZTRA 7

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$. Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: ECZTRA 7 efficacy tables [49]. Data in this figure are academic-in-confidence.

B.2.6.2.4 Patient-reported outcomes and health-related quality of life

B.2.6.2.4.1 Pruritus

Improvements in pruritus significantly favoured tralokinumab plus TCS over placebo plus TCS from week 4

In ECZTRA 7, the reduction from baseline in the weekly mean of worst daily pruritus NRS scores was significantly higher in the tralokinumab Q2W plus TCS group than in the placebo group from week 4, and increased throughout the 26-week treatment period (Figure 11) [49].

Among patients treated with tralokinumab Q2W plus TCS, [redacted] had clinically meaningful improvements in pruritus

A 4-point reduction in worst daily pruritus NRS is considered to be a clinically meaningful change [79]. In ECZTRA 7, [redacted] of patients in the tralokinumab Q2W plus TCS group had a decrease of ≥ 4 points in worst daily pruritus NRS score, calculated as a weekly mean, at week 16, compared with [redacted] in the placebo plus TCS group (difference, [redacted]; Table 14) [49]. Similar reductions in pruritus were seen at week 26 (Table 14) [49].

B.2.6.2.4.2 Sleep

Tralokinumab plus TCS was associated with early improvements in eczema-related sleep disruption

In ECZTRA 7, mean eczema-related sleep NRS scores began to decline within the first week of treatment. The difference between the tralokinumab Q2W plus TCS and placebo

plus TCS groups was statistically significant at week 4 and was maintained throughout the 26-week treatment period (Figure 11) [49].

B.2.6.2.4.3 POEM

Tralokinumab plus TCS was associated with early improvements in mean POEM scores

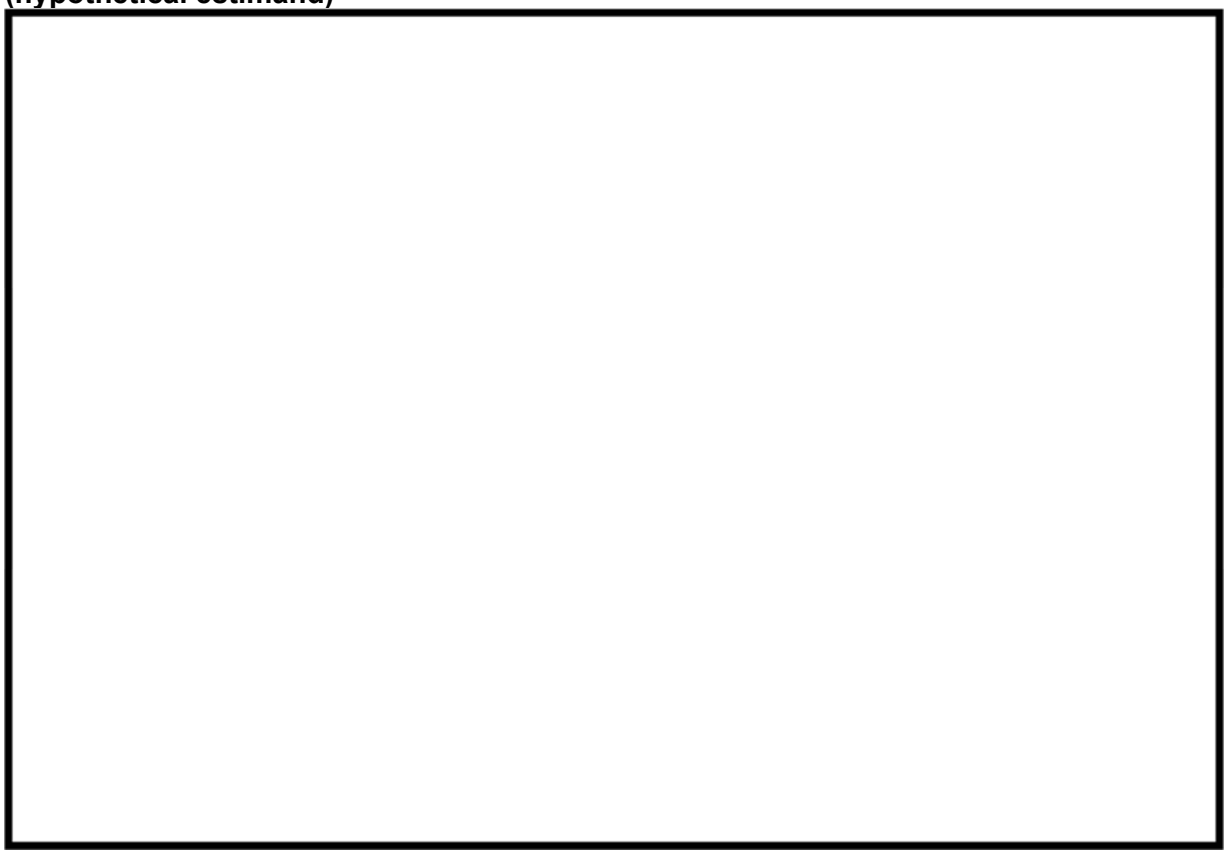
In ECZTRA 7, mean POEM scores were significantly lower among patients treated with tralokinumab Q2W plus TCS, compared with those receiving placebo plus TCS, as early as week 2 (Figure 11) [49]. The differences between groups were statistically significant throughout the 26-week treatment period [49].

B.2.6.2.4.4 DLQI

Tralokinumab plus TCS was associated with improvements in mean DLQI

In ECZTRA 7, improvements in DLQI were statistically significantly greater with tralokinumab plus TCS than with placebo plus TCS from week 8 onward, with a [redacted] difference at week 16 which was maintained up to week 26 (Figure 11, Table 14) [49].

Figure 11 Mean change from baseline in patient-reported outcomes in ECZTRA 7 (hypothetical estimand)



* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.
Hypothetical estimand: data collected after permanent discontinuation of IMP, initiation of rescue medication or prolonged interruption of IMP due to the SARS-CoV-2 pandemic were not included; missing data imputed.
DLQI, Dermatology Life Quality Index; IMP, investigational medicinal product; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCS, topical corticosteroids.
Source: ECZTRA 7 efficacy tables [49]. Data in this figure are academic-in-confidence.

B.2.6.2.4.5 EQ-5D-3L

Tralokinumab plus TCS was associated with improvements in EQ-5D-3L utility scores, compared with placebo plus TCS

At baseline, mean EQ-5D-3L index scores were [redacted] and [redacted] in the tralokinumab Q2W plus TCS and placebo plus TCS groups, respectively [49]. Mean scores increased from baseline to week 16, with significantly higher increases in the tralokinumab Q2W plus TCS group than in the placebo plus TCS group (Table 20); this increase was maintained at week 26 [49].

Table 20 Change in EQ-5D-3L from baseline to week 16 and week 26 in ECZTRA 7 (hypothetical estimand)

EQ-5D-3L index score	Tralokinumab Q2W plus TCS	Placebo
Baseline, mean (SD) [N]	[redacted]	[redacted]
Change from baseline to week 16, mean (SE) Mean difference (95% CI) and *p* value vs placebo plus TCS	[redacted]	[redacted]
Change from baseline to week 26, mean (SE) Mean difference (95% CI) and *p* value vs placebo plus TCS	[redacted]	[redacted]

Hypothetical estimand: data collected after permanent discontinuation of IMP, initiation of rescue medication or prolonged interruption of IMP due to the SARS-CoV-2 pandemic were not included; missing data imputed.
CI, confidence interval; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; Q2W, every 2 weeks; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SE, standard error; TCS, topical corticosteroids. Source: ECZTRA 7 efficacy tables [49].

B.2.6.3 ECZTRA 3

B.2.6.3.1 Statistical significance of primary and key secondary endpoints

In ECZTRA 3, all primary and all week 16 secondary endpoints showed statistically significantly greater efficacy with tralokinumab Q2W plus TCS than with placebo plus TCS [30].

Table 21 Statistical significance of comparisons between tralokinumab and placebo in ECZTRA 3 (composite/hypothetical estimand)

Endpoint	*p* value
Primary endpoints	
IGA 0/1 at week 16	**0.015**
EASI 75 at week 16	**< 0.001**
Secondary endpoints	
Reduction in weekly average of worst daily pruritus NRS from baseline to week 16	**0.037**
Change in SCORAD score from baseline to week 16	**< 0.001**
Change in DLQI from baseline to week 16	**< 0.001**

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NT, not formally tested; SCORAD, Scoring Atopic Dermatitis. Source: Silverberg *et al.* 2020a [30].

B.2.6.3.2 Clinical results during initial treatment period

B.2.6.3.2.1 IGA response

Significantly more patients achieved IGA 0/1 with tralokinumab plus TCS than with placebo plus TCS

In ECZTRA 3, the proportion of patients with an IGA 0/1 response at week 16 was significantly higher in the tralokinumab Q2W plus TCS group than in the placebo plus TCS

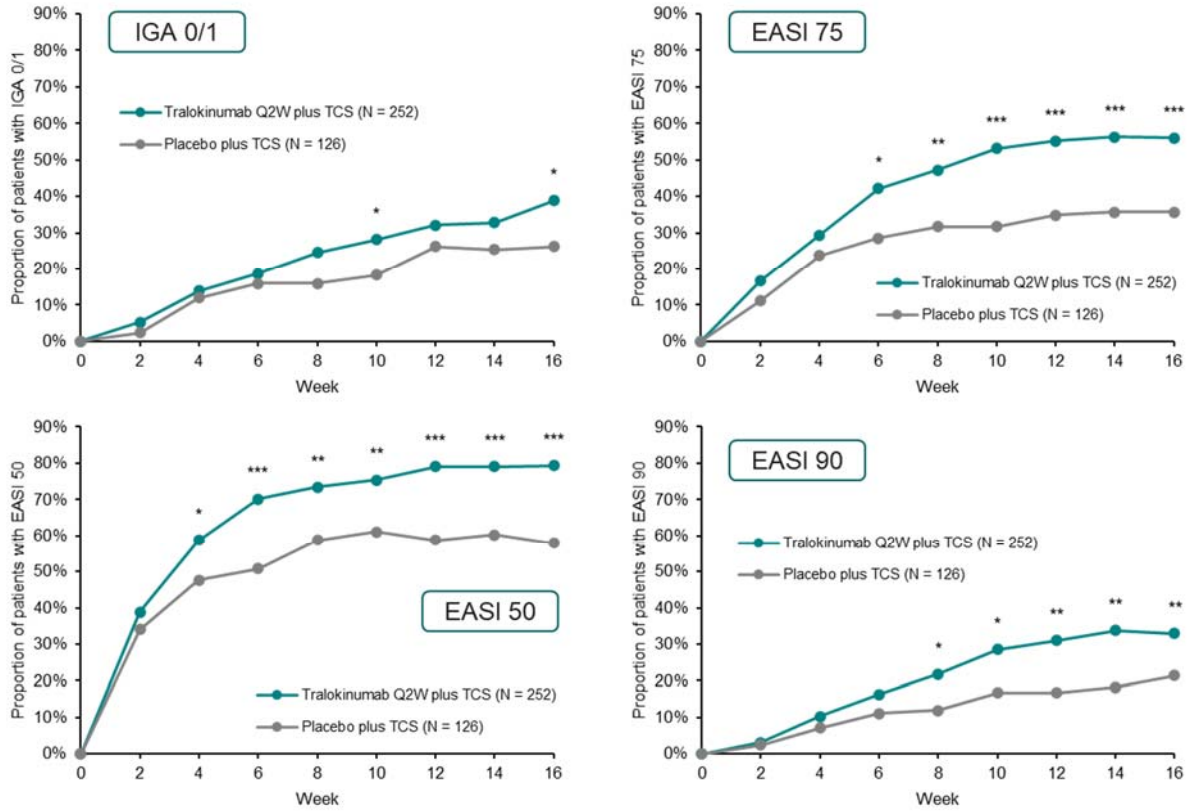
group (38.9% vs 26.2%; difference, 12.4% [95% CI, 2.9–21.9]; $p = 0.015$; Table 15; Figure 12) [30].

B.2.6.3.2.2 EASI responses

Significantly more patients achieved EASI 75 with tralokinumab plus TCS than with placebo plus TCS

In ECZTRA 3, the proportion of patients with an EASI 75 response at week 16 was significantly higher in the tralokinumab Q2W plus TCS group than in the placebo plus TCS group (56.0% vs 35.7%; difference, 20.2% [95% CI, 9.8–30.6]; $p < 0.001$; Table 15; Figure 12) [30].

Figure 12 IGA and EASI responses in ECZTRA 3 (composite estimand)



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs placebo plus TCS.
Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks.
Source: Silverberg *et al.* 2020a [30].

Patients treated with tralokinumab plus TCS were significantly more likely to achieve EASI 50 than those receiving placebo plus TCS

In ECZTRA 3, the proportion of patients with an EASI 50 response at week 16 was significantly higher in the tralokinumab Q2W plus TCS group than in the placebo plus TCS group (79.4% vs 57.9%; difference, 21.3% [95% CI, 11.3–31.3]; $p < 0.001$; Table 15) [30].

Significantly more patients achieved EASI 90 with tralokinumab plus TCS than with placebo plus TCS

In ECZTRA 3, the proportion of patients with an EASI 90 response at week 16 was significantly higher in the tralokinumab Q2W plus TCS combination therapy group than in the

placebo plus TCS group (32.9% vs 21.4%; difference, 11.4% [95% CI, 2.1–20.7]; $p = 0.022$; Table 15) [30].

B.2.6.3.2.3 SCORAD

At week 16, patients treated with tralokinumab plus TCS had significantly greater reductions in SCORAD score, compared with those receiving placebo plus TCS

In ECZTRA 3, use of tralokinumab Q2W plus TCS was associated with an adjusted mean change (SD) in SCORAD score of −37.7 (1.25), compared with −26.8 (1.80) among patients receiving placebo ($p < 0.001$; Table 15) [30].

B.2.6.3.2.4 Combined endpoint – EASI 50 plus DLQI improvement

At week 16, EASI 50 plus a DLQI improvement of ≥ 4 points was significantly more common among patients treated with tralokinumab plus TCS, compared with placebo plus TCS

In ECZTRA 3, [redacted] of patients in the tralokinumab Q2W plus TCS group achieved the combined endpoint of EASI 50 & ΔDLQI ≥ 4 at week 16, compared with [redacted] in the placebo plus TCS group (difference, [redacted]; Table 15) [51].

B.2.6.3.3 Rescue medication and TCS use

B.2.6.3.3.1 Use of rescue medication during initial treatment period

Fewer patients treated with tralokinumab plus TCS used rescue mediation, compared with those receiving placebo plus TCS

In ECZTRA 3, few patients receiving tralokinumab Q2W plus TCS used rescue medication in the initial treatment period (2.8%), with a higher rate of rescue medication use in the placebo group (10.2%) (Table 22) [30].

Table 22 Rescue medication use in initial treatment period, ECZTRA 3

Type of rescue medication, n (%)	Tralokinumab Q2W plus TCS (N = 253)	Placebo plus TCS (N = 127)
Any rescue medication	7 (2.8)	13 (10.2)
Topical		
Corticosteroids	5 (2.0)	10 (7.9)
Other	1 (0.4)	0
Systemic		
Corticosteroids	3 (1.2)	3 (2.4)
Immunosuppressants	0	3 (2.4)
Other	0	0

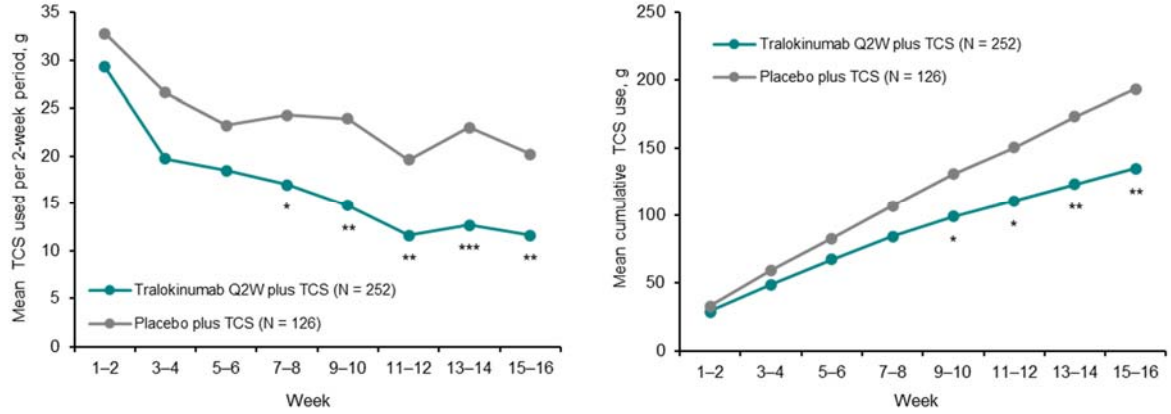
Q2W, once every 2 weeks; TCS, topical corticosteroids. Source: Silverberg *et al.* 2020a [30].

B.2.6.3.3.2 TCS use in initial treatment period

Tralokinumab therapy was associated with a reduction in TCS use, compared with placebo

In ECZTRA 3, cumulative TCS use was lower among patients treated with tralokinumab Q2W than among those receiving placebo during the initial treatment period ($p = 0.004$; Figure 13). At weeks 15–16, patients treated with tralokinumab Q2W used approximately 40% less of the supplied TCS, compared with patients receiving placebo ($p = 0{\cdot}002$; Figure 13) [55]; 55.3% and 36.7% in the tralokinumab Q2W and placebo groups, respectively, used no or very limited amounts (0–5 g) of TCS [30, 55].

Figure 13 Mean TCS use (left) and mean cumulative use of TCS (right) in the initial treatment period in ECZTRA 3



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs placebo plus TCS. Q2W, once every 2 weeks; TCS, topical corticosteroids.
Source: Silverberg *et al.* 2020a [30].

B.2.6.3.4 Clinical results during maintenance/continuation period

B.2.6.3.4.1 Responses among patients with a response to initial treatment

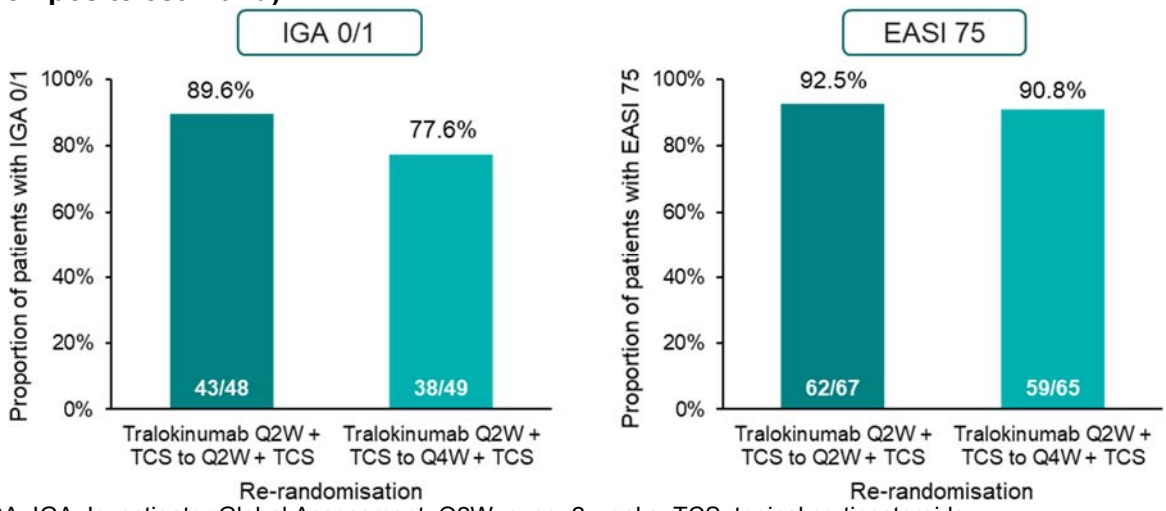
Most patients receiving maintenance therapy with tralokinumab Q2W or Q4W plus TCS retained their week 16 IGA 0/1 response at week 32

In ECZTRA 3, 89.6% of patients with IGA 0/1 at week 16 still had IGA 0/1 after a further 16 weeks of treatment with tralokinumab Q2W plus TCS, without use of rescue medication. Similarly 77.6% of patients retained a week 16 IGA 0/1 response after 16 weeks of maintenance treatment with tralokinumab Q4W plus TCS (Table 17; Figure 14) [30].

Most patients receiving maintenance therapy with tralokinumab Q2W or Q4W plus TCS retained their week 16 EASI 75 response at week 32

Among patients with an EASI 75 response at week 16, 92.5% and 90.8% still had EASI 75 after a further 16 weeks of treatment with tralokinumab Q2W or Q4W, respectively, in combination with TCS, without use of rescue medication (Table 17; Figure 14) [30].

Figure 14 ECZTRA 3 week 32 IGA 0/1 responses among patients with IGA 0/1 at week 16 (left), and EASI 75 responses among patients with EASI 75 at week 16 (right) (composite estimand)



IGA, IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids.
Source: Silverberg *et al.* 2020a [30].

B.2.6.3.4.2 Responses to continuation treatment among patients without initial responses

Patients without EASI 75 or IGA 0/1 at week 16 were assigned to tralokinumab Q2W plus TCS for 16 weeks of additional treatment (see section B.2.3.1.1) [30].

Among patients without EASI 75 or IGA 0/1 at week 16, [redacted] achieved EASI 75 after a further 16 weeks of treatment with tralokinumab Q2W plus TCS

In ECZTRA 3, [redacted] patients who were treated with tralokinumab Q2W plus TCS in the initial treatment period and did not have EASI 75 or IGA 0/1 at week 16 were assigned to continuation treatment with tralokinumab Q2W [57]. Of these, [redacted] had achieved EASI 75 at week 24, and [redacted] by week 32; among patients with EASI 50, but not EASI 75, at week 16, [redacted] had EASI 75 at weeks 24 and 32 (Table 23) [57].

Table 23 Clinical responses during continuation treatment among tralokinumab-treated patients without EASI 75 or IGA 0/1, or with EASI 50–74, at week 16 in ECZTRA 3 (composite estimand)

Outcome	All patients without EASI 75 or IGA 0/1 at week 16			Patients with EASI 50–74 at week 16		
Week 16 N		[redacted]			[redacted]	
Week 24 EASI 75, n (%)		[redacted]			[redacted]	
Week 32 EASI 75, n (%)		[redacted]			[redacted]	

No statistical analysis was performed.
Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Sources: ECZTRA 3 CSR [55]; ECZTRA 3 statistical appendix, 3 Oct 2020 [57].

B.2.6.3.4.3 Use of rescue medication during maintenance/continuation period

In the ECZTRA 3 continuation phase, [redacted] received rescue medication (systemic corticosteroids, in the tralokinumab Q4W plus TCS arm) [55].

B.2.6.3.5 Patient-reported outcomes and health-related quality of life

B.2.6.3.5.1 Pruritus

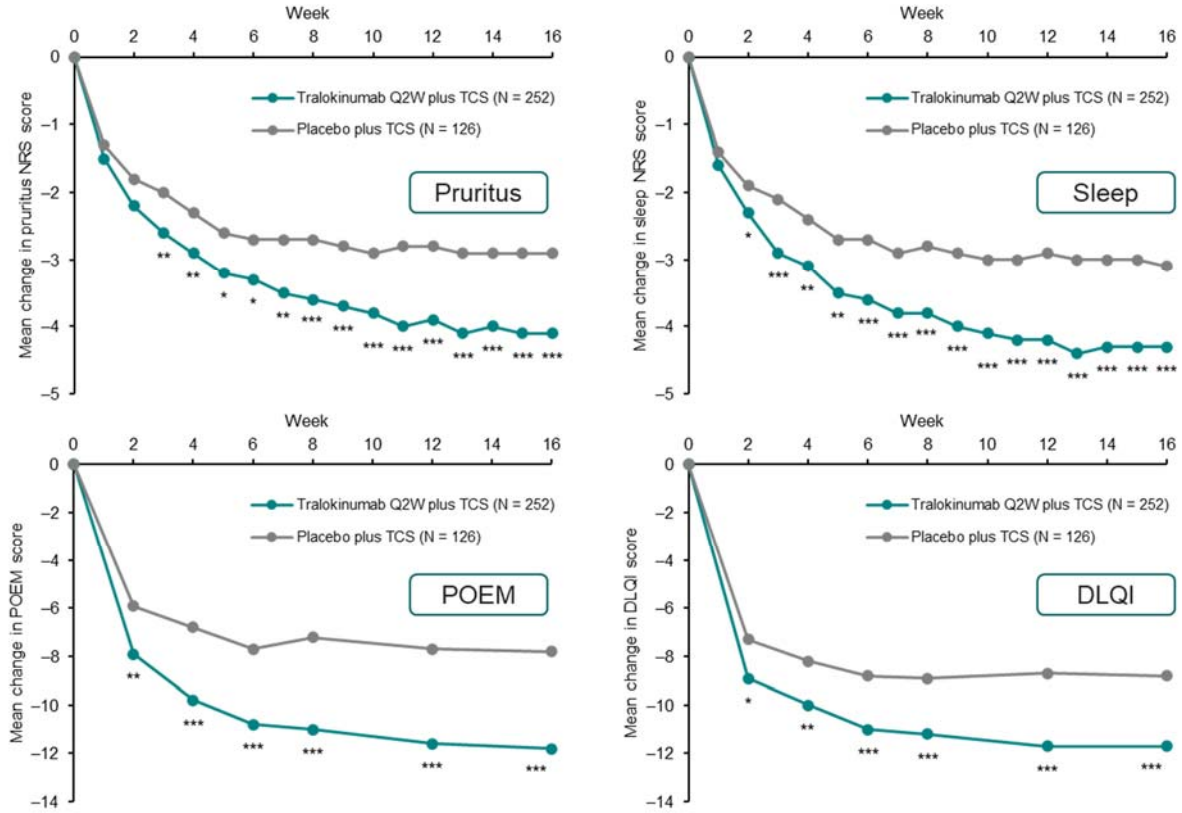
Significantly more patients achieved a clinically meaningful improvement in pruritus with tralokinumab plus TCS than with placebo plus TCS

In ECZTRA 3, the proportion of patients with ≥ 4-point improvement in worst daily pruritus NRS score at week 16 was significantly higher in the tralokinumab Q2W plus TCS combination therapy group than in the placebo plus TCS group (45.4% vs 34.1%; difference, 11.3% [95% CI, 0.9–21.6]; p = 0.037; Table 16) [30].

Improvements in pruritus significantly favoured tralokinumab plus TCS over placebo plus TCS from week 3

In ECZTRA 3, mean improvement in worst daily pruritus NRS scores was greater with tralokinumab Q2W plus TCS than with placebo plus TCS by week 3; this difference continued to be statistically significant throughout the initial treatment period (Figure 15) [30].

Figure 15 Mean change from baseline in patient-reported outcomes in ECZTRA 3 (hypothetical estimand)



* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.
Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed.
DLQI, Dermatology Life Quality Index; IMP, investigational medicinal product; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: Silverberg *et al.* 2020a,b [30, 80]; ECZTRA 3 CSR [55].

During the continuation period, mean improvements in worst daily pruritus NRS scores were seen in all tralokinumab-treated groups, with numerically larger improvements in patients who had not had an EASI 75 or IGA 0/1 response at week 16 (Table 24) [55].

Table 24 Mean worst daily pruritus NRS during ECZTRA 3 continuation period

Weekly mean of worst daily pruritus NRS, mean (SD) [N]	Week 16 tralokinumab responders		Week 16 tralokinumab non-responders	Week 16 placebo non-responders
	Q2W to Q2W	Q2W to Q4W	Q2W to Q2W	Placebo to Q2W
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive data, based on observed cases; no statistical analysis was performed. All treatment was in combination with TCS.
NRS, numerical rating scale; Q2W, once every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: ECZTRA 3 CSR [55].

B.2.6.3.5.2 Sleep disruption

Tralokinumab plus TCS was associated with early improvements in eczema-related sleep disruption

In ECZTRA 3, the mean eczema-related sleep NRS score for patients treated with tralokinumab Q2W plus TCS declined within the first week of treatment, with a significant difference versus placebo at week 2 (Figure 15) [80]. Improvements were maintained throughout the initial treatment period [55].

During the continuation period, mean improvements in eczema-related sleep NRS scores were seen in all tralokinumab-treated groups, with numerically larger improvements in patients who had not had an EASI 75 or IGA 0/1 response at week 16 (Table 25) [55].

Table 25 Mean eczema-related sleep NRS during ECZTRA 3 continuation period

Weekly mean of eczema-related sleep NRS, mean (SD) [N]	Week 16 tralokinumab responders		Week 16 tralokinumab non-responders	Week 16 placebo non-responders
	Q2W to Q2W	Q2W to Q4W	Q2W to Q2W	Placebo to Q2W
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive data, based on observed cases; no statistical analysis was performed. All treatment was in combination with TCS.
NRS, numerical rating scale; Q2W, once every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: ECZTRA 3 CSR [55].

B.2.6.3.5.3 POEM

Tralokinumab plus TCS was associated with early improvements in mean POEM scores

In ECZTRA 3, the mean POEM scores were significantly lower among patients treated with tralokinumab Q2W plus TCS, compared with those receiving placebo plus TCS, as early as week 2 (Figure 15). The differences between groups were statistically significant throughout the initial treatment period [55].

In the continuation period, mean POEM scores were stable among patients with a week 16 response to tralokinumab plus TCS, and improved among those without a week 16 response to tralokinumab Q2W plus TCS or placebo plus TCS (Table 26) [55].

Table 26 Mean POEM scores during ECZTRA 3 continuation period

POEM score, mean (SD) [N]	Week 16 tralokinumab responders		Week 16 tralokinumab non-responders	Week 16 placebo non-responders
	Q2W to Q2W	Q2W to Q4W	Q2W to Q2W	Placebo to Q2W
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive data, based on observed cases; no statistical analysis was performed. All treatment was in combination with TCS.
POEM, Patient-Oriented Eczema Measure; Q2W, once every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: ECZTRA 3 CSR [55].

B.2.6.3.5.4 DLQI

Tralokinumab plus TCS was associated with improvements in mean DLQI

In ECZTRA 3, improvements in DLQI were statistically significantly greater with tralokinumab plus TCS than with placebo plus TCS from week 2 onward, with a 2.9-point ($p < 0.001$) difference at week 16 (Figure 15, Table 16) [30]. In the continuation period, mean DLQI was stable among patients with a week 16 response to tralokinumab plus TCS, and improved among those without a week 16 response to tralokinumab Q2W plus TCS or placebo plus TCS (Table 26) [55].

Table 27 Mean DLQI during ECZTRA 3 continuation period

DLQI, mean (SD) [N]	Week 16 tralokinumab responders		Week 16 tralokinumab non-responders	Week 16 placebo non-responders
	Q2W to Q2W	Q2W to Q4W	Q2W to Q2W	Placebo to Q2W
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive data, based on observed cases; no statistical analysis was performed. All treatment was in combination with TCS.
DLQI, Dermatology Life Quality Index; Q2W, once every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: ECZTRA 3 CSR [55].

Patients treated with tralokinumab plus TCS were significantly more likely to have clinically meaningful improvements in DLQI, compared with those receiving placebo plus TCS

A 4-point improvement in DLQI is defined as a clinically meaningful change [75]. In ECZTRA 3, 83.5% of patients treated with tralokinumab Q2W plus TCS, and 65.9% of those receiving placebo plus TCS, had a decrease of ≥ 4 points in DLQI at week 16 (difference, 17.6% [95% CI, 8.0–27.1%]; $p < 0.001$) (Table 16) [30]. DLQI reductions of ≥ 4 points were also assessed in the continuation period: among patients who had EASI 75 or IGA 0/1 at week 16 and were re-randomised to tralokinumab Q2W plus TCS (n = 69), [redacted] and [redacted] had a DLQI reduction of ≥ 4 points from baseline at week 16 and week 32, respectively [56].

B.2.6.3.5.5 HADS

Patients treated with tralokinumab plus TCS were significantly more likely than those receiving placebo plus TCS to have improvements in clinically significant HADS scores

Approximately [redacted] of patients in ECZTRA 3 had baseline HADS anxiety and/or depression scores of ≥ 8 – the threshold for possible anxiety or depressive disorders (Table 28) [55, 56, 81]. At week 16, [redacted] and [redacted] of relevant patients in the tralokinumab Q2W plus TCS and placebo plus TCS groups, respectively, had both HADS scores < 8 [55].

Table 28 HADS anxiety and depression scores < 8 at week 16 in ECZTRA 3 (composite estimand)

Outcome	Tralokinumab Q2W plus TCS	Placebo plus TCS
Patients with HADS anxiety and/or depression score ≥ 8 at baseline, N	[redacted]	[redacted]
Both HADS anxiety and depression scores < 8 at week 16, n (%)	[redacted]	[redacted]
Difference (95% CI) and *p* value vs placebo plus TCS	[redacted]	

Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; Q2W, once every 2 weeks; TCS, topical corticosteroids. Source: ECZTRA 3 CSR [55].

B.2.6.3.5.6 EQ-5D-3L

Tralokinumab plus TCS was associated with significant improvements in EQ-5D-3L utility scores, compared with placebo plus TCS

At baseline, mean EQ-5D-3L index scores were [redacted] and [redacted] in the ECZTRA 3 tralokinumab Q2W plus TCS and placebo plus TCS groups, respectively (Table 29) [55]. Mean EQ-5D-3L index scores increased from baseline to week 16, with significantly higher increases in the tralokinumab Q2W plus TCS group than in the placebo plus TCS group [55]. Improvements in EQ-5D-3L index scores during the initial treatment period were maintained to week 32 in patients with an EASI 75 or IGA 0/1 response at week 16 who received tralokinumab Q2W or Q4W plus TCS in the continuation period (Table 29) [55].

Table 29 Change from baseline in mean EQ-5D-3L index scores in ECZTRA 3 (hypothetical estimand)

EQ-5D-3L index	Tralokinumab Q2W plus TCS			Placebo plus TCS
Initial treatment period				
Baseline, mean (SD) [N]	[redacted]			[redacted]
Change from baseline to week 16, mean (95% CI) [N]	[redacted]			[redacted]
Mean difference (95% CI) and *p* value vs placebo plus TCS	[redacted]			
Continuation treatment period (observed values)				
Week 16 response	**Responders**		**Non-responders**	
	Q2W plus TCS	**Q4W plus TCS**	**Q2W plus TCS**	
Week 16, mean (SD) [N]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32, mean (SD) [N]	[redacted]	[redacted]	[redacted]	[redacted]

Data after rescue medication or discontinuation of IMP were excluded. N values indicate the number of included responses at baseline and week 16.
EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; IMP, investigational medicinal product; Q2W, once every 2 weeks; TCS, topical corticosteroids. Source: ECZTRA 3 CSR [55].

B.2.6.4 ECZTRA 1 and ECZTRA 2

B.2.6.4.1 Statistical significance of primary and key secondary endpoints

In ECZTRA 1 and ECZTRA 2, all primary and all week 16 secondary endpoints showed statistically significantly greater efficacy with tralokinumab Q2W than with placebo [52]. In ECZTRA 2, IGA 0/1 and EASI 75 endpoints at week 52 were statistically significant versus placebo for the tralokinumab Q2W arm, but not for the tralokinumab Q4W arm [52]. There were no significant differences between tralokinumab and placebo in the ECZTRA 1 52-week secondary endpoints [30].

Table 30 Statistical significance of comparisons between tralokinumab and placebo in ECZTRA 1 and ECZTRA 2 (composite/hypothetical estimand)

	p value (nominal *p* value)	
Endpoint	**ECZTRA 1**	**ECZTRA 2**
Primary endpoints		
IGA 0/1 at week 16	**0.002**	**< 0.001**
EASI 75 at week 16	**< 0.001**	**< 0.001**
Secondary endpoints		
Reduction in weekly average of worst daily pruritus NRS from baseline to week 16	**0.002**	**< 0.001**
Change in SCORAD score from baseline to week 16	**< 0.001**	**< 0.001**
Change in DLQI from baseline to week 16	**0.002**	**< 0.001**
IGA 0/1 at week 52 between tralokinumab Q2W and placebo	0.68	**0.004**
EASI 75 at week 52 between tralokinumab Q2W and placebo	NT (0.056)	**< 0.001**
IGA 0/1 at week 52 between tralokinumab Q4W and placebo	NT (0.50)	0.084
EASI 75 at week 52 between tralokinumab Q4W and placebo	NT (0.27)	NT (0.001)

Nominal *p* values are shown for comparisons not formally tested due to being lower in the statistical testing hierarchy than a non-significant comparison.
DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NT, not formally tested; SCORAD, Scoring Atopic Dermatitis.
Source: Wollenberg *et al.* 2020 [52].

B.2.6.4.2 Clinical results during initial treatment period

B.2.6.4.2.1 IGA response

Twice as many patients achieved IGA 0/1 with tralokinumab than with placebo

In ECZTRA 1, 15.8% of patients in the tralokinumab Q2W group achieved IGA 0/1 at week 16, compared with 7.1% in the placebo group (difference, 8.6% [95% CI, 4.1–13.1%]; $p = 0.002$; Table 15) [52]. In ECZTRA 2, a week 16 IGA 0/1 response was achieved by 22.2% of patients treated with tralokinumab Q2W and 10.9% of those receiving placebo (difference, 11.1% [95% CI, 5.8–16.4%]; $p < 0.001$) [52].

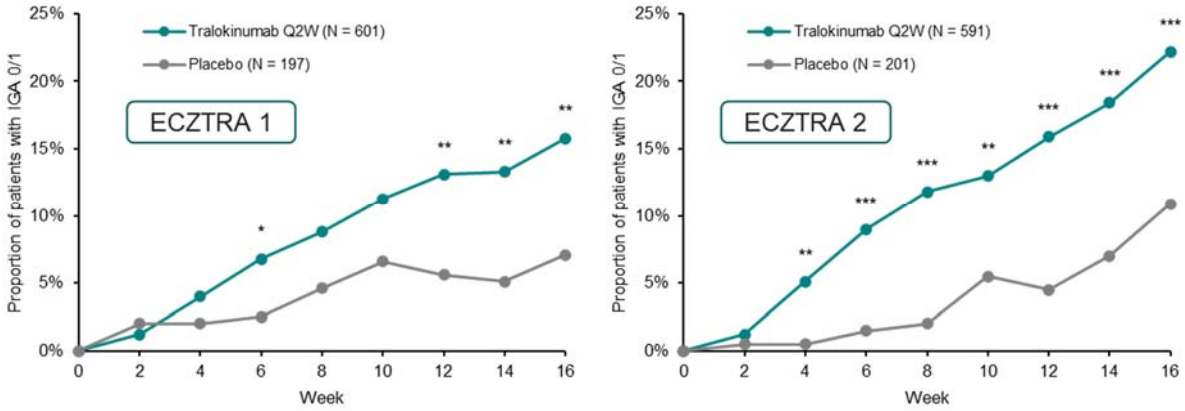
In the pooled ECZTRA 1 and ECZTRA 2 population, the difference between tralokinumab Q2W and placebo groups was [redacted]; Table 15) [51].

The proportion of patients treated with tralokinumab who achieved IGA 0/1 increased steadily during the initial treatment period

In ECZTRA 1 and ECZTRA 2, the proportion of patients with an IGA 0/1 response was significantly higher in the tralokinumab Q2W group than in the placebo group from week 4 in

ECZTRA 2 and week 12 in ECZTRA 1. In ECZTRA 2, [redacted] of patients receiving tralokinumab Q2W achieved an IGA 0/1 response at week 4, compared with [redacted] in the placebo group ($p < 0.01$) [52, 54]. At week 12 in ECZTRA 1, an IGA response was seen for [redacted] and [redacted] of patients in the tralokinumab Q2W and placebo groups, respectively ($p < 0.01$) [52, 53].

Figure 16 IGA 0/1 responses in ECZTRA 1 and ECZTRA 2 (composite estimand)



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs placebo. IGA, Investigator Global Assessment; Q2W, every 2 weeks. Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Source: Wollenberg *et al.* 2020 [52].

B.2.6.4.2.2 EASI responses

Significantly more patients achieved EASI 75 with tralokinumab than with placebo

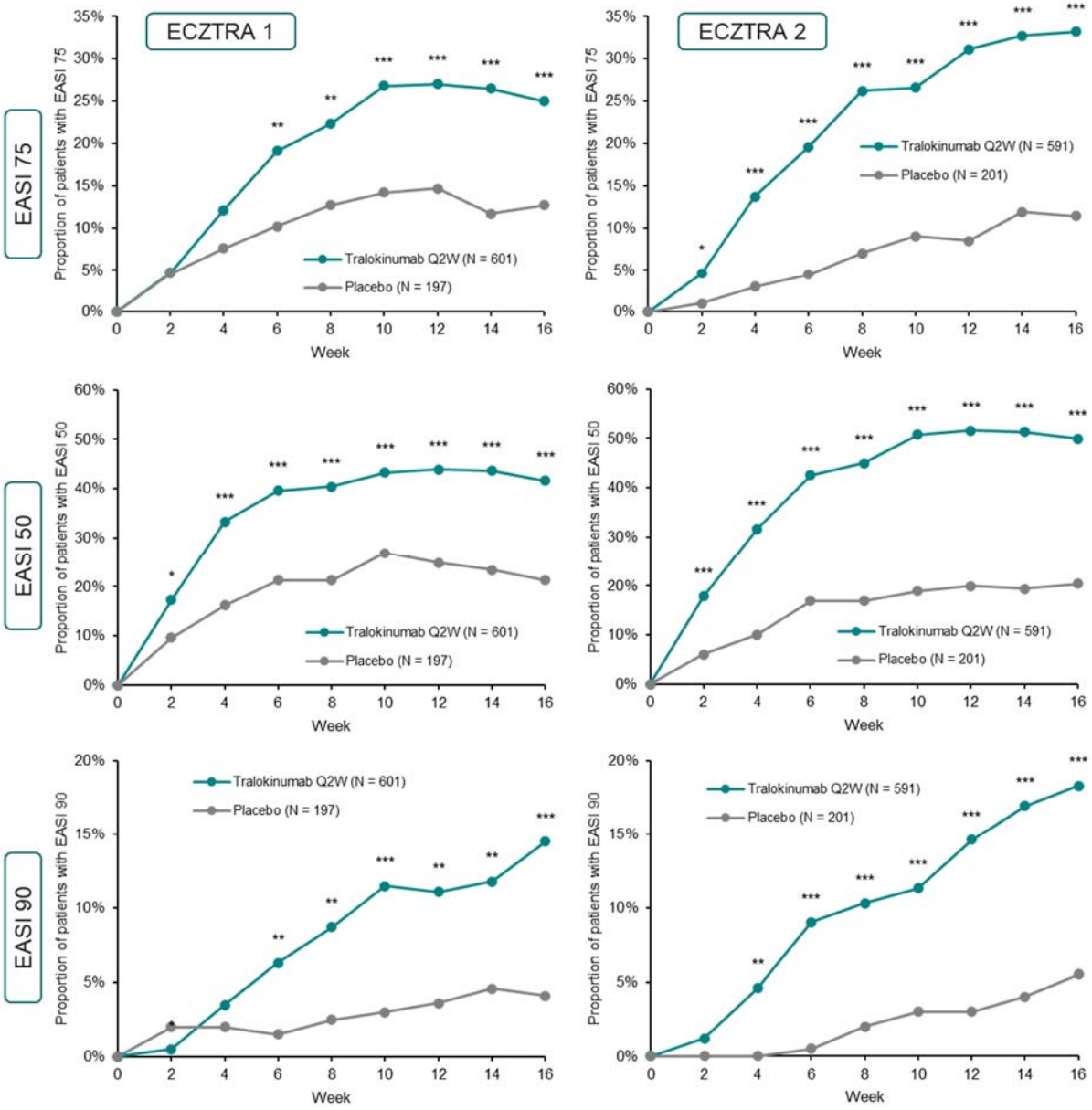
In ECZTRA 1, 25.0% of patients in the tralokinumab Q2W group achieved EASI 75 at week 16, compared with 12.7% in the placebo group (difference, 12.1% [95% CI, 6.5–17.7%]; $p < 0.001$; Table 15) [52]. In ECZTRA 2, a week 16 EASI 75 response was achieved by 33.2% of patients treated with tralokinumab Q2W and 11.4% of those receiving placebo (difference, 21.6% [95% CI, 15.8–27.3%]; $p < 0.001$) [52].

In the pooled ECZTRA 1 and ECZTRA 2 population, the difference between tralokinumab Q2W and placebo groups was [redacted]; Table 15) [51].

The proportion of patients with EASI 75 was significantly higher with tralokinumab than with placebo by week 2 or week 6

In ECZTRA 1 and ECZTRA 2, the proportion of patients with an EASI 75 response was statistically significantly higher in the tralokinumab Q2W group than in the placebo group from week 2 (ECZTRA 2) and week 6 (ECZTRA 1) (Figure 17) [52]. In ECZTRA 2, [redacted] of patients receiving tralokinumab Q2W achieved EASI 75 at week 2, compared with [redacted] in the placebo group ($p < 0.05$) [52, 54]. At week 6 in ECZTRA 1, EASI 75 was seen for [redacted] and [redacted] of patients in the tralokinumab Q2W and placebo groups, respectively ($p < 0.01$) [52, 53].

Figure 17 EASI responses in ECZTRA 1 and ECZTRA 2 (composite estimand)



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs placebo. EASI, Eczema Area and Severity Index; Q2W, every 2 weeks. Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Source: Wollenberg *et al.* 2020 [52].

Significantly more patients achieved EASI 50 with tralokinumab than with placebo

In ECZTRA 1, 41.6% of patients in the tralokinumab Q2W group achieved EASI 50 at week 16, compared with 21.3% in the placebo group (difference, 20.1% [95% CI, 13.3–26.8%]; $p < 0.001$; Table 15) [52]. In ECZTRA 2, a week 16 EASI 50 response was achieved by 49.9% of patients treated with tralokinumab Q2W and 20.4% of those receiving placebo (difference, 29.3% [95% CI, 22.5–36.1%]; $p < 0.001$) [52].

In the pooled ECZTRA 1 and ECZTRA 2 population, the difference between tralokinumab Q2W and placebo groups was [redacted]; Table 15) [51].

The proportion of patients with EASI 50 was significantly higher with tralokinumab than with placebo by week 2

In ECZTRA 1 and ECZTRA 2, the proportion of patients with an EASI 50 response was statistically significantly higher in the tralokinumab Q2W group than in the placebo group from week 2 (Figure 17) [52]. EASI 50 was achieved at week 2 by [redacted] and [redacted] of patients receiving tralokinumab Q2W in ECZTRA 1 and ECZTRA 2, respectively, compared with [redacted] and 9.6% in the corresponding placebo groups ($p < 0.001$ and $p < 0.01$, respectively) [52-54].

Three times as many patients achieved EASI 90 with tralokinumab monotherapy than with placebo

In ECZTRA 1, 14.5% of patients in the tralokinumab Q2W group achieved EASI 90 at week 16, compared with 4.1% in the placebo group (difference, 10.3% [95% CI, 6.4–14.1%]; $p < 0.001$; Table 15) [52]. In ECZTRA 2, a week 16 EASI 90 response was achieved by 18.3% of patients treated with tralokinumab Q2W and 5.5% of those receiving placebo (difference, 12.7% [95% CI, 8.4–17.0%]; $p < 0.001$) [52].

In the pooled ECZTRA 1 and ECZTRA 2 population, the difference between tralokinumab Q2W and placebo groups was [redacted]; Table 15) [51].

The proportion of patients with EASI 90 was significantly higher with tralokinumab than with placebo by week 4 or week 6

In ECZTRA 1 and ECZTRA 2, the proportion of patients with an EASI 90 response was statistically significantly higher in the tralokinumab Q2W group than in the placebo group from week 4 (ECZTRA 2) and week 6 (ECZTRA 1) (Figure 17) [52]. In ECZTRA 2, [redacted] of patients receiving tralokinumab Q2W achieved EASI 90 at week 4, compared with [redacted] in the placebo group ($p < 0.01$) [52, 54]. At week 6 in ECZTRA 1, EASI 90 was seen for [redacted] and [redacted] of patients in the tralokinumab Q2W and placebo groups, respectively ($p < 0.01$) [52, 53].

B.2.6.4.2.3 SCORAD

At week 16, patients treated with tralokinumab had significantly greater reductions in SCORAD score, compared with those receiving placebo

In ECZTRA 1 and ECZTRA 2, the adjusted mean (SD) change in SCORAD scores were −25.2 (0.94) and −28.1 (0.92), respectively, in the two tralokinumab groups, compared with −14.7 (1.80) and −14.0 (1.79) in the corresponding placebo groups (both $p < 0.001$; Table 16) [52].

B.2.6.4.2.4 Combined endpoint – EASI 50 plus DLQI improvement

At week 16, EASI 50 plus a DLQI improvement of ≥ 4 points was significantly more common among patients treated with tralokinumab, compared with placebo

In ECZTRA 1, [redacted] of patients in the tralokinumab Q2W group achieved the combined endpoint of EASI 50 & ΔDLQI ≥ 4 at week 16, compared with [redacted] in the placebo group (difference, [redacted]; Table 15) [51]. In ECZTRA 2, an EASI 50 & ΔDLQI ≥ 4 response was achieved at week 16 by [redacted] of patients treated with

tralokinumab Q2W and [redacted] of those receiving placebo (difference, [redacted]; Table 15) [51].

B.2.6.4.3 Rescue medication

B.2.6.4.3.1 Use of rescue medication during initial treatment period

Fewer patients treated with tralokinumab used rescue mediation, compared with those receiving placebo

In the initial treatment period from baseline to week 16, fewer patients in ECZTRA 1 and ECZTRA 2 who were treated with tralokinumab Q2W used rescue medication, compared with those receiving placebo (Table 22) [52]. Most rescue medication use in ECZTRA 1 and ECZTRA 2 was TCS, and use of systemic rescue treatment was more common in the placebo groups than in the tralokinumab Q2W groups [52]. Comparing tralokinumab Q2W groups, rescue medication use was more common in ECZTRA 1 than in ECZTRA 2 [53, 54].

Table 31 Rescue medication in initial treatment period, ECZTRA 1 and ECZTRA 2

Type of rescue medication, n (%)	ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W (N = 603)	Placebo (N = 199)	Tralokinumab Q2W (N = 593)	Placebo (N = 201)
Any rescue medication	216 (35.8)	92 (46.2)	135 (22.8)	89 (44.3)
Topical				
Corticosteroids	203 (33.7)	90 (45.2)	115 (19.4)	74 (36.8)
Other	29 (4.8)	13 (6.5)	24 (4.0)	11 (5.5)
Systemic				
Corticosteroids	18 (3.0)	13 (6.5)	9 (1.5)	18 (9.0)
Immunosuppressants	6 (1.0)	3 (1.5)	6 (1.0)	15 (7.5)
Other	2 (0.3)	1 (0.5)	0	0

Q2W, once every 2 weeks; TCS, topical corticosteroids.
Source: Wollenberg *et al.* 2020 [52].

B.2.6.4.4 Clinical results during maintenance/continuation period

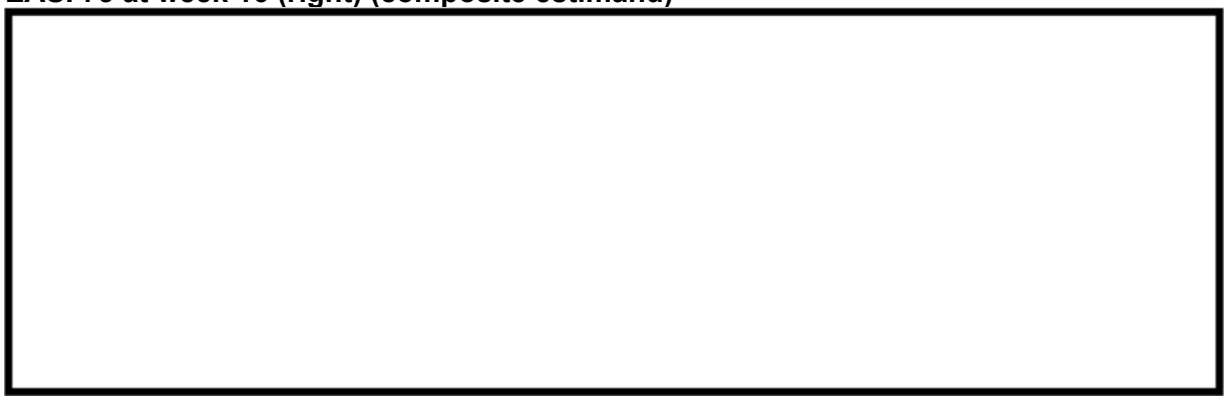
B.2.6.4.4.1 Responses among patients with a response to initial treatment

Significantly more patients receiving maintenance therapy with tralokinumab Q2W retained their week 16 IGA 0/1 response at week 52, compared with placebo

Among patients who had IGA 0/1 at week 16, 51.3% and 59.3% of those receiving tralokinumab Q2W maintenance therapy in ECZTRA 1 and ECZTRA 2, respectively, had IGA 0/1 at week 52 (Table 17) [52], without use of rescue medication. In the pooled patient population, significantly more patients retained their week 16 IGA 0/1 response with tralokinumab Q2W than with placebo ([redacted]; Table 17; Figure 18) [56].

Week 52 IGA 0/1 response rates among patients re-randomised to tralokinumab Q4W maintenance therapy were 38.9% and 44.9% in ECZTRA 1 and ECZTRA 2, respectively (pooled population, [redacted]) [52, 56].

Figure 18 Pooled ECZTRA 1 and ECZTRA 2 week 52 IGA 0/1 responses among patients with IGA 0/1 at week 16 (left), and EASI 75 responses among patients with EASI 75 at week 16 (right) (composite estimand)



* $p < 0.05$ vs placebo; ** $p < 0.01$ vs placebo; *** $p < 0.001$ vs placebo. EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: monotherapy pool statistical appendix [56]. Data in this figure are commercial-in-confidence.

Significantly more patients receiving maintenance therapy with tralokinumab retained their week 16 EASI 75 response at week 52, compared with placebo

Among patients who had EASI 75 at week 16, 59.6% and 55.8% of those receiving tralokinumab Q2W maintenance therapy in ECZTRA 1 and ECZTRA 2, respectively, had EASI 75 at week 52, without any use of rescue medication, compared with 33.3% and 21.4% in the respective placebo groups (Table 17) [52]. In the pooled patient population, significantly more patients retained their week 16 EASI 75 response with tralokinumab Q2W than with placebo ([redacted] Table 17; Figure 18) [56]. EASI 75 response rates at week 52 for patients treated with tralokinumab Q4W maintenance therapy were 49.1% and 51.4% in ECZTRA 1 and ECZTRA 2, respectively, and [redacted] in the pooled patient population (pooled difference versus placebo, [redacted]) [52, 56].

B.2.6.4.4.2 Responses to continuation treatment among patients without initial responses

Among patients without EASI 75 or IGA 0/1 at week 16, 31.9% achieved EASI 75 after a further 8 weeks of tralokinumab

Patients without EASI 75 or IGA 0/1 at week 16 were transferred to continuation treatment with tralokinumab Q2W, plus optional TCS, for 36 weeks (see section B.2.3.1.1) [52].

In total, 686 patients (ECZTRA 1, n = 360; ECZTRA 2, n = 326) who did not have EASI 75 or IGA 0/1 at week 16 received continuation treatment with tralokinumab Q2W. Of these, half (49.3%) used additional anti-inflammatory treatment, mainly TCS, which was allowed by the study protocol [78]. In total, 31.9% of patients had an EASI 75 response at week 24, and 42.9% had an EASI 75 response at week 52 (Table 32). EASI 75 responses were achieved without use of TCS by 25.7% of patients. Among patients with an EASI 50 response (but not EASI 75 or IGA 0/1) at week 16, the majority (53.2%) achieved EASI 75 at week 52 [78].

Table 32 Clinical responses during continuation treatment among tralokinumab-treated patients without EASI 75 or IGA 0/1, or with EASI 50–74, at week 16 in pooled ECZTRA 1 and ECZTRA 2 population (multiple estimands)

Outcome	Patients without EASI 75 or IGA 0/1 at week 16	Patients with EASI 50–74 at week 16
Week 16 N	686	269
Treatment policy sensitivity analysis estimand		
Week 24 EASI 75, n (%)	219 (31.9)	[redacted]
Week 52 EASI 75, n (%)	294 (42.9)	143 (53.2)
Composite estimand		
Week 52 EASI 75 without optional TCS, n (%)	176 (25.7)	[redacted]

No statistical analysis was performed.
Treatment policy sensitivity analysis estimand: treatment difference regardless of permanent discontinuation of IMP or initiation of rescue medication (including TCS); missing data imputed as non-responders. Composite estimand: patients who received rescue medication (including TCS) considered non-responders; patients with missing data imputed as non-responders.
Sources: Simpson *et al.* 2020a [78]; monotherapy pool statistical appendix [56].

B.2.6.4.4.3 Use of rescue medication during maintenance/continuation period

During the maintenance period in ECZTRA 1 and ECZTRA 2, rescue medication use was lower among patients receiving tralokinumab than among those in the placebo group (Table 33) [53, 54].

Table 33 Rescue medication use in maintenance period in ECZTRA 1 and ECZTRA 2

Type of rescue medication, n (%)	ECZTRA 1			ECZTRA 2		
	Tralokinumab Q2W (N = 71)	Tralokinumab Q4W (N = 78)	Placebo (N = 36)	Tralokinumab Q2W (N = 91)	Tralokinumab Q4W (N = 90)	Placebo (N = 46)
Any rescue medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topical						
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Systemic						
Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Q2W, once every 2 weeks; Q4W, every 4 weeks.
Sources: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

B.2.6.4.5 Patient-reported outcomes and health-related quality of life

B.2.6.4.5.1 Pruritus

Patients treated with tralokinumab were significantly more likely than those receiving placebo to have a clinically meaningful improvement in pruritus

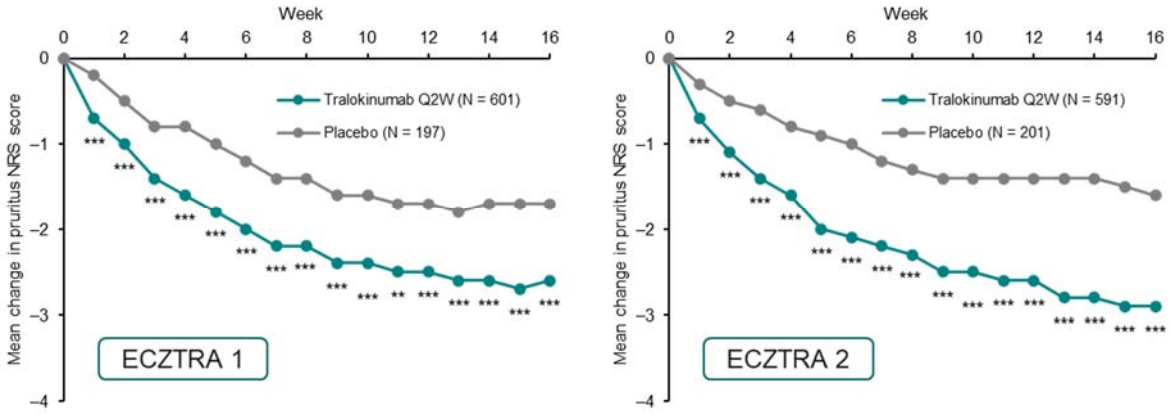
In ECZTRA 1, 20.0% of patients in the tralokinumab Q2W group had a decrease of ≥ 4 points in worst daily pruritus NRS score, calculated as a weekly mean, at week 16, compared with 10.3% in the placebo group (difference, 9.7% [95% CI, 4.4–15.0%]; $p < 0.001$; Table 16) [52]. In ECZTRA 2 a ≥ 4-point improvement at week 16 was reported by 25.0% of patients treated with tralokinumab Q2W and 9.5% of those receiving placebo (difference, 15.6% [95% CI, 10.3–20.9%]; $p < 0.001$; Table 16) [52].

Improvements in pruritus significantly favoured tralokinumab over placebo from week 1

In ECZTRA 1 and ECZTRA 2, the reduction from baseline in the weekly mean of worst daily pruritus NRS scores was significantly higher in the tralokinumab Q2W groups than in the placebo groups from week 1, and increased throughout the initial treatment period (Figure 19) [52].

Patients who had IGA 0/1 or EASI 75 responses at week 16 had improvements in mean daily pruritus NRS scores during ongoing treatment with tralokinumab Q2W or Q4W which were numerically greater than those in the placebo maintenance groups (Table 34) [53, 54].

Figure 19 Mean change in weekly mean of worst daily pruritus NRS scores from baseline to week 16 in ECZTRA 1 and ECZTRA 2 (hypothetical estimand)



** $p < 0{\cdot}01$; *** $p < 0{\cdot}001$ vs placebo. Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed. IMP, investigational medicinal product; NRS, numeric rating scale; Q2W, every 2 weeks.
Sources: Wollenberg *et al.* 2020 [52].

Table 34 Mean worst daily pruritus NRS during maintenance period among patients with IGA 0/1 or EASI 75 at week 16 in ECZTRA 1 and ECZTRA 2

Weekly mean of worst daily pruritus NRS, mean (SD) [N]	ECZTRA 1			ECZTRA 2		
	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16	[redacted]					
Week 52	[redacted]					

Descriptive data, based on observed cases; no statistical analysis was performed.
NRS, numerical rating scale; Q2W, once every 2 weeks; Q4W, every 4 weeks.
Source: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

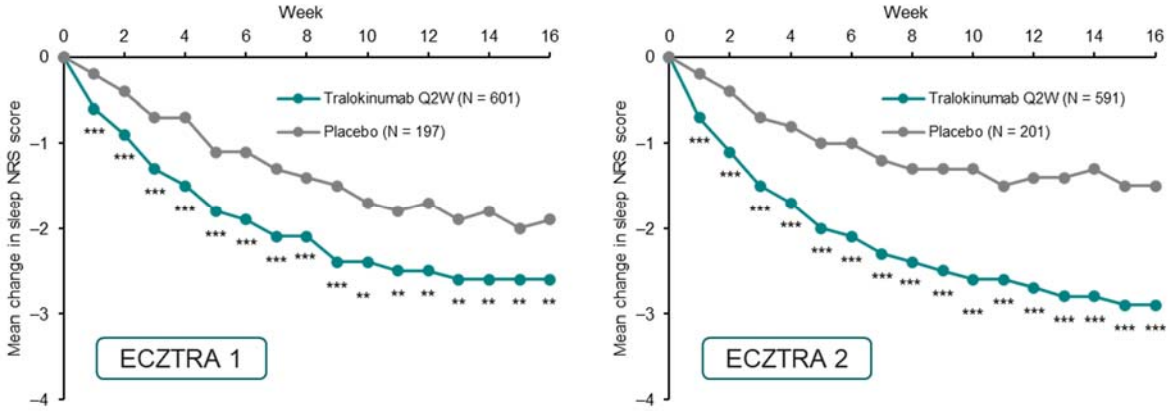
B.2.6.4.5.2 Sleep disruption

Tralokinumab was associated with early improvements in eczema-related sleep disruption

Mean eczema-related sleep NRS scores declined within the first week of treatment. The difference between the tralokinumab Q2W and placebo groups was statistically significant at week 1, and was maintained throughout the initial treatment period (Figure 20) [52].

Patients who had IGA 0/1 or EASI 75 responses at week 16 had improvements in eczema-related sleep NRS scores during ongoing treatment with tralokinumab Q2W which were numerically greater than those seen in the placebo maintenance groups; smaller mean improvements were seen with tralokinumab Q4W (Table 35) [53-55].

Figure 20 Mean change in weekly mean of eczema-related sleep NRS scores from baseline to week 16 in ECZTRA 1 and ECZTRA 2 (hypothetical estimand)



** $p < 0.01$; *** $p < 0.001$ vs placebo. Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed. IMP, investigational medicinal product; NRS, numeric rating scale; Q2W, every 2 weeks
Sources: Wollenberg *et al.* 2020 [52].

Table 35 Mean eczema-related sleep NRS during maintenance period among patients with IGA 0/1 or EASI 75 at week 16 in ECZTRA 1 and ECZTRA 2

Weekly mean of eczema-related sleep NRS, mean (SD) [N]	ECZTRA 1			ECZTRA 2		
	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16	[redacted]					
Week 52	[redacted]					

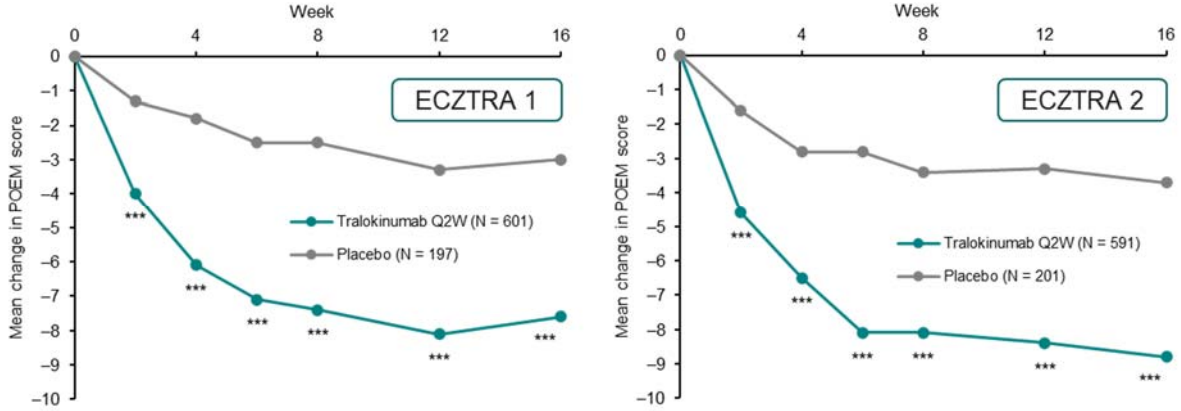
Descriptive data, based on observed cases; no statistical analysis was performed.
NRS, numerical rating scale; Q2W, once every 2 weeks; Q4W, every 4 weeks.
Source: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

B.2.6.4.5.3 POEM

Tralokinumab was associated with early improvements in mean POEM scores

Mean POEM scores were significantly lower among patients treated with tralokinumab Q2W, compared with those receiving placebo, as early as week 2 (Figure 21). The differences between groups were statistically significant throughout the initial treatment period [53, 54].

Figure 21 Mean change in POEM scores from baseline to week 16 in ECZTRA 1 and ECZTRA 2 (hypothetical estimand)



*** $p < 0.001$ vs placebo. Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed.
IMP, investigational medicinal product; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks.
Sources: Silverberg *et al.* 2020b [80].

Table 36 Mean POEM scores during maintenance period among patients with IGA 0/1 or EASI 75 at week 16 in ECZTRA 1 and ECZTRA 2

POEM score, mean (SD) [N]	ECZTRA 1			ECZTRA 2		
	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16	[redacted]					
Week 52	[redacted]					

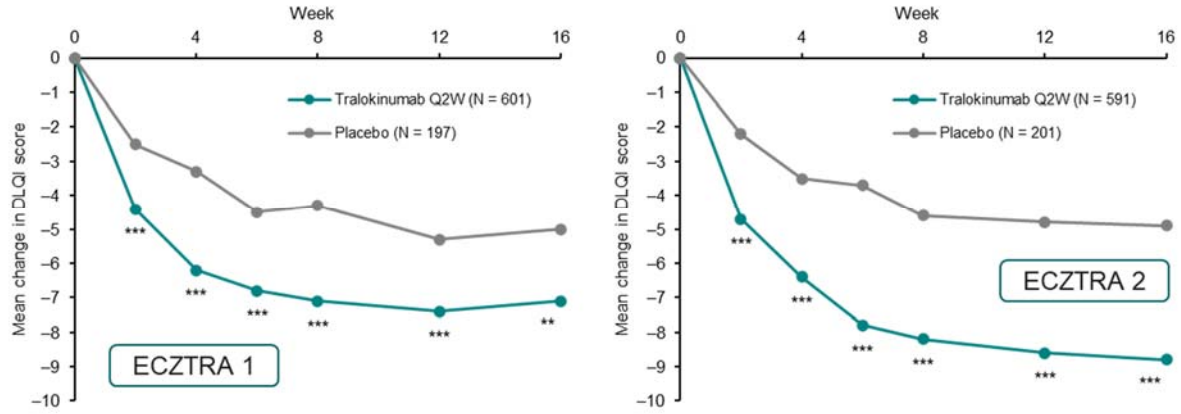
Descriptive data, based on observed cases; no statistical analysis was performed.
POEM, Patient-Oriented Eczema Measure; Q2W, once every 2 weeks; Q4W, every 4 weeks.
Source: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

B.2.6.4.5.4 DLQI

Tralokinumab was associated with improvements in mean DLQI

In ECZTRA 1 and ECZTRA 2, patients treated with tralokinumab Q2W had significant improvements in mean DLQI, compared with placebo, as early as week 2 (Figure 22) [52]. The differences between groups were statistically significant throughout the initial treatment period, with 2.1-point ($p = 0.002$) and 3.9-point ($p < 0.001$) differences between tralokinumab Q2W and placebo in ECZTRA 1 and ECZTRA 2, respectively, at week 16 (Table 16) [52]. In ECZTRA 1 and ECZTRA 2, DLQI improved during maintenance therapy in all treatment arms (Table 37) [53, 54].

Figure 22 Mean change in DLQI from baseline to week 16 in ECZTRA 1 and ECZTRA 2 (hypothetical estimand)



** $p < 0.01$; *** $p < 0.001$ vs placebo. Hypothetical estimand: data collected after permanent discontinuation of IMP or initiation of rescue medication not included; missing data imputed.
DLQI, Dermatology Life Quality Index; IMP, investigational medicinal product; Q2W, every 2 weeks.
Sources: Wollenberg *et al.* 2020 [52].

Table 37 Mean DLQI during maintenance period among patients with IGA 0/1 or EASI 75 at week 16 in ECZTRA 1 and ECZTRA 2

DLQI, mean (SD) [N]	ECZTRA 1			ECZTRA 2		
	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16	[redacted]					
Week 52	[redacted]					

Descriptive data, based on observed cases; no statistical analysis was performed.
DLQI, Dermatology Life Quality Index; Q2W, once every 2 weeks; Q4W, every 4 weeks.
Source: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

Patients treated with tralokinumab were significantly more likely to have clinically meaningful improvements in DLQI, compared with those receiving placebo

In ECZTRA 1, 44.6% of patients in the tralokinumab Q2W group had a clinically meaningful decrease of ≥ 4 points in DLQI at week 16, compared with 31.6% in the placebo group (difference, 13.0% [95% CI, 5.4–20.5%]; p = 0.001; Table 16) [52]. In ECZTRA 2 a ≥ 4-point improvement at week 16 was reported by 56.3% of patients treated with tralokinumab Q2W and 27.3% of those receiving placebo (difference, 28.9% [95% CI, 21.4–36.3%]; p < 0.001; Table 16) [52].

In the pooled ECZTRA 1 and ECZTRA 2 population, the difference between tralokinumab Q2W and placebo groups was [redacted]; Table 16) [56].

B.2.6.4.5.5 HADS

Patients treated with tralokinumab significantly more likely than those receiving placebo to have improvements in clinically significant HADS scores

Approximately [redacted] of patients in ECZTRA 1 and ECZTRA 2 had baseline HADS anxiety and/or depression scores of ≥ 8 – the threshold for possible anxiety or depressive disorders (Table 28) [55, 56, 81]. In the pooled ECZTRA 1 and ECZTRA 2 population with either baseline HADS score ≥ 8, [redacted] of patients treated with tralokinumab Q2W had both scores < 8 at week 16, compared with [redacted] in the placebo group (difference, [redacted]) [56].

Table 38 HADS anxiety and depression scores < 8 at week 16 in ECZTRA 1 and ECZTRA 2 (composite estimand)

Outcome	Tralokinumab Q2W	Placebo
Patients with HADS anxiety and/or depression score ≥ 8 at baseline, N	[redacted]	[redacted]
Both HADS anxiety and depression scores < 8 at week 16, n (%)	[redacted]	[redacted]
Difference (95% CI) and p value vs placebo	[redacted]	

Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; Q2W, once every 2 weeks; TCS, topical corticosteroids.
Source: monotherapy pool statistical appendix [56].

B.2.6.4.5.6 EQ-5D-3L

Tralokinumab was associated with significant improvements in EQ-5D-3L utility scores, compared with placebo

At baseline, mean EQ-5D-3L index scores ranged from [redacted] across randomised groups in ECZTRA 1 and ECZTRA 2 (Table 29) [53-55]. Mean EQ-5D-3L index scores increased from baseline to week 16, with significantly higher increases in the tralokinumab Q2W groups than in the placebo groups (Table 29). EQ-5D-3L scores were stable or improved during maintenance therapy in all treatment arms [53, 54].

Table 39 Change from baseline to week 16 in mean EQ-5D-3L index scores in ECZTRA 1 and ECZTRA 2 (hypothetical estimand)

EQ-5D-3L index, mean change from baseline	ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W	Placebo	Tralokinumab Q2W	Placebo
Baseline, mean (SD) [N]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to week 16, mean (95% CI) [N] Mean difference (95% CI) and *p* value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]

Data after rescue medication or discontinuation of IMP were excluded. N values indicate the number of included responses at baseline and week 16.
EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; IMP, investigational medicinal product; Q2W, once every 2 weeks; TCS, topical corticosteroids.
Sources: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

Table 40 Mean EQ-5D-3L index scores during maintenance/continuation period among patients with IGA 0/1 or EASI 75 at week 16 in ECZTRA 1 and ECZTRA 2

EQ-5D-3L index score, mean (SD) [N]	ECZTRA 1			ECZTRA 2		
	Q2W to Q2W	Q2W to Q4W	Q2W to placebo	Q2W to Q2W	Q2W to Q4W	Q2W to placebo
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Descriptive data, based on observed cases; no statistical analysis was performed.
DLQI, Dermatology Life Quality Index; Q2W, once every 2 weeks; TCS, topical corticosteroids.
Source: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

B.2.6.5 Summary of additional trial data

B.2.6.5.1 Phase 2b study

Key 12-week results for tralokinumab 300 mg Q2W combination therapy in the phase 2b study were consistent with the findings of the phase 3 trials (Table 41) [33]. Additional information on the phase 2b trial is given in Appendix D.3.

Table 41 Summary of key endpoint results at week 12 in the phase 2b study

Outcome	Tralokinumab 300 mg Q2W + TCS (N = 52)	Placebo + TCS (N = 51)
IGA 0/1, % Difference (95% CI) and *p* value vs placebo plus TCS	26.7% 14.5% (0.0–29.7) $p = 0.06$	11.8%
EASI 75, % *p* value vs placebo plus TCS	42.5% $p = 0.003$	15.5%
EASI 50, % *p* value vs placebo plus TCS	73.4% $p = 0.03$	51.9%

Data for other tralokinumab doses are not shown.
EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids.
Source: Wollenberg *et al.* 2019 [33].

B.2.6.5.2 ECZTRA 5

The primary endpoint of the ECZTRA 5 trial was the proportion of patients with moderate-to-severe AD who had an antibody response to meningococcal vaccine. Week 16 efficacy data showed that the proportion of patients with IGA 0/1 and EASI 75 responses was higher in the tralokinumab 300 mg Q2W group than in the placebo group (Table 42). Additional information on the ECZTRA 5 trial is given in Appendix D.3.

Table 42 Summary of key efficacy results at week 16 in ECZTRA 5

Outcome	Tralokinumab 300 mg Q2W (N = 107)	Placebo (N = 108)
IGA 0/1, % Difference (95% CI) and *p* value vs placebo	31.1% 11.4% (0.2–22.6%) *p* = 0.049	19.4%
EASI 75, % *p* value vs placebo	49.1% 12.7% (−0.2, 25.7%) *p* = 0.057	36.1%

EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks.
Source: Merola *et al.* 2020 [63].

B.2.6.5.3 ECZTEND – interim analysis

As of the data cut-off date of 30 April 2020, 1174 patients had been enrolled in ECZTEND, originating from ECZTRA 1 (38.3%), ECZTRA 2 (25.0%), ECZTRA 3 (24.0%) and ECZTRA 5 (12.7%), of whom [redacted] ([redacted]) were still in the study [64]. An interim efficacy analysis was conducted including the 513 patients treated for at least 60 weeks (Table 43) [64]. At week 56 in ECZTEND, 95.1% of patients had an EASI 50 response, relative to the start of their parent trial, and 82.8% had an EASI 75 response. Similar results were seen in a subset of patients who had received at least 2 years of treatment with tralokinumab, starting in ECZTRA 1 or ECZTRA 2 (Table 43) [64]. Additional information on the ECZTEND trial is given in Appendix D.3.

Table 43 Summary of key efficacy results at week 56 in ECZTEND

Endpoint	Full cohort (observed cases; N = [redacted]) [a]	Patients treated for ≥ 2 years (observed cases; N = [redacted]) [b]
EASI 50 relative to baseline in the parent trial, n (%)	[redacted]	[redacted]
EASI 75 relative to baseline in the parent trial, n (%)	[redacted]	[redacted]
EASI 90 relative to baseline in the parent trial, n (%)	[redacted]	[redacted]
IGA 0/1, n (%)	[redacted]	[redacted]

[a] All patients enrolled in ECZTEND trial ≥ 60 weeks prior to data cut-off date; including both recently tralokinumab- and placebo-treated.
[b] Patients from ECZTRA 1 and 2 trials enrolled in ECZTEND trial ≥ 60 weeks prior to data cut-off date and receiving treatment with tralokinumab for ≥ 2 years.
EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment.
Source: ECZTEND data tables, 22 March 2021 [64].

B.2.7 Subgroup analysis

B.2.7.1 Subgroup analyses conducted

Subgroup data relevant to the decision problem come from *post hoc* analyses of ECZTRA 1, ECZTRA 2 and ECZTRA 3 patients who do not have adequate control with, or have intolerance or contraindications to, CSA ('ECZTRA 7-like' subgroup) [59].

The full definition for the ECZTRA 7-like subgroup was patients who:

- had not received CSA because the risk of important side effects was too high, or there were contraindications to CSA use; or
- had received CSA but stopped because of inadequate efficacy (after at least 12 weeks of treatment) or side effects.

For use in the NMA and economic model, ECZTRA 7-like subgroup data from ECZTRA 3 were combined with data for the overall population from ECZTRA 7. Similarly, ECZTRA 7-like subgroup data from ECZTRA 1 and ECZTRA 2 were pooled together. Results for the resultant ECZTRA 7-like combination therapy and monotherapy populations are shown in Table 44 [61, 62].

B.2.7.2 Subgroup analysis results

Tralokinumab as monotherapy or combination therapy with TCS was associated with a greater likelihood of improvement in AD, compared with placebo, in patients who do not have adequate control with, or have intolerance or contraindications to, CSA

In both composite and treatment policy sensitivity analysis estimand analyses for the ECZTRA 7-like combination therapy and monotherapy subgroups (Table 44) [61, 62], results for key efficacy endpoints at week 16 were generally consistent with the overall populations (Table 14 and Table 15) [30, 49, 51, 52].

The differences between tralokinumab Q2W plus TCS and placebo plus TCS in the ECZTRA 7-like combination therapy subgroup were generally similar to those in the overall ECZTRA 7 population [49, 51, 61].

In the ECZTRA 7-like monotherapy subgroup, the proportions of patients with IGA 0/1, EASI 75, EASI 50 and the combined endpoint of EASI 50 & ΔDLQI ≥ 4 were similar to the overall monotherapy population analysis [56, 62]. The difference between tralokinumab Q2W and placebo was slightly higher than in the overall monotherapy population [56, 62].

Results for the individual trial populations for the ECZTRA 7-like subgroup and for a similar analysis of patients who do not have adequate control with, or have intolerance or contraindications to, any systemic therapy are summarised in Appendix E, Table 143 and Table 144, respectively [59, 60].

Table 44 Key outcomes at week 16 in ECZTRA 7-like combination therapy and monotherapy subgroups (multiple estimands)

Outcome	Combination therapy (ECZTRA 7 overall population plus ECZTRA 3 ECZTRA 7-like subgroup)		Monotherapy (ECZTRA 1 plus ECZTRA 2 ECZTRA 7-like subgroups)	
	Tralokinumab Q2W plus TCS (N = 257)	Placebo (N = 199)	Tralokinumab Q2W (N = 417)	Placebo (N = 120)
Composite estimand				
IGA 0/1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator				
EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator				
EASI 50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator				
EASI 50 and DLQI improvement ≥ 4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	[redacted]		[redacted]	
Treatment policy sensitivity analysis estimand				
IGA 0/1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator				
EASI 75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator				
EASI 50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and p value vs comparator				
EASI 50 and DLQI improvement ≥ 4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI) and *p* value vs comparator	[redacted]		[redacted]	

Composite estimand: patients who received rescue medication considered non-responders; patients with missing data imputed as non-responders.
Treatment policy sensitivity analysis estimand: treatment difference regardless of permanent discontinuation of IMP or initiation of rescue medication; missing data imputed as non-responders.
CI, confidence interval; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA; IGA, Investigator Global Assessment; IMP, investigational medicinal product; Q2W, every 2 weeks; TCS, topical corticosteroids.
Sources: payer submission statistical appendices, combination therapy, ECZTRA 7-like [61] and monotherapy, ECZTRA 7-like [62].

B.2.8 Meta-analysis

No pairwise meta-analysis was conducted. Head-to-head evidence is not available comparing tralokinumab with all of the comparators in the assessment scope; therefore, an NMA was conducted to estimate the relative efficacy of all relevant therapies (see section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

Full details of the methodology for the NMA and the SLR that was used to identify studies for inclusion in the evidence network are reported in Appendix D.1.5.

B.2.9.1 Evidence network for network meta-analysis

Head-to-head RCTs between all comparators specified in the NICE scope have not been conducted; therefore, an NMA was undertaken to estimate the relative efficacy between these treatments. Use of an NMA in preference to pairwise meta-analysis allowed for the inclusion of all available and relevant evidence, although there was considerable heterogeneity and uncertainty in the analysis, and the results should be interpreted in the context of limitations described in section B.2.9.3. The results from the NMA feed into the economic model described in section B.3, providing evidence for the cost-effectiveness of tralokinumab against relevant comparators.

Efficacy outcomes included in the NMA and used in the cost-effectiveness model described in section B.3 were EASI 50, EASI 75 and the combined endpoint of EASI 50 & ΔDLQI ≥ 4. IGA 0/1 responses were also assessed in the NMA for completeness. Analyses were conducted separately for monotherapy and combination therapy with TCS, and for induction therapy and maintenance treatment. Where data were available, networks were constructed for patients who do not have adequate control with, or have intolerance or contraindications to, CSA (the ECZTRA 7-like subgroup); these are the main source of treatment response data for the cost-effectiveness model. Results for the overall trial populations provide supplementary evidence for the relative efficacy of the comparators. The incidence of injection-site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes was also synthesised – the results of these analyses are described in section B.2.10.9.

The study selection process is described in detail in Appendix D.1.5; studies included in the efficacy NMAs are summarised in Table 45. For the induction therapy analyses, evidence across efficacy and safety outcomes was available from nearly all studies of dupilumab, baricitinib and tralokinumab. Non-responder imputation (NRI) following receipt of rescue therapy was the primary method of analysis across the majority of studies, though many also reported outcomes ‘as observed’ regardless of rescue therapy. In the ECZTRA 7-like subgroup, data from dupilumab, baricitinib and tralokinumab studies were available to inform analyses. For the maintenance phase analyses, evidence was available for tralokinumab and dupilumab as monotherapy and combination therapy. No evidence for maintenance efficacy was available from studies of baricitinib.

Inclusion criteria, baseline characteristics, background treatments and reported efficacy and safety results for the included trials are detailed in Appendix D.1.4 and discussed in section B.2.9.3.1.

Table 45 Summary of trials included in efficacy and safety NMAs

Study	Treatment							All randomised patients								ECZTRA 7-like patients			
	Placebo	Tralokinumab		Dupilumab		Baricitinib		EASI 50	EASI 75	IGA 0/1	EASI 50 + DLQI ≥ 4	Injection-site reactions	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	EASI 50	EASI 75	IGA 0/1	EASI 50 + DLQI≥ 4
		Q2W	Q4W	Q2W	QW	2 mg	4 mg												
Induction therapy – monotherapy trials (week 12–16)																			
ECZTRA 1 [52]	X	X						NRI; AO	NRI; AO	NRI; AO	NRI; AO	X	X	X	X	NRI; AO	NRI; AO	NRI; AO	NRI; AO
ECZTRA 2 [52]	X	X						NRI; AO	NRI; AO	NRI; AO	NRI; AO	X	X	X	X	NRI; AO	NRI; AO	NRI; AO	NRI; AO
Thaci 2016 [82]	X			X	X			NRI	NRI	NRI		X							
SOLO 1 [83]	X			X	X			NRI; AO	NRI; AO	NRI; AO		X	X	X	X	NRI; AO	NRI; AO		NRI: AO
SOLO 2 [83]	X			X	X			NRI; AO	NRI; AO	NRI; AO		X	X	X	X				
Beck 2014 [84]	X				X			NRI	NRI	NRI									
BREEZE-AD 1 [85]	X					X	X	NRI	NRI; AO	NRI; AO									
BREEZE-AD 2 [85]	X					X	X	NRI	NRI; AO	NRI; AO									
BREEZE-AD 5 [86]	X					X	X	NRI	NRI	NRI									
Induction therapy – combination therapy trials (week 12–16)																			
ECZTRA 3 [30]	X	X						NRI; AO	NRI; AO	NRI; AO	NRI; AO	X	X	X	X	NRI; AO	NRI; AO	NRI; AO	NRI; AO
Wollenberg 2019 [33]	X	X						NRI	NRI	NRI									
ECZTRA 7 [a] [47]	X	X						NRI; AO	NRI; AO	NRI; AO	NRI; AO	X	X	X	X	NRI; AO	NRI: AO	NRI; AO	NRI; AO
CHRONOS [87]	X			X	X			NRI; AO	NRI; AO	NRI; AO		X	X	X	X	NRI: AO	NRI: AO		NRI: AO
CAFÉ [a] [88]	X			X	X			NRI; AO	NRI; AO	NRI; AO		X	X	X	X			NRI; AO	
JADE COMPARE [89]	X			X				NRI	NRI	NRI									

Study	Treatment							All randomised patients								ECZTRA 7-like patients			
	Placebo	Tralokinumab		Dupilumab		Baricitinib		EASI 50	EASI 75	IGA 0/1	EASI 50 + DLQI ≥ 4	Injection-site reactions	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	EASI 50	EASI 75	IGA 0/1	EASI 50 + DLQI≥ 4
		Q2W	Q4W	Q2W	QW	2 mg	4 mg												
BREEZE-AD 4 [90]	X					X	X	NRI	NRI	NRI						NRI	NRI	NRI	
BREEZE-AD 7 [91]	X					X	X	NRI	NRI; AO	NRI; AO									
Guttman-Yassky 2019a [92]	X					X	X	NRI	NRI	NRI									
Induction therapy – combination therapy trials (week 24–26)																			
ECZTRA 7 [a] [47]	X	X							NRI	NRI							NRI	NRI	
CHRONOS [87]	X			X	X				NRI	NRI									
BREEZE-AD 4 [90]	X					X	X		NRI	NRI							NRI	NRI	
Maintenance therapy – monotherapy trials (week 52)																			
ECZTRA 1 [52]	X	X	X						NRI	NRI									
ECZTRA 2 [52]	X	X	X						NRI	NRI									
SOLO-CONTINUE [93]	X			X	X				NRI	NRI									
Maintenance therapy – combination therapy trials (weeks 24–52)																			
ECZTRA 3 (week 32) [30]	X	X	X						NRI		NRI								
ECZTRA 7 [a] (week 26) [47]	X	X						NRI	NRI		NRI								
CHRONOS (week 52) [87]	X			X				AO	AO		AO								

[a] All patients were ECZTRA 7-like: patients who have inadequate control with, or intolerance or contraindications to, CSA.

AO, as observed (all observed outcomes regardless of rescue therapy); CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA; IGA 0/1, Investigator global assessment; NRI, non-responder imputation (following rescue therapy); TCS, topical corticosteroids; QW, every week; Q2W, every 2 weeks.

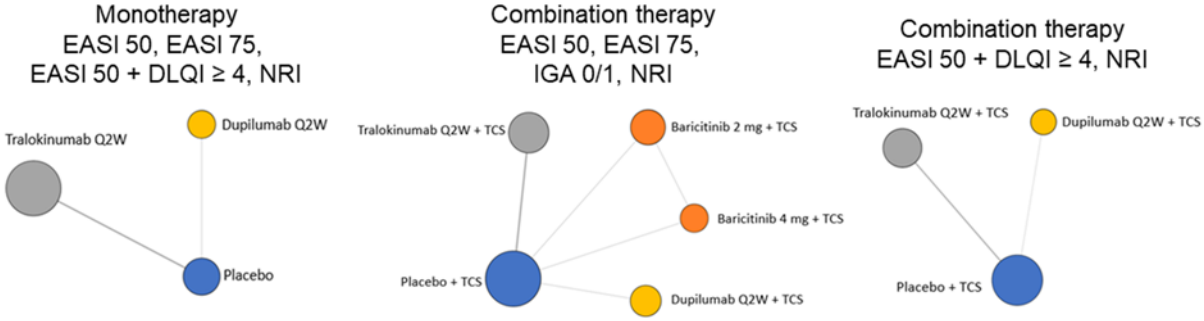
B.2.9.2 Base-case network meta-analyses

B.2.9.2.1 Induction therapy

B.2.9.2.1.1 Networks

For the ECZTRA 7-like subgroup analyses, networks including baricitinib could be constructed only for EASI 50, EASI 75 and IGA 0/1 responses to combination therapy; the monotherapy networks and the assessment of EASI 50 & ΔDLQI ≥ 4 responses to combination therapy included only tralokinumab and dupilumab (Figure 23).

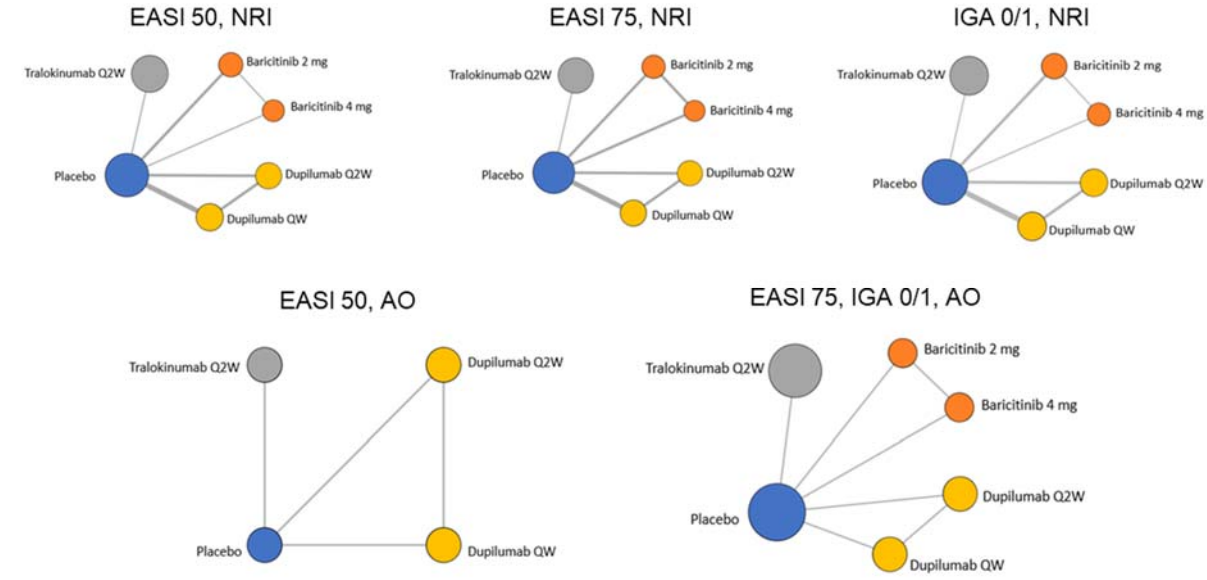
Figure 23 Induction evidence networks, ECZTRA 7-like



DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IR, inadequate control with, or intolerance or contraindications to; NRI, non-responder imputation; Q2W, every 2 weeks; TCS, topical corticosteroids.

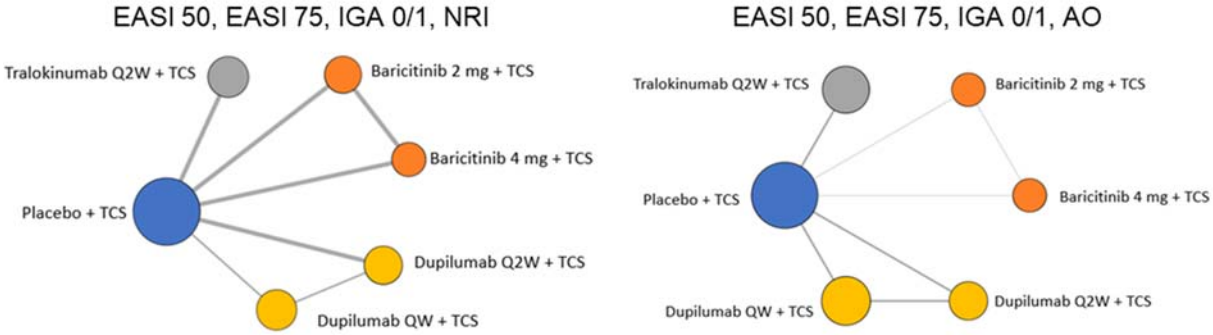
For the overall population induction phase analyses, it was possible to construct networks of evidence for tralokinumab, dupilumab and baricitinib for EASI 50, EASI 75 and IGA 0/1 responses (monotherapy, Figure 24; combination therapy, Figure 25); insufficient data were available for assessment of the EASI 50 & ΔDLQI ≥ 4 combined endpoint.

Figure 24 Induction evidence networks, overall populations, monotherapy



AO, as observed; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRI, non-responder imputation; QW, every week; Q2W, every 2 weeks.

Figure 25 Induction evidence networks, overall populations, combination therapy



AO, as observed; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRI, non-responder imputation; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroids.

Three of the included trials reported responses to induction therapy at week 24 or week 26 [47, 87, 90]. Accordingly, week 24/26 networks could be created for EASI 75 and IGA 0/1 responses for tralokinumab, dupilumab and baricitinib – in the corresponding ECZTRA 7-like analysis, evidence was available only for tralokinumab and baricitinib (Figure 26).

Figure 26 Induction evidence networks, week 24/26

EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IR, inadequate control with, or intolerance or contraindications to; NRI, non-responder imputation; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroids.

B.2.9.2.1.2 ECZTRA 7-like subgroups – monotherapy

The random-effects models were preferred for EASI 50 and EASI 75 responses; for EASI 50 & ΔDLQI ≥ 4, the fixed-effects model was preferred (Appendix D.1.5.3, Table 124).

Results indicate that as monotherapy both tralokinumab and dupilumab Q2W are [redacted] placebo at inducing EASI 50, EASI 50 & ΔDLQI ≥ 4, and EASI 75, regardless of how outcomes are handled after receipt of rescue therapy (Table 46). Across outcomes, risk ratios for tralokinumab and dupilumab versus placebo are [redacted] when patients receiving rescue therapy are [redacted]

B.2.9.2.1.3 ECZTRA 7-like subgroups – combination therapy

There were several potential sources of heterogeneity in the combination therapy analysis (see Appendix D.1.4). Accordingly, the random-effects model was considered more plausible (model fit is shown in Appendix D.1.5.3, Table 125), although not all heterogeneity could be addressed (see section B.2.9.3).

Results indicate that in combination with TCS tralokinumab, dupilumab Q2W and baricitinib are [redacted] placebo at inducing EASI 50, EASI 50 & ΔDLQI ≥ 4 (no evidence was available for baricitinib for this endpoint), EASI 75 and IGA 0/1, regardless of how outcomes are handled after receipt of rescue therapy, [redacted] (Table 46; IGA 0/1 results are shown in Appendix D.1.5.5, Table 134). Dupilumab plus TCS was [redacted] placebo plus TCS across all outcomes regardless of the handling of data following rescue therapy. Tralokinumab plus TCS [redacted] than placebo plus TCS for the outcomes of EASI 50 & ΔDLQI ≥ 4 and IGA 0/1. For EASI 50, tralokinumab was [redacted] than placebo where [redacted]. Only for the outcome of IGA 0/1 and only at a dose of 4 mg was baricitinib plus TCS [redacted] than placebo plus TCS. [redacted]

B.2.9.2.1.4 Overall populations – monotherapy

The fixed- and random-effects model were comparable in terms of results and goodness of fit; the fixed-effects model was preferred due to a lower deviance information criterion (DIC; Appendix D.1.5.3, Table 126).

Results indicate that as monotherapy tralokinumab, dupilumab (QW and Q2W) and baricitinib are [redacted] placebo at inducing EASI 50, EASI 75 and IGA 0/1, regardless of how outcomes are handled after receipt of rescue therapy (Table 47; IGA 0/1 results are shown in Appendix D.1.5.5, Table 134). Across all outcomes, risk ratios for tralokinumab, dupilumab, and baricitinib versus placebo are [redacted] when patients receiving rescue therapy are [redacted]. As receipt of rescue was more common in the placebo arms of the trials than the intervention arms, the analyses which included responses after rescue [redacted]

B.2.9.2.1.5 Overall populations – combination therapy

There were several potential sources of heterogeneity in the combination therapy analysis (see Appendix D.1.4). Accordingly, the random-effects model was considered more plausible (model fit is shown in Appendix D.1.5.3, Table 127).

Results indicate that in combination with TCS tralokinumab, dupilumab (QW and Q2W) and baricitinib are [redacted] placebo at inducing EASI 50, EASI 75 and IGA 0/1, regardless of how outcomes are handled after receipt of rescue therapy (Table 47; IGA 0/1 results are shown in Appendix D.1.5.5, Table 134). Across outcomes, risk ratios for tralokinumab and dupilumab versus placebo are [redacted] when patients receiving rescue therapy are [redacted]

[redacted]

Table 46 Induction therapy NMA results, ECZTRA 7-like subgroups

Treatment	Probability, %		Risk ratio vs placebo (± TCS)		Risk ratio, tralokinumab vs comparator	
	NRI	AO	NRI	AO	NRI	AO
Monotherapy						
EASI 50 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 & ΔDLQI ≥ 4 – fixed-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination therapy						
EASI 50 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 & ΔDLQI ≥ 4 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).

AO, as observed; CrI, credible interval; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA; IGA, Investigator's Global Assessment; IR, inadequate control with, or intolerance or contraindications to; mg, milligram; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks.

Table 47 Induction therapy NMA results, overall populations

Treatment	Probability, %		Risk ratio vs placebo (± TCS)		Risk ratio, tralokinumab vs comparator	
	NRI	AO	NRI	AO	NRI	AO
Monotherapy						
EASI 50 – fixed-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 – fixed-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination therapy						
EASI 50 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 – random-effects model						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).
AO, as observed; CrI, credible interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; mg, milligram; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks.

B.2.9.2.1.6 ECZTRA 7-like subgroups – combination therapy at week 24/26

Due to limited data at week 24/26, the random-effects model could not be run; model fit for the fixed-effects model is shown in Appendix D.1.5.3, Table 128.

On the outcome of EASI 75 and IGA 0/1 among ECZTRA 7-like patients, tralokinumab in combination with TCS was [redacted] placebo plus TCS at week 24–26 (Table 48; IGA 0/1 results are shown in Appendix D.1.5.5, Table 135). [redacted]

B.2.9.2.1.7 Overall populations – combination therapy at week 24/26

Due to limited data at week 24/26, the random-effects model could not be run; model fit for the fixed-effects model is shown in Appendix D.1.5.3, Table 129.

Both tralokinumab and dupilumab in combination with TCS were [redacted] placebo and TCS at week 24–26 (Table 48; IGA 0/1 results are shown in Appendix D.1.5.5, Table 135). The proportion of responders to baricitinib at week 24–26 was [redacted] the proportion of responders to placebo. [redacted]

Table 48 Induction therapy NMA results (combination therapy, 24–26 weeks)

Treatment	Probability, %	Risk ratio vs placebo (± TCS)	Risk ratio, tralokinumab vs comparator
Combination therapy – ECZTRA 7-like subgroup			
EASI 75 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]
Combination therapy - overall population			
EASI 75 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]

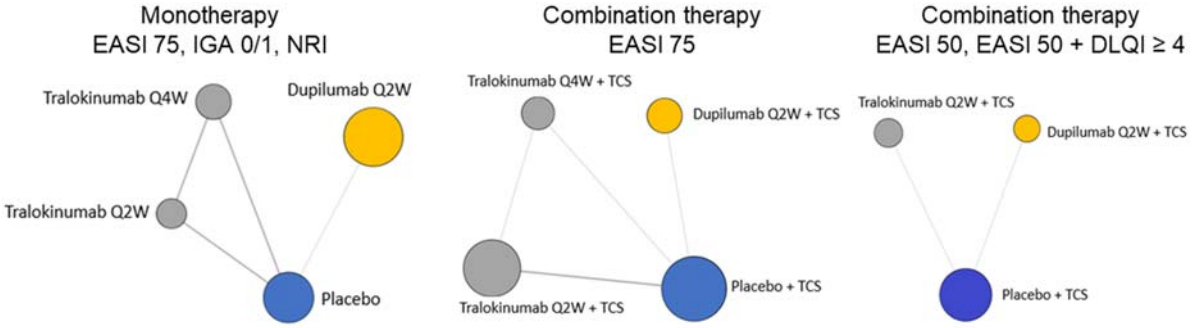
Data are median (95% CrI). The included trials used an NRI approach.
AO, as observed; CrI, credible interval; EASI, Eczema Area and Severity Index; IR, inadequate control with, or intolerance or contraindications to; mg, milligram; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks.

B.2.9.2.2 Maintenance therapy

B.2.9.2.2.1 Networks

The maintenance phase evidence networks included only trials of tralokinumab and dupilumab, with no evidence available for baricitinib. The included monotherapy trials used an NRI approach, while the combination therapy networks include a mixture of NRI and 'as observed' data.

Figure 27 Maintenance evidence networks



EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IR, inadequate control with, or intolerance or contraindications to; NRI, non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

B.2.9.2.2.2 Overall populations – monotherapy

The fixed- and random-effects model were comparable in terms of results and goodness of fit; the fixed-effects model was preferred due to a lower DIC; Appendix D.1.5.3, Table 130).

Results indicate that patients who achieve EASI 75 at week 16 are [redacted] tralokinumab (Q2W and Q4W) or dupilumab (QW/Q2W) [redacted] placebo (Table 49). Only [redacted] of placebo responders are expected to sustain EASI 75 responses, compared to [redacted] of patients receiving tralokinumab Q4W, [redacted] of patients receiving tralokinumab Q2W and [redacted] of patients receiving either a QW or Q2W dose of dupilumab. [redacted]

[redacted] both tralokinumab Q2W and dupilumab (QW/Q2W) were [redacted] placebo to be associated with sustained IGA 0/1 responses at week 52 (Appendix D.1.5.5, Table 136).

B.2.9.2.2.3 Overall populations - combination therapy

Fixed-effects models were preferred for all combination therapy outcomes due to lower DIC (EASI 75) or insufficient data to run the random-effects model (EASI 50 & ΔDLQI ≥ 4 and IGA 0/1; model fit statistics are shown in Appendix D.1.5.3, Table 131).

Results indicate that patients who achieve EASI 50 or EASI 50 & ΔDLQI ≥ 4 at week 16 [redacted] (Table 49). Around [redacted] of patients treated with placebo plus TCS are expected to maintain an EASI 50 response, rising to [redacted] and [redacted] of those treated with tralokinumab and dupilumab, respectively. [redacted] patients are expected to sustain EASI 50 & ΔDLQI ≥ 4 responses achieved at week 16: [redacted] with placebo, [redacted] with tralokinumab and [redacted] with dupilumab, all in combination with TCS. [redacted]

Patients who achieve EASI 75 at week 16 are [redacted] with tralokinumab Q2W plus TCS [redacted] placebo plus TCS. The likelihood of sustained EASI 75 is [redacted]

[redacted] Around [redacted] of tralokinumab-treated patients (Q2W and Q4W) are expected to maintain their EASI 75 response, compared with [redacted] of dupilumab-treated patients and [redacted] of placebo-treated patients. [redacted]

Table 49 Maintenance therapy NMA results, overall populations

Treatment	Probability, %	Risk ratio vs placebo (± TCS)	Risk ratio, tralokinumab vs comparator
Monotherapy (week 16 to 52)			
EASI 75 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Tralokinumab Q4W	[redacted]	[redacted]	[redacted]
Dupilumab QW/Q2W	[redacted]	[redacted]	[redacted]
Combination therapy (week 16 to 26, 32 or 52)			
EASI 50 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]
EASI 50 & ΔDLQI ≥ 4 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]
EASI 75 – fixed-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Tralokinumab Q4W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]

Data are median (95% CrI). The included trials used an NRI approach.
AO, as observed; CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IR, inadequate control with, or intolerance or contraindications to; mg, milligram; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

B.2.9.3.1 Sources of uncertainty

As described in Appendix D.1.4, there are a number of sources of potential heterogeneity in the induction NMA which should be considered whilst interpreting the results.

The eligibility criteria of studies included in the NMA appear similar; however, a few key differences are noted. The tralokinumab and baricitinib trials required a shorter duration of chronic AD at baseline, compared with the dupilumab trials (≥1 year vs ≥3 years), and the time since an inadequate response to TCS was longer in the tralokinumab trials than in the dupilumab and baricitinib trials (previous 12 months vs 6 months).

Although the baseline characteristics of the patients are broadly similar across the included trials, they differ in a few important ways. Higher proportions of participants in the tralokinumab trials reported exposure to treatments such as systemic corticosteroids than patients in the other trials, while tralokinumab trial participants had higher mean DLQI scores

at baseline; both of these differences are suggestive of more severe disease at baseline in the tralokinumab studies.

In terms of study design, the duration and procedure of a pre-randomisation washout period for prohibited therapies varied across the trials, particularly with regard to TCS and TCI. A 2-week washout was required prior to randomisation in ECZTRA 1, 2 and 3 and the BREEZE-AD trials; by contrast, the similarly designed phase 3 dupilumab trials (SOLO 1 and 2, CHRONOS and JADE COMPARE) only required a 1-week washout. These differences may have affected patients' baseline characteristics as well as the disease course and response to treatment post-randomisation. The 2-week washout period in the tralokinumab and baricitinib trials might have been long enough to exacerbate AD in some patients, leading to early use of rescue medication in the monotherapy trials. It may also have influenced a response to TCS in the combination therapy trials, as TCS was re-initiated after a longer break than in the dupilumab CHRONOS trial.

Among the studies recruiting only patients with an inadequate response, intolerance or contraindication to ciclosporin – ECZTRA 7, CAFÉ and BREEZE-AD 4, there was even more variation in the run-in to randomisation. BREEZE-AD 4 required a 2-week washout of TCS, whereas both CAFÉ and ECZTRA 7 allowed for the use of stable TCS in the weeks between screening and randomisation, but the procedure was different. In ECZTRA 7, the use of any type or potency of TCS was permitted, but not mandated. In CAFÉ, the run-in comprised a mandatory 2-week TCS standardisation period, during which all patients used medium-potency TCS (or low-potency TCS on areas of thin skin or where continued treatment with medium-potency TCS was considered unsafe). This procedure would select out those patients responding well to TCS as they would not have met the inclusion criteria of EASI ≥ 20 at baseline. By contrast, such patients would have been included in ECZTRA 7, thereby influencing the level of response in the placebo plus TCS group.

Several differences in the type of TCS used and instructions for TCS use, along with differences in the frequency of follow-up between tralokinumab, dupilumab and baricitinib trials, have been described in Appendix D.1.4.2.3 – these could have influenced response to treatment, particularly in the placebo arms. This seems to be confirmed by observed differences in placebo response in the included combination therapy trials, which would have been expected to be more similar if the trials were more closely aligned in terms of design, patients, concomitant therapies and methods of handling rescue medication.

Although these differences may have a minimal impact on the within-trial comparisons, it is possible they might affect between-trial comparisons. Options to account for these potential design differences in the NMA are limited due to the relatively sparse networks of evidence and the fact that many differences occur at the level of trial programme (e.g. ECZTRA, LIBERTY AD or BREEZE-AD) rather than individual RCT.

Variation in the placebo response rates across the included studies suggests that there may be some measured and unmeasured patient- and trial-level characteristics that could modify the observed treatment effect and introduce heterogeneity in a meta-analysis. Variation in placebo responses in the monotherapy studies (Appendix D.1.5.4.1, Figure 35) appears greatest for the outcomes of EASI 50 – ranging from less than 13% in the BREEZE-AD2 and BREEZE-AD5 [86, 94] to 20–25% in the phase 3 trials of tralokinumab and dupilumab [52, 83] and more than 30% in the phase 2 dupilumab studies [82, 84] – and IGA 0/1 (2% in Thaci

2016 [82] vs 11% in ECZTRA 2 [52]), but is less prominent for EASI 75 and is reduced in the ECZTRA 7-like subgroup, compared with the overall population (Appendix D.1.5.4.1, Figure 36).

The variation is particularly pronounced among the studies comparing tralokinumab, dupilumab and baricitinib in combination with TCS, appearing consistently across all definitions of response (Appendix D.1.5. 4.1, Figure 37) and in the subgroup of patients who have inadequate control with, or intolerance or contraindications to, CSA (ciclosporin-IR; equivalent to the tralokinumab ECZTRA 7-like subgroups; Appendix D.1.5.4.1, Figure 38). For all randomised patients, the difference between the study with the highest and lowest placebo response rates is 49% for EASI 50, 32% for EASI 75 and 18% for IGA 0/1. Similar ranges were seen in the ciclosporin-IR subgroup; in addition, responses according to the key reimbursement outcome of EASI 50 & ΔDLQI ≥ 4 ranged from 59% in ECZTRA 7 to just 21% in the pooled CAFÉ and CHRONOS-CAFÉ-like subgroup.

This variation in placebo arm response rates has the potential to be a source of significant bias in cross-trial comparisons of biological therapy outcomes [95-97]

B.2.9.3.2 Sensitivity analysis conducted (induction NMA)

To address the difference in placebo arm response rates, an additional analysis was undertaken to assess the comparative efficacy using a model that includes an adjustment for reference arm response rates. This adjustment has the potential to account for heterogeneity across trials in the network and improve the degree to which the NMA model fits the available data [98-101]. This baseline-risk-adjusted analysis was performed only for the outcomes for which there were sufficient data: EASI 50, EASI 75 and IGA 0/1 among all patients using NRI following rescue therapy. In accordance with NMA guidelines [99], fit was informed by the statistical significance of the regression coefficient and whether there was a reduction in between-trial heterogeneity. The methodology for the baseline-risk-adjusted analysis is described in detail in Appendix D.1.5.4.2. Although the adjusted analysis addresses some of the heterogeneity in the NMA, significant uncertainty remains and the results should still be interpreted with caution.

B.2.9.3.3 Sensitivity analysis results (induction NMA)

[redacted] (Appendix D.1.5.5.2, Table 137).

[redacted]

[redacted]

Table 50 EASI 50 and EASI 75 treatment effects (combination therapy, all patients, NRI, 12–16 weeks) – with and without baseline risk adjustment

Treatment	Risk ratio vs placebo plus TCS		Risk ratio, tralokinumab vs comparator	
	Unadjusted	Baseline risk-adjusted	Unadjusted	Baseline risk-adjusted
EASI 50 – random-effects model				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75 – random-effects model				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).
CrI, credible interval; EASI, Eczema Area and Severity Index; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks.

Table 51 Probabilities of EASI 50, EASI 75 and IGA 0/1 (combination therapy, all patients, NRI, 12–16 weeks) – with and without baseline risk adjustment

Treatment	Probability, %		
	Unadjusted	Baseline risk-adjusted	Average observed in trials
EASI 50 – random-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]
EASI 75 – random-effects model			
Placebo	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]
Dupilumab QW	[redacted]	[redacted]	[redacted]
Baricitinib 2 mg QD	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg QD	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).

CrI, credible interval; EASI, Eczema Area and Severity Index; NRI, non-responder imputation; QD, once daily; QW, once weekly; Q2W, every 2 weeks.

B.2.9.4 Overview of NMA results

[redacted]

There are a number of sources of potential heterogeneity in the induction NMA which should be considered whilst interpreting the results. Although the baseline characteristics of the patients are broadly similar across the included trials, important differences concerning study design have been highlighted above. These relate to the eligibility criteria of the trials, the requirement for and duration of TCS washout and the type of TCS used, as well as to the discretion given to clinical investigators and the timing and frequency of follow-up, all of which varied significantly across trials and could affect TCS use and adherence. The impact of observed and unobserved differences is apparent, as variation in placebo response rates across the included studies was found to constitute an important source of heterogeneity and uncertainty (see also section B.2.13.2). [redacted]

[redacted]

The results of the maintenance treatment analyses should be interpreted with caution. For monotherapy, the analysis relies on the assumption that weekly and fortnightly dosing of dupilumab have similar efficacy. If the unlicensed weekly dose of dupilumab is more efficacious than the licensed Q2W dosing, the treatment effect for dupilumab may be overestimated. For combination therapy, there are at least three potential sources of heterogeneity. First, the maintenance periods of the included tralokinumab trials (ECZTRA 3 and ECZTRA 7) were shorter than those of the dupilumab trial CHRONOS; the direction of potential bias caused by this is uncertain. Based on the visual inspection of trends over time, this may benefit dupilumab over tralokinumab. Second, the evidence from CHRONOS includes data observed after rescue therapy. This may slightly underestimate the relative

efficacy of dupilumab because placebo arm responses would include outcomes achieved with rescue instead of imputing them as non-responses. Third, the tralokinumab evidence for the EASI 50 & ΔDLQI ≥ 4 endpoint comes only from ECZTRA 7, a study of patients who had inadequate control with, or intolerance or contraindications to CSA; as such, this may represent a conservative scenario for tralokinumab. The analyses are also limited by the lack of relevant data for baricitinib, and by the re-randomised responder design of four of the included trials (ECZTRA 1, ECZTRA 2, ECZTRA 3 and SOLO-CONTINUE), which means that comparisons of EASI 50 and EASI 50 & ΔDLQI ≥ 4 responses were based only on ECZTRA 7 and CHRONOS.

Finally, with so few trials, there was no way to formally explore or account for potential design differences in the maintenance NMA, but many of the same sources of heterogeneity that apply to the induction phase analysis should be considered when interpreting the results of tralokinumab and dupilumab as maintenance therapy.

B.2.10 Adverse reactions

B.2.10.1 Summary of safety data for tralokinumab in atopic dermatitis

Safety data in this submission comprise a pooled analysis of tralokinumab trials in AD (ECZTRA 1, ECZTRA 2, ECZTRA 3, ECZTRA 5 [NCT03562377; a vaccine response trial] and the phase 2b trial [58, 102]), and detailed safety data from the individual phase 3 trials [30, 47, 52-55].

Of the included trials, the largest are ECZTRA 1 and ECZTRA 2, in which tralokinumab monotherapy was compared with placebo [52-54]. In all of the included trials, the safety analysis set (SAS) included all randomised patients who received one or more doses of investigational product [30, 47, 52-55].

Additional evidence comes from a network meta-analysis that compared adverse events (AEs) of interest in the tralokinumab clinical trial programme with those in the dupilumab trials SOLO 1, SOLO 2, CHRONOS and CAFÉ and the baricitinib trials BREEZE-AD, -2, -4, -5 and -7 (section B.2.10.9).

Supporting evidence for the safety profile of tralokinumab is provided by an interim analysis of the ECZTEND extension study [64] and a previous analysis of safety in the tralokinumab asthma trials (STRATOS 1, STRATOS 2 and CD-RI-CAT-354-1049; section B.2.10.7) [103].

B.2.10.2 Pooled safety analysis

B.2.10.2.1 Exposure

Overall, [redacted] patients were treated with tralokinumab 300 mg (± TCS) and [redacted] with placebo (± TCS), corresponding to 1404 and 273 patient-years of exposure (PYE), respectively [58, 102]. In total, [redacted] patients ([redacted]) were exposed to tralokinumab (± TCS) and [redacted] ([redacted]) to placebo (± TCS) for at least 16 weeks; [redacted] ([redacted]) were exposed to tralokinumab (± TCS) and [redacted] ([redacted]) to placebo (± TCS) for at least 52 weeks [58].

B.2.10.2.2 Summary of adverse events

AEs during the initial treatment period (weeks 0–16) are summarised in Table 52 [58, 102]. The overall incidence and rate of AEs were similar for tralokinumab Q2W (± TCS) and placebo (± TCS). Serious AEs (SAEs) were infrequent and reported at a slightly lower incidence and rate with tralokinumab than with placebo.

B.2.10.2.3 Common adverse events

Among the most frequent AEs in the initial treatment period, 'viral upper respiratory tract infection', 'upper respiratory tract infection', 'conjunctivitis', and 'injection-site reaction' were reported with a higher frequency for tralokinumab than placebo. 'Headache' occurred at a similar frequency in both treatment arms, whereas 'atopic dermatitis', 'skin infections' and 'pruritus' were reported less frequently with tralokinumab than placebo (Table 52) [58, 102].

B.2.10.2.4 Adverse events of special interest

Based on potential and established areas of safety interest for monoclonal antibodies in the treatment of AD, the following AEs of special interest were pre-defined in the ECZTRA 1, ECZTRA 2, ECZTRA 2 and ECZTRA 5 trials: eye disorders (conjunctivitis, keratoconjunctivitis, and keratitis); skin infections requiring systemic treatment; eczema herpeticum; and malignancies diagnosed after randomisation (excluding basal cell carcinoma, squamous cell carcinoma of the skin, and carcinoma *in situ* of the cervix) [58, 102].

The incidence and rate of eye disorder AEs of special interest were higher with tralokinumab than placebo in the initial treatment period (7.9% vs 3.4%; 31.1 vs 12.9 events per 100 PYE). Most of the events were mild or moderate in severity (98%), and none were serious. The incidence and rate of skin infections requiring systemic treatment were lower with tralokinumab than placebo in the initial treatment period (2.6% vs 5.5%; 9.7 vs 22.8 events per 100 PYE). Few of the events were serious ([redacted] in each treatment group). Few events of eczema herpeticum were reported as AEs of special interest in the initial treatment period (tralokinumab: 6 events; placebo: 10 events), with a lower incidence and rate for tralokinumab than for placebo (0.3% vs 1.5%; 1.2 vs 5.2 events per 100 PYE). None of the events were serious [58, 102].

The pooled safety analysis revealed no indication that treatment with tralokinumab is associated with a higher risk of malignancies.

Table 52 Safety results at week 16 (pooled safety data, ECZTRA 1–3, 5 and phase 2b study)

Key safety parameters, n (%) [a] [rate] [b]	Safety pool	
	Tralokinumab (± TCS) N = 1605, PYE = 473.19	Placebo (± TCS) N = 680, PYE = 193.1
Overall AEs		
Total	1080 (65.7) [639.5]	449 (67.2) [678.3]
Serious	37 (2.1) [7.4]	18 (2.8) [11.9]
Mild	881 (53.2) [429.8]	326 (49.0) [391.0]
Moderate	518 (31.5) [189.5]	258 (39.0) [254.3]
Severe	77 (4.6) [20.2]	40 (6.3) [33.0]
AEs related to study drug	[redacted]	[redacted]

AEs leading to permanent discontinuation of study drug	38 (2.3) [9.9]	20 (2.8) [13.3]
Most frequent AEs, ≥ 2% in any treatment groups		
Atopic dermatitis	[redacted] (15.4) [68.0]	[redacted] (26.2) [139.7]
Viral URTI	[redacted] (15.7) [65.1]	[redacted] (12.2) [53.5]
URTI	[redacted] (5.6) [20.8]	[redacted] (4.8) [18.5]
Conjunctivitis	[redacted] (5.4) [21.0]	[redacted] (1.9) [6.9]
Headache	[redacted] (4.6) [21.6]	[redacted] (3.9) [19.6]
Injection-site reaction	[redacted] (3.5) [22.9]	[redacted] (0.3) [4.0]
Pruritus	[redacted] (2.6) [10.6]	[redacted] (3.0) [13.1]
Skin infection	[redacted] (1.1) [4.0]	[redacted] (2.5) [9.0]
Injection-site pain	[redacted] (2.3) [13.4]	[redacted] (1.7) [11.8]

AE, adverse event; PYE, patient-years of exposure; TCS, topical corticosteroid; URTI, upper respiratory tract infection.
[a] Adjusted percentage calculated using Cochran–Mantel–Haenszel weights.
[b] Adjusted rate (number of events divided by PYE multiplied by 100) calculated using Cochran–Mantel–Haenszel weights.
Source: Simpson *et al.* 2020b [102]; tralokinumab AD pool tables 19 March 2020 [58].

B.2.10.3 Safety results in ECZTRA 7

B.2.10.3.1 Exposure

In ECZTRA 7, the 138 patients treated with tralokinumab had a mean exposure of [redacted] years (Table 53) [50].

Table 53 Exposure to tralokinumab in ECZTRA 7

Exposure	Tralokinumab Q2W plus TCS	Placebo plus TCS
Number exposed	[redacted]	[redacted]
PYE, years Mean (SD) Median (IQR)	[redacted]	[redacted]
Exposure time, n (%) < 6 weeks 6–11 weeks 12–15 weeks ≥ 16 weeks	[redacted]	[redacted]

IQR, interquartile range; PYE, patient-years of exposure; Q2W, every 2 weeks; SD, standard deviation; TCS, topical corticosteroids.
Source: ECZTRA 7 safety tables [50].

B.2.10.3.2 Summary of adverse events

In ECZTRA 7, the incidence of AEs was similar with tralokinumab Q2W plus TCS and placebo plus TCS (Table 54) [50]; of the most frequently reported AEs, 'headache' was more common with tralokinumab Q2W plus TCS than with placebo plus TCS [50].

B.2.10.3.3 Common adverse events

The most frequently reported AEs in ECZTRA 7 were 'atopic dermatitis', 'viral upper respiratory tract infection', 'upper respiratory tract infection' and 'headache' (Table 54 and Appendix F, Table) [50]. 'Atopic dermatitis' was less common with tralokinumab plus TCS than with placebo plus TCS, but 'headache' was more common. The frequency of upper respiratory tract infections was similar in the two groups (Table 54) [50].

Table 54 Summary of adverse events in ECZTRA 7 (SAS)

Event, n (%)	Tralokinumab Q2W plus TCS (N = 138, PYE = 65.4)	Placebo plus TCS (N = 137, PYE = 65.4)
AEs		
Total AEs	[redacted]	[redacted]
Total SAEs	[redacted]	[redacted]
Patients with AEs		
≥ 1 AE	[redacted]	[redacted]
≥ 1 SAE	[redacted]	[redacted]
AE severity		
Mild	[redacted]	[redacted]
Moderate	[redacted]	[redacted]
Severe	[redacted]	[redacted]
AE leading to permanent discontinuation of IMP	[redacted]	[redacted]
Frequent AEs [a]		
Atopic dermatitis	[redacted]	[redacted]
Viral URTI	[redacted]	[redacted]
URTI	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
AEs of special interest [b]		
Conjunctivitis	[redacted]	[redacted]
Keratoconjunctivitis	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Skin infections requiring systemic treatment	[redacted]	[redacted]
Eczema herpeticum	[redacted]	[redacted]
Malignancies [c]	[redacted]	[redacted]

[a] Frequent AEs were defined as those occurring in ≥ 5% of patients in any treatment group; classification was according to MedDRA 20.0.
[b] AEs of special interest include multiple MedDRA 20.0 preferred terms (e.g. conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic).
[c] Malignancies diagnosed after randomisation.
AE, adverse event; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PYE, patient-years of exposure; SAE, serious adverse event; SAS, safety analysis set; TCS, topical corticosteroids; URTI, upper respiratory tract infection.
Source: ECZTRA 7 safety tables [50].

B.2.10.3.4 Serious adverse events

In total, there were [redacted] SAEs in ECZTRA 7, of which [redacted] occurred in the placebo plus TCS group (Table 54 and Appendix F, Table 146) [50]. The SAE that occurred in the tralokinumab Q2W plus TCS group was appendicitis. The only system organ classes in which more than one SAE were reported were 'nervous system disorders' (one cerebrovascular accident and one seizure) and 'psychiatric disorders' (depressed mood and suicidal ideation, in the same patient in the placebo plus TCS group).

B.2.10.3.5 Adverse events of special interest

AEs of special interest are summarised in Table 54 [50]. Conjunctivitis occurred more frequently among patients treated with tralokinumab Q2W plus TCS than among those receiving placebo plus TCS. Skin infections requiring systemic treatment were less common among patients treated with tralokinumab plus TCS than in the placebo plus TCS group [50]. Other AEs of special interest were rare, and no malignancies were reported [50].

B.2.10.3.6 Deaths

[redacted]

B.2.10.3.7 Adverse events leading to discontinuation

Discontinuation due to AEs was rare, affecting [redacted] patient in the tralokinumab Q2W plus TCS group and [redacted] patients in the placebo plus TCS group (Table 54) [50].

B.2.10.4 Safety results in ECZTRA 3

B.2.10.4.1 Exposure

Exposure to tralokinumab in ECZTRA 3 is summarised in Table 55 and Table 56. In total, [redacted] patients received tralokinumab, with a mean exposure of [redacted] years [55].

Table 55 Exposure to tralokinumab in initial treatment period in ECZTRA 3 (SAS)

Exposure	Tralokinumab Q2W plus TCS	Placebo plus TCS
Number exposed	252	126
PYE, years Mean (SD) Median (IQR)	[redacted]	[redacted]
Exposure time, n (%) < 6 weeks 6–11 weeks 12–15 weeks ≥ 16 weeks	[redacted]	[redacted]

IQR, interquartile range; PYE, patient-years of exposure; Q2W, every 2 weeks; SAS, safety analysis set; SD, standard deviation; TCS, topical corticosteroids.
Sources: ECZTRA 3 CSR [47].

Table 56 Exposure to tralokinumab in continuation phase in ECZTRA 3 (SAS)

Exposure	Tralokinumab responders		Tralokinumab non-responders	Placebo non-responders	Placebo responders
	TRA Q2W plus TCS	TRA Q4W plus TCS	TRA Q2W plus TCS	TRA Q2W plus TCS	Placebo plus TCS
Number exposed	69	69	95	79	41
PYE, years Mean (SD) Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure time, n (%) ≥ 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 16 response definition was IGA 0/1 or EASI 75.
IQR, interquartile range; PYE, patient-years of exposure; Q2W, every 2 weeks; Q4W, every 4 weeks; SAS, safety analysis set; SD, standard deviation; TCS, topical corticosteroids; TRA, tralokinumab.
Source: ECZTRA 3 CSR [47].

B.2.10.4.2 Summary of adverse events

The overall frequency of AEs was comparable between tralokinumab Q2W plus TCS and placebo plus TCS; of the most frequently reported AEs, ‘viral upper respiratory tract infection’, ‘conjunctivitis’, ‘headache’, ‘upper respiratory tract infection’, and ‘injection-site reaction’ were more common with tralokinumab Q2W plus TCS than with placebo plus TCS (Table 57) [30].

During prolonged treatment with tralokinumab plus TCS from 16 weeks to 32 weeks, the rate of AEs decreased compared with the initial treatment period (Table 58). In the off-treatment safety follow-up period, the incidence and rate of AEs were generally lower than in the treatment periods (Appendix F, Table 147).

B.2.10.4.3 Common adverse events

In the initial treatment period, the most frequently reported AEs in both treatment groups were 'viral upper respiratory tract infection' (Table 57 and Appendix F, Table 148) [30, 52-55].

'Viral upper respiratory tract infection' had a higher frequency and rate in the tralokinumab Q2W + TCS group than in the placebo plus TCS group [55]. The most frequent AEs during prolonged treatment (Table 58) with tralokinumab plus TCS were generally in line with those reported in the initial treatment period, with no clinically relevant increase in the rate of any of the events. Upper respiratory tract infections and injection-site-related preferred terms were consistently reported at a higher rate for tralokinumab plus TCS compared with placebo plus TCS (Table 62) [30].

B.2.10.4.4 Serious adverse events

In the initial treatment period, there were six SAEs in ECZTRA 3 (Table 57 and Appendix F, Table 149) [30]. The incidence (and rate per 100 PYE) of SAEs was lower with tralokinumab Q2W plus TCS than with placebo plus TCS. All SAEs were reported as single events within each system organ class. During randomised continuation treatment, there were seven SAEs in ECZTRA 3, with a further [redacted] events during the safety follow-up period (Table 58 and Appendix F, Table 150, Table 151 and Table 152).

B.2.10.4.5 Adverse events of special interest

AEs of special interest are summarised in Table 57 and Table 58. In ECZTRA 3, conjunctivitis as an AE of special interest was reported more frequently in the tralokinumab plus TCS group than the placebo plus TCS group during the initial treatment period (Table 62) [30]. All conjunctivitis AEs were mild or moderate in severity and most patients had recovered by the end of the initial treatment period, with one patient discontinuing tralokinumab due to conjunctivitis [30]. There was no difference between groups in the frequency of eczema herpeticum. Skin infections requiring systemic treatment were less common among patients treated with tralokinumab plus TCS than in the placebo plus TCS group [30].

Two AEs of special interest of 'malignancies diagnosed after randomisation' were reported in ECZTRA 3, both during the continuation period: one non-serious prostate cancer in one tralokinumab-treated patient and one serious invasive ductal breast carcinoma in one placebo-treated patient [30]. [redacted]

B.2.10.4.6 Deaths

[redacted]

B.2.10.4.7 Adverse events leading to discontinuation

Discontinuation due to AEs was rare, affecting a maximum of 2.4% of patients in any tralokinumab-treated group (Table 57 and Table 58) [30].

Table 57 Summary of adverse events in initial treatment period in ECZTRA 3 (SAS)

Event, n (%)	Tralokinumab Q2W plus TCS (N = 252, PYE = 75.0)	Placebo plus TCS (N = 126, PYE = 37.9)
AEs		
Total AEs	[redacted]	[redacted]
Total SAEs	[redacted]	[redacted]
Patients with AEs		
≥ 1 AE	180 (71.4)	84 (66.7)
≥ 1 SAE	2 (0.8)	4 (3.2)
AE severity		
Mild	157 (62.3)	69 (54.8)
Moderate	66 (26.2)	30 (23.8)
Severe	7 (2.8)	7 (5.6)
AE leading to permanent discontinuation of IMP	6 (2.4)	1 (0.8)
Frequent AEs [a]		
Atopic dermatitis	6 (2.4)	10 (7.9)
Viral URTI	49 (19.4)	14 (11.1)
URTI	19 (7.5)	6 (4.8)
Conjunctivitis	28 (11.1)	4 (3.2)
Headache	22 (8.7)	6 (4.8)
Injection-site reaction	17 (6.7)	0
AEs of special interest [b]		
Conjunctivitis	33 (13.1)	7 (5.6)
Keratoconjunctivitis	1 (0.4)	0
Keratitis	0	0
Skin infections requiring systemic treatment	4 (1.6)	7 (5.6)
Eczema herpeticum	1 (0.4)	1 (0.8)
Malignancies [c]	0	0

[a] Frequent AEs were defined as those occurring in ≥ 5% of patients in any treatment group; classification was according to MedDRA 20.0.
[b] AEs of special interest include multiple MedDRA 20.0 preferred terms (e.g. conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic).
[c] Malignancies diagnosed after randomisation.
AE, adverse event; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PYE, patient-years of exposure; SAE, serious adverse event; TCS, topical corticosteroids; URTI, upper respiratory tract infection.
Sources: Silverberg *et al.* 2020a [30]; ECZTRA 3 CSR [55].

Table 58 Summary of adverse events in continuation period in ECZTRA 3 (SAS)

Event, n (%)	Tralokinumab responders		Placebo responders	Tralokinumab non-responders	Placebo non-responders
	Tralokinumab Q2W + TCS (*N* = 69, PYE = 21.5)	Tralokinumab Q4W + TCS (*N* = 69, PYE = 20.7)	Placebo + TCS (*N* = 41, PYE = 12.3)	Tralokinumab Q2W + TCS (N = 95, PYE = 28.3)	Tralokinumab Q2W + TCS (N = 79, PYE = 23.0)
AEs					
Total number of AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of SAEs					
Patients with AEs					
≥ 1 AE	48 (69.6)	41 (59.4)	26 (63.4)	62 (65.3)	55 (69.6)
≥ 1 SAE	3 (4.3)	0	1 (2.4)	2 (2.1)	0
AE severity, number of patients					
Mild	41 (59.4)	35 (50.7)	17 (41.5)	51 (53.7)	41 (51.9)
Moderate	16 (23.2)	12 (17.4)	12 (29.3)	30 (31.6)	25 (31.6)
Severe	2 (2.9)	0	2 (2.5)	1 (1.1)	2 (2.5)
AE leading to withdrawal from trial	0	1 (1.4)	1 (2.4)		2 (2.2)
Frequent AEs [a]					
Atopic dermatitis	1 (1.4)	1 (1.4)	2 (4.9)	8 (8.4)	6 (7.6)
Viral URTI	12 (17.4)	9 (13.0)	7 (17.1)	20 (21.1)	15 (19.0)
URTI	7 (10.1)	3 (4.3)	2 (4.9)	6 (6.3)	3 (3.8)
Oral herpes	3 (4.3)	4 (5.8)	1 (2.4)	4 (4.2)	2 (2.5)
Injection-site reaction	5 (7.2)	4 (5.8)	0	5 (5.3)	2 (2.5)
Headache	2 (2.9)	5 (7.2)	1 (2.4)	7 (7.4)	2 (2.5)
Nausea	3 (4.3)	4 (5.8)	0	3 (3.2)	1 (1.3)
AEs of special interest [b]					
Conjunctivitis	3 (4.3)	1 (1.4)	1 (2.4)	4 (4.2)	6 (7.6)
Keratoconjunctivitis	0	0	0	0	0
Keratitis	0	0	1 (2.4)	0	1 (1.3)
Skin infections requiring systemic treatment	0	0	0	1 (1.1)	2 (2.5)
Eczema herpeticum	0	0	0	1 (1.1)	1 (1.3)
Malignancies [c]	0	1 (1.4)	1 (2.4)	0	0

Responder definition: patients with IGA 0/1 or EASI 75 at week 16. [a] Frequent AEs were defined as those occurring in ≥ 5% of patients in any re-randomised treatment group; classification was according to MedDRA 20.0. [b] AEs of special interest include multiple MedDRA 20.0 preferred terms (e.g. conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic). [c] Malignancies diagnosed after randomisation.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PYE, patient-years of exposure; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TCS, topical corticosteroids; URTI, upper respiratory tract infection.

Source: Silverberg *et al.* 2020a [30]; ECZTRA 3 CSR [55].

B.2.10.5 Safety results in ECZTRA 1 and ECZTRA 2

B.2.10.5.1 Exposure

Exposure to tralokinumab in the ECZTRA 1 and ECZTRA 2 trials is summarised in Table 59 and Table 60. In ECZTRA 1, the [redacted] patients treated with tralokinumab at some point during the trial had a mean exposure of [redacted] years [53]. Similarly, [redacted] patients in ECZTRA 2 had a mean exposure to tralokinumab of [redacted] years [54].

B.2.10.5.2 Summary of adverse events

In the initial treatment period, the incidence and rate of AEs were similar with tralokinumab Q2W and placebo in ECZTRA 1 and ECZTRA 2 (Table 61) [52]. During prolonged treatment with tralokinumab from 16 up to 52 weeks, the rate of AEs decreased compared with the initial treatment period (Table 62). In the off-treatment safety follow-up period, the incidence and rate of AEs were generally lower than in the treatment periods (Appendix F, Table 153 and Table 154).

B.2.10.5.3 Common adverse events

In the initial treatment period, the most frequently reported AEs in both treatment groups were: 'atopic dermatitis' and 'viral upper respiratory tract infection' in ECZTRA 1; and 'atopic dermatitis', 'upper respiratory tract infection', 'viral upper respiratory tract infection' and 'injection-site pain' in ECZTRA 2 (Table 61; Appendix F, Table 155 and Table 156) [52-54].

'Atopic dermatitis' and 'skin infection' were less common with tralokinumab than with placebo, and 'viral upper respiratory infection' was reported at a similar incidence and rate between treatment groups [53, 54]. The most frequent AEs during prolonged treatment (Table 62) with tralokinumab were generally in line with those reported in the initial treatment period, with no clinically relevant increase in the rate of any of the events. Upper respiratory tract infections and injection-site-related preferred terms were consistently reported at a higher rate for tralokinumab compared with the placebo (Table 62).

B.2.10.5.4 Serious adverse events

In the initial treatment period, there were 51 SAEs in ECZTRA 1 and ECZTRA 2 (Table 61 and Appendix F, Table 157 and Table 158). The incidence (and rate per 100 PYE) of SAEs was lower with tralokinumab Q2W than with placebo in both studies. Most SAEs in ECZTRA 1 and all SAEs in ECZTRA 2 were reported as single events within each system organ class; in ECZTRA 1, the most frequently reported SAE was 'atopic dermatitis'. During randomised maintenance or continuation treatment, there were 10 SAEs in ECZTRA 1 and ECZTRA 2 (Table 62, and Appendix F, Table 159 and Table 160). During open-label treatment, there were [redacted] SAEs in ECZTRA 1 and ECZTRA 2 (mostly reported as single events within each system organ class) (Table 62 and Appendix F, Table 161 and Table 162). During the safety follow-up period, there were [redacted] SAEs in ECZTRA 1 and ECZTRA 2 (mostly reported as single events within each system organ class) (Appendix F, Table 163 and Table 164).

Table 59 Exposure to tralokinumab in initial treatment period in ECZTRA 1 and ECZTRA 2 (SAS)

Exposure	ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W	Placebo	Tralokinumab Q2W	Placebo
Number exposed	602	196	592	200
PYE, years Mean (SD) Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]
Exposure time, n (%) < 6 weeks 6–11 weeks 12–15 weeks ≥ 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]

IQR, interquartile range; PYE, patient-years of exposure; Q2W, every 2 weeks; SAS, safety analysis set; SD, standard deviation; TCS, topical corticosteroids.
Sources: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

Table 60 Exposure to tralokinumab in maintenance/open-label treatment period in ECZTRA 1 and ECZTRA 2 (SAS)

Exposure	ECZTRA 1					ECZTRA 2				
	Tralokinumab responders			Placebo responders	Open-label	Tralokinumab responders			Placebo responders	Open-label
	TRA Q2W	TRA Q4W	Placebo	Placebo	TRA Q2W + optional TCS	TRA Q2W	TRA Q4W	Placebo	Placebo	TRA Q2W + optional TCS
Number exposed	68	76	35	29	563	91	89	46	31	558
PYE, years Mean (SD) Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure time, n (%) ≥ 36 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 16 response definition was IGA 0/1 or EASI 75.
IQR, interquartile range; PYE, patient-years of exposure; Q2W, every 2 weeks; Q4W, every 4 weeks; SAS, safety analysis set; SD, standard deviation; TCS, topical corticosteroids; TRA, tralokinumab.
Sources: ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

Table 61 Summary of adverse events in initial treatment period in ECZTRA 1 and ECZTRA 2 (SAS)

Event, n (%)	ECZTRA 1		ECZTRA 2	
	Tralokinumab Q2W (N = 602, PYE = 177.6)	Placebo (N = 196, PYE = 57.1)	Tralokinumab Q2W (N = 592, PYE = 176.9)	Placebo (N = 200, PYE = 57.4)
AEs				
Total AEs	1482	491	997	408
Total SAEs	24	11	10	6
Patients with AEs				
≥ 1 AE	460 (76.4)	151 (77.0)	364 (61.5)	132 (66.0)
≥ 1 SAE	23 (3.8)	8 (4.1)	10 (1.7)	5 (2.5)
AE severity				
Mild	385 (64.0)	111 (56.6)	288 (48.6)	93 (46.5)
Moderate	241 (40.0)	98 (50.0)	168 (28.4)	84 (42.0)
Severe	41 (6.8)	16 (8.2)	24 (4.1)	16 (8.0)
AE leading to permanent discontinuation of IMP	20 (3.3)	8 (4.1)	9 (1.5)	3 (1.5)
Frequent AEs [a]				
Atopic dermatitis	156 (25.9)	75 (38.3)	98 (16.6)	67 (33.5)
Viral URTI	139 (23.1)	41 (20.9)	49 (8.3)	17 (8.5)
URTI	9 (1.5)	2 (1.0)	59 (10.0)	17 (8.5)
Conjunctivitis	43 (7.1)	4 (2.0)	18 (3.0)	3 (1.5)
Skin infection	6 (1.0)	3 (1.5)	12 (2.0)	11 (5.5)
Pruritus	32 (5.3)	10 (5.1)	12 (2.0)	5 (2.5)
Headache	28 (4.6)	10 (5.1)	16 (2.7)	6 (3.0)
AEs of special interest [b]				
Conjunctivitis	60 (10.0)	7 (3.6)	31 (5.2)	5 (2.5)
Keratoconjunctivitis	1 (0.2)	0	2 (0.3)	0
Keratitis	3 (0.5)	0	1 (0.2)	1 (0.5)
Skin infections requiring systemic treatment	13 (2.2)	4 (2.0)	21 (3.5)	22 (11.0)
Eczema herpeticum	3 (0.5)	2 (1.0)	2 (0.3)	5 (2.5)
Malignancies [c]	0	0	1 (0.2)	0

[a] Frequent AEs were defined as those occurring in ≥ 5% of patients in any treatment group; classification was according to MedDRA 20.0.
[b] AEs of special interest include multiple MedDRA 20.0 preferred terms (e.g. conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic).
[c] Malignancies diagnosed after randomisation.
AE, adverse event; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PYE, patient-years of exposure; Q2W, every 2 weeks; SAE, serious adverse event; SAS, safety analysis set; URTI, upper respiratory tract infection.
Sources: Wollenberg *et al.* 2020 [52].

Table 62 Summary of adverse events in maintenance/open-label treatment period in ECZTRA 1 and ECZTRA 2 (SAS)

Event, n (%)	ECZTRA 1					ECZTRA 2				
	Tralokinumab responders			Placebo responders	Open-label	Tralokinumab responders			Placebo responders	Open-label
	Tralokinumab Q2W (N = 68, [redacted])	Tralokinumab Q4W (N = 76 [redacted])	Placebo (N = 35 [redacted])	Placebo (N = 29 [redacted])	TRA Q2W + optional TCS (N = 563 [redacted])	Tralokinumab Q2W (N = 91 [redacted])	Tralokinumab Q4W (N = 89 [redacted])	Placebo (N = 46 [redacted])	Placebo (N = 31 [redacted])	TRA Q2W + optional TCS (N = 558 [redacted])
AEs										
Total number of AEs	214	209	70	[redacted]	[redacted]	209	154	99	[redacted]	[redacted]
Total number of SAEs	1	5	0			0	3	0		
Patients with AEs				[redacted]	[redacted]				[redacted]	[redacted]
≥ 1 AE	54 (79·4)	53 (69·7)	25 (71·4)			62 (68·1)	56 (62·9)	32 (69·6)		
≥ 1 SAE	1 (1·5)	3 (3·9)	0			0	3 (3·4)	0		
AE severity, number of patients				[redacted]	[redacted]				[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Moderate										
Severe										
AE leading to withdrawal from trial	1 (1·5)	1 (1·3)	0	[redacted]	[redacted]	2 (2·2)	1 (1·1)	0	[redacted]	[redacted]
Frequent AEs [a]				[redacted]	[redacted]				[redacted]	[redacted]
Atopic dermatitis	11 (16·2)	14 (18·4)	13 (37·1)			13 (14·3)	14 (15·7)	9 (19·6)		
Viral URTI	14 (20·6)	18 (23·7)	4 (11·4)			9 (9·9)	6 (6·7)	7 (15·2)		
URTI	1 (1·5)	2 (2·6)	1 (2·9)			14 (15·4)	9 (10·1)	3 (6·5)		
Bronchitis	3 (4·4)	7 (9·2)	2 (5·7)			1 (1·1)	3 (3·4)	0		
Injection-site reaction	5 (7·4)	7 (9·2)	1 (2·9)			4 (4·4)	4 (4·5)	0		
Headache	6 (8·8)	2 (2·6)	3 (8·6)			2 (2·2)	2 (2·2)	0		
Asthma	4 (5·9)	1 (1·3)	0			2 (2·2)	3 (3·4)	3 (6·5)		
Dry eye	0	0	0			1 (1·1)	0	3 (6·5)		
Hypertension	1 (1·5)	2 (2·6)	0			1 (1·1)	1 (1·1)	3 (6·5)		
Influenza	4 (5·9)	3 (3·9)	1 (2·9)			2 (2·2)	1 (1·1)	1 (2·2)		
Nasopharyngitis	0	3 (3·9)	2 (5·7)			3 (3·3)	2 (2·2)	0		
Allergic conjunctivitis	3 (4·4)	1 (1·3)	2 (5·7)			2 (2·2)	3 (3·4)	1 (2·2)		
Liver function test increased/abnormal	0	0	2 (5·7)			1 (1·1)	1 (1·1)	0		
Oropharyngeal pain	1 (1·5)	0	2 (5·7)	[redacted]	[redacted]	1 (1·1)	2 (2·2)	0	[redacted]	[redacted]
Conjunctivitis	3 (4·4)	4 (5·3)	0			5 (5·5)	1 (1·1)	2 (4·3)		
Back pain	3 (4·4)	4 (5·3)	0			3 (3·3)	2 (2·2)	0		
Pruritus	2 (2·9)	4 (5·3)	1 (2·9)			2 (2·2)	2 (2·2)	2 (4·3)		

Event, n (%)	ECZTRA 1					ECZTRA 2				
	Tralokinumab responders			Placebo responders	Open-label	Tralokinumab responders			Placebo responders	Open-label
	Tralokinumab Q2W (N = 68, [redacted])	Tralokinumab Q4W (N = 76 [redacted])	Placebo (N = 35 [redacted])	Placebo (N = 29 [redacted])	TRA Q2W + optional TCS (N = 563 [redacted])	Tralokinumab Q2W (N = 91 [redacted])	Tralokinumab Q4W (N = 89 [redacted])	Placebo (N = 46 [redacted])	Placebo (N = 31 [redacted])	TRA Q2W + optional TCS (N = 558 [redacted])
AEs of special interest [b]	8 (11·8)	5 (6·6)	2 (5·7)	[redacted]	[redacted]	8 (8·8)	5 (5·6)	3 (6·5)	[redacted]	[redacted]
Conjunctivitis	6 (8·8)	5 (6·6)	2 (5·7)			8 (8·8)	5 (5·6)	3 (6·5)		
Keratoconjunctivitis	2 (2·9)	0	0			1 (1·1)	0	0		
Keratitis	1 (1·5)	0	0			0	0	0		
Skin infections requiring systemic treatment	2 (2·9)	2 (2·6)	0			2 (2·2)	1 (1·1)	1 (2·2)		
Eczema herpeticum	0	0	0	[redacted]	[redacted]	1 (1·1)	0	0	[redacted]	[redacted]
Malignancies [c]	0	0	0			0	1 (1·1)	0		

Responder definition: patients with IGA 0/1 or EASI 75 at week 16.

[a] Frequent AEs were defined as those occurring in ≥ 5% of patients in any re-randomised treatment group; classification was according to MedDRA 20.0.

[b] AEs of special interest include multiple MedDRA 20.0 preferred terms (e.g. conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic).

[c] Malignancies diagnosed after randomisation.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PYE, patient-years of exposure; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TCS, topical corticosteroids; URTI, upper respiratory tract infection.

Sources: Wollenberg *et al.* 2020 [52]; ECZTRA 1 CSR [53]; ECZTRA 2 CSR [54].

B.2.10.5.5 Adverse events of special interest

In ECZTRA 1 and ECZTRA 2, conjunctivitis occurred more frequently among patients treated with tralokinumab than among those receiving placebo (Table 61 and Table 62) [52]. Most cases of conjunctivitis were mild and resolved by the end of the treatment period; one case led to treatment discontinuation [52]. Tralokinumab-treated patients had lower rates of eczema herpeticum than those receiving placebo in both ECZTRA 1 and ECZTRA 2. In addition, in ECZTRA 2 lower rates of skin infections requiring systemic treatment were seen among patients treated with tralokinumab than in the placebo group; the frequency of skin infections requiring systemic treatment was similar across groups in ECZTRA 1 [52].

There were a total of [redacted] AEs of special interest of 'malignancies diagnosed after randomisation' (Table 61 and Table 62): [redacted] [53, 54]. [redacted] [53, 54].

B.2.10.5.6 Deaths

[redacted]

B.2.10.5.7 Adverse events leading to discontinuation

Discontinuation due to AEs was rare, affecting a maximum of 3.3% of patients in any tralokinumab-treated group (Table 61 and Table 62) [30, 52].

B.2.10.6 Analysis of anti-drug antibodies

The presence of anti-drug antibodies was measured at weeks [redacted] in ECZTRA 7 [47], at weeks 0, 4, 16, 32 and 46 in ECZTRA 3 [55], and at weeks 0, 4, 16, 28, 52 and 66 in ECZTRA 1 and ECZTRA 2 (as well as at weeks 68 and 82 for selected Japanese patients in ECZTRA 1) [53, 54].

In ECZTRA 7, [redacted] had detectable anti-tralokinumab antibodies after initiation of tralokinumab; antibodies were transient and non-neutralising [50].

In ECZTRA 3, [redacted] patients were positive for anti-tralokinumab antibodies at some point during the trial; of these, [redacted] patients had anti-tralokinumab antibodies before exposure to tralokinumab [55]. A total of [redacted] patients in ECZTRA 3 had neutralising antibodies [55]. In total, [redacted] and [redacted] patients had detectable anti-tralokinumab antibodies after initiation of

tralokinumab in ECZTRA 1 and ECZTRA 2, respectively [53, 54]. Among these, three and eight patients, respectively, had neutralising antibodies [52].

Based on examination of tralokinumab concentrations, anti-drug antibody titre levels, AEs and EASI/IGA scores, it was considered that the presence of neutralising antibodies did not have an impact on the pharmacokinetics, efficacy or safety of tralokinumab for any patients in any of the trials [52-55].

B.2.10.7 Summary of safety in ECZTEND

The safety of tralokinumab was evaluated in an interim analysis of 1174 patients in the ECZTEND long-term extension trial who received at least 1 dose of tralokinumab (data cut-off, 30 April 2020), corresponding to a total combined patient exposure of 1236 years.

The exposure-adjusted incidence rate of AEs declined over time, compared with the initial treatment periods of the parent trials: there were 237.8 AEs per 100 PYE reported in the ECZTEND study, compared to 639.5 AEs per 100 PYE observed with tralokinumab in the initial treatment period in the AD pool (section B.2.10.2.2). Most AEs were mild or moderate (96.3%), and 75.8% were considered unrelated to tralokinumab. Discontinuation due to AEs was infrequent (1.6%). The most commonly reported AEs were ‘viral upper respiratory tract infection’ (most commonly reported as a common cold; 21.3%; 29.3 events per 100 PYE), ‘upper respiratory tract infections’ (7.1%; 9.1 events per 100 PYE) and ‘dermatitis atopic’ (13.5%; 20.6 events per 100 PYE). Conjunctivitis or allergic conjunctivitis were reported by 3.8% and 2.0% of patients, respectively; 2.4% reported injection site reactions [64]. No new safety issues were identified.

B.2.10.8 Summary of safety in tralokinumab asthma trials

Safety results from the AD trial programme are supported by a pooled analysis of [redacted] patients ([redacted] PYE) in three phase 3 trials of tralokinumab for the treatment asthma [103].

[redacted]

B.2.10.9 Safety network meta-analysis

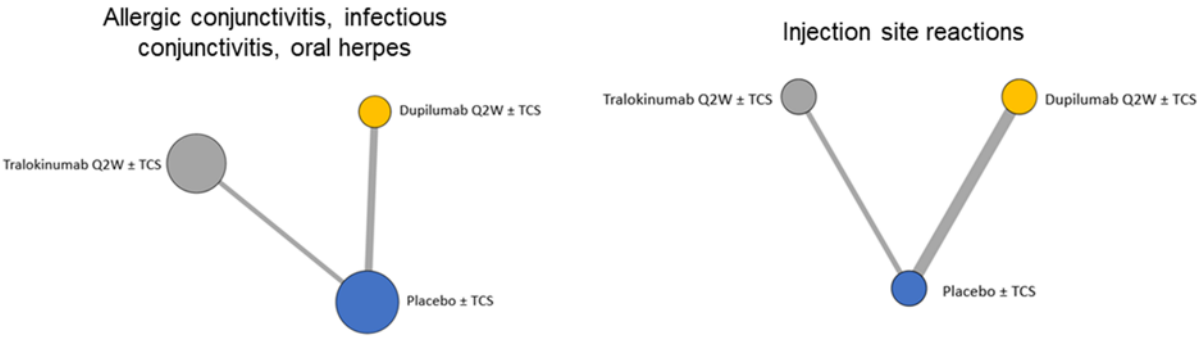
Identification of relevant studies for the safety NMA is described in Appendix D.1. The safety NMA network for allergic conjunctivitis, infectious conjunctivitis and oral herpes (Table 45; Figure 28) consisted of eight RCTs of tralokinumab (two monotherapy, two combination therapy with TCS) and dupilumab (two monotherapy, two combination therapy with TCS).

Baricitinib could not be added to the evidence network. Although data on the risk of allergic conjunctivitis was available for baricitinib from a pooled safety analysis [90], these were not

immediately comparable to the rate data reported in the tralokinumab and dupilumab trials. Combining these data would ignore the potentially recurrent nature of events in the baricitinib trial whilst accounting for it in the tralokinumab and dupilumab trials. This assumption was considered too strong and not worth the bias it might introduce to the analysis.

The NMA was conducted as described in Appendix D.1.5.1. Model fit statistics are shown in Appendix D.1.5.3, Table 132). In addition to these studies, the evidence network for injection-site reactions included one additional study of dupilumab monotherapy (Table 45; Figure 28). Because there were zero injection-site reactions in the placebo arms of ECZTRA 1, ECZTRA 3 and ECZTRA 7, the NMA results for these data were implausible. Instead, a simple Bucher analysis based on the Peto odds ratios was undertaken, which reduced the imprecision and positive skew of the distribution and correspondingly decreased the mean point estimate of the treatment effects relative to placebo and dupilumab.

Figure 28 Safety evidence networks



Q2W, every 2 weeks; TCS, topical corticosteroids.

Allergic conjunctivitis

[redacted]

Infectious conjunctivitis

[redacted]

Oral herpes

[redacted]

[redacted]

Injection-site reactions

[redacted]

Table 63 Safety NMA results – allergic conjunctivitis, infections conjunctivitis and oral herpes

Treatment	Rate per patient per year)	Hazard ratio vs placebo (± TCS)	Hazard ratio, tralokinumab vs comparator
Allergic conjunctivitis – fixed-effects model			
Placebo ± TCS	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Dupilumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Infectious conjunctivitis – fixed-effects model			
Placebo ± TCS	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Dupilumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Oral herpes – fixed-effects model			
Placebo ± TCS	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Dupilumab Q2W ± TCS	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).
CrI, credible interval; Q2W, every 2 weeks; TCS, topical corticosteroids.

Table 64 Safety NMA results – injection-site reactions

Treatment	Probability, %	Treatment effect vs placebo (± TCS)	Treatment effect, tralokinumab vs comparator
Injection-site reactions – Bucher ITC			
Placebo ± TCS	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Dupilumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Injection-site reactions – fixed-effects model			
Placebo ± TCS	[redacted]	[redacted]	[redacted]
Tralokinumab Q2W ± TCS	[redacted]	[redacted]	[redacted]
Dupilumab Q2W ± TCS	[redacted]	[redacted]	[redacted]

Data are median (95% CrI).
CrI, credible interval; ITC, indirect treatment comparison; Q2W, every 2 weeks; TCS, topical corticosteroids.

B.2.10.10 Overview of safety in relation to the decision problem

In total, the safety analysis of the tralokinumab AD clinical trial programme includes 1742 PYE [47, 48, 58]. Overall, the most frequent AEs were upper respiratory tract infections (most commonly reported as a common cold) – there was no consistent trend across studies

towards these events being more common among patients treated with tralokinumab (± TCS) than among those receiving placebo (± TCS) [30, 52]. In all four trials, conjunctivitis was more common in the tralokinumab (± TCS) groups than in the placebo (± TCS) groups [30, 50, 52]. Most cases of conjunctivitis were mild and resolved by the end of the treatment period [30, 52].

In all four trials, the incidence of SAEs during randomised treatment was lower with tralokinumab (± TCS) than with placebo (± TCS) [30, 50, 52].

[redacted]

Conclusion

The results of the safety analyses from the ECZTRA trials and the ECZTEND extension study show that tralokinumab Q2W is generally well tolerated. XXXXXXXXXXXXXXXX [redacted]

B.2.11 Ongoing studies

The long-term ECZTEND study (NCT03587805) is ongoing [65]. This study is not expected to be completed within 12 months of this submission, but the results of an interim analysis are summarised in section B.2.6.5.

B.2.12 Innovation

The cost-effectiveness analysis described in section B.3 models the benefits of tralokinumab based on EASI and DLQI response rates in the ECZTRA trials. In addition to the utility gains associated with improvements in EASI and DLQI, tralokinumab has a number of benefits that may not be included in the incremental cost-effectiveness ratio (ICER): tralokinumab has a mechanism of action targeting underlying inflammation; may reduce symptoms of anxiety and depression; relieves pruritus; improves sleep; does not require monitoring; reductions in skin infections, provides benefits to society, family and carers; allows for flexible dosing with the option of Q4W maintenance treatment; significantly reduces TCS use; and provides an alternative choice of targeted therapy.

The mechanism of action of tralokinumab targets underlying inflammation driving atopic dermatitis symptoms

Tralokinumab has been developed to specifically target a primary mediator of the type II inflammatory response in the skin, IL-13 (described in section B.1.3) [32, 35, 39]. Tralokinumab specifically binds with high affinity to circulating IL-13, preventing receptor binding and inhibiting downstream signalling [32, 40].

The targeted nature of tralokinumab means it has lower toxicity than conventional systemic therapies such as CSA, contributing to the favourable side effect profile seen in the ECZTRA and ECZTEND trials (described in section B.2.10).

Treatment with tralokinumab is associated with a reduction in clinically significant eczema-related anxiety and depression

Around 1 in 6 patients with AD have clinically significant anxiety, and 1 in 10 have clinically significant depression [16, 21]. Evidence from the ECZTRA trials showed that among patients with possible anxiety or depressive disorders, those treated with tralokinumab were more likely than those receiving placebo to have HADS scores below the threshold for these disorders at week 16 (sections B.2.6.3.5.5 and B.2.6.4.5.5). This benefit of tralokinumab may not be fully captured in the ICER calculation.

Pruritus, a particularly debilitating symptom of atopic dermatitis, is significantly improved after initiation of tralokinumab

The most frequently reported therapeutic need among patients with AD is to be free of itch [19]. In the ECZTRA trials, patients treated with tralokinumab had significant improvements in pruritus in the first 1–3 weeks, and were significantly more likely to have clinically meaningful improvements, compared with placebo (sections B.2.6.2.4.1, B.2.6.3.5.1 and B.2.6.4.5.1).

Tralokinumab treatment significantly reduces eczema-related sleep disruption

As a result of the symptoms of AD, a substantial proportion of patients have difficulty sleeping. In all four ECZTRA trials, patients treated with tralokinumab (± TCS) had significantly greater improvements in sleep, compared with those receiving placebo (± TCS; sections B.2.6.2.4.2, B.2.6.3.5.2 and B.2.6.4.5.2). This benefit of tralokinumab may not be fully captured in the ICER calculation.

Compared with baricitinib, tralokinumab is associated with fewer listed cautions about side effects and no monitoring

In a recent study of treatment-related patient needs, 72.5% of patients with AD (n = 1619) described having a treatment with fewer side-effects as an important goal [19]. However, baricitinib is associated with infections and changes in lipid parameters, while a risk of venous thromboembolism (VTE) and diverticulitis means it should be used with caution in patients with risk factors for these conditions [104, 105] – this may be particularly problematic for patients with AD, which has recently been shown to be associated with an increased risk of VTE [106]. In addition, long-term efficacy and safety data for baricitinib are currently lacking.

Initiation of baricitinib requires blood tests every 2 weeks until the dose is stable, then monthly for 3 months, followed by 12-weekly ongoing tests [107]. These additional blood tests incur significant costs and are inconvenient for patients, particularly during the SARS-CoV-2 pandemic. The benefits of having fewer listed cautions about side effects may not be captured in the ICER calculation.

Targeted treatment with tralokinumab may be preferred to broad-acting agents during the SARS-CoV-2 pandemic

Immunosuppressants may interact with defence mechanisms against viral disease. The European Task Force on Atopic Dermatitis has suggested that targeted treatment selectively interfering with type 2 inflammation, such as dupilumab – and, by extension, tralokinumab – is not considered to increase the risk for viral infections and might therefore be preferred to conventional systemic immunosuppressive treatments, such as CSA, in a situation such as the SARS-CoV-2 pandemic [108].

Tralokinumab reduces skin infections

Patients with AD are predisposed to skin infections [1], including eczema herpeticum, an acute, potentially life-threatening viral infection caused by the *Herpes simplex* virus, which occurs in approximately 3% of AD patients, particularly those with severe disease [109]. In the ECZTRA trials, eczema herpeticum events were rare, with a lower incidence among patients treated with tralokinumab than in those receiving placebo. In addition, skin infections requiring systemic treatment were generally less common among patients treated with tralokinumab than in the placebo groups (see section B.2.10).

Tralokinumab provides benefits to society and to patients' family and careers

AD has a substantial impact on patients' HRQoL and sleep, particularly as a result of intense pruritus [16-18]. The results of the ECZTRA trials demonstrate significant reductions in pruritus, as well as significant improvements in both HRQoL and sleep (sections B.2.6.2.4 and B.2.6.3.5). It is common for patients with moderate-to-severe AD to avoid social interactions and limit activities [110]. In a survey of 530 adults with AD in the UK, 21% reported their relationships being impacted by AD [25]. As a result, it is likely that improving the symptoms and HRQoL of patients with AD will also have a positive impact on the quality of life of their family. The symptoms of AD also impact patients' working life, including effects on absenteeism, presenteeism and career choice [111]; in the UK survey described above, 9% reported having lost a job due to AD, and 13% believed they had been overlooked for promotion [25]. Consequently, the benefits of tralokinumab treatment could be expected to provide employment benefits, including reduced patients' absence from work and, increased productivity. These benefits of tralokinumab are not included in the results of the economic model.

During maintenance therapy with tralokinumab, efficacy may be sustained with a lower dosing frequency

The ECZTRA trials demonstrated sustained efficacy of tralokinumab maintenance therapy. For many patients, IGA 0/1 and EASI 75 responses were maintained to week 32 or week 52 following a switch from tralokinumab Q2W (± TCS) to tralokinumab Q4W (± TCS) at week 16. The potential for less frequent treatment would benefit patients, would reduce the cost of treatment, and could contribute to an improved safety profile. Of these potential benefits, only cost is incorporated into the ICER calculation.

Tralokinumab significantly reduces topical corticosteroid use

The need to regularly use topical therapy contributes to the burden of AD for patients. In ECZTRA 7, patients with severe AD treated with tralokinumab initially applied TCS on a

mean of [redacted] days per week (see section B.2.6.2.3.1) [49]. By week 16, the need for TCS application was reduced to a mean of [redacted] days per week (compared with a change from [redacted] to [redacted] days per week in the placebo group) [49]; this benefit to patients may not be fully captured in the ICER calculation. In addition, the amount of TCS used was reduced by approximately 40% at weeks 15–16 in ECZTRA 3, compared with placebo (see section B.2.6.3.3.2).

Use of TCS may cause side effects including local adverse effects such as skin atrophy, while with prolonged use there is potential for adverse events due to systemic absorption [112]. The potential benefits of reducing the side effects by cutting patients' TCS use are not captured in the economic model for tralokinumab.

With a different mechanism of action, tralokinumab provides an alternative choice of targeted biological therapy for moderate-to-severe atopic dermatitis

Biological therapies can target the specific pathways involved in the pathophysiology of inflammatory diseases [113]. AD pathogenesis is driven by the type 2 inflammatory response, mediated by the IL-4 and IL-13 cytokines, which share receptors and biological activity [31, 32]. The only biological agent for AD currently recommended by NICE is dupilumab, an inhibitor of IL-4 signalling through both type 1 and type 2 receptors [32, 38, 46]. By contrast, tralokinumab acts only on IL-13, which has a prominent role in the skin, and acts through type 2 receptors only (section B.1.3.2) [32, 39]. The small-molecule targeted therapy baricitinib inhibits the JAK pathway, which mediates cellular responses to multiple cytokines [41, 42]. Consequently, tralokinumab has a mechanism of action that is different from those of dupilumab and baricitinib. This provides clinicians and patients with an alternative choice of targeted therapy. Potentially, each therapeutic approach may be associated with greater effectiveness and tolerability for different subsets of patients, increasing the likelihood of achieving disease control for patients with moderate-to-severe AD [37].

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the ECZTRA clinical studies

The efficacy of tralokinumab Q2W (± TCS) for the treatment of moderate-to-severe AD in adults was demonstrated in four phase 3 trials: ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7. The primary endpoints were met in all four studies, with significantly higher EASI 75 response rates at week 16 with tralokinumab Q2W (± TCS) than with placebo (± TCS; section B.2.6.1).

ECZTRA 7 showed that tralokinumab plus TCS combination therapy was superior to placebo plus TCS in a difficult-to-treat population of patients with severe AD who did not have adequate control with, or had contraindications to, CSA (section B.2.6.2.2.1). Significantly more patients in the tralokinumab plus TCS group had an EASI 75 response at week 16, compared with the placebo plus TCS group; this response rate was maintained until week 26. In addition, [redacted] of patients treated with tralokinumab Q2W plus TCS achieved an EASI 90 response by the end of the treatment period.

In ECZTRA 3, there was a significant increase in EASI 75 response rate with tralokinumab Q2W plus TCS, compared with placebo plus TCS, in patients with moderate-to-severe AD, a broader patient population than ECZTRA 7 (section B.2.6.3.2.2); among patients with an EASI 75 response at week 16, 92.5% and 90.8% of those treated with tralokinumab Q2W and tralokinumab Q4W, respectively, retained their EASI 75 status after a further 16 weeks of treatment (section B.2.6.3.4.1).

ECZTRA 1 and ECZTRA 2 demonstrated the superiority of tralokinumab monotherapy over placebo in patients with moderate-to-severe AD. Significantly more patients achieved EASI 75 at week 16 with tralokinumab than with placebo (ECZTRA 1, 25.0% vs 12.7%; ECZTRA 2, 33.2% vs 11.4%; both $p < 0.001$; section B.2.6.4.2.2). The majority of those with a week 16 response retained that response at week 52 without any use of TCS (pooled population, EASI 75: Q2W, [redacted]; Q4W, [redacted]; placebo, [redacted]; section B.2.6.4.4.1).

The efficacy of tralokinumab over a further year of treatment has been demonstrated in an interim analysis of the ongoing ECZTEND trial. Most patients ([redacted]) who received at least 60 weeks of extension treatment had an EASI 75 response at week 56. Similar results were seen in a subset of patients who had been treated with tralokinumab (± TCS) for 2 years (52 weeks in ECZTRA 1 or ECZTRA 2 followed by 56 weeks in ECZTEND): [redacted] had an EASI 75 response [64].

To complement results in the ECZTRA 7 population, subgroup analyses were used to investigate the efficacy of tralokinumab in patients in ECZTRA 1, ECZTRA 2 and ECZTRA 3 who had inadequate control with, or intolerance or contraindications to, either CSA or any systemic therapy. Results for key endpoints at week 16 were generally consistent with the overall populations, suggesting that tralokinumab is efficacious in these patient groups (section B.2.7.2).

The open-label treatment periods in ECZTRA 1, ECZTRA 2 and ECZTRA 3 also explored the response to tralokinumab among patients who did not have a response at week 16. In ECZTRA 1 and ECZTRA 2, 31.9% of patients without a response at week 16 achieved EASI 75 after a further 8 weeks of treatment with tralokinumab and optional TCS, and 42.9% had an EASI 75 response at week 52 (25.7% without use of TCS). The majority (53.2%) of ECZTRA 1/ECZTRA 2 patients who had an EASI 50 response but not EASI 75 or IGA 0/1 at week 16 achieved EASI 75 at week 52 (section B.2.6.4.4.2) [78]. Similarly, in ECZTRA 3 [redacted] of patients without a protocol-defined response at week 16 achieved EASI 75 after a further 16 weeks of tralokinumab plus TCS combination therapy (section B.2.6.3.4.2). The use of EASI 75 to define week 16 responders in the ECZTRA trials may mean that some patients who did not have a protocol-defined response at week 16, but who did have a partial response, may in clinical practice have continued to receive treatment on the basis of having achieved an EASI 50 & ΔDLQI ≥ 4 response, which is routinely used as a stopping rule [46]. Consequently, the high rate of EASI 75 responses achieved after week 16 is relevant to the expected effectiveness of tralokinumab in clinical practice. These effects of tralokinumab are consistent with the clinical goal of long-term, stable disease control with a generally well-tolerated therapy.

In all four ECZTRA trials, use of tralokinumab (± TCS) was associated with clinically meaningful improvements in pruritus that were statistically significant versus placebo (± TCS) from week 1 (ECZTRA 1 and ECZTRA 2), week 3 (ECZTRA 3) or week 4 (ECZTRA 7). Patients treated with tralokinumab also had statistically significant improvements, compared with placebo, in sleep disruption, patient-reported AD symptoms and HRQoL. In addition, patients in the tralokinumab groups who had possible anxiety or depressive disorders were significantly more likely than those in the placebo groups to have improvements in the symptoms of anxiety and depression, measured with the HADS, during treatment (sections B.2.6.2.4 and B.2.6.3.5).

In ECZTRA 3 and ECZTRA 7, patients were provided with TCS in addition to their treatment with tralokinumab or placebo. In ECZTRA 3, patients treated with tralokinumab used statistically significantly less TCS than those receiving placebo, while patients with severe AD in the tralokinumab arm of ECZTRA 7 had significantly more TCS-free days than those randomised to placebo (sections B.2.6.2.3.1 and B.2.6.3.3.2).

An NMA was conducted to compare tralokinumab with dupilumab and baricitinib. However, there are a number of sources of potential heterogeneity in the induction NMA which should be considered whilst interpreting the results. Although the baseline characteristics of the patients are broadly similar across the included trials (differences are described in section B.2.9.3), important differences concerning study design have been highlighted. These relate to the eligibility criteria of the trials, the requirement for and duration of TCS washout and the type of TCS used, as well as to the discretion given to clinical investigators and the timing and frequency of follow-up, all of which varied significantly across trials and could affect TCS use and adherence. The maintenance NMA relies on a number of assumptions and includes multiple sources of heterogeneity. With so few trials, there was no way to formally explore or account for potential design differences in the maintenance NMA. [redacted] The impact of observed and unobserved differences is apparent, as variation in placebo response rates across the included studies was found to constitute an important source of heterogeneity and uncertainty (section B.2.9.3). Placebo response rates could be partially accounted for in an adjusted analysis of the combination therapy network, but this could not be conducted for monotherapy induction treatment, for maintenance therapy, or in the ECZTRA 7-like population (section B.2.9.3.3). [redacted] The results of the adjusted analysis demonstrate the potential impact of controlling for observed and unobserved sources of heterogeneity in the other networks of evidence and illustrate that the

unadjusted analyses may paint a conservative picture regarding the absolute and relative efficacy of tralokinumab.

The results of the safety analyses show that tralokinumab Q2W is generally well tolerated (section B.2.10). Consistent with the fully human nature of tralokinumab, few patients had neutralising anti-drug antibodies (ECZTRA 3, 8 patients; ECZTRA 1, 3 patients; ECZTRA 2, 8 patients), and these were not considered to have an impact on efficacy or safety (section B.2.10.6). The safety NMA shows that adverse events of interest are expected to occur [redacted] with tralokinumab, compared with dupilumab (section B.2.10.9).

Although the studies are not directly comparable, the rate of conjunctivitis was numerically lower in the ECZTRA trials than in the dupilumab phase 3 studies (5.4% in the pooled safety analysis for tralokinumab [section B.2.10.2.3] vs 9.3% in the dupilumab primary safety pool [46]). In addition, the rate of conjunctivitis was numerically lower in ECZTEND than in the dupilumab extension study ([redacted] across all relevant terms [64], compared with 10.7% across all terms [114]); as for the phase 3 trials, the extension studies are not directly comparable. In clinical practice, the prevalence of conjunctivitis among patients receiving dupilumab was found to be 55% in an Italian cohort [115]. In England, the clinical experience of dermatologists consulted during an advisory board meeting is that around 60% of patients with AD treated with dupilumab develop conjunctivitis, with 30% needing to consult an ophthalmologist. Consistent with this experience, a recent retrospective analysis of patients at Southampton General Hospital found that of 28 patients prescribed dupilumab for AD between 2017 and 2019, 14 were referred to the ophthalmology department with symptoms of eye redness, soreness, itch and epiphora, and nine were diagnosed with conjunctivitis [116]. Similarly, a prospective study of the first 100 patients treated with dupilumab at a specialist eczema clinic reported that ophthalmic AEs were common (29.3% of all AEs, affecting 76% of patients): predominantly allergic/dupilumab-associated conjunctivitis (32%), conjunctivitis (unspecified; 7%) or dry eyes (23%) [117].

In contrast to tralokinumab, the other currently available targeted therapy, baricitinib, is associated with a risk of infections, VTE and diverticulitis, and should be used with caution in patients with risk factors for these conditions [104].

B.2.13.2 Strengths and limitations of the clinical evidence base for tralokinumab

Study design

The clinical evidence provided by the four ECZTRA trials demonstrates the efficacy and safety of tralokinumab monotherapy and combination therapy in the treatment of moderate-to-severe AD. All four trials met their primary endpoints, with tralokinumab providing improvements in AD symptoms and HRQoL which were sustained to the end of the trial periods.

A strength of the tralokinumab clinical programme is that ECZTRA 7 showed that tralokinumab plus TCS was superior to placebo plus TCS in patients with severe AD who did not have adequate control with, or had contraindications to, CSA. These results were

supported by subgroup analyses of ECZTRA 7-like patients from the ECZTRA 3 combination therapy trial and from the ECZTRA 1 and ECZTRA 2 monotherapy trials.

A further strength of the clinical programme is that the two identical ECZTRA 1 and ECZTRA 2 trials included a 52-week treatment period, providing a robust assessment of sustained response to tralokinumab therapy. In addition, the design of the ECZTRA studies allowed the effect of tralokinumab to be investigated beyond week 16 in patients who did not have a response in the initial treatment period, showing that many patients obtain benefits from a longer period of treatment.

One limitation of ECZTRA 1 and ECZTRA 2 is the high level of rescue medication use (see section B.2.6.3.3.1). The greater use of rescue medication in ECZTRA 1 than in ECZTRA 2 may explain the smaller difference between tralokinumab Q2W and placebo seen in the former trial. One explanation for the difference between ECZTRA 1 and ECZTRA 2 is differences in clinical practice across regions. Use and choice of rescue medication were based on investigators' decisions, which might have been affected by local practice and availability of rescue medication options. For example, Japanese clinical practice favours TCS use, including high-potency TCS, rather than systemic agents; this is consistent with the [redacted]

A possible explanation for the high level of rescue medication use overall is the inclusion of a 2-week washout period in these trials, which may have led to an early need for additional treatment [52]. In contrast to some other trials in AD, in ECZTRA 1 and ECZTRA 2 there was no penalty for use of rescue medication in the first 2 weeks, and patients with early use of additional treatment were able to continue in the trials. Further, even a single use of TCS was classified as a treatment failure in ECZTRA 1 and ECZTRA 2. This does not reflect real-world use of systemic therapies – use of tralokinumab in combination with TCS, as in ECZTRA 3 and ECZTRA 7, is likely to be common in clinical practice, although TCS use may be more intensive in clinical trials than in real-life practice [52].

All of the ECZTRA trials had generally high response rates in the placebo arms; this was particularly evident in the combination therapy studies, but was also seen in ECZTRA 1 and ECZTRA 2, in which 13% and 11% of placebo-treated patients, respectively, achieved EASI 75 at week 16 [52]. Patients may have unstable disease after a 2-week washout period, and might be expected to have a greater response to the reintroduction of TCS than would be seen after a 1-week washout, as used in the phase 3 dupilumab studies LIBERTY AD CHRONOS, SOLO 1 and SOLO 2 [87, 118]. However, high placebo response rates were also seen in the dupilumab phase 3 trials, as noted in noted in NICE TA534 [46], and may reflect the stringent emollient regime in the trials, as well as increased contact with healthcare professionals. The use of a potent steroid in ECZTRA 3 and ECZTRA 7 may also contribute to high placebo response rates in these trials. All patients were given tubes of a potent steroid in ECZTRA 3 and ECZTRA 7, with little discretion given to the trial clinicians to substitute other products. By contrast, rather than tubes of steroid, patients in the LIBERTY AD programme were given prescriptions, which some patients may not have filled. In addition, several steroid options were used in the LIBERTY AD programme, including

different potencies for different areas; if any were unavailable clinicians could substitute locally available options. Although these effects would affect both study arms, high placebo response rates may reduce the scope for demonstrating the full clinical potential of tralokinumab.

An additional strength of the clinical trial programme is that data were available from the ongoing ECZTEND extension study, demonstrating continued efficacy and safety of tralokinumab for a further year of treatment.

Appropriateness of therapy and comparators

The tralokinumab clinical trial programme investigated both monotherapy and combination therapy with TCS. There is agreement that novel therapies for AD should be investigated as monotherapy [119], since interpretation of treatment effects is complicated by use of TCS, which differs between treatment and placebo arms (as shown in ECZTRA 3 and ECZTRA 7). In clinical practice, however, tralokinumab is likely to be commonly used in combination with TCS. Both treatment scenarios are assessed in the ECZTRA trials.

One limitation of the tralokinumab trial programme is the lack of direct comparisons with an active comparator. The only relevant active comparators – dupilumab and baricitinib – were not available in the UK at the time the tralokinumab phase 3 trial programme was initiated, making head-to-head studies infeasible. This limitation has been partly addressed by conducting an NMA based on a comprehensive systematic review. Although an NMA was conducted based on a comprehensive systematic review, this has important limitations (sections B.2.9.3 and B.2.9.4). There is considerable uncertainty in the NMA results, and there exists a risk that observed and unobserved differences in trial design may bias the treatment effect estimates against tralokinumab in the unadjusted comparisons. Consequently, the NMA results should be interpreted with a high degree of caution.

Relevance of outcomes

The main efficacy outcome assessed in the ECZTRA trials was the EASI, an investigator-assessed, validated measure of the physical signs of AD [67, 68]. A 50% improvement in EASI (EASI 50) is considered to be a clinically significant treatment response [120], and was assessed in the ECZTRA trials, in which the primary endpoint was a more stringent 75% reduction (EASI 75).

In addition to improvements in EASI, the consensus-based Harmonising Outcome Measures for Eczema (HOME) initiative [121] recommends the use of the POEM and DLQI instruments to assess patient-reported symptoms and HRQoL, respectively [121]. Both of these measures were used to evaluate the efficacy of tralokinumab, with all four trials demonstrating consistent, statistically significant improvements with tralokinumab, compared with placebo.

The combined endpoint of EASI 50 & ΔDLQI ≥ 4, which is used in the economic model, is relevant to clinical practice as a routine stopping rule [29, 46].

A strength of the clinical studies is that in addition to the composite estimand, in which patients using rescue medication were conservatively considered to be non-responders,

data were also calculated for the treatment policy sensitivity analysis estimand. This estimand attempts to mimic treatment effects in the real-life clinical setting as closely as possible. Key endpoint results were generally similar in both analyses.

A limitation of the ECZTRA 7 trial was disruption caused by the SARS-CoV-2 pandemic. However, the impact on the trial results appears to have been limited, with similar results obtained in the primary analysis and in an analysis using a modified composite estimand, as described in section B.2.6.1.

Trial populations

The decision problem population is adults with moderate-to-severe AD that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated. The ECZTRA 7 trial provides evidence for tralokinumab combination therapy in this population (patients who do not have adequate control with, or have contraindications to, CSA). ECZTRA 1, ECZTRA 2 and ECZTRA 3 were conducted in the full licence population (all patients with moderate-to-severe AD). To generate evidence for the decision problem population, subgroup analyses of these trials were conducted focussing on patients who had inadequate control with, or intolerance or contraindications to, CSA. The results for key efficacy endpoints in these subgroups were generally consistent with the overall populations.

The ECZTRA 7 trial was conducted at 68 sites in Europe, including five sites in Great Britain, and the other phase 3 trials were conducted at multiple locations in Europe, North America and Asia. The results achieved in this broad population are expected to be applicable to patients in England.

B.2.13.3 Life expectancy of people with atopic dermatitis

The published evidence on the impact of AD on life expectancy is limited. AD has recently been shown to be associated with an increased likelihood of hospitalisation for VTE [106]. A recent UK study using electronic health records from the Clinical Practice Research Datalink (CPRD) and mortality data from the Office for National Statistics found that from 1998–2016 there was limited evidence of an increased hazard of all-cause mortality among people with AD (hazard ratio [HR], 1.04; 99% CI, 1.03–1.06) [122]. There was a stronger association between severe AD and all-cause mortality (HR, 1.62; 99% CI, 1.54–1.71), with particular increases in the hazard of death due to infection (HR, 2.85; 99% CI, 1.78–4.55), respiratory disease (HR, 2.20;99% CI, 1.91–2.53) and diseases of the genitourinary system (HR, 2.10; 99% CI, 1.43–3.07) [122].

Tralokinumab is not considered to be a ‘life-extending treatment at the end of life’.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Identification and selection of relevant cost-effectiveness studies is described in Appendix G. In brief, searches of relevant publication databases and grey literature sites were conducted on 16 February 2021. The SLR identified 17 relevant studies, comprising five health technology assessments (HTAs; four for dupilumab and one for baricitinib), three published UK economic evaluations and nine non-UK evaluations (described in Appendix G). The five economic evaluations identified that assessed the cost-effectiveness of dupilumab and baricitinib in moderate-to-severe AD were used to inform the development of the economic model. Published UK-based cost-effectiveness studies relevant to the decision problem are summarised in Table 65.

B.3.2 Economic analysis

The objective of this economic analysis is to assess the cost-effectiveness of tralokinumab, with and without TCS, versus the currently approved targeted therapies (dupilumab and baricitinib) and best supportive care (BSC) in a population of adults with moderate-to-severe AD who are candidates for systemic therapy but for whom conventional systemic therapies, including CSA, have been inadequately effective, not tolerated or contraindicated, in line with the anticipated positioning of tralokinumab in UK clinical practice. No previous cost-effectiveness analysis of tralokinumab in the treatment of moderate-to-severe AD was identified. Therefore, a *de novo* economic model was constructed.

B.3.2.1 Patient population

The base-case economic evaluation considered patients who failed to respond to prior conventional systemic therapies and were eligible to receive systemic biological therapies approved in the UK. Therefore, the model base case uses data for a subgroup of patients in the ECZTRA 1, ECZTRA 2 and ECZTRA 3 trials [30, 52] who had inadequate control with, or intolerance or contraindications to, CSA (ECZTRA 7-like; see section B.2.2, Figure 4), as well as all ECZTRA 7 patients [47]. Data for all randomised patients regardless of prior CSA exposure, was used in scenario analysis C (section B.3.8.3.4).

Hypothetical patients were based on the patient cohorts from the ECZTRA trials [30, 47, 52]. Hence, they varied depending on whether the model was assessing monotherapy or combination therapy, with baseline characteristics of the pooled populations of ECZTRA 1 and ECZTRA 2 assumed for monotherapy and those of the pooled populations of ECZTRA 3 and ECZTRA 7 used for combination therapy (Table 66).

Table 65 Summary of published UK-based cost-effectiveness studies relevant to the decision problem

Study (year of publication)		Summary of model	Patient population	QALYs	Costs (GBP)	ICER (cost per QALY gained – GBP)
TA534 (2018) [119]	1st submission	Type of EE: Decision tree and Markov model Time horizon: lifetime Perspective: UK NHS Costing year: 2017 Discounting: 3.5% Conflicts of interest: Sanofi-Regeneron manufacturer submission	Adults with moderate-to-severe AD	NR	NR	Dupilumab vs BSC (PAS price): Monotherapy: £28,874 Combination therapy: £24,703
	ERG analyses	Type of EE: Decision tree and Markov model Time horizon: 10 years Perspective: UK NHS Costing year: NR Discounting: 3.5% Conflicts of interest: Sanofi-Regeneron manufacturer submission	Adults with moderate-to-severe AD who are ciclosporin-experienced	NR	NR	Dupilumab vs BSC (PAS price): Monotherapy: £29,468 Combination therapy: £33,297
	2nd submission	Type of EE: Decision tree and Markov model Time horizon: 10 years Perspective: UK NHS Costing year: NR Discounting: 3.5% Conflicts of interest: Sanofi-Regeneron manufacturer submission	Adults with moderate-to-severe AD who are ciclosporin-experienced	NR	NR	Dupilumab vs BSC (PAS price): Combination therapy: £28,495

Study (year of publication)		Summary of model	Patient population	QALYs	Costs (GBP)	ICER (cost per QALY gained – GBP)
TA681 (2021) [123]	1st submission	Type of EE: Markov model Time horizon: lifetime Perspective: UK NHS Costing year: 2019 Discounting: 3.5% Conflicts of interest: Eli Lilly and Company manufacturer submission	Adults with moderate-to-severe AD who have experienced failure with, are intolerant of, or have contraindications to, ciclosporin	NR	NR	Baricitinib vs BSC (PAS price): Base Case: £17,941 Dupilumab vs BSC (list price): Base Case: £88,842 Baricitinib vs dupilumab (baricitinib PAS, dupilumab list prices): Base Case: £203,525 (cost saving per QALY foregone)
	ERG analyses	Type of EE: Markov model Time horizon: lifetime Perspective: UK NHS Costing year: NR Discounting: 3.5% Conflicts of interest: Eli Lilly and Company manufacturer submission	Adults with moderate-to-severe AD who have experienced failure with, are intolerant of, or have contraindications to, ciclosporin	NR	NR	Baricitinib vs BSC (PAS price): Base Case: £64,710 Baricitinib + dupilumab vs baricitinib sequence (baricitinib PAS, dupilumab list prices): Base Case: £174,071 Dupilumab vs baricitinib + dupilumab sequence (baricitinib PAS, dupilumab list prices): Base Case: Dominated Dupilumab + baricitinib sequence vs baricitinib + dupilumab sequence (baricitinib PAS, dupilumab list prices): Base Case: £334,999
	2nd submission	Type of EE: Markov model Time horizon: lifetime Perspective: UK NHS Costing year: 2019 Discounting: 3.5% Conflicts of interest: Eli Lilly and Company manufacturer submission	Adults with moderate-to-severe AD who have experienced failure with, are intolerant of, or have contraindications to, ciclosporin	NR	NR	Baricitinib vs BSC (PAS price): Base Case: £27,037 Dupilumab vs BSC (list price): Base Case: £89,350 Baricitinib vs dupilumab (baricitinib PAS, dupilumab list prices): Base Case: £113,459 (cost saving per QALY foregone)

AD, atopic dermatitis; BSC, best supportive care; EE, economic evaluation; GBP, Great British Pound; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY, quality-adjusted life year; SoC, Standard of Care.

Table 66 Baseline patient characteristics

Mean baseline characteristic	Monotherapy		Combination therapy	
	All patients	ECZTRA 7-like	All patients	ECZTRA 7-like
Age, years	37.8	37.7	38.0	38.3
Male sex	59.3%	60.0%	56.9%	58.3%
EQ-5D utility index	0.551	0.513	0.588	0.590
Weekly average worst daily pruritus NRS score	7.80	7.95	7.58	7.49
EASI	32.30	33.54	30.87	31.80

CSA, ciclosporin A; EASI, Eczema Area and Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA EQ-5D, 5-dimension EuroQol questionnaire; NRS, numeric rating scale.

B.3.2.2 Treatment responses

In the base case analysis, patients were defined as responders if they achieved the combined endpoint of EASI 50 plus a DLQI ≥ 4-point change (EASI 50 & ΔDLQI ≥ 4). This was not a primary endpoint within the tralokinumab trials. However, results for dupilumab for this endpoint were generated for the purposes of TA534 [119], as it was argued that using the primary endpoint of EASI 75 might exclude some patients who were receiving a benefit from continuing to receive the biologic, and could go on to achieve a higher level of response at a later timepoint. EASI 50 & ΔDLQI ≥ 4 was the preferred response definition in the NICE appraisals for dupilumab and baricitinib [29, 46], and was used in the base-case analysis within these submissions. For tralokinumab, this precedent has been followed, to ensure the analyses are comparable. Other response definitions, including EASI 50 and EASI 75 were considered in scenario analysis B (section B.3.8.3.3)

B.3.2.3 Model structure

A cohort model, comprised of a 1-year decision tree followed by a Markov chain with annual cycles and half-cycle correction, was developed in Microsoft Excel for Office 365®. The model structure is shown in Figure 29.

In the first year, patients receive treatment with the intervention or comparators, and transition at week 16 to either continue their biological therapy or switch to BSC depending on whether they achieve a response. For patients continuing on biological therapy, a similar branch between the biologic and BSC occurs at week 52. Patients receiving long-term maintenance with biological therapy have an annual risk of discontinuation, upon which they switch to BSC. After moving to BSC, patients continue receiving BSC until the end of the modelled time horizon or death.

Death is an absorbing state to which patients can transition from any model state at any time. Mortality is not conditioned on treatment or level of response as AD and its treatment were assumed not to affect overall mortality. Background mortality was derived from life tables for the UK [124].

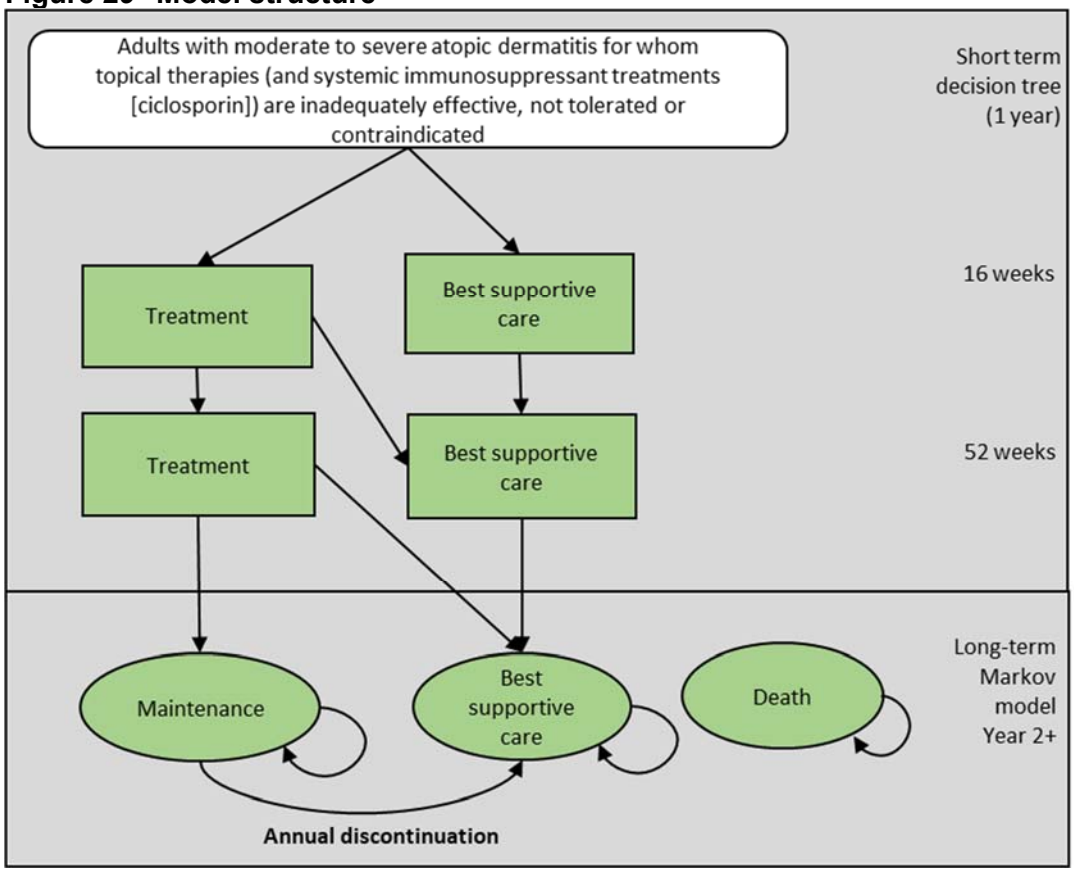
The key features of the economic analysis are summarised in Table 67. This was a cost–utility analysis with health outcomes expressed in terms of quality-adjusted life years

(QALYs). Cost outcomes include treatment, monitoring and adverse event costs. Results are reported in terms of incremental cost-effectiveness ratios (ICERs).

The perspective of the analysis is that of England and Wales NHS and Personal Social Services (PSS), consistent with the NICE Reference Case [125].

A lifetime horizon was used in the base case. The impact of fixed time horizons of 2, 5 and 10 years on the results of the model were explored in scenario analysis F (section B.3.8.3.7). A discount rate of 3.5% was applied to both costs and QALYs, as recommended in the NICE Reference Case [125].

Figure 29 Model structure



B.3.2.4 Intervention technology and comparators

Comparators in the model are tralokinumab, dupilumab, and BSC. BSC consists of emollients, with the addition of TCS in the combination therapy analyses.

The comparators were modelled as per their marketing authorisations and doses, as monotherapy or with TCS. Tralokinumab and dupilumab are both administered using a 600 mg loading dose followed by 300 mg Q2W. Tralokinumab maintenance therapy can also be administered Q4W, a dosing option which has been accepted by EMA as a treatment option for patients who achieve ‘clear or almost clear’ skin [126].

In the base case [redacted] of patients on tralokinumab switched to Q4W dosing at week 52. This assumption was based on UK market research which found that [redacted] of 50 HCPs would consider lowering the tralokinumab dose in their clinical practice, after an average of

28 weeks. The proportion of patients switching was also informed by the [redacted] of tralokinumab-treated patients in ECZTRA 7 who met the EASI 50 & ΔDLQI ≥ 4 response definition and had both IGA 0/1 ('clear or almost clear' skin) and worst daily pruritus NRS < 3 at week 26. The rationale for this assumption is described in more detail in Appendix I.2. The proportion of patients switching to Q4W dosing is explored in scenario analysis E (section B.3.8.3.6).

RCT data for baricitinib were not available for the EASI 50 & ΔDLQI ≥ 4 endpoint from the study publications, and were redacted in the NICE submission documents. Accordingly, baricitinib could not be included in the base-case analysis. Baricitinib was included in the scenario analyses in which responses were based on the NMA of EASI 50 and EASI 75 responses (scenario analysis B, section B.3.8.3.3).

Neither CSA, nor any other systemic immunosuppressant, could be included in the model as a comparator since relevant data were not available.

B.3.3 Clinical parameters and variables

B.3.3.1 Estimands and imputation

In the base case, patients who received rescue treatments are assumed to discontinue biologics; this aligns with the NRI approach used for the primary estimand ('composite') in the clinical trials (see section B.2.4.3). This is in line with the preference expressed by NICE as part of the dupilumab NICE appraisal (TA534) [46]. Probabilities derived from the tertiary estimand ('treatment policy', referred to in this section as 'all-observed' data), in which outcomes were recorded for patients regardless of receipt of rescue therapy, were used in scenario analysis A (section B.3.8.3.2).

B.3.3.2 Treatment responses

B.3.3.2.1 Initial response

The proportions of patients achieving EASI 50 & ΔDLQI ≥ 4 responses at week 16 in the NRI analysis for tralokinumab, dupilumab and BSC are presented in Table 68; response rates for other response definitions are presented in section B.3.8.3.3, Table 90.

The probabilities of response are informed by NMA data, using ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7, as well as the relevant dupilumab trials, with the exception of the EASI 50 & ΔDLQI ≥ 4 response measure for the overall patient populations, for which there were no data available to perform an NMA.

The probabilities of achieving this response at week 16 for tralokinumab and BSC were taken from ECZTRA 1 and ECZTRA 2 (for monotherapy) and ECZTRA 3 and ECZTRA 7 (for combination therapy). In the absence of data, it was assumed that the relationship between dupilumab and placebo on the outcome of EASI 50 & ΔDLQI ≥ 4 is the same in the overall population and in the ECZTRA 7-like subgroup. Therefore, the odds ratio for dupilumab vs BSC estimated in the NMA of EASI 50 & ΔDLQI ≥ 4 response in the ECZTRA 7-like subgroup was applied to the probability of response for BSC in the all-patient population.

Table 67 Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TA534 [46]	TA681 [29]	Chosen approach	Justification
Patient population	Moderate-to-severe AD patients. Analyses conducted in the all-patient population and ciclosporin-IR subgroup.	Moderate-to-severe AD patients. Analyses conducted in the all-patient population and ciclosporin-IR subgroup.	Moderate-to-severe AD patients. Analyses conducted in the all-patient population and ECZTRA 7-like subgroup.	Consistent with TA534 [46] and tralokinumab's expected position in the treatment pathway.
Model structure	1-year decision tree followed by a three-state Markov model	Markov state transition model with 4-week cycles	1-year decision tree followed by a three-state Markov model	Consistent with TA534 [46] and reflecting long-term treatment of AD
Time horizon	Lifetime	Lifetime	Lifetime	NICE reference case [125]
Treatment waning effect and discontinuation	Annual probability of discontinuation based on clinical trials (SOLO, 6.3%; CHRONOS EASI 50 & ΔDLQI ≥ 4, 3.7%; EASI 50, 5.5%; EASI 75, 5.1%) In the 2nd submission, a 3.7% rate was used in monotherapy and combination therapy. A further proportion of patients are assumed to lose the treatment benefit of biological therapy and discontinue to BSC (range, 0–3% per year)	Annual probability of discontinuation based on dupilumab clinical trials (EASI 50 & ΔDLQI ≥ 4, 3.7%; EASI 75, 5.1%)	During maintenance treatment, an annual rate of discontinuation of 2.6% was assumed for all biologics A further proportion of patients are assumed to lose the treatment benefit of biological therapy and discontinue to BSC (range, 0–3% per year)	Discontinuation was based on data from the ECZTEND trial Loss of response was based on TA534 [46]
Source of utilities	A mixed model regression was performed to derive health state utility values from the trial data. Change in utility values was modelled as a function of response to treatment at week 16. The utility values were adjusted multiplicatively for the impact of ageing on HRQoL	Utility values were derived by cross-walking EQ-5D-5L scores collected in the BREEZE-AD trials to EQ-5D-3L scores. A mixed model regression was performed to derive health state utility values from the trial data. Change in utility values was modelled as a function of response to treatment at week 16. At the	Utility values were derived by cross-walking EQ-5D-5L scores collected in the ECZTRA trials to EQ-5D-3L, valued with the UK tariff. A mixed model regression was performed to derive health state utility values from the trial data. Change in utility values was modelled as a function of response to treatment at week 16.	Consistent with TA534, TA681 and the NICE reference case [125]

		Final Appraisal Determination stage, health state utility values from TA534 were applied based on ERG feedback.		
Source of costs	BNF (2017), National Schedule of Reference Costs (2015–16), NHS reference costs (2014–2015), PSSRU and National Reference Costs (2015)	BNF (2019), National schedule of NHS Costs (2018–19), PSSRU and National Reference Costs (2019)	BNF (2019), MIMS (2020) [127], NHS Reference Costs (2018–2019) [128] and PSSRU (2019) [129]	Established sources of costs within the NHS. In line with the NICE reference case [125] and previous TAs
Adverse events	AEs based on dupilumab clinical trials	AEs based on TA534	AEs based on NMAs	It was feasible to carry out safety NMAs for tralokinumab compared to dupilumab for the AEs considered relevant for biologics in TA534 [46]
Health effects measure	QALYs	QALYs	QALYs	NICE reference case [125]
Half-cycle correction applied?	Yes – annual cycles with half-cycle correction	No	Yes – annual cycles with half-cycle correction	NICE reference case [125]

AE, adverse event; BNF, British National Formulary; EQ-5D-3L, 3-level, 5-dimension EuroQol questionnaire; EQ-5D-5L, 5-level, 5-dimension EuroQol questionnaire; ERG, evidence review group; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.3.2.2 Sustained response

The probability of EASI 50 & ΔDLQI ≥ 4 responses at week 52 among patients with a response at week 16, shown in Table 68, were based on the NMA results (section B.2.9.2.2). Response rates for other response definitions are shown in section B.3.8.3.3, Table 90. No evidence was available for the ECZTRA 7-like subgroup: accordingly, response probabilities for these patients were assumed to be the same as those for the overall population. The impact of these assumptions was explored in deterministic sensitivity analysis (section 0) and in a scenario analysis in which the probabilities of sustained response to tralokinumab and dupilumab were assumed to be equal (scenario analysis F, section B.3.8.3.7).

Table 68 Proportion of patients with EASI 50 & ΔDLQI ≥ 4 responses (NRI)

Treatment	Week 16		Week 52
	ECZTRA 7-like [a]	All patients	All patients [b]
Monotherapy			
Tralokinumab Q2W	0.372	[redacted]	0.813
Tralokinumab Q4W	–	[redacted]	0.813 [c]
Dupilumab Q2W	0.556	[redacted]	0.948
BSC	0.126	[redacted]	0.793
Combination therapy			
Tralokinumab Q2W + TCS	0.579	[redacted]	0.813
Tralokinumab Q4W + TCS	–	[redacted]	0.813 [c]
Dupilumab Q2W + TCS	0.862	[redacted]	0.948
BSC + TCS	0.426	[redacted]	0.793

[a] Any differences between these probabilities and those presented in Table 46 are due to rounding based on the synthesis of median baseline (A) and treatment effects (d) in the model. [b] Week 52 sustained response values are assumed to apply for the ECZTRA 7-like subgroup and for the all-observed estimand. [c] Assumed to be the same as tralokinumab Q2W.
BSC, best supportive care; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA; NRI, non-responder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

B.3.3.3 Discontinuation and drug survival (year 2 onwards)

Patients treated with BSC are assumed to lose their treatment benefit over time. This assumption is based on the inclusion criteria in AD clinical trials: in order to be eligible for the trials, patients were required to have had an inadequate response to the treatments included in BSC. Therefore, it is expected that after the trial these patients would return to their baseline HRQoL and resource use. Loss of treatment benefit is assumed to occur linearly, with all patients having lost the BSC treatment benefit from year 5 onward. This was the ERG's preferred assumption in TA534. Scenario analysis F (section B.3.8.3.7) explores assumptions around loss of treatment benefits after year 1.

For patients entering the maintenance phase while receiving biological therapy, discontinuation is assumed to occur for two reasons. First, patients treated with biologics who lose their response are assumed to discontinue treatment, the likelihood of which varies over time. Second, patients may discontinue for other reasons, of which there is a constant risk.

For the first cause of discontinuation, data from the dupilumab submission (TA534) were used, described in Table 69. For the constant risk of discontinuation, open-label data on discontinuation from an interim analysis of the ongoing ECZTEND study were used (see

sections B.2.2 and B.2.6.5.3) [64]. The annual rate of discontinuation from tralokinumab due to adverse events or lack of efficacy in ECZTEND was 2.6% among patients who achieved EASI 50 & ΔDLQI ≥ 4 in their parent study. The rate was similar when using other definitions of response, so the same discontinuation rate was used across all response definitions. This was the same discontinuation rate reported in the dupilumab open-label extension [46]. Therefore, in the base-case analysis the constant discontinuation rate associated with all biologics was 2.6%. Scenario analysis F (section B.3.8.3.7) investigates the impact of increasing the discontinuation rate for tralokinumab Q4W, compared with Q2W dosing, and of setting the biological therapy discontinuation rate to the ECZTEND all-cause drop-out rate among patients who achieved EASI 50 & ΔDLQI ≥ 4 in their parent study.

Table 69 Annual proportion of patients who lose response

Year	Biologic			BSC
	Annual risk of discontinuation (ECZTEND)	Probability of loss of response (TA534)	Cumulative total: patients who lose response	Cumulative total: patients who lose response (TA534)
Year 2	2.6%	2%	4.5%	25%
Year 3	2.6%	3%	9.8%	50%
Year 4	2.6%	2%	13.9%	75%
Year 5+	2.6%	1%	17.0%	100%

BSC, best supportive care.

B.3.3.4 Adverse events

The adverse events included within the model are injection-site reactions, oral herpes, allergic conjunctivitis and infectious conjunctivitis. An NMA was conducted for each of these events, using data from the tralokinumab and dupilumab trials (section B.2.10.9). Adverse event rates were used instead of risks, as some patients experienced more than one event – the cost of adverse events should reflect the total number of events, to ensure they are not under-counted. Data, pooled for monotherapy and combination therapy, were taken from the first 16 weeks of each trial and adjusted to estimate the annual rate.

Rate data were not available for injection site reactions in the dupilumab trials. As described in section B.2.10.9, the likelihood of experiencing at least one injection-site reaction with dupilumab compared to tralokinumab was calculated using a simple Bucher analysis, using the Peto odds ratio. This Peto odds ratio was applied to the odds of experiencing an injection-site reaction by week 16 in ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7 and adjusted to estimate the annual rate of injection-site reactions.

A rate network was constructed for each of the other adverse events, as described in section B.2.10.9. The resulting annual event rates are shown in Table 70.

Table 70 Annual adverse event risks/rates (NMA)

Adverse event	Tralokinumab	Dupilumab	BSC
Injection-site reactions [a]	[redacted]	[redacted]	[redacted]
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]
Infectious conjunctivitis	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]

[a] Calculated using Bucher analysis of the Peto odds ratio.
BSC, best supportive care; NMA, network meta-analysis.

Clinician expert opinion was that adverse events would affect resource use (section B.3.5.2.1).

B.3.3.5 Mortality

For completeness, age-dependent all-cause mortality rates were obtained from UK life tables and applied to the model as a background risk of death to all patients [124]. AD and its treatment were assumed not to affect overall mortality.

B.3.4 Measurement and valuation of health effects

Health effects in the analysis were expressed in QALYs, in accordance with the NICE Reference Case [125].

B.3.4.1 Health-related quality-of-life studies

Identification and selection of relevant cost-effectiveness studies is described in Appendix H. In brief, searches of relevant publication databases and grey literature sites were conducted on 16 February 2021. A summary of the EQ-5D utility values reported in the included studies is presented in Appendix H.1.3.1, Table 172.

B.3.4.2 Health-related quality-of-life data from clinical trials

Utility data from the ECZTRA trial programme were collected using the EQ-5D-5L and cross-walked using the van Hout *et al.* 2012 mapping function [77] to obtain index scores for the EQ-3D-3L. These data have been acquired directly from patients with AD, making them the most suited for inclusion in the base case cost-effectiveness analysis. The utility data were collected every 2 weeks up to the week-16 assessment point in ECZTRA 1, ECZTRA 2 and ECZTRA 3 and week 16 in ECZTRA 7.

B.3.4.3 Derivation of HRQoL data for use in the economic model

Following best practice, the economic analysis used a mixed model with repeated measures (MMRM) on EQ-5D-3L data collected in ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7 in order to determine the extent to which response to treatment at week 16 affected change in EQ-5D from baseline. As shown below, change in EQ-5D from baseline to week 16 was modelled as a function of age, sex, EASI and worst pruritus NRS score. These covariates were selected to align with the dupilumab appraisal (TA534).

$$\text{EQ-5D} = \alpha + \beta_1 \text{BaselineEQ-5D} + \beta_2 \text{Age} + \beta_3 \text{Sex} + \beta_4 (\text{EASIscore}) + \beta_5 (\text{WorstPruritusScore}) + \beta_6 (\text{EASIscore*WorstPruritiusScore}) + \beta_7 \text{Treatment}$$

Female was the reference category for sex; therefore, β_3 corresponds to the improvement from baseline EQ-5D for males. The total EASI and average weekly worst daily pruritus NRS scores were derived by applying mean change from baseline values to the baseline scores. Placebo was the reference category for treatment; therefore, β_7 corresponds to the improvement from baseline EQ-5D from receiving tralokinumab.

Mixed effects models were generated at the trial level (ECZTRA 1 and ECZTRA 2 combined; ECZTRA 3; and ECZTRA 7), not the base-case population level (ECZTRA 7-like), for both the NRI and all-observed data sets. This is because HRQoL is dependent on the EASI score and pruritus reduction and any differences in populations are adjusted for by accounting for baseline utility. Weights are generated for the base-case population using the mean change in EASI score and change in pruritus from the base case population in the appropriate utility regression (see Table 71).

Table 71 Summary of sources of regression inputs

Analysis	Source of input data
Monotherapy, all patients	All ECZTRA 1 and ECZTRA 2 data
Monotherapy, ECZTRA 7-like subgroup	ECZTRA 1 and ECZTRA 2 ECZTRA 7-like subgroup
Combination therapy, all patients	All ECZTRA 7 and ECZTRA 3 data
Combination therapy, ECZTRA 7-like subgroup	All ECZTRA 7 data and ECZTRA 3 ECZTRA 7-like subgroup data

IR, inadequate control with, or intolerance or contraindications to.

Parameter coefficients used in the utility calculations were varied in probabilistic sensitivity analysis, as described in section B.3.8.1.

Baseline data used in the utility regressions are presented in section B.3.2.1, Table 66. Change from baseline to week 16 in EASI and pruritus NRS score for the EASI 50 & ΔDLQI ≥ 4 response definition are shown in Appendix H.2.1, Table 175 and Table 176. Estimated model coefficients are reported in Table 72. Model goodness-of-fit was assessed using the AIC, the BIC statistics and diagnostic plots. AICs and BICs for each model fit are shown in Appendix H.2.2, Figure 47, Figure 48 and Figure 49. Variance–covariance matrices for each model are shown in Appendix H.2.3, Table 181, Table 182 and Table 176.

B.3.4.4 Disutilities associated with adverse reactions

The model does not include any utility effects of adverse events as it was judged that any impact would be mild and would be captured by the fortnightly utility measurement within the trials.

Table 72 Parameter coefficients from mixed-effects model

Mixed-effects model	Coefficient	Standard error	Individual *p* value
Monotherapy – ECZTRA 7-like and all-patient populations (ECZTRA 1 & 2)			
NRI (base-case)			
Intercept	0.68719	0.01925	< 0.0001
Baseline EQ-5D	0.34719	0.01486	0.0100
Age	-0.00069	0.00027	0.7865
Sex	0.00214	0.00791	< 0.0001
EASI	0.00146	0.00059	0.0136
Change in worst pruritus	-0.01872	0.00173	< 0.0001
EASI*Change in worst pruritus interaction	-0.00063	0.00009	< 0.0001
Treatment	0.03027	0.00945	0.0014
Combination therapy – all-patient population (ECZTRA 3)			
NRI (base-case)			
Intercept	0.84124	0.02700	< 0.0001
Baseline EQ-5D	0.18576	0.02163	0.0636
Age	-0.00072	0.00039	0.4227
Sex, F	-0.00974	0.01214	< 0.0001
EASI	-0.00027	0.00095	0.7787
Change in worst pruritus	-0.01859	0.00252	< 0.0001
EASI*Change in worst pruritus interaction	-0.00049	0.00015	0.0014
Treatment	0.00703	0.01302	0.5895
Combination therapy – ECZTRA 7-like population (ECZTRA 7)			
NRI (base-case)			
Intercept	0.81779	0.02842	< 0.0001
Baseline EQ-5D	0.19069	0.02833	0.7933
Age	−0.00012	0.00046	0.8140
Sex, F	0.00312	0.01327	< 0.0001
EASI	−0.00051	0.00097	0.5951
Change in worst pruritus	−0.02536	0.00279	< 0.0001
EASI*Change in worst pruritus interaction	−0.00031	0.00017	0.0730
Treatment	0.00471	0.01315	0.7205

EASI, Eczema Area and Severity Index.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.5.1 Health state utility values

Health state utility values estimated using the MMRM described in section B.3.4.3 are shown in Table 73. The method used to derive and apply health state utility values was in line with previous appraisals.

Induction therapy – responders

In the model, the utility value assumed for patients who have a week 16 response to biological therapy is the mean of the biologic responder utility and the baseline utility up to

16 weeks, to account for them achieving a response over time. Likewise, patients who respond to BSC receive the mean of the baseline utility value and BSC responder utility.

Induction therapy – non-responders

Patients who do not respond to treatment still, on average, receive a utility improvement compared to baseline in the ECZTRA trials. This was modelled by assigning patients who do not respond to a biologic, or BSC, the respective utility benefit modelled using the utility regressions. Patients receiving biological induction therapy who do not achieve the response threshold are assumed to receive some treatment benefit despite non-response; therefore, these patients are given the mean of the biologic non-responder and BSC non-responder utility values. This assumption is explored in scenario analysis F (section B.3.8.3.7). Patients treated with BSC who do not achieve a response receive the BSC non-responder utilities.

Maintenance therapy

After week 16, patients treated with a biological therapy who respond to treatment receive the biologic responder utility value until they lose response, discontinue treatment, or die. Patients receiving BSC are given the BSC responder or non-responder utilities, depending on whether they achieve the response definition threshold. A proportion of BSC patients revert to receiving baseline utility each year, such that all BSC patients are receiving baseline utility by year 5. This is detailed in section B.3.3.3.

Table 73 Health state utility values for EASI 50 & ΔDLQI ≥ 4 response definition, by treatment and response

Response definition	Biologic		BSC	
	Responders	Non-responders	Responders	Non-responders
Monotherapy – all patients	0.808	0.699	0.765	0.632
Monotherapy – ECZTRA 7-like	0.787	0.677	0.753	0.599
Combination therapy – all patients	0.860	0.769	0.843	0.745
Combination therapy – ECZTRA 7-like	0.851	0.757	0.833	0.738

BSC, best supportive care; CSA, ciclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; ECZTRA 7-like, patients who have inadequate control with, or intolerance or contraindications to, CSA.

B.3.4.5.2 Utility value age adjustment

In addition, an age adjustment was applied to the baseline utility estimate using the multiplicative method detailed in Ara and Brazier, 2010 [130]. The EQ-5D regression model, with EASI 50 & ΔDLQI ≥ 4 selected as the response definition, is:

$$u = multiplier * \sum_{i=1}^{j} response_i * u_{response_i} + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

Although EQ-5D population norms for the UK general population have been shown to decline with age, survival was assumed to be equal across all treatments, thus this was not expected to have an impact on the incremental results.

Scenario analysis F (section B.3.8.3.7) explores the impact of removing this age adjustment.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

In order to identify resource utilisation and unit costs most appropriate to this submission, several activities were undertaken:

- A systematic review of the literature to identify published and unpublished studies of relevant cost-effectiveness studies is described in Appendix I. In brief, searches of relevant publication databases and grey literature sites were conducted on 16 February 2021 to identify direct costs in a UK setting.
- Market research to evaluate the circumstances under which UK clinicians would consider switching patients from a Q2W to a Q4W maintenance dosing strategy.

Cost and healthcare resource use inputs considered in the base-case analysis were:

- biological treatment acquisition cost
- biological treatment administration
- monitoring costs
- adverse event management costs
- BSC.

As specified in the NICE Reference Case [125], only direct medical costs were included in the model. Costs were sourced from the NHS Reference Costs 2018–19 [128], Monthly Index of Medical Specialties (MIMS) [127], Personal Social Services Research Unit (PSSRU) [129] and published literature [131].

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs were derived from MIMS [127]. Unit costs as well as trial and treatment period total costs for each comparator are summarised in Table 74. Both dupilumab and tralokinumab begin with a 600 mg loading dose, before patients progress to receiving 300 mg doses at regular intervals (Q2W or Q4W for a portion of tralokinumab patients).

The total annual cost for tralokinumab, at list price, is £14,445 in year 1, and: £13,910 in subsequent years assuming all patients follow a Q2W dosing scheme from week 52 onward; and £6,955 in subsequent years assuming all patients follow a Q4W dosing scheme from week 52 onward.

B.3.5.1.2 Treatment administration

All therapies are administered as a subcutaneous (SC) injection. Based on the resource use assumptions from previous technology appraisals [46], it was assumed that patients treated with SC formulations would receive training regarding how to self-administer the drug. It was assumed that each patient only received one self-injection training session, requiring 1 hour of trained nurse time at a cost of £55.50 [129], incurred when they are first prescribed a

subcutaneously injected biologic. Training will be provided free of charge for tralokinumab, so is not included for this comparator.

Table 74 Drug acquisition costs

Drug	Pack size	Dose (mg)	Pack cost	Cost per dose	Total cost (to week 16)	Total cost (week 16 to end of year 1)	Total annual cost (maintenance)
Tralokinumab Q2W dosing (list price)	2 [a]	300	£1,070	£535	£4,815	£9,630	£13,910 [b] £6,955 [c]
Tralokinumab Q2W dosing (PAS price)	2 [a]	300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab (list price)	2	300	£1,265	£632	£5,748 [d]	£11,384	£16,444

[a] 4-syringe pack, making up two doses. [b] Assumes no patients switch to Q4W at week 52. [c] Assumes all patients switch to Q4W at week 52. [d] Includes one-off training cost of £55.50.
mg, milligram; PAS, patient access scheme; Q4W, every 4 weeks.

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Treatment monitoring

Resource use data associated with treatment monitoring were taken from the dupilumab NICE appraisal [46] as they were considered most relevant to the patient population and treatments under consideration. Monitoring includes regular outpatient visits and laboratory tests, with unit costs as shown in Table 75. The annual frequency of monitoring and the total costs are shown in Table 76 and Table 77. Alternate frequency estimates from the literature [132] were explored in scenario analysis F (section B.3.8.3.7). Frequency of monitoring was assumed to be the same across treatments, with the exception of tests and investigations, which are not required by biologic responders.

Table 75 NHS unit costs of treatment monitoring

Type of cost	Unit cost	Source
Primary care visits	£39.19	NHS Reference costs 2018–19 [128]
Consultant dermatologist visits	£114.57	
Accident and emergency attendances	£166.05	
Inpatient hospitalisations	£2,832.23	
Day case	£454.67	
Dermatology nurse visit	£10.50	
Social worker visit	£51.00	
Dermatologist nurse phone conversation	£10.50	
Visit to a medical specialist	£144.39	
Dermatologist phone conversation	£27.25	Unit Costs of Health and Social Care 2019 [129]
Phototherapy	£103.00	NHS Reference costs 2018–19 [128]
Psychological support	£297.50	
Tests and investigations (full blood count)	£2.78	

NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Table 76 Frequency and total cost of treatment monitoring during trial and treatment periods for each drug

Parameter description	Base case (TA534)		Ameen 2020 [132]	
	Responders	Non-responders	Responders	Non-responders
Primary care visits	2	12.81	12.22	18.09
Consultant dermatologist visits (Year 1)	4	6.09	0.13	0.51
Consultant dermatologist visits (Year 2+)	2	6.09	0.13	0.51
Accident and emergency attendances	0.02	0.09	0	0
Inpatient hospitalisations	0.02	0.12	0.78	1.02
Day case	0	0.21	0	0
Dermatology nurse visit	0.42	0.55	0	0
Social worker visit	0	0	0	0
Dermatologist nurse phone conversation	0	0	0	0
Visit to a medical specialist	0	0	2.53	3.41
Dermatologist phone conversation	0	0	0	0
Phototherapy	0.06	0.06	0	0
Psychological support	0.07	0.07	0	0
Tests and investigations [a]	4	4	0	0

[a] none for biologic responders.

Table 77 Annual monitoring costs by treatment

Treatment	Responders	Non-responders
Biologic (Year 1)	£628.05	£1,692.54
Biologic (Year 2+)	£398.90	n/a
Best supportive care (Year 1)	£639.17	£1,692.54
Best supportive care (Year 2+)	£410.02	£1,692.54

B.3.5.2.2 Best supportive care

BSC cost estimates were taken from the dupilumab NICE appraisal (TA534) [46], which included market research to establish the most common bathing and emollient products used by patients with AD. The up-to-date unit costs of these treatments were obtained from MIMS or inflated where this was not possible [127]. The costs of bathing products are excluded, based on recommendations by the committee for the baricitinib NICE appraisal [29]. It is assumed that patients use the eight most commonly prescribed emollients, and the assumed quantity used is based on the label recommendation. The rate of background treatment use is assumed to be reduced by half for responders, compared with BSC non-responders, at a corresponding cost of £142.14 and £284.28, respectively. This follows the expert opinion referenced in TA534 [46].

B.3.5.3 Adverse reaction unit costs and resource use

Resource use associated with the management of AEs is summarised in Table 78 and is informed by TA534. Injection-site reactions were associated with a consultant-led appointment [128]. Allergic conjunctivitis was associated with a 9.22-minute general practitioner (GP) visit, as was oral herpes. Infectious conjunctivitis is associated with an

11.7-minute GP visit [129], an ophthalmology visit [128] and prescription of 1% prednisolone eye drops [127].

Patients could also experience flares, in which case they received rescue therapy (consisting of high-potency topical treatments or systemic therapy). The cost associated with rescue was informed by the quantity and unit costs of rescue therapy used in ECZTRA 1, ECZTRA 2 and ECZTRA 3 (Table 79). The quantity of rescue therapy used was higher in the monotherapy trials; this may be as a result of TCS being classed as rescue therapy. It was assumed that each product was used for an average of 14 days, following the label recommended quantities.

The total costs associated with AEs are shown in Table 79 and are calculated by multiplying adverse event rates in Table 70 by the corresponding unit costs in Table 78.

Table 78 Unit costs of treatment for adverse events

Adverse event	Resource use	Cost	Source
Injection-site reaction	1 consultant led episode (WF01)	£114.57	Unit Costs of Health and Social Care 2019 [129] NHS Reference costs [128]
Oral herpes	9.22-minute GP visit	£39.19	Unit Costs of Health and Social Care 2019 [129]
Allergic conjunctivitis			
Infectious conjunctivitis	11.7-minute GP visit Ophthalmology visit (WF01B) Prescription of 1% prednisolone eye drops	£50.20	Unit Costs of Health and Social Care 2019 [129] NHS Reference costs [128] MIMS 2020 [127]

GP, general practitioner; MIMS, Monthly Index of Medical Specialties.

Table 79 Annual adverse event costs

Treatment	Monotherapy	Combination therapy
Cost to treat flares		
Tralokinumab	£63.89	£2.43
Dupilumab [a]	£63.89	£2.43
Best supportive care	£82.23	£12.52
Total annual adverse event costs		
Tralokinumab	£91.91	£30.36
Dupilumab	£97.31	£35.86
Best supportive care	£89.99	£20.28

[a] assumed to be the same as tralokinumab.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Variables used in the economic model, together with the distributions used in probabilistic sensitivity analysis (PSA), are shown in Table 80.

Table 80 Summary of variables applied in the economic model

Parameter	Mean	Precision parameters			Distribution	Section of submission
		SE (95% CI)	LLCI	HLCI		
General						
Model parameters						
Discount rate for costs, %	3.5	–	–	–	Fixed	B.3.2.2
Discount rate for outcomes, %	3.5	–	–	–		
Time horizon	Lifetime	–	–	–		
Perspective	NHS/PSS	–	–	–		
Include mortality	Yes	–	–	–		B.3.3.5
Age-adjusted utility	Yes	–	–	–		B.3.4.5.2
Definition of response	EASI 50 & ΔDLQI ≥ 4	–	–	–		B.1.1.1.1
Population						
Monotherapy, ECZTRA 7-like					Fixed – varied in OWSA only	B.3.2.1
Male sex, %	60.0	–	50.0	70.0		
Age, years	37.7	–	27.7	47.7		
Combination therapy, ECZTRA 7-like						
Male sex, %	58.3	–	48.3	68.3		
Age, years	38.3	–	28.3	48.3		
Discontinuation						
Annual rate for all biologics, %	2.6	–	1.8	3.0	Beta – varied in OWSA for tralokinumab only	B.3.3.3
Clinical response (NRI) [a]						
Week 16						
Monotherapy, ECZTRA 7-like, EASI 50 & ΔDLQI ≥ 4					CODA, log-odds scale, anchored against BSC – also varied in OWSA	B.1.1.1.1
Tralokinumab Q2W	1.418	–	0.873	2.022		
Dupilumab Q2W	2.163	–	1.427	2.979		
BSC	−1.940	–	−2.917	−0.959		
Combination therapy, ECZTRA 7-like, EASI 50 & ΔDLQI ≥ 4						
Tralokinumab Q2W	0.618	–	0.056	1.206		
Dupilumab Q2W	2.133	–	1.354	2.920		
BSC	−0.299	–	−3.096	2.474		
Week 52						
Monotherapy and combination therapy, EASI 50 & ΔDLQI ≥ 4					CODA, log-odds scale, anchored against BSC – also varied in OWSA	B.3.3.2.2
Tralokinumab Q2W	0.123	–	−0.670	0.910		
Tralokinumab Q4W	0.123	–	0.440	1.703		
Dupilumab Q2W	1.551	–	0.481	2.701		
BSC	1.346	–	0.555	2.140		
Adverse events [a]						
Allergic conjunctivitis, tralokinumab	0.453	–	−0.061	0.990	CODA, values on log hazard scale, anchored against BSC – also varied in OWSA	B.3.3.4
Allergic conjunctivitis, dupilumab	0.838	–	0.462	1.234		
Allergic conjunctivitis, BSC	−2.641	–	−4.918	−0.362		
Infectious conjunctivitis, tralokinumab	1.222	–	0.810	1.669		

Parameter	Mean	Precision parameters			Distribution	Section of submission
		SE (95% CI)	LLCI	HLCI		
Infectious conjunctivitis, dupilumab	1.619	–	1.026	2.298		
Infectious conjunctivitis, BSC	−2.954	–	−4.457	−1.451		
Oral herpes, tralokinumab	−0.342	–	−0.864	0.168		
Oral herpes, dupilumab	1.051	–	0.373	1.808		
Oral herpes, BSC	−2.815	–	−4.603	−1.025		
Injection site reaction, tralokinumab	0.037	–	0.027	0.046	Beta, odds ratio applied to week 16 risk	
Injection site reaction, OR tralokinumab vs dupilumab	3.810	–	1.200	12.090	Log-normal, odds ratio applied to week 16 risk	
Utilities (NRI)						
Baseline utility						
Ciclosporin IR, monotherapy	0.513	0.013	0.488	0.538	Beta – also varied in OWSA	B.3.2.1
Ciclosporin IR, combination therapy	0.590	0.011	0.569	0.610		
Monotherapy, ECZTRA 7-like						
Intercept	0.687	0.019	0.649	0.725	Normal, Cholesky decomposition – change in EASI and pruritus were also varied in OWSA	B.3.4.5
Baseline utility effect	0.347	0.015	0.318	0.376		
Age	−0.001	0.000	−0.001	0.000		
Sex, Female	0.002	0.008	−0.013	0.018		
EASI	0.001	0.001	0.000	0.003		
Change in pruritus	−0.019	0.002	−0.022	−0.015		
Pruritus*EASI	−0.001	0.000	−0.001	0.000		
Tralokinumab	0.030	0.009	0.012	0.049		
Combination therapy, ECZTRA 7-like						
Intercept	0.818	0.028	0.762	0.873	Normal, Cholesky decomposition – change in EASI and pruritus were also varied in OWSA	B.3.4.5sec
Baseline utility effect	0.191	0.028	0.135	0.246		
Age	0.000	0.000	−0.001	0.001		
Sex, Female	0.003	0.013	−0.023	0.029		
EASI	−0.001	0.001	−0.002	0.001		
Change in pruritus	−0.025	0.003	−0.031	−0.020		
Pruritus*EASI	0.000	0.000	−0.001	0.000		
Tralokinumab	0.005	0.013	−0.021	0.030		
Costs						
Treatment costs						
Biological therapy costs						
Tralokinumab 300mg pre-filled syringe	[redacted]	–	–	–	Fixed	B.3.5.1.1
Dupilumab 300mg pre-filled syringe	£632.45	–	–	–		
One-off self-injection training cost	£55.50	–	–	–		

Parameter	Mean	Precision parameters			Distribution	Section of submission
		SE (95% CI)	LLCI	HLCI		
Emollient costs						
Aveeno cream (Johnson & Johnson Ltd)	£6.47	£0.65	£5.26	£7.80	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	B.3.5.2.2
Cetraben ointment (Thornton & Ross Ltd)	£5.39	£0.54	£4.39	£6.50		
Dermol cream (Dermal Laboratories Ltd)	£6.63	£0.66	£5.39	£7.99		
Diprobase ointment (Bayer Plc)	£5.99	£0.60	£4.87	£7.22		
Epaderm ointment (Molnlycke Health Care Ltd)	£12.25	£1.23	£9.97	£14.76		
Hydromol ointment (Alliance Pharmaceuticals Ltd)	£8.20	£0.82	£6.67	£9.88		
White soft paraffin 50% / Liquid paraffin 50% ointment (A A H Pharmaceuticals Ltd)	£3.49	£0.35	£2.84	£4.21		
Oilatum cream (GlaxoSmithKline Consumer Healthcare)	£11.08	£1.11	£9.02	£13.35		
Topical corticosteroid costs						
Mometasone 0.1% ointment	£10.37	£1.04	£8.44	£12.50	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	B.1.1.1
Rescue therapy costs						
Azathioprine 50 mg x56	£2.59	£0.26	£2.11	£3.12	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	0
Benzoic acid 25 g x1	£2.69	£0.27	£2.19	£3.24		
Betamethasone 30 g x1	£19.84	£1.98	£16.14	£23.91		
Capsorin (Ciclosporin) 100 mg x30	£41.59	£4.16	£33.84	£50.13		
Clobetasol 30 g x1	£7.90	£0.79	£6.43	£9.52		
Flumetasone (Triclosan) 10 ml x1	£15.13	£1.51	£12.31	£18.24		
Hydrocortisone 100 mg x1	£4.93	£0.49	£4.01	£5.94		
Hydrocortisone Butyrate 100 mg x1	£4.93	£0.49	£4.01	£5.94		
Methotrexate 10 mg x100	£52.01	£5.20	£42.32	£62.69		
Methylprednisolone 4 mg x30	£6.19	£0.62	£5.04	£7.46		
Mycophenolate Mofetil 500 mg x50	£6.17	£0.62	£5.02	£7.44		
Prednisolone 30 mg x28	£23.43	£2.34	£19.06	£28.24		
Prednisone 30 mg x28	£23.43	£2.34	£19.06	£28.24		
Tacrolimus 60 g x1	£34.52	£3.45	£28.09	£41.61		
Triamcinolone 5 mg x1	£3.63	£0.36	£2.95	£4.38		

Parameter	Mean	Precision parameters			Distribution	Section of submission
		SE (95% CI)	LLCI	HLCI		
Adverse event related costs						
1% Prednisolone eye drops	£3.66	£0.37	£2.98	£4.41	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	0
Ophthalmology, non-consultant led	£93.08	£9.31	£75.73	£112.19		
Ophthalmology, consultant led	£114.75	£11.47	£93.36	£138.30		
Healthcare-related resource use						
Healthcare related resource unit costs						
Consultant dermatologist visit [b]	£114.57	–	–	–	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	B.3.5.2.1
GP Dr hourly cost [b]	£255	–	–	–		
GP nurse hourly cost [b]	£42	–	–	–		
Day case [b]	£454.67	–	–	–		
Non-elective Inpatient [b]	£2,832.23	–	–	–		
Emergency attendances [b]	£166.05	–	–	–		
Full blood count cost	£2.78	£0.28	£2.26	£3.35		
Tests and monitoring cost	£55.50	£5.55	£45.16	£66.89		
Visit to a medical specialist	£144.39	£14.44	£117.48	£174.03		
Phototherapy	£103.00	£10.30	£83.80	£124.14		
Psychological support	£297.50	£29.75	£242.06	£358.57		
Healthcare related resource use (responders)						
Primary care visits	2.000	0.200	1.683	2.340	Gamma, SE assumed to be 0.1 x mean – also varied in OWSA	B.3.5.2.1
Consultant dermatologist visits (Year 1)	4.000	0.400	3.366	4.680		
Consultant dermatologist visits (Year 2+)	2.000	0.200	1.683	2.340		
Accident and emergency attendances	0.020	0.002	0.017	0.023		
Inpatient hospitalisations, Responder	0.020	0.002	0.017	0.023		
Dermatology nurse visit, Responder	0.420	0.042	0.353	0.491		
Phototherapy	0.060	0.006	0.050	0.070		
Psychological support	0.070	0.007	0.059	0.082		
Healthcare related resource use (non-responders)						
Primary care visits	12.810	0.211	12.466	13.158	Gamma, SE derived from SD in TA534 revised submission or TA534 ERG report – also varied in OWSA	B.3.5.2.2
Consultant dermatologist visits	6.090	0.489	5.309	6.916		
Accident and emergency attendances	0.090	0.031	0.045	0.146		
Inpatient hospitalisations	0.120	0.068	0.031	0.248		
Day case	0.210	0.097	0.073	0.387		

Parameter	Mean	Precision parameters			Distribution	Section of submission
		SE (95% CI)	LLCI	HLCI		
Dermatology nurse visit	0.550	0.102	0.393	0.728		
Phototherapy	0.060	0.029	0.021	0.114		
Psychological support	0.065	0.024	0.032	0.109		
Psychological support	0.065	0.024	0.032	0.109		
Tests and investigations	4.0	No distribution assumed per TA534 ERG analysis				

[a] induction and maintenance phase efficacy and adverse event parameters are taken from the NMA. Data are presented as A (baseline) and d (treatment effect) parameters. Risks are presented on the log-odds scale and rates are presented on the log hazard scale. Clinical responses are anchored against BSC. [b] These are weighted averages, which each cost component varied individually as part of PSA.
BSC, best supportive care; CODA, Convergence Diagnostics and Output Analysis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, evidence review group; g, grams; HLCI, higher limit of confidence interval; IR, inadequate control with, or intolerance or contraindications to; LLCI, lower limit of confidence interval; mg, milligrams; MIMS, Monthly Index of Medical Specialties; n/a, not applicable; NHS, National Health Service; OR, Odds-ratio; OWSA, one-way sensitivity analysis; SD, standard deviation; SE, Standard error; Q2W, every 2 weeks; Q4W, every 4 weeks.

B.3.6.2 Assumptions

Table 81 Base-case economic model assumptions

Parameter	Assumptions	Justification
Treatment mix	[redacted] of tralokinumab responders are assumed to switch to Q4W dosing after week 52	This proportion is based on feedback from clinicians about the number of patients for whom maintenance Q4W treatment is likely to be suitable, and is varied in scenario analysis E Switching is permitted by the tralokinumab label after 16 weeks, and UK HCP opinion is that most clinicians would consider switching at approximately 6 months, based on patients' responses; therefore, this assumption may be conservative
Discontinuation	During maintenance treatment, an annual rate of discontinuation of 2.6% was assumed for all biologics	Discontinuation was based on data from the ECZTEND trial and was similar across all response definitions The same discontinuation rate was reported in the dupilumab open-label extension [46]
	A proportion of patients are assumed to lose the biologic treatment benefit and discontinue to BSC	Discontinuation due to loss of response was informed by the dupilumab appraisal (TA534) [46]
Estimands	In the base case, patients who received rescue treatments are assumed to discontinue biologics	This aligns with the NRI approach used for the clinical trial primary 'composite' estimand
Response definition	Treatment response is based on EASI 50 & ΔDLQI ≥ 4 at week 16	This response definition is consistent with the dupilumab and baricitinib appraisals (TA534, TA681) [29, 46], and is relevant to clinical practice in the NHS
Sustained response	Sustained response probabilities are assumed to be the same in the ECZTRA 7-like subgroup and the overall population	No evidence was available for the ECZTRA 7-like subgroup; this assumption is based on the consistent week 16 responses in the ECZTRA 1, ECZTRA 2 and ECZTRA 3 ECZTRA 7-like subgroups and in the overall trial populations

Parameter	Assumptions	Justification
	Sustained EASI 50 and EASI 50 & ΔDLQI ≥ 4 responses for tralokinumab Q4W are assumed to be the same as for Q2W	Data for these endpoints were not available for tralokinumab Q4W, because these were derived from ECZTRA 7 which did not include Q4W dosing
	Patients treated with biologics are assumed to maintain their response until they discontinue treatment	Loss of response is assumed to result in treatment discontinuation; this is consistent with the dupilumab and baricitinib appraisals (TA534, TA681) [29, 46]
	Patients treated with BSC are assumed to lose their treatment benefit over time	This assumption is based on the inclusion criteria in AD clinical trials: in order to be eligible for the trials, patients were required to have had an inadequate response to the treatments included in BSC. Therefore, it is expected that after the trial these patients would return to their baseline HRQoL
Mortality	AD and its treatment are assumed not to affect overall mortality	The published evidence on the impact of AD on life expectancy is limited The assumption of no impact on mortality is consistent with the dupilumab and baricitinib appraisals (TA534, TA681) [29, 46]
Utility values	Disutilities of AEs are not included	The utility impact of AEs was judged to be mild and to be captured by the fortnightly utility measurement within the trials; this is consistent with the dupilumab appraisal (TA534) [46]
	Patients receiving biological induction therapy who do not achieve the response threshold are assumed to receive some treatment benefit despite non-response; therefore, these patients are given the mean of the biologic non-responder and BSC non-responder utility values	This is consistent with the dupilumab appraisal (TA534) [46] This assumption is explored in scenario analysis F
	Utility values are adjusted to decline with age	This is consistent with multiple previous NICE appraisals including the baricitinib appraisal (TA681) [29]
Treatment administration costs	Patients treated with SC dupilumab are assumed to receive training regarding how to self-administer the drug	This is based on the resource use assumptions from the dupilumab and baricitinib appraisals (TA534, TA681) [29, 46]
BSC costs	The costs of bathing products are excluded	This is based on recommendations by the committee for the baricitinib appraisal (TA681) [29, 133]
	Patients are assumed to use the eight most commonly prescribed emollients	This is consistent with the dupilumab and baricitinib appraisals (TA534, TA681) [29, 46]

AD, atopic dermatitis; AE, adverse event; BSC, best supportive care; HCP, healthcare provider; HRQoL, health-related quality of life; IR, inadequate control with, or intolerance or contraindications to; NHS, National Health Service; NMA, network meta-analysis; NRI, non-responder imputation; SC, subcutaneous; Q4W, every 4 weeks.

B.3.7 Base-case results

The economic analysis results are presented below for treatment with the comparators as monotherapy and combination therapy with TCS.

All results include the tralokinumab PAS confidential discount.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Clinical outcomes from the model and disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix J.

B.3.7.2 Base-case results

B.3.7.2.1 Monotherapy

Base-case cost-effectiveness results for monotherapy are shown in Table 82. The ICER for tralokinumab compared with BSC was £24,666 per QALY. When compared with tralokinumab, dupilumab provided more QALYs, at a higher cost, with a fully incremental ICER of £115,545.

Table 82 Base-case results for monotherapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,666	£24,666
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£115,545

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.7.2.2 Combination therapy with TCS

As combination therapy, the ICER for tralokinumab plus TCS versus BSC plus TCS was £26,969 per QALY (Table 83). In a fully incremental analysis, the ICER for dupilumab plus TCS versus tralokinumab plus TCS was £125,178.

Table 83 Base-case results for combination therapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,969	£26,969
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£125,178

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

A PSA with 1000 model simulations was conducted to explore the uncertainty in model variables. A full list of all parameters included in the PSA, including mean values, standard errors and distributions, is presented in section B.3.6.1, Table 80. Probability distributions were based on estimates of uncertainty from data sources, such as confidence intervals. In the absence of data on the variability around the sampling distribution of mean values, the standard error is assumed to be equal to 10% of the mean. PSA was conducted for both monotherapy and combination therapy, using the base-case response definition (EASI 50 & ΔDLQI ≥ 4) and population (ECZTRA 7-like).

B.3.8.1.1 Monotherapy

PSA results for monotherapy are shown in Table 84. The mean ICER for tralokinumab compared with BSC was £25,260 per QALY. Dupilumab provided more QALYs, at a higher cost, with a mean ICER versus BSC of £64,393. A graphical representation of the simulations and the resultant cost-effectiveness acceptability curves are shown in Figure 30. At a cost-effectiveness threshold of £30,000 per QALY, tralokinumab has the highest likelihood of the comparators of being cost effective (98%).

Table 84 PSA results for monotherapy in ECZTRA 7-like population

Treatment	Total, mean (95% CrI)		ICER vs BSC (£/QALY), mean (95% CrI)
	Costs (£)	QALYs	
BSC	[redacted]	[redacted]	–
Tralokinumab	[redacted]	[redacted]	£25,260 (£21,845–29,379)
Dupilumab	[redacted]	[redacted]	£64,393 (£53,582–69,000)

BSC, best supportive care; CrI, credible interval; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B.3.8.1.2 Combination therapy with TCS

As combination therapy, the mean ICER for tralokinumab plus TCS versus BSC plus TCS was £29,155 per QALY (Table 85). The mean ICER for dupilumab plus TCS versus BSC plus TCS was £70,686 per QALY. A graphical representation of the simulations and the resultant cost-effectiveness acceptability curves are shown in Figure 30. At a cost-effectiveness threshold of £30,000 per QALY, tralokinumab has the highest likelihood of the comparators of being cost effective (77%). The PSA results for dupilumab were slightly different from the deterministic analysis due to a negative skew in the distribution of dupilumab costs and effects. This appears to be driven by its high probability of response at week 16 which constrains the distribution at 100%.

Table 85 PSA results for combination therapy in ECZTRA 7-like population

Treatment	Total, mean (95% CrI)		ICER vs BSC (£/QALY), mean (95% CrI)
	Costs (£)	QALYs	
BSC + TCS	[redacted]	[redacted]	-
Tralokinumab + TCS	[redacted]	[redacted]	£29,155 (£23,789–41,931)
Dupilumab + TCS	[redacted]	[redacted]	£70,686 (£56,379–72,650)

BSC, best supportive care; CrI, credible interval; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was undertaken to assess the impact of key variables on the outcomes of the model. The parameters that were assessed are noted in section B.3.6.1, Table 80; inputs were varied to the limits of their 95% credible intervals/confidence intervals. OWSA was conducted for tralokinumab versus BSC and tralokinumab versus dupilumab for both monotherapy and combination therapy, using the base-case outcome definition and population. The results of the ten parameters with the greatest impact are reported in terms of incremental net monetary benefit (INMB), calculated at a willingness-to-pay of £30,000 per QALY; positive values suggest that tralokinumab is more cost-effective at this threshold than the comparator. The full OWSA results are also reported in a tabular format in Appendix J.

B.3.8.2.1 Monotherapy

Figure 31 shows the ten inputs with the greatest impact on the INMB of tralokinumab compared with BSC and tralokinumab compared with dupilumab. For reference, the INMB in the base case is £5,243 for tralokinumab versus BSC and £63,510 for tralokinumab versus dupilumab. The week 16 response probabilities had the highest impact on the INMB for tralokinumab (tralokinumab vs BSC) or dupilumab (tralokinumab vs dupilumab). In all comparisons the INMB of tralokinumab was positive, suggesting that tralokinumab is associated with a net-monetary benefit relative to its comparators and is therefore cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

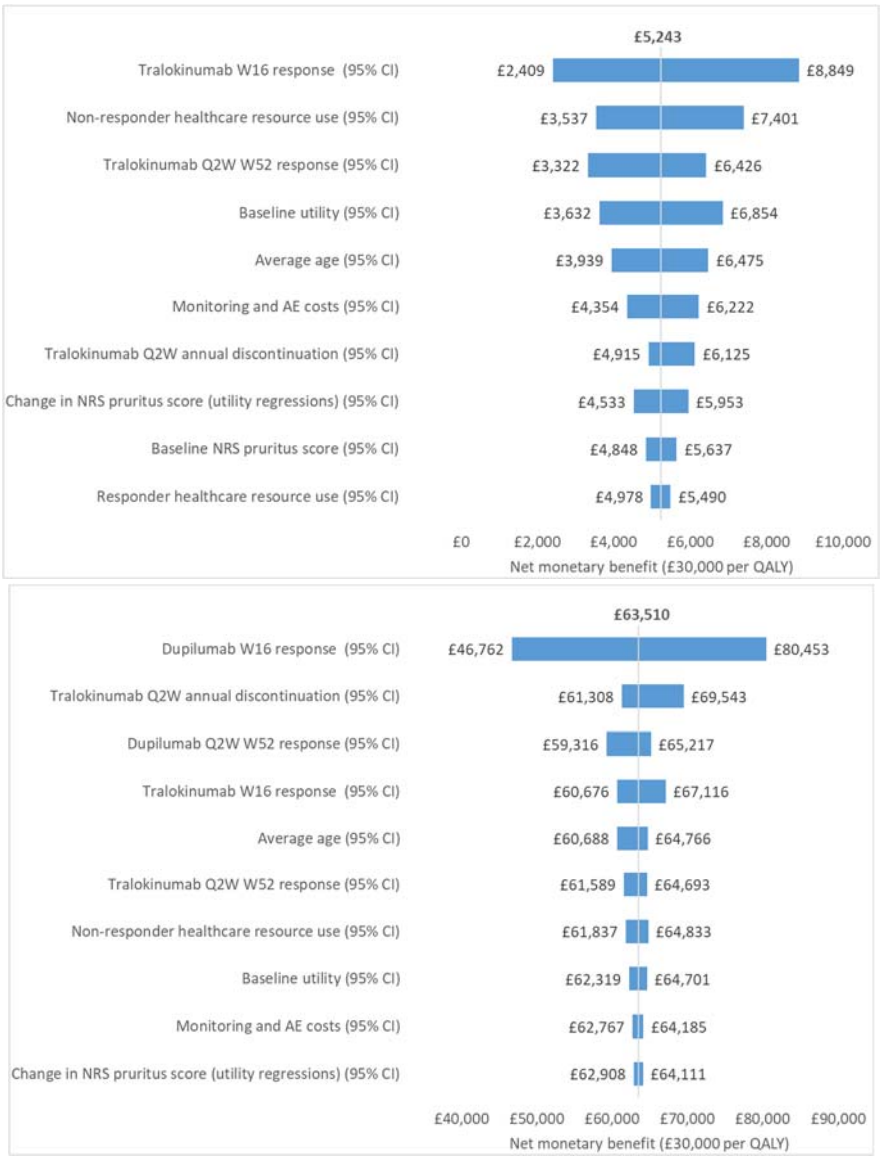
B.3.8.2.2 Combination therapy with TCS

Figure 32 shows the ten inputs with the greatest impact on the INMB of tralokinumab compared with BSC and tralokinumab compared with dupilumab. For reference, the INMB in the base case is £4,122 for tralokinumab versus BSC and £99,454 for tralokinumab versus dupilumab. In all comparisons the INMB of tralokinumab was positive, suggesting that tralokinumab is associated with a net-monetary benefit relative to its comparators and is therefore cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

Figure 30 PSA cost-effectiveness plane scatterplots and cost-effectiveness acceptability curves

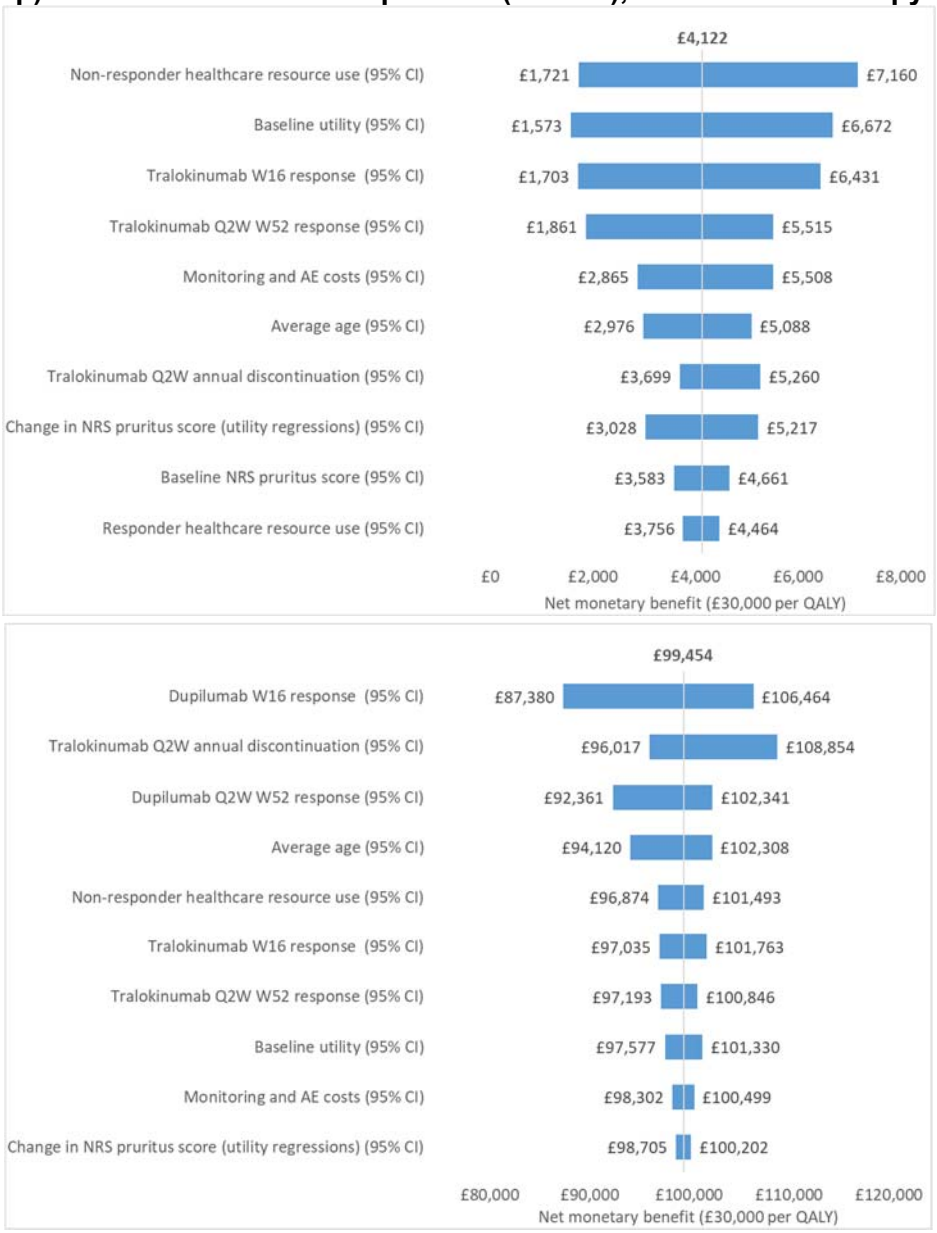
CEAC, cost-effectiveness acceptability curve.

Figure 31 Most impactful variables in one-way sensitivity analysis for tralokinumab vs BSC (top) and tralokinumab vs dupilumab (bottom), monotherapy



AE, adverse event; BSC, best supportive care; Q2W, every 2 weeks; W16, week 16; W52, week 52.

Figure 32 Most impactful variables in one-way sensitivity analysis for tralokinumab vs BSC (top) and tralokinumab vs dupilumab (bottom), combination therapy



AE, adverse event; BSC, best supportive care; Q2W, every 2 weeks; W16, week 16; W52, week 52.

B.3.8.3 Scenario analyses

As described in the following sections, a series of scenario analyses were performed in order to test particular assumptions and/or data sources.

B.3.8.3.1 Inclusion of baricitinib in scenario analyses

Data were not available for baricitinib using the EASI 50 & ΔDLQI ≥ 4 response definition, so it could not be included in the base case analysis. Several scenario analyses were conducted using alternative response definitions, for which some evidence for baricitinib was available from the NMA (see section B.2.9). In scenario analyses in the base-case ECZTRA 7-like population, baricitinib could be included in the EASI 50 and EASI 75 response definition analyses for combination therapy only. In scenario analysis C, which explored cost-effectiveness in the overall trial populations, baricitinib could be included as monotherapy and as combination therapy (see section B.2.9.2.1.1).

B.3.8.3.1.1 Baricitinib-specific assumptions

In addition to the assumptions described in section B.3.6.2, inclusion of baricitinib in the scenario analyses required several additional modelling assumptions (Table 86).

Table 86 Baricitinib modelling assumptions

Aspect	Approach
Response rates	In the absence of relevant data, the week 52 conditional response rate for baricitinib monotherapy was assumed to be the same as that for tralokinumab (see section B.3.8.3.1.2) The week 52 conditional response rate for baricitinib combination therapy was assumed to be the same as that for BSC (see section B.3.8.3.1.2)
Discontinuation	For baricitinib there was limited information regarding long-term discontinuation since only data for 68 weeks of continuous treatment were available [134]. This was not considered long enough to determine the discontinuation rate beyond week 52. Therefore, the long-term discontinuation rate for baricitinib was assumed to equal that of tralokinumab
Adverse events	In the absence of comparable data on safety for baricitinib, it was assumed to be associated with the same risk of conjunctivitis and oral herpes as tralokinumab. Baricitinib is an oral tablet; therefore, the rate of injection site reactions was set to zero
Treatment costs	The cost of baricitinib was modelled using the list price, taken from MIMS: £805.56 for 28 4-mg tablets Baricitinib is a 4-milligram oral tablet and does not have any associated treatment administration costs
Monitoring costs	Per the NICE Clinical Knowledge Summary for baricitinib [107], additional primary care monitoring is recommended with the following schedule: fortnightly for 6 weeks of baricitinib treatment, monthly for the subsequent 3 months and then subsequently every 12 weeks on an ongoing basis. In the model this additional monitoring was included as extra primary care visits; it was assumed that the visits would be in addition to visits related to management of atopic dermatitis All other monitoring costs were assumed to be the same as for biologics

MIMS, Monthly Index of Medical Specialties.

B.3.8.3.1.2 Model inputs for baricitinib analyses

The probabilities of EASI 50 and EASI 75 responses at week 16 were informed by the NMA (section B.2.9.2.1), and are presented in scenario analysis B (section B.3.8.3.3, Table 90).

Data were not available to include baricitinib in the maintenance phase NMA. The only data available for the efficacy of baricitinib over the long term came from the BREEZE AD-3 long-term extension study which enrolled patients who completed BREEZE AD-1, AD-2 or AD-7 (and therefore reflected an all-patient population rather than a ECZTRA 7-like subpopulation). The BREEZE AD-4 trial reported data on the effectiveness of baricitinib in the ECZTRA 7-like population up to week 24, but responses were not conditional on outcomes at week 16 and are therefore not comparable to data from the other maintenance phase trials.

The best available data for estimating the conditional response for baricitinib in a combination therapy regimen at Week 52 was judged to be the subgroup of the BREEZE AD-3 trial who enrolled via the BREEZE AD-7 trial. For this subgroup, the proportion of patients achieving EASI 75 was reported up to week 40 with response decreasing steadily over time and with values lower than placebo reported at week 32 and week 40 (overall weeks on treatment). By extrapolating this trend to week 52 it was assumed that the baricitinib conditional response rate is equivalent to BSC for combination therapy in the all-patient population. In lieu of other data, the same assumption was applied to the ECZTRA 7-like subgroup, and was also used for the EASI 50 response definition.

A similar approach for the monotherapy analysis was not considered valid since the use of TCS was allowed in the BREEZE AD-3 trial which meant that the results may not reflect a true monotherapy population. In lieu of other data it was assumed that the conditional response of baricitinib at week 52 was equivalent to tralokinumab in both the all-patient and ECZTRA 7-like populations as well as for the EASI 50 response definition.

The probabilities of EASI 50 and EASI 75 responses at week 52 are presented in scenario analysis B (section B.3.8.3.3, Table 91).

B.3.8.3.2 Scenario analysis A: use of all-observed data

In the base case, the probability of response was estimated using the NRI data set ('composite' estimand), in which all patients who used rescue therapy were treated as non-responders. In this scenario, the probability of response was estimated using the 'all-observed' estimand instead, in which patients who used rescue therapy were still included in the analysis as biologic patients.

B.3.8.3.2.1 Scenario A inputs

The proportion of patients achieving each response definition at week 16, based on all-observed data in the NMA, is shown in Table 87. Probabilities of sustained responses at week 52 are assumed to be the same as in the NRI analysis (section B.3.3.2.2, Table 68).

Table 87 Proportion of patients achieving each response definition at week 16 (all-observed)

Treatment	ECZTRA 7-like			All patients		
	EASI 50 & ΔDLQI ≥ 4	EASI 50	EASI 75	EASI 50 & ΔDLQI ≥ 4	EASI 50	EASI 75
Monotherapy						
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination therapy						
Tralokinumab Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC + TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IR, inadequate control with, or intolerance or contraindications to; Q2W, every 2 weeks; TCS, topical corticosteroids.

B.3.8.3.2.2 Scenario A results

Results for the all-observed scenario are shown in Table 88 and Table 89 for monotherapy and combination therapy, respectively. Costs and QALYs for tralokinumab were higher than the base case, but the ICERs versus BSC were similar or slightly lower. The ICERs for dupilumab versus tralokinumab were higher than the base-case analysis.

Table 88 All-observed scenario for monotherapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,305	£23,305
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£61,717	£159,620

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 89 All-observed scenario results for combination therapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,978	£26,978
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£70,248	£136,938

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.3.3 Scenario analysis B: use of alternative outcome definitions

The responder definition used in the base-case analysis was EASI 50 & ΔDLQI ≥ 4. Although this definition is relevant to clinical practice in the UK [46], published data for this endpoint are limited. This scenario investigated the use of the alternative response definitions EASI 50 and EASI 75 in the ECZTRA 7-like population. As described in section B.3.8.3.1, baricitinib could be included in the combination therapy analysis (assumptions required to include baricitinib are shown in Table 86), but not in the monotherapy analysis.

B.3.8.3.3.1 Scenario B inputs

The proportion of patients achieving EASI 50 and EASI 75 responses at week 16, based on the NMA (section B.2.9.2.1), is shown in Table 90 (response probabilities for the all-patient population are used in scenario analysis C; section B.3.8.3.4). Conditional response probabilities at week 52, based on the NMA (section B.2.9.2.2) and additional assumptions for baricitinib (section B.3.8.3.1.2), are shown in Table 91.

Table 90 Proportion of patients achieving week 16 EASI 50 and EASI 75 responses (NRI)

Treatment	ECZTRA 7-like		All patients	
	EASI 50	EASI 75	EASI 50	EASI 75
Monotherapy				
Tralokinumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Combination therapy				
Tralokinumab Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib 4 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W + TCS	[redacted]	[redacted]	[redacted]	[redacted]
BSC + TCS	[redacted]	[redacted]	[redacted]	[redacted]

[a] estimated by applying the treatment effect from the all-patient population (baricitinib 4 mg vs BSC odds ratio of 3.65).
[b] estimated by applying the treatment effect from the all-patient population (baricitinib 4 mg vs BSC odds ratio of 4.07).
BSC, Best supportive care; EASI, Eczema Area and Severity Index; IR, inadequate control with, or intolerance or contraindications to; NRI, non-responder imputation; Q2W, every 2 weeks; TCS, topical corticosteroids.

Table 91 Proportion of patients maintaining each response definition at week 52 (NRI) [a]

Treatment	EASI 50	EASI 75
Monotherapy		
Tralokinumab Q2W	[redacted]	[redacted]
Tralokinumab Q4W	[redacted]	[redacted]
Baricitinib 4mg	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Combination therapy		
Tralokinumab Q2W + TCS	[redacted]	[redacted]
Tralokinumab Q4W + TCS	[redacted]	[redacted]
Baricitinib 4mg	[redacted]	[redacted]
Dupilumab Q2W + TCS	[redacted]	[redacted]
BSC + TCS	[redacted]	[redacted]

[a] These values are also assumed to apply to both the ECZTRA 7-like subgroup and the all-patient population, as well as for the all-observed estimand. [b] Assumed to be the same as tralokinumab. [c] Assumed to be the same as BSC.
BSC, best supportive care; EASI, Eczema Area and Severity Index; Q2W, every 2 weeks; Q4W, every four weeks; TCS, topical corticosteroids.

Utility inputs for the alternative definitions were calculated as for the base-case analysis, using the trial data inputs described in Appendix H.2.1, Table 177, Table 178, Table 179 and Table 180, and are summarised in Table 92.

Table 92 Health state utility values for alternative response definitions, by treatment and response

Response definition	Biologic		BSC	
	Responders	Non-responders	Responders	Non-responders
Monotherapy – all patients				
EASI 50	0.798	0.689	0.755	0.624
EASI 75	0.812	0.713	0.766	0.639
Monotherapy – ECZTRA 7-like				
EASI 50	0.780	0.664	0.742	0.592
EASI 75	0.791	0.689	0.745	0.605
Combination therapy – all patients				
EASI 50	0.855	0.750	0.837	0.720
EASI 75	0.863	0.797	0.853	0.753
Combination therapy – ECZTRA 7-like				
EASI 50	0.844	0.743	0.827	0.709
EASI 75	0.852	0.783	0.841	0.743

BSC, best supportive care; EASI, Eczema Area and Severity Index.

B.3.8.3.3.2 Scenario B results

Results for the alternative outcome definitions are shown in Table 93 and Table 94 for monotherapy and combination therapy, respectively. The ICERs for tralokinumab and dupilumab versus BSC were similar to the base case. The ICERs for dupilumab versus tralokinumab were higher than the base-case analysis. Using the EASI 50 response definition, baricitinib combination therapy was dominated by tralokinumab, which provided more QALYs at a lower cost. In the EASI 75 analysis, baricitinib combination therapy was extendedly dominated by tralokinumab and dupilumab.

Table 93 Scenario results for monotherapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
EASI 50						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,298	£24,298
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£65,697	£214,230
EASI 75						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,172	£26,172
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£66,182	£135,897

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year.

Table 94 Scenario results for combination therapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
EASI 50						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,997	£26,997
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£47,879	Dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£71,404	£166,214
EASI 75						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,883	£26,883
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£43,677	Extendedly dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£70,484	£143,283

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.3.4 Scenario analysis C: use of overall trial populations

The base-case analysis was conducted in the ECZTRA 7-like population. This scenario analysis investigated the cost-effectiveness of the comparators in the overall trial populations.

For dupilumab, the probability of an EASI 50 & ΔDLQI ≥ 4 response in the all-patient population is calculated using the odds ratio for dupilumab versus BSC in the ECZTRA 7-like subgroup (see section B.1.1.1.1) and relies on the assumption that the relationship between dupilumab and placebo is the same in all patients and the ECZTRA 7-like subgroup for this endpoint.

As described in section B.3.8.3.1, for the all-patient population baricitinib could be included in both monotherapy and combination therapy analyses, but only for the response definitions of EASI 50 and EASI 75 (assumptions required to include baricitinib are shown in Table 86).

B.3.8.3.4.1 Scenario C inputs

Baseline characteristics of the all-patient population are summarised in section B.3.2.1, Table 66. Response probabilities are shown in section B.1.1.1.1, Table 68 and section B.3.8.3.3.1, Table 90 and Table 91.

B.3.8.3.4.2 Scenario C results

Results for the all-patient population are shown in Table 95 and Table 96 for monotherapy and combination therapy, respectively. The ICERs for tralokinumab and dupilumab versus BSC were generally similar to the base case and to the scenario results for the EASI 50 and EASI 75 response definitions. Baricitinib was dominated or extendedly dominated in all analyses except monotherapy using the EASI 75 response definition, in which it had an ICER versus tralokinumab of £75,120 per QALY.

Table 95 Scenario results for monotherapy in all-patient population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
EASI 50 & ΔDLQI ≥ 4						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,478	£26,478
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£67,922	£113,885
EASI 50						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,645	£26,645
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	£41,771	Extendedly dominated
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£70,723	£156,450
EASI 75						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,591	£28,591
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	£37,423	£75,120
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£70,136	£130,347

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 96 Scenario results for combination therapy in all-patient population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
EASI 50 & ΔDLQI ≥ 4						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£25,254	£25,254
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£67,119	£168,800
EASI 50						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£25,403	£25,403
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£45,058	Dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£68,278	£211,073
EASI 75						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£25,280	£25,280
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£45,880	Dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£67,467	£167,889

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.3.5 Scenario analysis D: baseline-risk-adjusted analysis

As described in section B.2.9.3, variation in placebo response rates across the studies included in the NMA are an important source of heterogeneity and uncertainty. A baseline-

risk-adjusted analysis provided a closer reproduction of reported clinical trial data (section B.2.9.3.3), but could not be run for the EASI 50 & ΔDLQI ≥ 4 endpoint due to insufficient data. In this scenario, baseline-risk-adjusted week 16 EASI 50 and EASI 75 response rates were used. As in the NMA, this analysis was conducted for combination therapy in the overall patient population only.

B.3.8.3.5.1 Scenario D inputs

Baseline-risk-adjusted week 16 response rates are shown in Table 97.

Table 97 Baseline-risk-adjusted response probabilities at week 16, combination therapy (NRI)

Treatment	Baseline-risk-adjusted
EASI 50	
Placebo	[redacted]
Tralokinumab Q2W	[redacted]
Dupilumab Q2W	[redacted]
Baricitinib 4 mg QD	[redacted]
EASI 75	
Placebo	[redacted]
Tralokinumab Q2W	[redacted]
Dupilumab Q2W	[redacted]
Baricitinib 4 mg QD	[redacted]

Data are median.
EASI, Eczema Area and Severity Index; mg, milligram; QD, once daily; QW, once weekly.

B.3.8.3.5.2 Scenario D results

Baseline-risk-adjusted results for combination therapy in the all-patient population are shown in Table 98. Compared with the corresponding unadjusted results (section B.3.8.3.4.2, Table 96), the ICERs for tralokinumab versus BSC were slightly reduced, and those for dupilumab versus tralokinumab were substantially increased. Baricitinib was dominated by tralokinumab.

Table 98 Baseline-risk-adjusted scenario results for combination therapy in all-patient population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
EASI 50						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£25,078	£25,078
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£53,964	Dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£68,303	£322,641
EASI 75						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£24,927	£24,927
Baricitinib + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£57,642	Dominated
Dupilumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£67,556	£234,656

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.3.6 Scenario analysis E: variation in tralokinumab maintenance dosing

In the base case, all patients receiving tralokinumab were treated with Q2W dosing until week 52, when [redacted] were assumed to switch to Q4W dosing (see section B.3.5.1.1 and Appendix H.2.1). In this scenario, alternative switching rates were used, including an analysis in which [redacted] of patients switched to Q4W dosing at week 16. The analysis was conducted in the ECZTRA 7-like population using the base-case response definition of EASI 50 & ΔDLQI ≥ 4.

Scenario results are shown in Table 99 and Table 100 for monotherapy and combination therapy, respectively. Tralokinumab QALYs, and both costs and QALYs for dupilumab, are not changed from the base case. Tralokinumab costs and cost effectiveness versus BSC are lower in scenarios with higher proportions of patients receiving Q4W dosing; the ICER was below £30,000 per QALY in all scenarios except combination therapy with [redacted].

Table 99 Q4W dosing scenario results for monotherapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
[redacted]						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,139	£29,139
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£109,623
[redacted] ***Q4W dosing from week 52***						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,157	£26,157
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£113,571
Base case – [redacted] Q4W dosing from week 52						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,666	£24,666
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£115,545
[redacted] ***Q4W dosing from week 52***						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,175	£23,175
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£117,519
[redacted] ***Q4W dosing from week 16***						
BSC	[redacted]	[redacted]	–	–	–	–
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,360	£24,360
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£63,771	£115,951

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; Q4W, every 4 weeks; QALY, quality-adjusted life year.

Table 100 Q4W dosing scenario results for combination therapy in ECZTRA 7-like population

Treatment	Total		Compared with BSC			Fully incremental
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)	ICER (£/QALY)
[redacted]						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£31,975	£31,975
Dupilumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£118,663
[redacted] ***Q4W dosing from week 52***						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£28,637	£28,637
Dupilumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£123,007
Base case – [redacted] ***Q4W dosing from week 52***						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,969	£26,969
Dupilumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£125,178
[redacted] ***Q4W dosing from week 52***						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£25,300	£25,300
Dupilumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£127,350
[redacted] ***Q4W dosing from week 16***						
BSC + TCS	[redacted]	[redacted]	–	–	–	–
Tralokinumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£26,624	£26,624
Dupilumab+ TCS	[redacted]	[redacted]	[redacted]	[redacted]	£69,641	£125,627

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; Q4W, every 4 weeks; QALY, quality-adjusted life year; TCS, topical corticosteroids.

B.3.8.3.7 Scenario analysis F: testing additional assumptions

A range of additional scenarios were tested in monotherapy and combination therapy, with results presented as the INMB of tralokinumab vs dupilumab and tralokinumab vs BSC (Table 101 and Table 102).

Results are shown in Table 101 and Table 102 for monotherapy and combination therapy, respectively. The INMB for tralokinumab versus dupilumab was positive in all scenarios. Against BSC, the tralokinumab INMB was positive in most scenarios; the exceptions were those with short time horizons, no loss of BSC utility benefit and increased biological therapy drop-out rates (combination therapy).

Table 101 Additional scenario analyses for monotherapy in ECZTRA 7-like population

Scenario	Tralokinumab vs dupilumab INMB	Tralokinumab vs BSC INMB
Base case	£63,510	£5,243
Conditional response at week 52		
Dupilumab equal to tralokinumab	£56,956	£5,243
Discontinuation		
Q4W discontinuation rate 20% higher than Q2W rate	£63,357	£5,089
Biological therapy discontinuation set to ECZTEND all-cause drop-out rate for EASI 50 & ΔDLQI ≥ 4 responders ([redacted] per annum)	£40,698	£1,683
Q4W discontinuation rate 20% higher than Q2W rate + biological therapy discontinuation set to ECZTEND all-cause drop-out rate for EASI 50 & ΔDLQI ≥ 4 responders	£40,497	£1,482
Time horizon		
2-year time horizon	£10,685	−£3,119
5-year time horizon	£21,776	−£1,662
10-year time horizon	£35,224	£886
Loss of response		
BSC patients lose HRQoL benefit more rapidly (50% in year 2 and 50% in year 3)	£63,057	£6,355
No loss of BSC HRQoL benefit	£69,781	−£14,540
Assume no loss of treatment benefit for biologics after year 1	£73,144	£6,692
Utility		
No age adjustment	£62,502	£6,618
Biologic non responders receive BSC non responder utility	£63,474	£5,119
Cost and resource use		
Ameen 2020 resource use	£64,112	£4,465

This table uses INMB. A positive INMB means tralokinumab is cost-effective versus the comparator and a negative INMB means tralokinumab is not cost-effective versus the comparator.
BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HRQoL, health-related quality of life; INMB, incremental net monetary benefit; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 102 Additional scenario analyses for combination therapy in ECZTRA 7-like population

Scenario	Tralokinumab + TCS vs dupilumab+ TCS INMB	Tralokinumab + TCS vs BSC + TCS INMB
Base case	£99,454	£4,122
Conditional response at week 52		
Dupilumab equal to tralokinumab	£88,368	£4,122
Discontinuation		
Q4W discontinuation rate 20% higher than Q2W rate	£99,255	£3,924
Biological therapy discontinuation set to ECZTEND all-cause drop-out rate for EASI 50 & ΔDLQI ≥ 4 responders ([redacted] per annum)	£63,705	−£509
Q4W discontinuation rate 20% higher than Q2W rate + biological therapy discontinuation set to ECZTEND all-cause drop-out rate for EASI 50 & ΔDLQI ≥ 4 responders	£63,443	−£771
Time horizon		
2-year time horizon	£16,068	−£6,068
5-year time horizon	£33,882	−£4,991
10-year time horizon	£55,142	−£1,568
Loss of response		
BSC patients lose HRQoL benefit more rapidly (50% in year 2 and 50% in year 3)	£98,252	£6,961
No loss of BSC HRQoL benefit	£116,011	−£45,221
Assume no loss of treatment benefit for biologics after year 1	£114,496	£5,996
Utility		
No age adjustment	£97,922	£6,273
Biologic non responders receive BSC non responder utility	£99,440	£4,102
Cost and resource use		
Ameen 2020 resource use	£100,382	£2,983

This table uses INMB. A positive INMB means tralokinumab is cost-effective versus the comparator and a negative INMB means tralokinumab is not cost-effective versus the comparator.
BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HRQoL, health-related quality of life; INMB, incremental net monetary benefit; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.

B.3.8.4 Summary of sensitivity analysis results

Overall, the sensitivity analysis showed that the economic model results were robust across a range of input parameters and assumptions. In PSA, tralokinumab was the intervention with the highest likelihood of being cost effective at willingness-to-pay thresholds close to those typical for the UK. Tralokinumab became the intervention with the highest likelihood of being cost effective at a threshold of approximately £25,000 per QALY in monotherapy and £30,000 per QALY in combination therapy. The probability of dupilumab being the most cost-effective comparator only started to increase at willingness-to-pay thresholds of above £70,000. In deterministic sensitivity analysis, in all comparisons the INMB of tralokinumab was positive, suggesting that it is associated with a net-monetary benefit relative to its

comparators and is therefore cost-effective at a willingness-to-pay threshold of £30,000 per QALY.

In general, scenario analysis results were similar to the base case. The results of the baseline-risk-adjusted scenario, based on the adjusted NMA model that was found to provide a closer reproduction of the trial data (see section B.2.9.3.3), were also similar to the base case. Where baricitinib could be included in scenario analyses, it was either dominated, extendedly dominated, or unlikely to be considered cost effective versus tralokinumab. The ICER for tralokinumab versus BSC was affected by assumptions around the use of Q4W maintenance therapy but was under £30,000 per QALY in all scenarios except combination therapy with [redacted]. In additional scenario analyses, the INMB for tralokinumab versus BSC was affected by assumptions around time horizon, biological therapy discontinuation rate and loss of treatment benefits with BSC.

B.3.9 Subgroup analysis

The base-case analysis was restricted to patients in the ECZTRA 7-like subgroup, reflecting the decision problem. The cost effectiveness of tralokinumab in the overall clinical trial populations is described in scenario analysis C (section B.3.8.3.4).

B.3.10 Validation

Face validity of the model concept was checked during an advisory board made up of clinical and health economic experts. Several quality control measures were undertaken to validate the model findings included in this submission. Internal quality control was undertaken by the developers of the model on behalf of the manufacturer. The model results were compared to the dupilumab and baricitinib NICE appraisals (TA534 and TA681) and any identified discrepancies were clarified and resolved. A second modeler, not involved in the programming, reviewed the model code and formulae, and conducted extreme value analysis to verify the model results. The lead modeler scrutinised the programming and references.

B.3.11 Interpretation and conclusions of economic evidence

This was a cost-effectiveness analysis of tralokinumab for the treatment of moderate-to-severe AD, considering use of the comparators as monotherapy or combination therapy with TCS. The population explored in the base-case analysis was adults with moderate-to-severe AD that has not responded to ciclosporin, or for whom ciclosporin is contraindicated or not tolerated. This is consistent with the proposed position of tralokinumab in the treatment pathway, which is narrower than the marketing authorisation; this population optimises the cost effectiveness of tralokinumab and is in line with the positioning and use of baricitinib and of dupilumab, the only currently available biologic therapy for the management of AD.

The cost-effectiveness analysis was based on a comprehensive evidence review and an NMA of the available evidence from randomised clinical trials. The structure of the economic

model was similar to the model used in several previous economic evaluations, including the dupilumab NICE appraisal (TA534) [46, 135, 136].

PSA results were similar to the deterministic base case analysis. There was a strong positive correlation between the cost and QALYs associated with the biologics in both monotherapy and combination therapy. This is because both costs and QALYs are heavily dependent on drug survival.

In the cost-effectiveness acceptability curve, tralokinumab becomes the intervention with the highest likelihood of being cost-effective at willingness-to-pay thresholds between £20,000 and £30,000 per QALY gained. Tralokinumab became the intervention with the highest likelihood of being cost effective at a threshold of approximately £25,000 per QALY in monotherapy and £30,000 per QALY in combination therapy. At willingness-to-pay thresholds of above £70,000 per QALY for monotherapy and combination therapy the probability that dupilumab becomes the most cost-effective comparator begins to increase.

In deterministic sensitivity analysis, the probabilities of response at week 16 had the greatest individual impact on the cost-effectiveness of comparators. Across both monotherapy and combination therapy, the parameters that affected the cost-effectiveness of tralokinumab versus BSC the most related to the long-term expense and benefit associated with BSC (e.g. non-responder costs and the value of baseline utility). Similarly, parameters related to prolonged drug survival (e.g. sustained response and discontinuation) were also important. These were also the parameters that mattered most in the comparison of tralokinumab and dupilumab, largely because they are the main sources of potential difference between active comparators in the model.

In general, scenario analysis results were similar to the base case; the ICER for tralokinumab versus BSC was robust to changes in population, response definition and how use of rescue medication was treated. The scenario with no use of Q4W dosing led to a higher ICER than the base case analysis. The base-case assumption that [redacted] of patients will switch to tralokinumab Q4W maintenance dosing after 52 weeks is based on market research conducted among UK physicians, which found that they would on average switch patients to less-frequent dosing after [redacted] weeks. Given that among patients with week 16 EASI 50 & ΔDLQI ≥ 4 responses in ECZTRA 7, [redacted] had an IGA 0/1 response at week 26, and [redacted] had both an IGA 0/1 response and a worst daily pruritus NRS score of < 3 at the same timepoint, the base-case assumption is likely to be conservative, at least for combination therapy.

The scenario with the largest impact on the cost-effectiveness of tralokinumab was the assumption that there would be no loss of treatment benefit over time for BSC. Given the clinical history of inadequate response to the types of treatment comprising BSC among the modelled patient population, this assumption may not be realistic.

A major source of heterogeneity and uncertainty in the combination therapy NMA is the variation in placebo arm response rates in the included trials. As described in section B.2.9.3, a baseline-risk-adjusted NMA provided a closer match to the underlying clinical trial data than the unadjusted analysis. Use of the adjusted analysis in the cost-effectiveness

model increased the number of QALYs produced by tralokinumab plus TCS, and slightly reduced the ICER for tralokinumab versus BSC. For dupilumab versus tralokinumab the ICERs were substantially increased and baricitinib was dominated by tralokinumab.

Because insufficient data were available for the key definition of response in the base-case population, baricitinib could not be included in the base-case analysis. Where possible, baricitinib was included in scenario analyses. However, limited baricitinib data were available for the ECZTRA 7-like subgroup, and sustained response estimates for baricitinib relied on additional modelling assumptions. The results including baricitinib are based on the best available data and consideration should be given to the limitations and sources of heterogeneity highlighted in section B.2.9.3.1. Extrapolation of the baricitinib scenario results to the base-case population, using the base-case definition of response, should be done with caution.

The current model was built on the strengths of previous models and addressed some of their limitations. The first strength of the model is that all the key inputs were drawn either directly from the ECZTRA trials, or from NMAs informed by SLRs that included the ECZTRA trials and recently published data for the comparators from JADE Compare and BREEZE-AD5. This means that the inputs are based on all the best available randomised evidence and highly relevant to the decision problem. Health state utility values were generated using the ECZTRA data and were linked to treatment, response, and baseline characteristics.

A second strength is that the model aligns closely with the dupilumab and baricitinib NICE submissions, meaning the results follow established precedents and are comparable with existing cost-effectiveness estimates within moderate-to-severe AD.

The main limitation of this analysis results from the fact that the design of the tralokinumab and dupilumab trials differed in a number of ways. In particular, limited data were published for dupilumab using the EASI 50 & ΔDLQI ≥ 4 response definition as this was not a primary endpoint in any of the trials. Also, there were very limited data available for the EASI 50 & ΔDLQI ≥ 4 response definition at week 52, as this was not a primary endpoint for the studies. This is discussed in more detail in sections B.2.9.2.1 and B.1.1.1.1. The data available for baricitinib were also limited, preventing its inclusion in the base-case analysis.

Another limitation is the uncertainty in the proportion of tralokinumab patients who will switch to a Q4W dosing regimen and at what timepoint they will switch. This uncertainty is exacerbated by two factors. First, the sustained response data for Q4W treatment were limited to the EASI 75 response definition. It was therefore assumed for the EASI 50 & ΔDLQI ≥ 4 and EASI 50 response definitions that the sustained response for Q4W treatment is equivalent to Q2W therapy. Second, there is a lack of long-term discontinuation data for Q4W treatment and so equivalence to Q2W dosing was assumed. To mitigate this second aspect a sensitivity analysis using an increased discontinuation rate for the Q4W dose regimen was explored.

A final limitation is that the values used to estimate the rate at which patients lose response following the first year were taken from the dupilumab submission and were informed by

expert opinion, since relevant trial data were not available. However, this assumption has been used previously in the NICE HTA process and is tested in sensitivity analysis.

The results of this analysis are expected to be applicable to clinical practice in England and Wales. The base-case response definition is used in clinical practice and NICE guidance as a routine stopping rule [46]. Furthermore, most of the evidence for unit costs and resource use was obtained from UK sources, while utility data from the ECZTRA clinical trial programme were valued using the UK tariff.

In conclusion, the results of the economic analysis suggested that, under the £30,000 per QALY threshold, tralokinumab is a cost-effective treatment option for patients with moderate-to-severe AD. Deterministic one-way sensitivity analysis, scenario analysis, and probabilistic sensitivity analysis suggested that the model results were robust to input range and assumption changes.

B.4 References

1. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care. 2017;23(8 Suppl):S115-s23.
2. NHS. Overview – Atopic eczema. 2019 [Available from: https://www.nhs.uk/conditions/atopic-eczema/. Accessed: 19 April 2021.]
3. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. J Am Acad Dermatol. 2019;80(6):1526-32.e7.
4. Thomsen SF. Epidemiology and natural history of atopic diseases. European clinical respiratory journal. 2015;2:10.3402/ecrj.v2.24642.
5. Weidinger S, Novak N. Atopic dermatitis. The Lancet. 2016;387(10023):1109-22.
6. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL*, et al.* Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.
7. Bos JD, Brenninkmeijer EE, Schram ME, Middelkamp-Hup MA, Spuls PI, Smitt JH. Atopic eczema or atopiform dermatitis. Exp Dermatol. 2010;19(4):325-31.
8. Werfel T, Schwerk N, Hansen G, Kapp A. The diagnosis and graded therapy of atopic dermatitis. Deutsches Arzteblatt international. 2014;111(29-30):509-20.
9. Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nograles K, Cardinale I*, et al.* Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. The Journal of allergy and clinical immunology. 2011;127(4):954-64.e644.
10. Silvestre Salvador JF, Romero-Pérez D, Encabo-Durán B. Atopic Dermatitis in Adults: A Diagnostic Challenge. J Investig Allergol Clin Immunol. 2017;27(2):78-88.
11. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1-11.
12. National Eczema Society. Our skin and eczema. [Available from: https://eczema.org/information-and-advice/our-skin-and-eczema/. Accessed: 20 October 2020.]
13. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL*, et al.* Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73(6):1284-93.
14. National Institute of Health and Care Excellence. Resource impact report: Dupilumab for treating moderate to severe atopic dermatitis (TA534). 2018 [Available from: https://www.nice.org.uk/guidance/ta534/resources/research-impact-report-pdf-4909806541. Accessed: 20 October 2020.]
15. Wei W, Anderson P, Gadkari A, Blackburn S, Moon R, Piercy J*, et al.* Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. The Journal of dermatology. 2018;45(2):150-7.
16. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM*, et al.* Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol. 2016;74(3):491-8.
17. Huet F, Faffa MS, Poizeau F, Merhand S, Misery L, Brenaut E. Characteristics of Pruritus in Relation to Self-assessed Severity of Atopic Dermatitis. Acta Derm Venereol. 2019;99(3):279-83.
18. de Bruin-Weller M, Gadkari A, Auziere S, Simpson EL, Puig L, Barbarot S*, et al.* The patient-reported disease burden in adults with atopic dermatitis: a cross-sectional study in Europe and Canada. J Eur Acad Dermatol Venereol. 2020;34(5):1026-36.
19. Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Ständer S*, et al.* Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. J Eur Acad Dermatol Venereol. 2020;34(1):142-52.

20. Jeon C, Yan D, Nakamura M, Sekhon S, Bhutani T, Berger T*, et al.* Frequency and Management of Sleep Disturbance in Adults with Atopic Dermatitis: A Systematic Review. Dermatol Ther (Heidelb). 2017;7(3):349-64.
21. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE*, et al.* The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984-91.
22. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. J Invest Dermatol. 2017;137(1):26-30.
23. Kimata H. Prevalence of suicidal ideation in patients with atopic dermatitis. Suicide Life Threat Behav. 2006;36(1):120-4.
24. Capucci S, Hahn-Pedersen J, Vilsbøll A, Kragh N. Impact of Atopic Dermatitis and Chronic Hand Eczema on Quality of Life Compared With Other Chronic Diseases. Dermatitis. 2020;31(3):178-84.
25. LEO Pharma and National Eczema Society. Eczema unmasked. 2020 [Available from: https://www.leo-pharma.co.uk/EczemaUnmasked-report. Accessed: 18 April 2021.]
26. Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venerol Suppl(Stockh). 1980;92:44-7.
27. Williams HC, Burney PG, Strachan D, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. Br J Dermatol. 1994;131(3):397-405.
28. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.
29. National institute of Health and Care Excellence. Baricitinib for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA681]. 2021 [Available from: https://www.nice.org.uk/guidance/TA681. Accessed: 18 March 2021.]
30. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE*, et al.* Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2020.
31. Junttila IS. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. Front Immunol. 2018;9:888.
32. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. Allergy. 2020;75(1):54-62.
33. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K*, et al.* Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. J Allergy Clin Immunol. 2019;143(1):135-41.
34. Furue K, Ito T, Tsuji G, Ulzii D, Vu YH, Kido-Nakahara M*, et al.* The IL-13–OVOL1–FLG axis in atopic dermatitis. Immunology. 2019;158(4):281-6.
35. Tazawa T, Sugiura H, Sugiura Y, Uehara M. Relative importance of IL-4 and IL-13 in lesional skin of atopic dermatitis. Arch Dermatol Res. 2004;295(11):459-64.
36. Bao K, Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. Cytokine. 2015;75(1):25-37.
37. Newsom M, Bashyam AM, Balogh EA, Feldman SR, Strowd LC. New and Emerging Systemic Treatments for Atopic Dermatitis. Drugs. 2020;80(11):1041-52.
38. Awosika O, Kim L, Mazhar M, Rengifo-Pardo M, Ehrlich A. Profile of dupilumab and its potential in the treatment of inadequately controlled moderate-to-severe atopic dermatitis. Clinical, cosmetic and investigational dermatology. 2018;11:41-9.
39. May RD, Monk PD, Cohen ES, Manuel D, Dempsey F, Davis NH*, et al.* Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. Br J Pharmacol. 2012;166(1):177-93.

40. Popovic B, Breed J, Rees DG, Gardener MJ, Vinall LM, Kemp B*, et al.* Structural Characterisation Reveals Mechanism of IL-13-Neutralising Monoclonal Antibody Tralokinumab as Inhibition of Binding to IL-13Rα1 and IL-13Rα2. J Mol Biol. 2017;429(2):208-19.
41. Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. JAK-STAT. 2013;2(3):e24137-e.
42. Napolitano M, Fabbrocini G, Cinelli E, Stingeni L, Patruno C. Profile of Baricitinib and Its Potential in the Treatment of Moderate to Severe Atopic Dermatitis: A Short Review on the Emerging Clinical Evidence. Journal of asthma and allergy. 2020;13:89-94.
43. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nature Reviews Drug Discovery. 2017;16(12):843-62.
44. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A*, et al.* Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82.
45. British Association of Dermatologists. Atopic eczema. 2020 [Available from: https://www.bad.org.uk/shared/get-file.ashx?id=69&itemtype=document. Accessed: 20 October 2020.]
46. National institute of Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA534]. 2018 [Available from: https://www.nice.org.uk/guidance/TA534/chapter/1-Recommendations. Accessed: 20 October 2020.]
47. LEO Pharma. Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A ECZTRA 7 (ECZema TRAlokinumab trial no. 7): Clinical study report. 2020.
48. LEO Pharma. LP0162-1346 ECZTRA7 Tables and Figures, Baseline Characteristics and IP Data. 2020.
49. LEO Pharma. LP0162-1346 ECZTRA7 Tables and Figures, Efficacy (and/or other as appropriate) Data. 2020.
50. LEO Pharma. LP0162-1346 ECZTRA7 Tables and Figures, Safety Data. 2020.
51. LEO Pharma. Payer submission statistical appendix, 9 April 2021. 2020.
52. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP*, et al.* Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2020.
53. LEO Pharma. Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 1 (ECZema TRAlokinumab trial no. 1): Clinical study report. 2020.
54. LEO Pharma. Tralokinumab monotherapy for moderate-to-severe atopic dermatitis ECZTRA 2 (ECZema TRAlokinumab trial no. 2): Clinical study report. 2020.
55. LEO Pharma. Tralokinumab in combination with topical corticosteroids for moderate-to-severe atopic dermatitis ECZTRA 3 (ECZema TRAlokinumab trial no. 3): Clinical study report. 2020.
56. LEO Pharma. Statistical tables for integrated summary of efficacy - monotherapy pool - 5.3.5.3. 2020.
57. LEO Pharma. Statistical appendix - binary responses in ECZTRA 3 - 3-Oct-2020. 2020 3 October 2020.
58. LEO Pharma. Statistical tables for integrated summary of safety - AD pool - 5.3.5.3. 2020.
59. LEO Pharma. Payer submission statistical appendix, cyclosporine-IR-subgroup population. 2020.
60. LEO Pharma. Payer submission statistical appendix, systemic-therapy-IR subgroup population. 2020.

61. LEO Pharma. Payer submission statistical appendix: pooled subgroup analysis - combination therapy ECZTRA 7-like - 11-Feb-2021. 2021.
62. LEO Pharma. Payer submission statistical appendix: pooled subgroup analysis - monotherapy ECZTRA 7-like 1-Sep-2020. 2021.
63. Merola JF, Bagel J, Almgren P, Røepke M, Grewal P. Vaccine antibody responses in tralokinumab-treated adult patients with moderate-to-severe atopic dermatitis: results from the 30-week Phase 2 ECZTRA 5 trial. E-poster at European Academy of Dermatology and Venereology (EADV) Virtual Congress; October 29-31, 2020 P0181; Abstract 8062020.
64. LEO Pharma. LP0162-1337 ECZTEND Tables and Figures, 15-Dec-2020. 2020.
65. clinicaltrials.gov. Long-term Extension Trial in Subjects With Atopic Dermatitis Who Participated in Previous Tralokinumab Trials - ECZTEND (NCT03587805). 2021 [Updated 14 January 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03587805. Accessed: 3 February 2021.]
66. clinicaltrials.gov. Tralokinumab in Combination With Topical Corticosteroids in Subjects With Severe Atopic Dermatitis Who Are Not Adequately Controlled With or Have Contraindications to Oral Cyclosporine A (ECZTRA 7). 2020 [Updated 20 October 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03761537. Accessed: 16 November 2020.]
67. Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K*, et al.* Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. J Allergy Clin Immunol. 2013;132(6):1337-47.
68. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M*, et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Experimental Dermatology. 2001;10(1):11-8.
69. Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. J Am Acad Dermatol. 2016;74(2):288-94.
70. Schram ME, Spuls PI, Leeflang MMG, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99-106.
71. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140(12):1513-9.
72. Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. The patient. 2019;12(5):445-59.
73. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
74. Patel KR, Singam V, Vakharia PP, Chopra R, Sacotte R, Patel N*, et al.* Measurement properties of three assessments of burden used in atopic dermatitis in adults. Br J Dermatol. 2019;180(5):1083-9.
75. Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the Minimal Clinically Important Difference and Responsiveness of the Dermatology Life Quality Index (DLQI): Further Data. Dermatology. 2015;230(1):27-33.
76. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
77. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.
78. Simpson E, Thyssen JP, Flohr C, Katoh N, Papp K, Abildgaard Steffensen L*, et al.* Tralokinumab provides progressive improvements beyond week 16 in patients with atopic dermatitis with an initial partial response. 29th Congress EADVirtual – New Frontiers in Dermatology and Venereology; 29–31 October 20202020.

79. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L*, et al.* Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761-9.
80. Silverberg JI, Cork M, Wollenberg A, Katoh N, Abildgaard Steffensen L, Kurbasic A*, et al.* Early changes in patient-relevant endpoints in three tralokinumab pivotal Phase 3 trials (ECZTRA 1−3) in adult patients with moderate-to-severe atopic dermatitis. DERM Virtual Congress; 6–9 August 20202020.
81. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
82. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K*, et al.* Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. The Lancet. 2016;387(10013):40-52.
83. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ*, et al.* Two Phase 3 Trials of dupilumab versus placebo in atopic dermatitis. New England Journal of Medicine. 2016;375(24):2335-48.
84. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R*, et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. New England journal of medicine. 2014;371(2):130‐9.
85. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R*, et al.* Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183(2):242-55.
86. Simpson EL, Forman S, Silverberg JI, Zirwas M, Maverakis E, Han G*, et al.* Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy Phase 3 trial in the United States and Canada (BREEZE-AD5). J Am Acad Dermatol. 2021.
87. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D*, et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. The Lancet. 2017;389(10086):2287-303.
88. de Bruin-Weller M, Thaçi D, Smith CH, Reich K, Cork MJ, Radin A*, et al.* Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFÉ). British Journal of Dermatology. 2018;178(5):1083-101.
89. Thaci D. A Phase 3 Study to Investigate the Efficacy and Safety of Abrocitinib and Dupilumab in Comparison With Placebo in Adults With Moderate-to-Severe Atopic Dermatitis. European Academy of Dermatology and Venereology. 2020.
90. Bieber T, Thyssen JP, Reich K, Simpson EL, Katoh N, Torrelo A*, et al.* Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. J Eur Acad Dermatol Venereol. 2021;35(2):476-85.
91. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T*, et al.* Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(12):1333-43.
92. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R*, et al.* Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol. 2019;80(4):913-21.e9.
93. Worm M, Simpson EL, Thaci D, Bissonnette R, Lacour JP, Beissert S*, et al.* Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(2):131-43.

94. Simpson E, Lacour J, Spelman L, Galimberti RL, Eichenfield L, Bissonnette NA*, et al.*, editors. Efficacy and safety of baricitinib in moderate to severe atopic dermatitis: results of two phase 3 monotherapy randomized, double-blind, placebo-controlled 16-week trials (BREEZE-AD1 and BREEZE-AD2). 24th World Congress of Dermatology; 2019; Milan.
95. Thompson SG, Smith TC, Sharp SJ. Investigating underlying risk as a source of heterogeneity in meta-analysis. Stat Med. 1997;16(23):2741-58.
96. Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. BMJ. 1996;313(7059):735-8.
97. Sharp SJ, Thompson SG. Analysing the relationship between treatment effect and underlying risk in meta-analysis: comparison and development of approaches. Stat Med. 2000;19(23):3251-74.
98. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Med Decis Making. 2013;33(5):618-40.
99. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making. 2013;33(5):607-17.
100. Achana FA, Cooper NJ, Dias S, Lu G, Rice SJ, Kendrick D*, et al.* Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. Stat Med. 2013;32(5):752-71.
101. Cameron C, Hutton B, Druchok C, McElligott S, Nair S, Schubert A*, et al.* Importance of assessing and adjusting for cross-study heterogeneity in network meta-analysis: a case study of psoriasis. Journal of Comparative Effectiveness Research. 2018;7(11):1037-51.
102. Simpson E, Merola JF, Silverberg JI, Zachariae R, Olsen CK, Wollenberg A. Safety of specifically targeting interleukin 13 with tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled Phase 3 and Phase 2 trials. Revolutionizing Atopic Dermatitis (RAD) Conference; 13–14 December 20202020.
103. LEO Pharma. Summary of clinical safety: tralokinumab in moderate-to-severe atopic dermatitis; section 2.7.4 of EMA submission. 2020.
104. British National Formulary. Baricitinib. 2020 [Available from: https://bnf.nice.org.uk/drug/baricitinib.html#importantSafetyInformations. Accessed: 19 February 2021.]
105. Eli Lilly. Important risk minimization information for healthcare professionals prescribing Olumiant® (baricitinib). 2020 [Available from: https://www.medicines.org.uk/emc/rmm/1864/Document. Accessed: 22 March 2021.]
106. Shaheen MS, Silverberg JI. Association of inflammatory skin diseases with venous thromboembolism in US adults. Arch Dermatol Res. 2021;313(4):281-9.
107. National institute of Health and Care Excellence. Clinical knowledge summary: DMARDS - baricitinib. 2020 [Available from: https://cks.nice.org.uk/topics/dmards/management/baricitinib/. Accessed: 19 February 2021.]
108. Wollenberg A, Flohr C, Simon D, Cork MJ, Thyssen JP, Bieber T*, et al.* European Task Force on Atopic Dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and atopic dermatitis. J Eur Acad Dermatol Venereol. 2020;34(6):e241-e2.
109. Damour A, Garcia M, Seneschal J, Lévêque N, Bodet C. Eczema Herpeticum: Clinical and Pathophysiological Aspects. Clin Rev Allergy Immunol. 2020;59(1):1-18.
110. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH*, et al.* Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340-7.
111. Chung J, Simpson EL. The socioeconomics of atopic dermatitis. Ann Allergy Asthma Immunol. 2019;122(4):360-6.
112. National Institute of Health and Care Excellence. Eczema - atopic: topical corticosteroids. 2021 [Updated January 2021. Available from:

https://cks.nice.org.uk/topics/eczema-atopic/prescribing-information/topical-corticosteroids/. Accessed: 17 February 2021.]
113. Cabanillas B, Brehler A-C, Novak N. Atopic dermatitis phenotypes and the need for personalized medicine. Current opinion in allergy and clinical immunology. 2017;17(4):309-15.
114. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S*, et al.* Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. Journal of the American Academy of Dermatology. 2020;82(2):377-88.
115. Nettis E, Bonzano L, Patella V, Detoraki A, Trerotoli P, Lombardo C. Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience. J Investig Allergol Clin Immunol. 2020;30(3):201-4.
116. Popiela MZ, Barbara R, Turnbull AMJ, Corden E, Martinez-Falero BS, O'Driscoll D*, et al.* Dupilumab-associated ocular surface disease: presentation, management and long-term sequelae. Eye (Lond). 2021.
117. Sears AV, Woolf RT, Gribaleva E, Abdelrahman W, Robbie S, Menon B*, et al.* Real-world effectiveness and tolerability of dupilumab in adult atopic dermatitis: a single-centre, prospective 1-year observational cohort study of the first 100 patients treated. Br J Dermatol. 2021;184(4):755-7.
118. Thaçi D, L. Simpson E, Deleuran M, Kataoka Y, Chen Z, Gadkari A*, et al.* Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). Journal of Dermatological Science. 2019;94(2):266-75.
119. National Institute of Clinical Excellence. National Institute for Health and Care Excellence Single Technology Appraisal: Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]. 2018.
120. Dermatologists BAo. Professional organisation submission: dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]. 2018 [Available from: https://www.bad.org.uk/shared/get-file.ashx?id=5903&itemtype=document. Accessed: 4 February 2021.]
121. Eczema HOMf. Core outcomes for trials [Available from: http://www.homeforeczema.org/research/index.aspx. Accessed: 4 February 2021.]
122. Silverwood RJ, Mansfield KE, Mulick A, Wong AYS, Schmidt SAJ, Roberts A*, et al.* Atopic eczema in adulthood and mortality: UK population-based cohort study, 1998-2016. J Allergy Clin Immunol. 2021.
123. National institute of Health and Care Excellence. National Institute for Health and Care Excellence Single technology appraisal: Baricitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis [ID1622]. 2021:1:570.
124. Office for National Statistics. National life tables: England, 2019. [Accessed: 2020.]
125. National Institute of Health and Care Excellence. Guide to the methods of technology appraisal. 2013 [Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed: 18 March 2021.]
126. LEO Pharma. Adtralza (tralokinumab) - summary of product characteristics. 2021.
127. Monthly Index of Medical Specialities (MIMS). 2020. [Available from: https://www.mims.co.uk. Accessed: 2020.]
128. NHS Improvement. National cost collection data: 2018–19. [Available from: https://www.england.nhs.uk/national-cost-collection/. Accessed: 2020.]
129. Curtis L, Burns A. Unit Costs of Health & Social Care 2019 Canterbury, Kent: Personal Social Services Research Unit 2019 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. Accessed: 2020.]
130. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.

131. Ariëns LFM, van Nimwegen KJM, Shams M, de Bruin DT, van der Schaft J, van Os-Medendorp H*, et al.* Economic Burden of Adult Patients with Moderate to Severe Atopic Dermatitis Indicated for Systemic Treatment. Acta Derm Venereol. 2019;99(9):762-8.
132. Ameen M, Rabe A, Blanthorn-Hazell S, Millward R. PSY17 The Prevalence and Clinical Profile of Atopic Dermatitis (AD) in England: A Population Based Linked Cohort Study Using Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). Value in Health. 2020;23:S745.
133. National institute of Health and Care Excellence. Final appraisal determination: Baricitinib for treating moderate to severe atopic dermatitis: Technology appraisal guidance [ID1622]. 2021 [Available from: https://www.nice.org.uk/guidance/gid-ta10562/documents/html-content-2. Accessed: 18 February 2021.]
134. European Medicines Agency. Assessment report: Olumiant 2020 [Available from: https://www.ema.europa.eu/en/documents/variation-report/olumiant-h-c-4085-ii-0016-epar-assessment-report-variation_en.pdf. Accessed: 11 April 2021.]
135. Canadian Agency for Drugs and Technologies in Health (CADTH). Pharmacoeconomic Review Report: Dupilumab (DUPIXENT). 2018.
136. Kuznik A, Bégo-Le-Bagousse G, Eckert L, Gadkari A, Simpson E, Graham CN*, et al.* Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. Dermatology and Therapy. 2017;7(4):493-505.
137. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M*, et al.* Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020;396(10246):255-66.
138. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C*, et al.* Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol. 2019;155(12):1371-9.
139. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K*, et al.* Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877-84.
140. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H*, et al.* Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. Journal of Allergy and Clinical Immunology. 2019;143(1):155-72.
141. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A*, et al.* Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis. New England Journal of Medicine. 2017;376(9):826-35.
142. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J*, et al.* Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol. 2020;156(4):411-20.
143. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C*, et al.* Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(8):863-73.
144. Schram ME, Roekevisch E, Leeflang MMG, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. Journal of Allergy and Clinical Immunology. 2011;128(2):353-9.
145. Lio P, Boguniewicz M, Alexis A, Lebwohl M, Reich K, Pink A*, et al.* Depth and Rapidity of Response With Abrocitinib and Dupilumab in Patients With Moderate-to-Severe Atopic Dermatitis (AD) in JADE COMPARE. Journal of Allergy and Clinical Immunology. 2021;147(2):AB34.
146. Blauvelt A, Simpson EL, Tyring SK, Purcell LA, Shumel B, Petro CD*, et al.* Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. Journal of the American Academy of Dermatology. 2019;80(1):158-67.e1.

147. Bieber T. Efficacy and Safety of Baricitinib in Combination with Topical Corticosteroids in Patients with Moderate-to-Severe Atopic Dermatitis Who Failed, are Intolerant to, or Have Contraindication to Cyclosporine: Results from a Randomized, Placebo-Controlled, Phase 3 Clinical Trial (BREEZEAD4). European Academy of Dermatology and Venereology. 2020.
148. Goujon C, Viguier M, Staumont-Sallé D, Bernier C, Guillet G, Lahfa M*, et al.* Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: a Phase III Randomized Noninferiority Trial. The journal of allergy and clinical immunology In practice. 2018;6(2):562‐9.e3.
149. Czech W, Bräutigam M, Weidinger G, Schöpf E. A body-weight-independent dosing regimen of cyclosporine microemulsion is effective in severe atopic dermatitis and improves the quality of life. Journal of the American Academy of Dermatology. 2000;42(4):653-9.
150. Granlund H, Erkko P, Remitz A, Langeland T, Helsing P, Nuutinen M*, et al.* Comparison of cyclosporin and UVAB phototherapy for intermittent one-year treatment of atopic dermatitis. Acta dermato-venereologica. 2001;81(1):22‐7.
151. Haeck IM, Knol MJ, Ten Berge O, Van Velsen SGA, De Bruin-Weller MS, Bruijnzeel-Koomen CAFM. Enteric-coated mycophenolate sodium versus cyclosporin a as long-term treatment in adult patients with severe atopic dermatitis: A randomized controlled trial. Journal of the American Academy of Dermatology. 2011;64(6):1074-84.
152. Munro CS, Levell NJ, Shuster S, Friedmann PS. Maintenance treatment with cyclosporin in atopic eczema. British journal of dermatology. 1994;130(3):376‐80.
153. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 5: the baseline natural history model. Med Decis Making. 2013;33(5):657-70.
154. Worm M, Simpson EL, Thaci D, Bissonnette R, Lacour JP, Beissert S*, et al.* Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. JAMA dermatology. 2019.
155. Cabout E ES, Launois R, Aslanian F, Taïeb C, Seité S. Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis. Clin Cosmet Investig Dermatol. 2020(13):987-96.
156. Green C, Colquitt JL, Kirby J, Davidson P, Payne E. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2004;8(47):iii,iv, 1-120.
157. Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: Twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. British Journal of Dermatology. 2011;164(2):387-95.
158. Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR*, et al.* Cost-effectiveness analysis of tacrolimus ointment versus high-potency topical corticosteroids in adults with moderate to severe atopic dermatitis. Journal of the American Academy of Dermatology. 2003;48(4):553-63.
159. Institute for Clinical and Economic Review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. 2017.
160. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic evaluation of dupilumab for moderate-to-severe atopic dermatitis: A cost-utility analysis. Journal of Drugs in Dermatology. 2018;17(7):750-6.
161. Hjalte F, Asseburg C, Tennvall GR. Cost-effectiveness of a barrier-strengthening moisturizing cream as maintenance therapy vs. no treatment after an initial steroid course in patients with atopic dermatitis in Sweden - With model applications for Denmark, Norway and Finland. Journal of the European Academy of Dermatology and Venereology. 2010;24(4):474-80.
162. Hjelmgren J, Svensson A, Jorgensen ET, Lindemalm-Lundstam B, Ragnarson Tennvall G. Cost-effectiveness of tacrolimus ointment vs. standard treatment in patients with

moderate and severe atopic dermatitis: a health-economic model simulation based on a patient survey and clinical trial data. Br J Dermatol. 2007;156(5):913-21.
163. Salo H, Pekurinen M, Granlund H, Nuutinen M, Erkko P, Reitamo S. An Economic Evaluation of Intermittent Cyclosporin A Therapy versus UVAB Phototherapy in the Treatment of Patients with Severe Atopic Dermatitis. Acta Dermato-Venereologica. 2004;84(2):138-41.
164. Wollenberg A, Sidhu MK, Odeyemi I, Dorsch B, Koehne-Volland R, Schaff M*, et al.* Economic evaluation of maintenance treatment with tacrolimus 0.1% ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2008;159(6):1322-30.
165. Almeida J, Vandewalle B, Silva MJ, Félix J. A new insight into cost-effectiveness analyses in atopic dermatitis: The tacrolimus 0.1% ointment versus ciclosporin comparison. Value in Health. 2012;15(7):A570-A1.
166. Cabout E, Eymere S, Delvigne V, Seité S, Taieb C, Reguiai Z*, et al.* PSS4 Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis in the French Setting. Value in Health. 2020;23:S733.
167. Fanelli F, Pedone MP, Serra A, Bitonti R, Furneri G. PBI11 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Atopic Dermatitis in Adolescent Patients in Italy. Value in Health. 2020;23:S412.
168. Simpson EL, Bieber T, De Bruin-Weller M, Blauvelt A, Chen Z, Ardeleanu M*, et al.* Dupilumab efficacy in atopic dermatitis in four randomized phase 3 trials (liberty ad solo 1&2, chromos, cafe). Journal of Investigative Dermatology. 2018;138(5):S83.
169. Andersen L, Nyeland ME, Nyberg F. Higher self-reported severity of atopic dermatitis in adults is associated with poorer self-reported health-related quality of life in France, Germany, the U.K. and the U.S.A. British Journal of Dermatology. 2019.
170. Nyberg F, Hansen JB, Andersen L. Greater severity of atopic dermatitis (AD) is associated with poorer patientreported outcomes among adults with moderate-to-severe AD. Pharmacoepidemiology and Drug Safety. 2018;27:334.
171. Simpson EL, Gadkari A, Worm M, Soong W, Blauvelt A, Eckert L*, et al.* Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). Journal of the American Academy of Dermatology. 2016;75(3):506-15.
172. Le PH, Vo TQ, Nguyen NH. Quality of life measurement alteration among Vietnamese: Impact and treatment benefit related to eczema. JPMA The Journal of the Pakistan Medical Association. 2019;69 2)(6):S49-S56.
173. Lee SH, Lee SH, Lee SY, Lee B, Lee SH, Park YL. Psychological health status and health-related quality of life in adults with atopic dermatitis: A nationwide cross-sectional study in South Korea. Acta Dermato-Venereologica. 2018;98(1):89-97.
174. Lio PA, Wollenberg A, Thyssen JP, Pierce EJ, Rueda MJ, DeLozier AM*, et al.* Impact of Atopic Dermatitis Lesion Location on Quality of Life in Adult Patients in a Real-world Study. Journal of drugs in dermatology : JDD. 2020;19(10):943-8.
175. Nguyen SH, Nguyen LH, Vu GT, Nguyen CT, Le THT, Tran BX*, et al.* Health-related quality of life impairment among patients with different skin diseases in Vietnam: A cross-sectional study. International Journal of Environmental Research and Public Health. 2019;16(3).
176. Poole CD, Chambers C, Sidhu MK, Currie CJ. Health-related utility among adults with atopic dermatitis treated with 0·1% tacrolimus ointment as maintenance therapy over the long term: Findings from the Protopic® CONTROL study. British Journal of Dermatology. 2009;161(6):1335-40.
177. Wollenberg A, Reitamo S, Atzori F, Lahfa M, Ruzicka T, Healy E*, et al.* Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy: European Journal of Allergy and Clinical Immunology. 2008;63(6):742-50.
178. Poole CD, Chambers C, Allsopp R, Currie CJ. Quality of life and health-related utility analysis of adults with moderate and severe atopic dermatitis treated with tacrolimus

ointment vs. topical corticosteroids. Journal of the European Academy of Dermatology and Venereology. 2010;24(6):674-8.
179. Reitamo S, Ortonne JP, Sand C, Cambazard F, Bieber T, Fölster-Holst R*, et al.* A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. British Journal of Dermatology. 2005;152(6):1282-9.
180. Vietri J, Nyberg F, Varol N. The impact of severity of atopic dermatitis on patient-reported outcomes of adults with moderate-to-severe atopic dermatitis. Journal of the American Academy of Dermatology. 2017;76(6):AB254.
181. Vilsbøll AW, Kragh N, Hahn-Pedersen J, Jensen CE. Mapping Dermatology Life Quality Index (DLQI) scores to EQ-5D utility scores using data of patients with atopic dermatitis from the National Health and Wellness Study. Quality of Life Research. 2020;29(9):2529-39.
182. Song HJ, Park H, Park SY, Lee EK, Ha SY, Park SY*, et al.* Estimation of Health Utilities Based on the Response to Treatment in Atopic Dermatitis: a Population-based Study. Clinical Therapeutics. 2019;41(4):700-13.
183. Simpson EL. Dupilumab Improves General Health-Related Quality-of-Life in Patients with Moderate-to-Severe Atopic Dermatitis: pooled Results from Two Randomized, Controlled Phase 3 Clinical Trials. Dermatology and therapy. 2017;7(2):243‐8.
184. Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L*, et al.* Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. Journal of Dermatological Treatment. 2020;31(6):606-14.
185. Misery L, Seneschal J, Reguiai Z, Merhand S, Heas S, Huet F*, et al.* The impact of atopic dermatitis on sexual health. J Eur Acad Dermatol Venereol. 2019;33(2):428-32.
186. Seneschal J, Ezzedine K, Reguiai Z, Heas S, Merhand S, Misery L*, et al.* Atopic Dermatitis In Adults: Impact on Sexuality. Value in Health. 2017;20(9):A808.
187. Marron SE, Alcalde-Herrero VM, Garcia-Latasa FJ, Moncin-Torres Dpharm CA, Fuentelsaz-del-Barrio MV. Dupilumab for the treatment of adult atopic dermatatis patients in routine clinical practice. Journal of the American Academy of Dermatology. 2019;81(4):AB48.
188. Cheng BT, Silverberg J. 599 Impact of atopic dermatitis on overall health-related quality of life and health utility scores in US adult patients. Journal of Investigative Dermatology. 2019;139(5):S103.
189. Cortesi PA, Ciampichini R, Mantovani LG, Scalone L. Preliminary Italian archive of EQ-5D data on individuals from the general population and with different disease conditions. Value in Health. 2013;16(7):A336.
190. de Bruin-Weller M, Pink AE, Patrizi A, Giménez-Arnau AM, Agner T, Roquet-Gravy P*, et al.* 161 EUROSTAD Prospective Observational Study: Baseline Characteristics, Atopic Dermatitis Severity, and Patient-Reported Outcomes. Journal of Investigative Dermatology. 2019;139(9):S241.
191. Dibonaventura M, Anderson P, Piercy J, Massey L, Cappelleri J, Llamado L*, et al.* The Relationship Between Pruritus, Sleep Disruption, and Quality of Life (QoL) Among Patients With Moderate-to-Severe Atopic Dermatitis (AD) in Europe. EADV conference abstract. 2020.
192. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. Journal of the American Academy of Dermatology. 2017;77(2):274-9.e3.
193. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan S. Impact of atopic dermatitis on patient self-reported quality of life, productivity loss, and activity impairment: An analysis using the National Health and Wellness survey. Journal of the American Academy of Dermatology. 2016;74(5):AB87.

194. Eckert L, Gupta S, Amand C, Mahajan S. Comparison of atopic dermatitis with psoriasis on patient self-reported quality of life and productivity loss: Analysis of the National Health and Wellness Survey. Journal of the American Academy of Dermatology. 2016;74(5):AB85.
195. Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72:44.
196. Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in atopic dermatitis (AD) patients by self-reported severity: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72:604.
197. Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. Journal of the American Academy of Dermatology. 2019;81(1):187-95.
198. Ikeda M, Uehara H, Tsuge M. Efficacy and safety of long-term treatment with dupilumab for moderate to severe atopic dermatitis. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74:182.
199. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: Results of the national health care study AtopicHealth. Journal of the European Academy of Dermatology and Venereology. 2014;28(6):719-26.
200. Steinke S, Langenbruch A, Ständer S, Franzke N, Augustin M. Therapeutic benefits in atopic dermatitis care from the patients' perspective: Results of the German national health care study 'atopic health'. Dermatology. 2014;228(4):350-9.
201. Franzke N, Langenbruch AK, Augustin M. Quality of health care of atopic dermatitis in Germany: Results of the national health care study atopic health 2010. Experimental Dermatology. 2012;21(3):e24.
202. Ock M, Han JW, Lee JY, Kim SH, Jo MW. Estimating quality-adjusted life-year loss due to noncommunicable diseases in Korean adults through to the year 2040. Value in Health. 2015;18(1):61-6.
203. Silverberg J, Gelfand J, Margolis D, Boguniewicz M, Fonacier L. Societal burden of atopic dermatitis in the US population. Journal of the American Academy of Dermatology 2019;81(4): AB125.
204. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH*, et al.* Validation and Interpretation of Short Form 12 and Comparison with Dermatology Life Quality Index in Atopic Dermatitis in Adults. J Invest Dermatol. 2019;139(10):2090-7.e3.
205. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH*, et al.* Health Utility Scores of Atopic Dermatitis in US Adults. Journal of Allergy and Clinical Immunology: In Practice. 2019;7(4):1246-52.e1.
206. Silverberg JI, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY*, et al.* Validation of five patient-reported outcomes for atopic dermatitis severity in adults. British Journal of Dermatology. 2019.
207. Silverberg JI, Gruben D, Neary MP, Smith TW, Fung S, Myers DE. 16882 The clinical and humanistic burden of mild to moderate atopic dermatitis in the United States: Analyses of the National Health and Wellness Survey. Journal of the American Academy of Dermatology. 2020;83(6):AB73.
208. Vilsbøll A, Kragh N, Hahn-Pedersen J, Jensen CE. An algorithm to generate EQ-5D-5L utility scores from the dermatology life quality index: A direct mapping study in a population with atopic dermatitis. Quality of Life Research. 2018;27:S28-S9.
209. Misery L, Reguiai Z, Seneschal J, Heas S, Merhand S. Atopic dermatitis is associated with poor quality of life in adult patients. Journal of the American Academy of Dermatology. 2018;79(3):AB50.

210. Seneschal J, Misery L, Reguiai Z, Heas S, Merhand S. Atopic dermatitis in adults: Impact on sexuality. Journal of the American Academy of Dermatology. 2018;79(3):AB50.
211. Barbieri JS, Chiesa Fuxench ZC, Shin DB, Takeshita J. Frequency and influence of "not relevant" responses on the Dermatology Life Quality Index among adults with atopic dermatitis. Quality of Life Research. 2021.
212. Carvalho D, Aguiar P, Mendes-Bastos P, Palma-Carlos A, Freitas J, Ferrinho P. Quality of Life and characterization of patients with atopic dermatitis in Portugal - QUADEP study. Journal of investigational allergology & clinical immunology. 2020;30(6):0.
213. Coghi S, Bortoletto MC, Sampaio SAP, De Andrade Jr HF, Aoki V. Quality of life is severely compromised in adult patients with atopic dermatitis in Brazil, especially due to mental components. Clinics. 2007;62(3):235-42.
214. Coyle D, Barbeau M. Cost effectiveness of elidel in the management of patients with atopic dermatitis in Canada. Journal of Cutaneous Medicine and Surgery. 2004;8(6):405-10.
215. Holm EA, Wulf HC, Stegmann H, Jemec GB. Life quality assessment among patients with atopic eczema. Br J Dermatol. 2006;154(4):719-25.
216. Huet F, Shourick J, Séité S, Taïeb C, Misery L. Pain in Atopic Dermatitis: An Online Population-based Survey. Acta Derm Venereol. 2020;100(14):adv00198.
217. Kiebert G, Sorensen SV, Revicki D, Fagan SC, Doyle JJ, Cohen J*, et al.* Atopic dermatitis is associated with a decrement in health-related quality of life. International Journal of Dermatology. 2002;41(3):151-8.
218. Kornmehl H, Singh S, Johnson M, Armstrong A. Direct-access online care for the management of atopic dermatitis: A randomized controlled clinical trial examining patient quality of life. Journal of Investigative Dermatology. 2017;137(5):S58.
219. Lam KM. Quality of life assessment among patients with atopic eczema attending dermatology clinics in Hong Kong. Hong Kong Journal of Dermatology and Venereology. 2010;18(4):181-8.
220. Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. British Journal of Dermatology. 1999;141(6):1067-75.
221. Maksimović N, Janković S, Marinković J, Sekulović LK, Živković Z, Spirić VT. Health-related quality of life in patients with atopic dermatitis. Journal of Dermatology. 2012;39(1):42-7.
222. Minami Y, Ito M, Shigeyama Y, Takeuchi N, Kato C, Ogino S*, et al.* Comparison of quality of life between patients with Japanese cedar pollinosis and atopic patients with the SF-8 Health status questionnaire. Allergy: European Journal of Allergy and Clinical Immunology. 2009;64:451.
223. Misery L, Finlay AY, Martin N, Boussetta S, Nguyen C, Myon E*, et al.* Atopic dermatitis: Impact on the quality of life of patients and their partners. Dermatology. 2007;215(2):123-9.
224. Misery L, Seneschal J, Ezzedine K, Heas S, Merhand S, Reguiai Z*, et al.* Atopic dermatitis is associated with poor quality of life in adult patients. Value in Health. 2017;20(9):A808.
225. Retzler J, Smith A, Reaney M, Rout R, Hudson R. Process utilities for topical treatment in atopic dermatitis. Quality of Life Research. 2019;28(9):2373-81.
226. Sand M, Bechara FG, Sand D, Radenhausen M, Tomi NS, Altmeyer P*, et al.* Extracorporeal photopheresis as a treatment for patients with severe, refractory atopic dermatitis. Dermatology. 2007;215(2):134-8.
227. Schmitt J, Meurer M, Klon M, Frick KD. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. Br J Dermatol. 2008;158(2):351-9.
228. Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. Ann Allergy Asthma Immunol. 2018;120(1):66-72.e11.

229. Silverberg JI, Gelfand, J., Margolis, D., et al. Measurement properties of Hospital Anxiety and Depression Scale used in atopic dermatitis in adults. Journal of Allergy and Clinical Immunology 2019;143(2): AB130.
230. Taieb C, Sibaud V, Merial-Kieny C. Impact of Avène hydrotherapy on the quality of life of atopic and psoriatic patients. Journal of the European Academy of Dermatology and Venereology. 2011;25(SUPPL. 1):24-9.
231. Taieb A, Taieb C, Boralevi F, Ezzedine K, Merhand S. Atopic dermatitis in adults: Design and validation of a specific burden questionnaire. Journal of the American Academy of Dermatology. 2014;70(5):AB62.
232. Taïeb A, Boralevi F, Seneschal J, Merhand S, Georgescu V, Taïeb C*, et al.* Atopic dermatitis burden scale for adults: Development and validation of a new assessment tool. Acta Dermato-Venereologica. 2015;95(6):700-5.
233. Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z, Oosting AJ, de Monchy JG, Bruijnzeel-Koomen CA*, et al.* The unfavorable effects of concomitant asthma and sleeplessness due to the atopic eczema/dermatitis syndrome (AEDS) on quality of life in subjects allergic to house-dust mites. Allergy. 2002;57(10):919-25.
234. Treudler R, Zeynalova S, Riedel-Heller SG, Zuelke AE, Roehr S, Hinz A*, et al.* Depression, anxiety and quality of life in subjects with atopic eczema in a population-based cross-sectional study in Germany. J Eur Acad Dermatol Venereol. 2020;34(4):810-6.
235. Thomson KF, Wilkinson SM, Sommer S, Pollock B. Eczema: Quality of life by body site and the effect of patch testing. British Journal of Dermatology. 2002;146(4):627-30.
236. Wolf P, Georgas D, Tomi NS, Schempp CM, Hoffmann K. Extracorporeal photochemotherapy as systemic monotherapy of severe, refractory atopic dermatitis: results from a prospective trial. Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology. 2013;12(1):174-81.
237. Ameen M, George S, Harwood C, Weller R, Lear J, Hudson R*, et al.* An Evaluation of the Current Treatment Pathways and Associated NHS Resource Use for the Management of Uncontrolled Moderate-to-severe Atopic Dermatitis Secondary Care. Value in Health. 2018;21:S430.
238. Ameen M, Blanthorn-Hazell S, Unal G, Alamgir G, Millward R, Rabe J. Healthcare Resource Utilisation of Atopic Dermatitis Patients in England: A Population Based Linked Cohort Study using Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). EADV conference abstract. 2020.
239. Cameron H, Yule S, Dawe RS, Ibbotson SH, Moseley H, Ferguson J. Review of an established UK home phototherapy service 1998-2011: Improving access to a cost-effective treatment for chronic skin disease. Public Health. 2014;128(4):317-24.
240. de Bruin-Weller M, Pink AE, Ferrucci AM, Arenberger P, Svensson A, Schutelaar L*, et al.* Baseline atopic comorbidities and healthcare resource utilisation (HCRU) among patients with atopic dermatitis (AD) in the EUROSTAD prospective observational registry World Congress of Dermatology2019.
241. Eckert L, Amand C, Gadkari A, Rout R, Hudson R, Ardern-Jones M. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). Journal of Dermatological Treatment. 2019.
242. Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P*, et al.* The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: A systematic review and economic evaluation. Health Technology Assessment. 2005;9(29):iii-122.
243. Moncrieff G, Lied-Lied A, Nelson G, Holy CE, Weinstein R, Wei D*, et al.* Cost and effectiveness of prescribing emollient therapy for atopic eczema in UK primary care in children and adults: A large retrospective analysis of the Clinical Practice Research Datalink. BMC Dermatology. 2018;18(1).

244. Oluwa F, Kragh N, Vilsbøel A. Real World Evidence of Ophthalmology Health Care Resource use in Patients with Atopic Dermatitis in England. EADV conference abstract. 2020.
245. Pitt M, Garside R, Stein K. A cost-utility analysis of pimecrolimus vs. topical corticosteroids and emollients for the treatment of mild and moderate atopic eczema. British Journal of Dermatology. 2006;154(6):1137-46.
246. Taylor K, Swan D, Affleck A, Flohr C, Reynolds N. Treatment of moderate-to-severe atopic eczema in adults within the U.K.: Results of a national survey. British Journal of Dermatology. 2015;173:65-6.
247. de Bruin-Weller M, Gadkari A, Auziere S, Puig L, Girolomoni G, Papp KA*, et al.* 714 Productivity losses in adults with atopic dermatitis (AD): A cross-sectional study from clinical practices in Europe and Canada. Journal of Investigative Dermatology. 2019;139(5):S122.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Abrocitinib for treating moderate to severe atopic dermatitis in people aged 12 and over [ID3768]

Document B

Company evidence submission

May 2021

File name	Version	Contains confidential information	Date
ID 3768 Abrocitinib Document B	V2	Yes	14 October 2021

Table of contents

Lists of tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

Atopic dermatitis (AD; also known as atopic eczema) is a chronic inflammatory disorder of the skin, characterised by the presence of red and itchy lesions that can occur anywhere on the body, in a persistent or relapsing manner (Sections B.1.3.1–B.1.3.4).

- The pathophysiology of AD is characterised by abnormalities of the structure and function of the epidermis and inappropriate immune responses to antigens in the skin.
- Many of the inappropriate immune responses are mediated by the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. JAK inhibitors improve the signs and symptoms of AD (including skin inflammation and itch) by inhibiting the cytokine signalling pathways implicated in AD pathogenesis.
- In a recent observational study, the prevalence of AD was estimated to be 6.4% and 4.3% in adolescents and adults in the UK, respectively. Moderate to severe disease is estimated to affect 7% of UK adults and adolescents with AD.

Atopic dermatitis results in a substantial clinical, health-related quality of life (HRQL) and psycho-social burden on patients, as well as an impact on families, caregivers, and society (Section B.1.3.5)

- An uncontrollable and relentless itch (pruritus) and the appearance of red and inflamed lesions on the skin are the two most critical contributors to clinical, HRQL and psycho-social burden for patients with AD.
- Together, itch and skin appearance play a causative role in many of the key features of AD including skin damage, risk of infection, sleep disturbance, difficulty with mood and attention, negative effects on social and intimate

relationships, depression and anxiety, and poor work or school performance.

- Atopic dermatitis can also have a large impact on the quality of life of families and caregivers; Eczema Outreach Support stated that parents/carers spend hours every day supporting adolescents in treating their skin with topical treatments, immunosuppressants, ultraviolet treatments or hospital admissions.

- The economic burden of disease is substantial and increases with disease severity. Costs for AD in the UK exceed £800 million annually including direct and indirect costs (adjusted for inflation). NICE do not typically consider indirect costs in health economic analyses. However, in surveys of patients with moderate to severe AD, absenteeism was three times higher than the general population; overall work impairment (capturing absenteeism and presenteeism) scores were as high as 67.9% for patients reporting extremely large effects of their disease on quality of life according to their DLQI score.

There is a significant unmet need for new treatments (Section B.1.3.7).

- Current treatment options for adults (≥18 years) with moderate to severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated, are limited to dupilumab and baricitinib. For adolescents (≥12 to <18 years) only dupilumab is available.

- Despite current treatment options there remains a substantial unmet need for treatments that better address the two major drivers of disease burden in AD: itch and the appearance of the skin.

- A proportion of patients in the Phase 3 dupilumab trials, 31%–56% of adults and 59% of adolescents treated with dupilumab did not achieve an EASI-75

response at Week 16, and patients can develop antidrug antibodies which may result in loss of efficacy over time.

- Dupilumab is also associated with injection site reactions, eye complications and face and neck erythema which can cause burning and itching, and therefore may not be appropriate for all patients. Further, it is available only as a subcutaneous injection, a dosage form often not preferred by patients.

- Baricitinib has recently been recommended by NICE as a treatment option in AD although it is not yet widely established in clinical practice. In the baricitinib appraisal the results of an indirect comparison informed the committee's view that baricitinib is less effective than dupilumab.

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation. The anticipated marketing authorisation for abrocitinib (CIBINQO®) is for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. However, the proposed positioning is for adult and adolescent patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated, which represents a subgroup of both the anticipated licensed population and the population studied in the clinical trial programme.

Given the current treatment landscape, there is a need for further efficacious, tolerable, and easily administered treatments at this point in the pathway of care (Section B.1.3.7).

In the submission adults and adolescents are explored separately; further, as per trial data the use of abrocitinib and comparator treatments in combination with background medicated topical therapy ("combination analysis") and as monotherapies ("monotherapy analysis") is considered in separate analyses. A summary of the four analyses and their relevance to the decision problem is presented in Table 1.

Table 1: Key analyses to support the decision problem

Analysis	Relevance to the decision problem
Adult combination therapy	Abrocitinib and comparator treatments are used in combination with medicated topical therapy. This is the primary analysis for adults and adolescents as it represents how these treatments are likely to be used in clinical practice.
Adolescent combination therapy	
Adult monotherapy	The adult and adolescent monotherapy comparisons are less relevant for decision-making but represent the effect of abrocitinib and comparator treatments without the confounding effect of medicated topical treatments
Adolescent monotherapy	

The company submission aligns with the preferred assumptions by committees in previous NICE submissions for dupilumab (TA534) and baricitinib (TA681) and the NICE reference case (1, 2). Further, the submission largely aligns with the final NICE scope. Elements of the submission that differ from the final scope are summarised in Table 2, with justification provided.

Two clinical experts were consulted to support development of the submission; their biographies are provided in Appendix R.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 and over with moderate to severe AD	• People aged 12 and over with moderate to severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated • Adults and adolescents are considered separately in the submission	• Pfizer is positioning abrocitinib as an alternative to dupilumab and baricitinib for patients whose disease has not responded to at least one other systemic therapy, such as ciclosporin, methotrexate, azathioprine or mycophenolate mofetil, or if these treatments are contraindicated or not tolerated • There is a substantial unmet need in this line of therapy given the limitations of existing treatments (Section B.1.3.7)
Intervention	Abrocitinib	Abrocitinib 200 mg and 100 mg with and without background medicated topical therapy	Abrocitinib 200 mg and 100 mg has been studied in clinical trials as a monotherapy and in combination with background medicated topical therapy
Comparator(s)	• Phototherapy including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA) • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) • Alitretinoin (in people with AD affecting the hands) • Dupilumab • Baricitinib • Best supportive care (including emollients, topical corticosteroids, phototherapy, education,	• Dupilumab • Baricitinib	There are several comparators that are not relevant to the decision problem, as accepted in the dupilumab (TA534) and baricitinib (TA681) appraisals (3, 4): **Phototherapy** • Typically used earlier in the treatment pathway than the proposed positioning for abrocitinib. The International Eczema Council recommends use of phototherapy after the failure of topical therapies and before the use of immunosuppressants (5). • Short-term treatment option to control symptoms; it is not usually used as a long-term treatment option for AD due to the potential increased risk of skin cancer (6). • Not available widely and only in specialist centres. **Conventional systemic immunosuppressants** • Given the availability of dupilumab and baricitinib, clinical experts confirmed that most patients would be treated with only one prior immunosuppressant therapy prior to initiating

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	psychological support and rescue therapy [for example oral corticosteroids or topical calcineurin inhibitors])		treatment with either dupilumab or baricitinib in clinical practice. If a patient discontinued a first line immunosuppressant therapy due to lack of response or safety concerns, it is unlikely they would be offered sequential lines of immunosuppressant therapy. • Immunosuppressant therapies are not considered relevant comparators; for reference, an STC for abrocitinib vs ciclosporin is presented within the appendices of the submission although this is not deemed relevant for decision making. **Alitretinoin** • Alitretinoin is indicated and recommended by NICE (TA177) for the treatment of adults with severe chronic hand eczema that has not responded to potent topical corticosteroids (7). AD affecting the hands and chronic hand eczema are not synonymous. They are separate conditions that have distinct treatment pathways in UK clinical practice. o AD is a multifaceted, chronic relapsing inflammatory skin condition that is commonly associated with other atopic manifestations. It affects typical anatomical sites at different ages. While most children and adults experience flexural involvement (e.g., backs of the knees/elbows), some adult patients display involvement of the face, hands, and feet. o Chronic hand eczema, defined as a hand eczema lasting for longer than three months or relapsing two or more times per year, is a distinct type of dermatitis that develops on the hands and wrists and is commonly related to contact allergies as well as domestic and occupational irritant exposures (8-10). • The trial data currently available for abrocitinib is for trials including patients with AD, not chronic hand eczema. Therefore, it would not be feasible to compare abrocitinib with alitretinoin in chronic hand eczema based on the currently available trial evidence.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			BSC • Clinician discussion confirmed that although some eligible patients may not receive dupilumab (e.g., due to needle phobia or concomitant medications) or baricitinib (e.g., due to concomitant medications) overall the population of patients unable receive dupilumab or baricitinib is likely to be negligible. • Although only dupilumab is available for adolescents, clinical experts commented that the proportion of patients who would be contraindicated to this treatment would be very small. • For these reasons BSC is not deemed a relevant comparator.
Outcomes	The outcome measures to be considered include: • measures of disease severity • measures of symptom control • disease free period/maintenance of remission • time to relapse/prevention of relapse • adverse effects of treatment • health-related quality of life		NA
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • people with AD affecting the hands • people with moderate dermatitis and those with severe dermatitis • people for whom systemic therapies have been inadequately effective or not tolerated, or are contraindicated • skin colour subgroups.	• People with moderate atopic dermatitis and those with severe atopic dermatitis • People for whom systemic immunosuppressants have been inadequately effective, not tolerated, or contraindicated (proposed positioning for abrocitinib) • Skin colour subgroups.	Pfizer is positioning abrocitinib as an alternative to dupilumab and baricitinib, so the submission presents data from the subgroup of patients from the trials for whom systemic immunosuppressants have been inadequately effective, not tolerated, or contraindicated (see 'Population' row above). Pre-specified full trial population data are presented for subgroups including those based on disease severity and race in Appendix E. People with AD affecting the hands is not considered a subgroup given that the clinical trial programme for abrocitinib was not designed to measure the effect on localised areas of the body such as hand eczema. Although it is plausible that abrocitinib would have an effect on hand eczema there were no outcomes for hand eczema in available clinical trial data against which this can be measured.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; NA, not applicable; NICE, National Institute for Health and Care Excellence; STC, simulated treatment comparison.

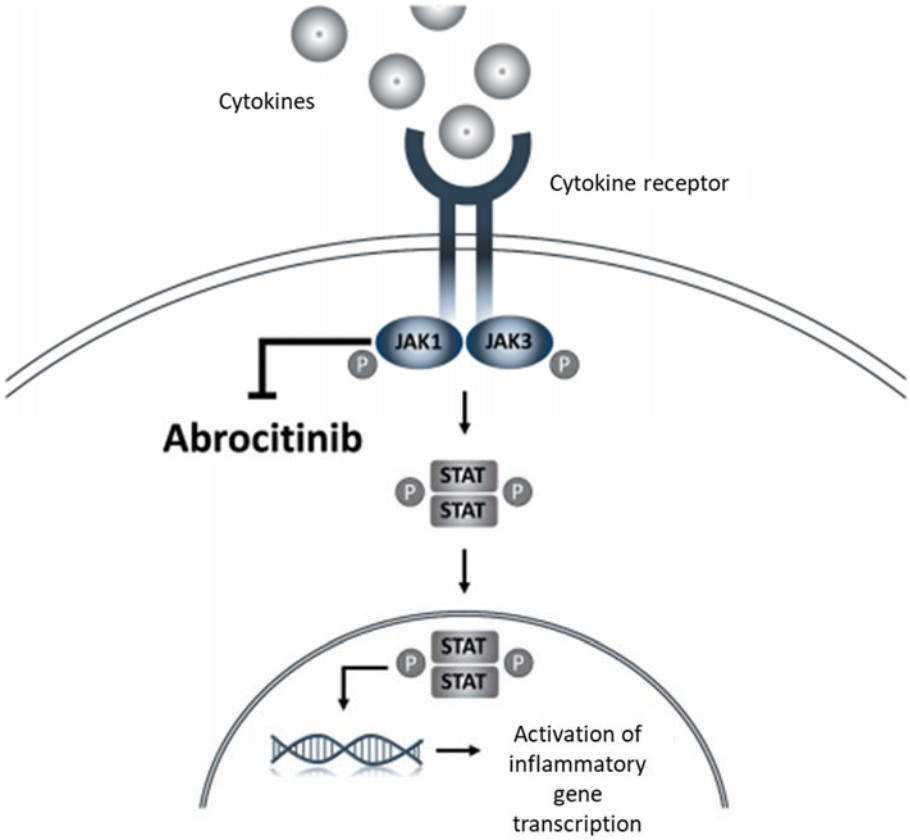
B.1.2 Description of the technology being appraised

The Medicines and Healthcare products Regulatory Agency (MHRA) is reviewing the evidence package for abrocitinib. The proposed UK summary of product characteristics (SmPC) is provided in Appendix C.

Table 3: Technology being appraised

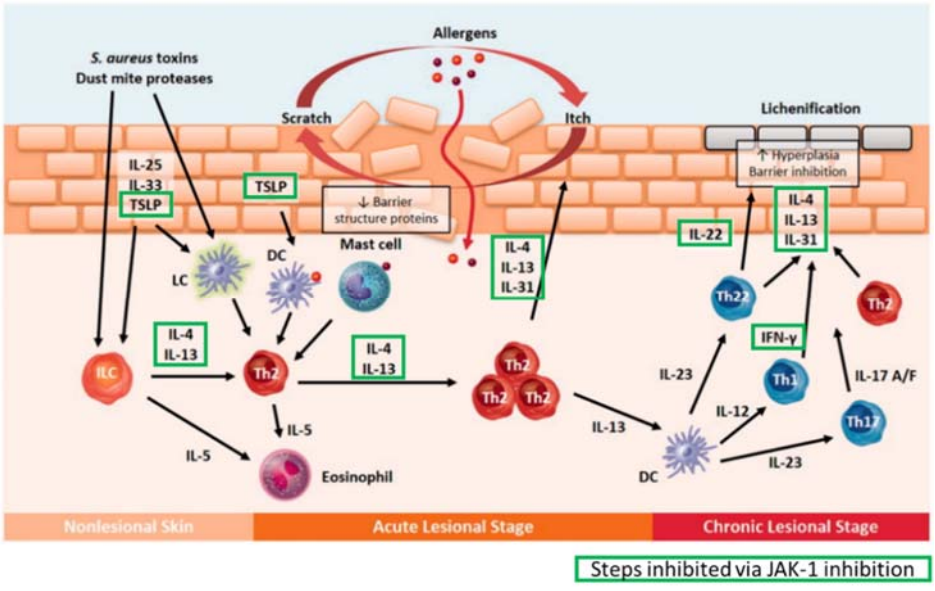
UK approved name and brand name	Abrocitinib (CIBINQO®)
Mechanism of action	Abrocitinib is an oral, Janus kinase 1 (JAK1)-selective inhibitor that inhibits several key cytokine signalling pathways known to have an important role in the pathophysiologic characteristics of atopic dermatitis (AD). The JAK family is a group of cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2) that mediate signalling pathways activated by various cytokines (11, 12). Upon cytokine binding and receptor activation JAKs dimerise (as homo-or heterodimers) to form receptor complexes for signal transducer and activator of transcription proteins (STATs), which then phosphorylate, dimerise and translocate to the nucleus to regulate transcription of genes involved in various inflammatory responses (Figure 1). Various cytokines relevant to the pathophysiology of atopic dermatitis, including interleukin (IL)-4, IL-13, IL-22, IL-31, thymic stromal lymphoprotein (TSLP) and interferon (IFN)-ɣ (11-13) activate JAK1-containing heterodimeric receptors. • IL-4 and IL-13 contribute to the negative effect on skin barrier integrity by downregulating barrier proteins filaggrin, loricrin and involucrin, making the epidermis more penetrable by allergens and pathogens. • IL-4 is also a key player in antibody switching to IgE class and promoting T helper type 2 (Th2) cell differentiation, which in turn produce additional cytokines e.g., IL-4, IL-5, IL-13 and IL-31, leading to further skin inflammation and worsening of the AD condition. • IL-22 is associated with epidermal thickening, skin barrier disruption and increased expression of other pro-inflammatory cytokines e.g., TSLP and IL-33. • IL-31 and TSLP are pruritogenic cytokines that are heavily involved in triggering of inflammatory itch (14). • Th1 cell-derived IFN-ɣ, which is dominant in the chronic phase of AD, promotes exaggerated production of proinflammatory cytokines in keratinocytes (Figure 2). Therefore, by inhibiting JAK1, abrocitinib inhibits the downstream functions of inflammatory cytokines in AD, reducing AD symptoms (including itch) and severity. Figure 1 depicts the inhibition of JAK-1 and JAK-STAT pathway by abrocitinib. Figure 2 presents an overview of the pathophysiology of AD, with the steps inhibited by JAK-1 inhibition outlined in green.

Figure 1: An example representation of the inhibition of JAK-1 and JAK-STAT pathway by abrocitinib



Adapted from: Crowley et al, 2020 (15).
Abbreviations: JAK, Janus kinase; STAT, signal transducer and activator of transcription.

Figure 2: Inflammatory cytokines implicated in skin barrier disruption and immune response in AD



Adapted from Cork et al, 2019 (16).
Abbreviations: AD, atopic dermatitis; DC, dendritic cell; IFN-γ, interferon gamma; ILC, innate lymphoid cell; IL, interleukin; IL-17 A/F, IL-17 A/F

	homodimer or heterodimer; LC, Langerhans cell; Th1, T helper type 1 cell; Th17, T helper type 17 cell; Th2, T helper type 2 cell; Th22, T helper type 22 cell; TSLP, thymic stromal lymphopoietin.
Marketing authorisation/ CE mark status	• Abrocitinib received a PIM designation from the MHRA on 21 July 2020, and an EAMS positive scientific opinion was awarded on 28 January 2021. • A National GB Marketing Authorisation Application (MAA) to the MHRA was submitted on the 29 April; marketing authorisation is anticipated in August 2021. • An application was submitted to the EMA on [redacted], with CHMP opinion expected on [redacted] and marketing authorisation anticipated to be granted on [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of atopic dermatitis. Contraindications included in the draft SmPC (Appendix C) for abrocitinib: • Hypersensitivity to the active substance or to any of the excipients • Active serious systemic infections, including tuberculosis • Severe hepatic impairment • Pregnancy and lactation
Method of administration and dosage	Abrocitinib is to be taken orally with or without food. It is recommended at 200 mg or 100 mg once daily. For most patients, particularly those with severe disease, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions. The maximum daily dose is 200 mg. During treatment, the dose may be decreased or increased based on tolerability and efficacy. Dose reduction can be considered after disease control is achieved in patients receiving 200 mg. Some patients may experience a disease flare after dose reduction. A higher risk of disease flare after dose reduction is associated with history of receiving systemic treatments for atopic dermatitis and extensive disease involving >50% of body surface area (BSA). Abrocitinib can be used with or without medicated topical therapies for AD.
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	List price: [redacted] Annual cost: [redacted] The SmPC advises that discontinuation of abrocitinib should be considered if no evidence of therapeutic benefit is shown after 12 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 12 weeks.
Patient access scheme (if applicable)	PAS price: [redacted] Annual cost: [redacted]

Abbreviations: AD, atopic dermatitis; CHMP, Committee for Medicinal Products for Human Use; EAMS, early access to medicines scheme; EMA, European Medicines Agency; MHRA, Medicines and

Healthcare products Regulatory Agency; PIM, promising innovative medicine; SmPC, summary of product characteristics.

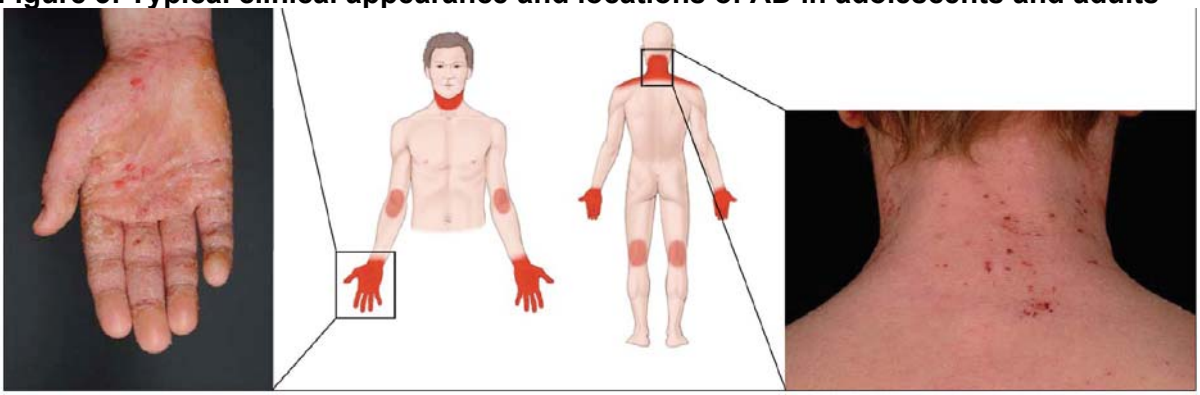
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Atopic dermatitis overview

Atopic dermatitis (also known as atopic eczema) is a chronic inflammatory disorder of the skin, characterised by the presence of red and itchy lesions that can occur anywhere on the body, in a persistent or relapsing manner (17). Eczema is an umbrella term for several skin conditions, of which AD is the most common (18).

The disease is heterogeneous, with variations in morphology, distribution and disease course between patients (19). In adolescents and adults, lesions tend to present on the neck and other areas including the knees, elbows, and wrists as depicted in Figure 3 (20).

Figure 3: Typical clinical appearance and locations of AD in adolescents and adults



Source: Weidinger 2016 (17).
Abbreviations: AD, atopic dermatitis.

The disease course may be relapsing-remitting with acute flares on top of a background of persistent skin inflammation. One study reported that patients with moderate and severe disease experienced on average 8.3 and 11.1 flares per year, respectively, with each flare lasting around 15 days (21). [redacted]

B.1.3.2 Pathophysiology

Atopic dermatitis has a complex pathophysiology that is not completely understood, but two major components have been described as pillars of the disease (16, 17). Evidence increasingly suggests that these components affect one another in a reciprocal manner to drive progression of the disease:

- abnormalities of the structure and function of the epidermis (the outer protective layer of the skin) can lead to disruption, enabling allergens to penetrate the skin more easily.
- inappropriate immune responses to antigens in the skin, resulting in inflammation.

As described fully in Table 3, the JAK-STAT signalling cascade is involved in modulating multiple immune pathways involved in AD. Many cytokines implicated in the pathophysiology of AD, including skin barrier disruption, inflammation, and itch, require JAK1 for signal transduction (17, 23, 24). Therefore, inhibition of JAK1 can block the downstream effects of cytokine signalling, leading to improvement in signs and symptoms of AD (23, 24).

B.1.3.3 Diagnosis and assessment of severity

According to NICE guidance on AD in children (25), diagnosis is typically based on the presence of an itchy skin condition plus three or more of the following:

- visible flexural dermatitis involving the skin creases, such as the bends of the elbows or behind the knees (or visible dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor areas in children aged 18 months or under)
- personal history of dry skin in the last 12 months
- personal history of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative of children aged under 4 years)

- onset of signs and symptoms under the age of two years (this criterion should not be used in children under 4 years of age).

Despite variability in how AD severity is defined, there is some consensus that a holistic approach is needed considering both the clinical manifestation of AD as well as the impact of symptoms on patients' quality of life and wellbeing. There are currently no NICE guidelines for adults, but the NICE guidelines on AD in children provide broad definitions of moderate and severe AD based on clinical factors and quality of life (Table 4) (25).

Table 4: Holistic assessment of AD severity

Skin/physical severity		**Impact on quality of life and psychosocial wellbeing**	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)	Mild	Little impact on everyday activities, sleep, and psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Source: NICE guideline CG57 (25).
Abbreviations: AD, atopic dermatitis.

Similarly, in the final guidance document for the NICE dupilumab appraisal, the committee referred to expert opinion suggesting that severity scoring should be based on both the clinical signs of disease as well as symptoms and their effect on sleep and work. The committee concluded that Eczema Area and Severity Index (EASI), Dermatology Life Quality Index (DLQI) and Patient Orientated Eczema Measure (POEM) are appropriate for assessing the severity of AD in NHS practice (3).

Given the practicalities of using different measures in a clinical trial setting, a range of scoring instruments are utilised (26). Commonly used instruments include the Investigator's Global Assessment (IGA)/Physician's Global Assessment (PGA), EASI and Scoring Atopic Dermatitis index (SCORAD).

In the JADE clinical trial programme for abrocitinib (Section B.2.3), patients with moderate to severe AD meeting the following criteria were included:

- Affected body surface area ≥10%,
- IGA ≥3,
- EASI ≥16,
- Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4[*].

These criteria combine clinical signs of disease (IGA, EASI) as well as a measure of itch intensity (PP-NRS) which is a key symptom of AD and a driver of health-related quality of life through its impact on sleep and work (Section B.1.3.5.2.1). Clinicians interviewed during development of this submission agreed that these eligibility criteria were generalisable to the population expected to be treated with abrocitinib in clinical practice. These eligibility criteria are also generally aligned with those used in the Phase 3 clinical trial programmes for dupilumab and baricitinib (2, 3).

B.1.3.4 Epidemiology

In a recent observational study using the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database, the prevalence of patients with AD receiving treatment was estimated to be 6.4% for adolescents (aged 12–17 years) and 4.3% for adults in the UK (27). There is variation in the estimated prevalence of AD in the literature. However, this is deemed a credible source given that it is a recent, large population-based study (covering 3.85 million people registered with 293 General Practitioner [GP] practices across England), providing a representative sample of the English population. Another strength of this study is that AD diagnosis is captured using a validated algorithm that ensures data accuracy.

The prevalence of moderate to severe disease is estimated to be 7% in UK adults with AD, based on Adelphi data presented in the NICE submission for dupilumab

[*]The PP-NRS was used with permission of Regeneron Pharmaceuticals, Inc. and Sanofi.

(TA534) (3); clinical experts confirmed that a similar proportion of adolescents patients have moderate to severe disease

B.1.3.5 Burden of disease

Atopic dermatitis and particularly the symptoms of itch and skin appearance results in a substantial clinical, health-related quality of life (HRQL) and psycho-social burden on patients, as well as an impact on families, caregivers, and society.

The following sections describe these impacts, with reference to key sources from the literature, studies conducted by Pfizer, and data from the abrocitinib clinical trial programme.

B.1.3.5.1 *Key studies*

A literature search was performed to identify studies reporting on the burden of disease in AD. Three key studies referenced in the submission are summarised below:

- 'Seeing Red' is a report developed by Allergy UK and Sanofi Genzyme, describing a survey of 305 patients in the UK undertaken between November–December 2016 (28).

- 'More Than Skin Deep' is the product of a collaboration of five patient organisations in the United States (29). The report presents findings from a one-day meeting of members of the eczema community, and results of a survey of 1,508 individuals in the US and 57 other countries including the UK (both were conducted in 2019).

- 'Itching for life' is a report produced by the European Federation of Allergy and Airways Diseases Patients' Associations (EFA) evaluating the humanistic and economic burden of AD (30). The report presents findings from a survey of 2,200 adults with AD; 200 patients were from the UK and 1,189 had severe disease.

In addition, Pfizer have conducted four bespoke studies exploring the burden of disease in moderate to severe AD. The studies (detailed in Appendix L) elicited opinions from patients around the burden of disease and treatment preferences:

- **The National Health and Wellness Survey (NHWS)** was a cross-sectional survey of 1,014 adults (including 283 from the UK) with moderate to severe AD (31). Outcomes included measures of HRQL and annual direct and indirect costs.

- **The Adelphi study** combined medical chart information with, if available, survey responses completed by adult patients with moderate to severe AD (32). Of the 631 patients enrolled, 89 were from the UK. Outcomes included measures of HRQL, work productivity, and other skin signs.

- **The patient preferences study for systemic treatments in moderate to severe AD** involved qualitative interviews with 41 patients >12 years with moderate to severe AD (20 from the UK) to explore treatment attributes that matter most to patients, and a discrete-choice experiment with 320 adults with moderate to severe AD (none from the UK) to elicit patients' preferences for specific treatment attributes, their relative importance, and the trade-offs patients were willing to make (33).

- **The 'Impact of Itch in AD' survey** comprised a survey of 34 UK adults with AD and prior use of oral corticosteroids, oral immunosuppressants, or other systemic treatments, and qualitative follow-up interviews with 9 individuals. The aim was to gather data and narratives on the burden of physical symptoms, impact of itch on life, and current management and support (22).

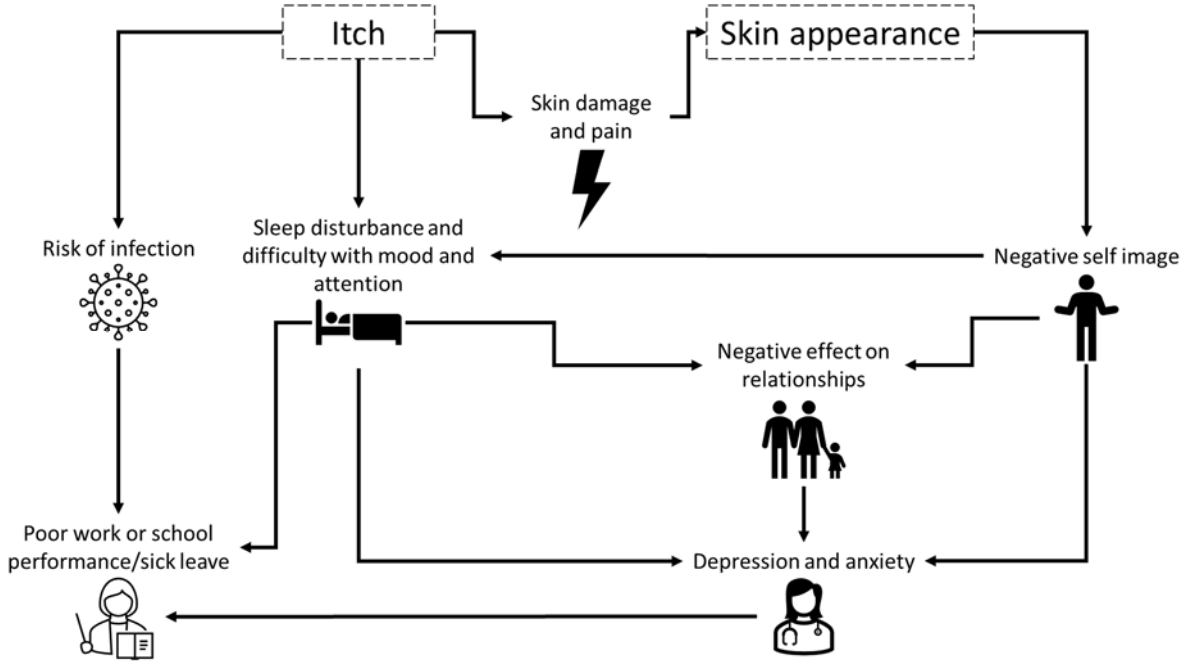
Outputs of these studies are described below. Where possible, UK data are presented, although where regression modelling has been used to explore relationships between variables, data are presented for the full sample.

B.1.3.5.2 *Clinical, HRQL and psycho-social burden of AD on patients*

An uncontrollable and relentless itch and the appearance of red and inflamed lesions on the skin are the two most critical contributors to clinical, HRQL and psycho-social

burden for patients with AD (29). They play a causative role in many of the key features of AD including skin damage, risk of infection, sleep disturbance, difficulty with mood and attention, negative effects on social and intimate relationships, depression and anxiety, and poor work or school performance (Figure 4).

Figure 4: Consequences of itch and skin appearance



Adapted from: More Than Skin Deep 2020 (29).

In the 'Impact of Itch in AD' survey [redacted]

[redacted]

Some of these impacts are particularly severe for adolescents with AD who are at an important stage in their lives; one study found that psychological wellbeing, activities

of daily living, social/leisure activities and interpersonal relationships are more commonly affected in adolescents compared with adults (34). In comments on the scope for this appraisal, the Eczema Outreach Support group noted:

"Eczema is often misunderstood and thought of as just a bit of itchy skin. For an adolescent with severe eczema the reality is very different; it includes recurrent infections, hospital admissions, enduring treatments such as 'wet wrapping' and immunosuppressants, missing school, not being able to take part in normal youth activities because their skin will flare, sleepless nights, and pain from broken itchy skin. Indeed, research shows that eczema impacts on their education, relationships, social life and the family as a whole" (35).

B.1.3.5.2.1 Impact of itch on patient wellbeing

Itch is consistently described by patients as the most burdensome symptom associated with AD (22, 29, 34, 36). In the 'Impact of Itch in AD' survey, [redacted]

As the most burdensome symptom, and given its unrelenting and unbearable nature, itch is associated with a significant impact on patient's wellbeing and quality of life(36, 37). In the patient preference study, patients indicated that reducing itch as quickly as possible was a key factor when considering treatment for their moderate to severe disease (33).

The effects of itch on skin damage, pain, risk of infection, sleep, mental health, relationships and wellbeing are fully described in Table 5.

Table 5: Impacts of itch

Impact	Supporting data
Skin damage, pain, and risk of infection	• Scratching can further exacerbate the condition; deep scratching can cause bleeding and increases the risk of infection (18). Consequently, individuals with AD can experience frequent infections that can lead to hospitalisation (29). • Skin pain has recently been recognised as an important symptom in AD. A prospective dermatology practice-based study of 305 adolescents and adults found that 42.7% of patients reported skin pain in the past week, with 13.8% reporting severe or very severe pain (38).

Impact	Supporting data
	• Patients with both severe itch and skin pain had even poorer quality of life and mental health symptoms than patients with either or neither being severe (38).
Sleep	• PP-NRS has been shown to be significantly associated with several sleep-related measures (SCORAD VAS, POEM sleep item, CDLQI sleep domain, and sleep disruption) in patients with moderate to severe AD (37, 39). • In the NHWS study 57.6% of UK adults reported sleep difficulties (31). Further, in the 'Impact of Itch in AD' survey [redacted]
Mental health, relationships and wellbeing	• The 'Impact of Itch in AD' survey, [redacted] • In the Adelphi study, [redacted]

Abbreviations: AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; NHWS, National Health and Wellness Survey; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCoring Atopic Dermatitis; VAS, visual analogue scale.

B.1.3.5.2.2 Impact of skin appearance on patient wellbeing

In the 'More Than Skin Deep' report, the effect of AD on the condition and appearance of the skin was found to be the second-most burdensome symptom after itch, leading to numerous negative impacts on daily life including low mood, poor self-image, and lack of confidence (29).

The appearance of the skin is linked to the development of anxiety and depression. In a study of patients with AD, psoriasis or acne who were taking systemic medication, cutaneous body image (CBI; a measure of how individuals perceive their hair, skin and nails) was found to be significantly correlated with global and appearance-related self-esteem (40).

The impact of skin appearance may be particularly disruptive in adolescents; in one study both adolescents and adults reported experiencing embarrassment about their skin, frustration, and sadness. Adults also reported experiencing anxiety, worry, and self-consciousness about their skin, whereas adolescents reported stress and disgust at their skin (34).

Higher thresholds of skin clearance is an important factor in making treatment choices: [redacted]

[redacted]

[redacted] B.3.4.5 [redacted]

B.1.3.5.2.3 Humanistic burden of AD compared with other conditions

Atopic dermatitis represents the skin disease with the greatest global skin disease burden as measured by disability-adjusted life years (41). Health-related quality of life scores are lower in AD compared with vitiligo, and patients with AD are more affected by skin discomfort than those with urticaria (hives) (42). More generally, the impact of AD on HRQL is similar to or greater than the impact of other chronic conditions such as visual disorders, hepatitis, and some types of cancer (43).

B.1.3.5.3 *Family and caregiver burden*

Atopic dermatitis can also have a large impact on the quality of life of families and caregivers; studies report significant correlation between Children's Dermatology Life Quality Index (CDLQI) scores of children/adolescents and Dermatitis Family Impact (DFI) scores of parents/guardians (44, 45). In comments on the draft scope for this appraisal, Eczema Outreach Support stated that parents/carers spend hours every day supporting adolescents in treating their skin with topical treatments, immuno-suppressants, ultraviolet treatments or hospital admissions (35).

Although less commonly recognised, AD can also have a significant burden on individuals living with adults with AD.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

B.1.3.5.4 *NHS and societal burden of AD*

The economic burden of disease is significant and increases with disease severity. Costs for AD in the UK exceed £800 million annually including direct and indirect costs (adjusted for inflation) (46, 47).

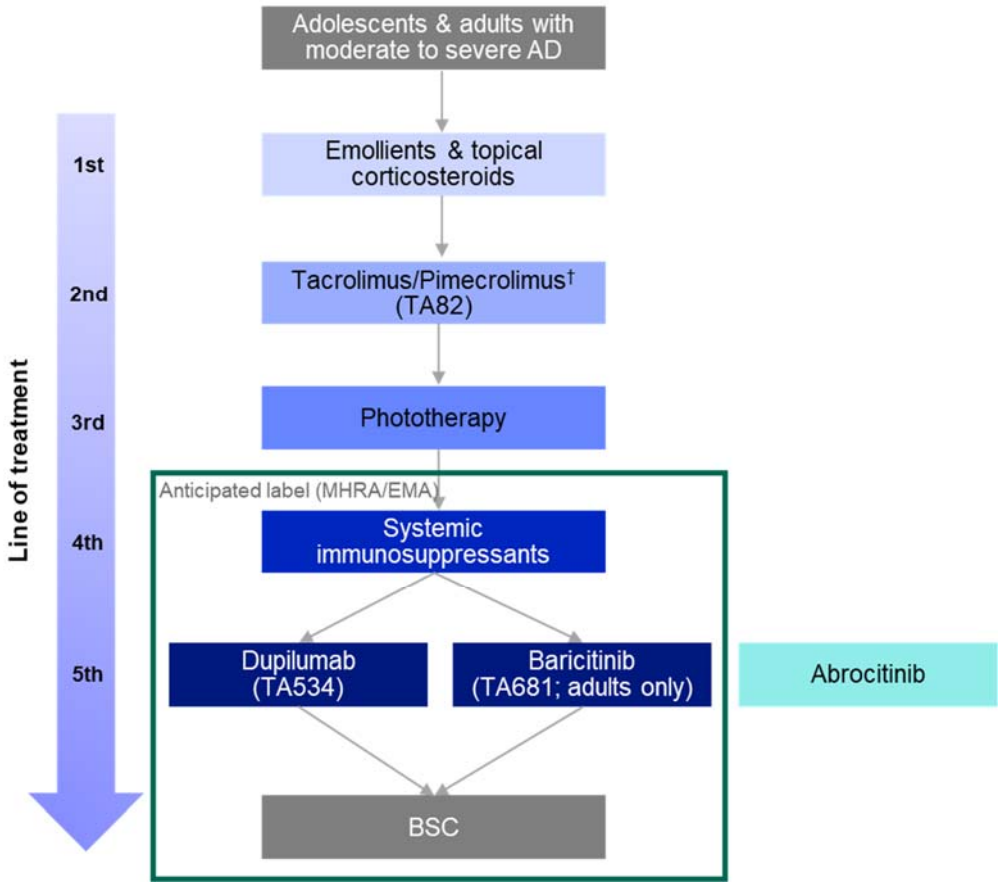
NICE do not typically consider indirect costs in health economic analyses. However, in surveys of patients with moderate to severe AD (NHWS surveys from 2013 and 2017), absenteeism was three times higher than the general population; overall work impairment (capturing absenteeism and presenteeism) scores ranged from 32.3 – 67.9% (31, 48).

Costs associated with work productivity loss in adults are included in the cost-effectiveness model (Section B.3.5).

B.1.3.6 Clinical pathway of care

An overview of the clinical pathway of care, highlighting the proposed positioning for abrocitinib, is presented in Figure 5. There is a NICE clinical guideline for the diagnosis and management of atopic eczema in children under 12 (CG57) (25) and a NICE Quality Standard for Atopic Eczema in under 12s (QS44) (49), but there are currently no NICE guidelines or quality standards on the diagnosis and management of moderate to severe AD in adults or adolescents. The treatment pathway in AD in England and Wales is well defined for adults based on previous appraisals for dupilumab (TA534) and baricitinib (TA681) (3, 4); advice from clinical experts in the UK was sought to explore the current treatment pathway for adolescents.

Figure 5: Proposed positioning of abrocitinib in the clinical pathway of care for AD



†Pimecrolimus is only recommend by NICE for moderate atopic dermatitis on the face and neck in children aged 2 to 16 years (50).
Abbreviations: AD, atopic dermatitis; BSC, best supportive care.

B.1.3.6.1 *Early lines of treatment in moderate to severe AD*

First-line treatment of adolescents and adults with moderate to severe AD involves use of emollients (51). Topical corticosteroids (TCS) are also used as first-line to address inflammation; potency should be tailored to the severity of AD and the area of the skin being treated.

NICE TA82 recommends topical calcineurin inhibitors (TCIs), tacrolimus (for moderate to severe disease in adults and children aged two years and older) and pimecrolimus (for moderate disease on the face and neck in children aged 2 to 16 years) as options for the second-line treatment of atopic eczema that has not been controlled by TCS, where there is a serious risk of important adverse effects from further TCS use, particularly irreversible skin atrophy (50).

Although topical therapies can be effective for some patients, in others they have limited efficacy (52). Prolonged use of potent TCS should be avoided due to potential

side effects including skin atrophy, skin bleaching, and the worsening or spreading of skin infections (53-55).

Phototherapy may be used after the failure of topical therapies (5). It can be effective in controlling AD, although it is associated with limitations, including the need for frequent applications by trained phototherapy nurses and expensive equipment that requires regular maintenance. Clinicians consulted for this submission explained that only around 10% of patients would be considered for phototherapy due to limited availability and difficulties in access (patients are required to attend two to three appointments per week for 8–16 weeks).

Patients may be prescribed a course of oral corticosteroids to manage flares however it is not a long-term treatment option; frequent or prolonged use is not recommended as these are associated with serious adverse effects (56).

B.1.3.6.2 *Conventional systemic immunosuppressants*

The only systemic immunosuppressant licensed for AD in the UK is ciclosporin, but other systemic therapies are also used outside of their marketing authorisation in UK clinical practice, such as methotrexate, azathioprine and mycophenolate mofetil (57). However, these treatments have poor safety profiles; ciclosporin use can lead to renal insufficiency, tremor, hypertension, and an increased risk of malignancies, particularly of the skin, and other systemic immunosuppressants are associated with a range of common side effects including skin and other malignancies, myelosuppression hepatotoxicity and gastrointestinal intolerance (58).

Clinicians consulted for this submission explained that methotrexate is the most prescribed systemic immunosuppressant for long-term maintenance treatment of AD. They stated that although ciclosporin is useful to gain rapid control of symptoms, it is usually used for no longer than 6–12 months because of its side-effect profile. Although ciclosporin is licensed for severe disease only, in practice it is also prescribed to patients with moderate disease.

B.1.3.6.3 *Dupilumab*

NICE TA534 recommends dupilumab as an option for treating moderate to severe AD in adults, only if the disease has not responded to at least one other systemic

therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated (3). The licence for dupilumab has since been extended to include younger age groups (aged six and above) and funding has been made available in the UK for adolescents through specialised commissioning (59, 60).

B.1.3.6.4 *Baricitinib*

Baricitinib has recently been recommended by NICE as a treatment option in AD (TA681) although it is not yet widely established in clinical practice (4). It is recommended as an option for treating moderate to severe AD in adults, only if the disease has not responded to at least one systemic immunosuppressant, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable (61). Baricitinib is not licensed for treatment of AD in people aged <18 years.

B.1.3.6.5 *Best supportive care*

For patients who do not respond or are intolerant to dupilumab or baricitinib, the only remaining treatment option is best supportive care.

In this submission, best supportive care is defined as including emollients, TCS, TCIs, phototherapy, psychological support, and rescue therapy associated with disease flares, which is composed of oral corticosteroids and potent or very potent TCS or TCI. This is based on consensus from the dupilumab and baricitinib NICE appraisals (3, 4). Education is not included because no reliable data are available; the ERG and committee agreed with this in the dupilumab appraisal (3). Emollient bathing additives are also excluded as the committee in the baricitinib appraisal noted information provided by the ERG that there has been a significant reduction in their use since no evidence of clinical benefit was found in a large scale study in the UK (4, 62).

B.1.3.7 Unmet need

There is a substantial unmet need in moderate to severe AD for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated given the limitations of existing treatments, as discussed in the sections below.

Notably, there is an unmet need for treatments that better address the two major drivers of disease burden in AD: itch (Section B.1.3.5.2) and the appearance of the skin (B.1.3.5.2.2).

Dupilumab may not be appropriate for some patients given some of its side effects and its route of administration – alternative treatment options are needed.

A proportion of patients in the Phase 3 dupilumab trials, 31%–56% of adults and 59% of adolescents treated with dupilumab did not achieve an EASI-75 response at Week 16 highlighting the need for additional treatment options (63-66). In a UK real-world study of dupilumab for the treatment of severe AD, some patients reported poor disease control prior to their fortnightly injections (67). The emergence of anti-drug antibodies seems to increase with shorter intervals in dupilumab dosing (68).

Furthermore, dupilumab treatment is also associated with injection site reactions, eye complications (e.g., dry eyes, conjunctivitis, keratitis) and face and neck erythema (associated with burning and itching), potentially limiting treatment for some patients (69-73). In a UK real-world study, 27 patients (42%) reported eye symptoms, some of whom required long-term ophthalmic follow-up (67). Other real-world studies have highlighted high rates of conjunctivitis, leading to discontinuation in some patients (74, 75).

Dupilumab is also only available as a subcutaneous injection, a dosage form often not preferred by patients, given the inconvenience of injections and for some needle phobia. A systematic literature review reported that multiple studies have shown that patients prefer oral formulations to injectable dosage forms, even when the oral medications were administered more frequently (75). In a discrete choice experiment, to analyse patient preferences in moderate to severe AD (Appendix L), oral pills taken once daily were strongly preferred over fortnightly injections (33).

Although recently recommended by NICE, NMA data suggest that baricitinib is less effective than dupilumab.

In the recommendation for baricitinib in TA681, the committee concluded that baricitinib is less effective than dupilumab based on the results of an indirect treatment comparison (61).

The committee also noted that the data showed a peak response to baricitinib at, or before, Week 12 for many outcomes. However, by Week 24 in a pivotal Phase 3 study on baricitinib in combination with background TCS (BREEZE-AD4) baricitinib was no longer statistically significantly more effective than placebo for EASI 75 or an IGA score of 0 or 1. The committee concluded that baricitinib was more clinically effective than placebo at week 16, but that this appeared to wane over time.

B.1.4 Equality considerations

The use of abrocitinib is not anticipated to raise any equality issues however, as highlighted in the Eczema Outreach Support comments on the draft scope adolescents and patients with AD with skin of colour may experience health inequalities in accessing/adhering to treatments (35). Adolescents have greater unmet need as only dupilumab is available as a treatment option in the proposed positioning. For patients with skin of colour, outcomes measures are less reliable and can result in an underestimation of the severity of AD. In addition, the cytokine pathways contributing to AD may differ across ethnicity groups; abrocitinib targets several immune pathways and provides therapeutic benefit across a broad range of patient populations (76).

B.2 Clinical effectiveness

The coprimary endpoints (IGA and EASI-75 response at Week 12) from the four pivotal Phase 3 RCTs (COMPARE, TEEN, MONO-1 and MONO-2) were met and superiority vs placebo was consistently demonstrated for both doses of abrocitinib (Section B.2.6).

Abrocitinib provides rapid onset of itch relief and skin clearance. In the full trial population of COMPARE, abrocitinib 200 mg appeared to be more effective than dupilumab across a range of endpoints, while abrocitinib 100 mg was comparable to dupilumab (Section B.2.6).

- Abrocitinib 200 mg was superior to dupilumab for the key secondary endpoint of achieving a PP-NRS ≥ 4-point improvement from baseline (PP-NRS4) at Week 2, suggesting it is more effective than dupilumab at achieving a rapid, clinically meaningful improvement in itch. Significantly greater proportions of PP-NRS4 responders were observed for abrocitinib 200 mg at all time points up to Week 8. At Week 12, statistically higher proportion of patients treated with abrocitinib 200 mg achieved PP-NRS 0/1 (illustrating itch-free or virtually itch-free status).
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

Data from the two supporting studies (EXTEND and REGIMEN) shows that the majority of patients on abrocitinib maintained the treatment responses in the long term (Sections B.2.6.4 and B.2.6.5). [redacted]

Abrocitinib is a novel, orally administered, JAK1-selective inhibitor (Section B.2.12).

- Abrocitinib has been recognised as a Promising Innovative Medicine by the MHRA.
- Abrocitinib offers a novel mode of action; two doses, which could be used with or without medicated topical therapies, offer dosing flexibility based on individual patients' tolerability and efficacy.
- The oral route of administration (as opposed to injection) is preferable for some patients and this could be a key factor when considering treatment for moderate to severe disease.
- [redacted]

[redacted]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical evidence on the efficacy and safety of abrocitinib and relevant comparators for the treatment of patients with moderate to severe AD. In total, the SLR identified 73 publications reporting on 38 unique studies; of these, 27 studies report on the key treatments considered in the decision problem (abrocitinib, dupilumab and baricitinib; Section B.1.1). Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Pivotal trials

The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD has been assessed in an extensive clinical trial programme, including four pivotal Phase 3 clinical trials (considering both 200 mg and 100 mg doses of abrocitinib). Importantly, JADE COMPARE included a comparison between abrocitinib 100 mg/200 mg and dupilumab.

- JADE COMPARE evaluated 200 mg and 100 mg abrocitinib in combination with background medicated topical therapy* vs each of dupilumab and placebo in adults (≥18 years).
- JADE TEEN also compared 200 mg and 100 mg abrocitinib in combination with background medicated topical therapy*, but with placebo only, and in an adolescent population (≥12 to <18 years).

*Background medicated topical therapy comprised medium/low potency TCS, TCIs e.g., tacrolimus, pimecrolimus or a PDE4 inhibitor (e.g., crisaborole)

- JADE MONO-1 and MONO-2 were identical trials comparing 200 mg and 100 mg abrocitinib monotherapy* with placebo in patients aged 12 years or older.

In all four trials, the use of rescue medication was prohibited.

COMPARE and TEEN support the adult and adolescent combination therapy analyses respectively and are therefore most relevant to decision making. However, the monotherapy studies (MONO-1 and MONO-2) represent the effect of abrocitinib without the confounding effect of medicated topical treatments, as summarised in Table 6. Only co-primary and key secondary endpoints from MONO-1 and -2 are presented in Section B.2, with the full monotherapy dataset summarised in Appendix M.

Table 6: Relevant abrocitinib trial data to support key analyses

Analysis	Relevance to the decision problem	Abrocitinib pivotal data
Adult combination therapy	Abrocitinib and comparator treatments are used in combination with medicated topical therapy. This is the primary analysis for adults and adolescents as it represents how these treatments are likely to be used in clinical practice.	COMPARE
Adolescent combination therapy		TEEN
Adult monotherapy	The adult and adolescent monotherapy comparisons are less relevant for decision-making but represent the effect of abrocitinib and comparator treatments without the confounding effect of medicated topical treatments	MONO-1/2 adult population
Adolescent monotherapy		MONO-1/2 adolescent population

B.2.2.2 Supporting trials

In addition to the four pivotal studies for abrocitinib, data from a long-term extension study (EXTEND) that feeds into the economic model are presented within Section B.2. This trial was designed to explore the long-term safety and efficacy of abrocitinib for patients who completed a qualifying parent trial. Patients received the same dose of abrocitinib as they received in the parent trials. Those who received placebo or active comparator in the parent trial were randomised to receive either 100 mg or 200 mg abrocitinib.

*In MONO-1 and MONO-2, concomitant use of only non-medicated emollient therapy was permitted.

A further study (REGIMEN) is also summarised; following an open-label run-in period with abrocitinib 200 mg, responders (defined as those achieving an IGA of clear [0] or almost clear [1], a reduction from IGA baseline of ≥2 points, and reaching an EASI-75 response compared to baseline) were randomised to “dose down” to 100 mg or placebo in the maintenance period. If at any time during the maintenance period a flare was experienced (defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2) the patient began a 12-week rescue treatment period (open-label abrocitinib 200 mg with concomitant medicated topical therapy). This study provides data on the ability to recapture response using abrocitinib 200 mg in combination with topical therapy as a rescue treatment for flares.

Data from REGIMEN on use of rescue medications was used to inform the flare rate used in the model for the 200 mg dose only; data for the 100 mg dose were not used directly but were used to inform selection of the flare rate (Section B.3.3.3). An overview of key findings is presented in this section as this study is relevant to the decision problem.

Table 7: Overview of pivotal studies

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
Study design	Phase 3, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel treatment group study	Phase 3, multicentre, randomised, double-blind, placebo-controlled study	Phase 3, multicentre, randomised, double-blind, placebo-controlled studies
Key objective	To compare the efficacy of abrocitinib 200 mg and 100 mg OD vs placebo in adults with moderate to severe AD who were receiving topical therapy†	To compare the efficacy of abrocitinib 200 mg and 100 mg OD vs placebo in adolescents aged 12 to <18 years with moderate to severe AD who were receiving topical therapy†	To compare the efficacy of abrocitinib 200 mg and 100 mg OD vs placebo in patients aged 12 years and older with moderate to severe AD
Population	≥18 years with moderate to severe AD and inadequate response to medicated topical therapy†, or who have required systemic therapies	≥12 to <18 years with moderate to severe AD and inadequate response to medicated topical therapy†, or who have required systemic therapies, or are candidates for systemic therapy	≥12 years with moderate to severe AD and inadequate response or contraindication to medicated topical therapy†, or who have required systemic therapies
Intervention(s)	Abrocitinib (100 mg or 200 mg, OD, oral) plus background medicated topical therapy‡	Abrocitinib (100 mg or 200 mg, OD, oral) plus background medicated topical therapy‡	Abrocitinib (100 mg or 200 mg, OD, oral) monotherapy
Comparator(s)	• Dupilumab (300 mg, Q2W, SC) plus background medicated topical therapy‡ • Matched placebo (OD, oral for abrocitinib placebo; Q2W, SC for dupilumab placebo) plus background medicated topical therapy‡	Placebo (OD, oral) plus background medicated topical therapy‡	Placebo (OD, oral)
Indicate if trial supports application for MA	Yes		
Indicate if trial used in the economic model	Yes – the economic model uses 12/16-week response data		
Rationale for use in the model	Sub-population data are directly relevant to the decision problem		

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
Reported outcomes specified in the decision problem *(outcomes included in the model marked bold)*	• **Measures of disease severity** • Measures of symptom control • **Adverse effects of treatment** • **Health-related quality of life**		
All other reported outcomes	NA		

†Defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over the counter or prescribed product). ‡Background medicated topical therapy comprised medium/low potency TCS, TCIs e.g., tacrolimus, pimecrolimus or a PDE4 inhibitor (e.g., crisaborole). Abbreviations: AD, atopic dermatitis; NA, not applicable; Q2W, every two weeks; MA, marketing authorisation; OD, once daily; RCT, randomised controlled trial; SC, subcutaneous.

Table 8: Supporting studies (EXTEND and REGIMEN)

Study	EXTEND (NCT03422822)	REGIMEN (NCT03627767)	
Study design	Phase 3, multicentre, long-term extension study	Phase 3, randomised withdrawal, double-blind, placebo-controlled, multicentre study	
Key objective	To estimate the long-term safety of abrocitinib 200 mg and 100 mg OD vs placebo with or without background medicated topical therapy† in patients aged 12 years and older who previously participated in qualifying AD trials‡	To evaluate and compare the maintenance of effect of two doses of abrocitinib (200 mg and 100 mg OD) and placebo in patients aged 12 years and above with moderate to severe AD who achieve the pre-defined response to initial open-label run-in treatment with 200 mg abrocitinib	
Population	≥12 years and completed the full treatment period of a qualifying parent study‡, or must have completed the full rescue treatment period of a qualifying parent study‡ (if applicable), or must have completed the full open-label run-in period in REGIMEN and did not meet the protocol-specified response criteria at Week 12	≥12 years with moderate to severe AD and inadequate response to topical therapy¶, or who have required systemic therapies, or are candidates for systemic therapy	
Intervention(s)	Abrocitinib (100 mg or 200 mg OD, oral; same dose as received in the parent study‡) with or without background medicated topical therapy† (regardless of use in the parent study‡)	**<u>Open-label run-in period (12 weeks)</u>** • Abrocitinib (200 mg OD, oral) monotherapy	Only responders from the open-label period were randomised. Response was defined as achieving an IGA of clear (0) or almost clear (1), a reduction from IGA baseline of ≥2 points,

Study	EXTEND (NCT03422822)	REGIMEN (NCT03627767)	
		Randomised, double-blind maintenance treatment period (40 weeks) • Abrocitinib (100 mg or 200 mg OD, oral) monotherapy	and reaching an EASI-75 response compared to baseline. If at any time during the maintenance period a flare was experienced (defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2) the patient began a 12-week rescue treatment period (open-label abrocitinib 200 mg with concomitant medicated topical therapy, including high or super-high potency, medium or low potency TCS, TCIs (e.g., tacrolimus, pimecrolimus) or PDE-4 inhibitor (e.g., crisaborole).
Comparator(s)	None	**Open-label run-in period (12 weeks)** • No comparator **Randomised, double-blind maintenance treatment period (40 weeks)** • Placebo OD	
Indicate if trial supports application for MA	Yes		
Indicate if trial used in the economic model	Yes – source of long-term efficacy data	Yes – flare rate for abrocitinib 200mg and 100mg doses informs the model	
Rationale for use in the model	Directly relevant to the decision problem		
Reported outcomes specified in the decision problem *(outcomes included in the model marked bold)*	• **Measures of disease severity** • Measures of symptom control • Adverse effects of treatment • **Health-related quality of life**	• Measures of disease severity • Measures of symptom control • Disease free period/maintenance of remission • Time to relapse/prevention of relapse • Adverse effects of treatment • Health-related quality of life	
All other reported outcomes	NA		

†Background medicated topical therapy comprised medium/low potency TCS, TCIs e.g., tacrolimus, pimecrolimus or a PDE4 inhibitor (e.g., crisaborole); ‡Qualifying parent studies were COMPARE, TEEN, MONO-1, MONO-2, REGIMEN and JADE MOA. Patients who received placebo or active comparator in the parent trial were randomised to receive either 100 mg or 200 mg abrocitinib; ¶Defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over the counter or prescribed product).
Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; MA, marketing authorisation; NA, not applicable; OD, once daily; PDE4, phosphodiesterase-4; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids.

B.2.2.3 Patient populations presented in the submission

As described in Section B.1.1, the proposed positioning for abrocitinib is for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. This represents a subgroup of both the anticipated license population and the population studied in the clinical trial programme for abrocitinib, which across all trials was patients who previously had inadequate response to medicated topical therapy or were eligible for systemic treatments.

B.2.2.3.1 *Full trial population*

Clinical data for the full trial populations are first presented in Section B.2.6 of this submission to align with data presented in previous submissions (TA534 and TA681 (1, 2)). The full population represent the largest sample size for assessment of the efficacy of abrocitinib. Co-primary, secondary, and other post-hoc analyses have been presented.

B.2.2.3.2 *Generalisable population*

Clinical data for the subgroup of patients relevant to the proposed positioning (referred to hereafter as the 'generalisable' population) are presented in Section B.2.7.2, with a specific emphasis on the endpoints that are relevant to the decision problem and modelling. The generalisable population is more reflective of the population who are likely to receive abrocitinib in UK clinical practice, namely patients who were previously treated with at least one systemic treatment for AD (Table 9). Generalisable population data were also used to inform the NMA (Section B.2.9) and used in the base case for modelling (B.3.2.1).

B.2.2.3.3 *Restricted population*

Data for a more restricted subgroup (hereafter referred to as the 'restricted' population) were also generated to align more closely with available comparator evidence for dupilumab and baricitinib, and to explore more of a like-for-like comparison within the NMA (Section B.2.9). The restricted population comprises patients who previously failed or were intolerant to ciclosporin. Data for this population are not presented within Section B.2.6 but these are incorporated in NMA

analyses (Section B.2.9) and in scenario analysis within the economic model (Section B.3.2.1).

Table 9 outlines how the generalisable and restricted populations are defined in terms of prior treatment(s).

Table 9: Subgroups considered in the submission

	Generalisable population (Sections B.2.7.2 and B.2.9)	Restricted population (Section B.2.9)
Prior exposure to systemic treatment(s)†		
Ciclosporin	✓	✓¶
Other non-biologics (e.g., mycophenolate mofetil, methotrexate, azathioprine)	✓	✗
Biologics (e.g., dupilumab‡)	✓	✗
Oral corticosteroids only (without prior exposure to any other systemic treatments)	✗	✗

†Patients may have received one or multiple prior systemic treatments; ‡[redacted] patients received prior treatment with dupilumab in MONO-1/-2 and TEEN; ¶In the restricted population, only patients who previously failed or did not tolerate ciclosporin were included. Contraindication was not captured within the clinical trial programme for abrocitinib.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Comparative summary of trial methodology

A full methodology for the pivotal and supporting trials is summarised in Table 10–Table 12, respectively. Study design schematics are presented below the tables.

Table 10: Comparative summary of pivotal trial methodology

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
Location	International (US, Poland, South Korea, Japan, Australia, Bulgaria, Canada, Germany, UK, Latvia, Hungary, Czech Republic, Chile, Spain, Italy, Mexico, Slovakia, Taiwan)	International (US, Australia, China, Czech Republic, Germany, Hungary, Italy, Japan, Latvia, Mexico, Poland, Spain, Taiwan)	**MONO-1:** International (US, Canada, Germany, Australia, Poland, Czech Republic, UK, Hungary) **MONO-2:** International (US, Canada, Australia, Bulgaria, China, Czech Republic, Germany, Hungary, Japan, South Korea, Latvia, Poland, UK)
Trial design	Phase 3, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel treatment group study	Phase 3, multicentre, randomised, double-blind, placebo-controlled study	Phase 3, multicentre, randomised, double-blind, placebo-controlled studies
Key inclusion criteria (full list presented in Appendix M)	• Adult patients ≥18 years with moderate to severe AD **(COMPARE only)** • Patients ≥12 years to <18 years with moderate to severe AD **(TEEN only)** • Patients ≥12 years with moderate to severe AD **(MONO trials only)** • Documented history (within 6 months before screening visit) of inadequate response to treatment with topical therapy† for ≥4 weeks, or for whom topical treatments are medically inadvisable, or who have required systemic therapies for control of their disease • If receiving concomitant medications for any reason other than AD, must be on a stable regimen, defined as not commencing treatment for a new drug or change of dose within 7 days or 5 half-lives prior to Day 1 and throughout duration of study • Willing and able to comply with standardised background medicated topical therapy **(COMPARE and TEEN only)** • During ≤7 days prior to Day 1, patient must have used only non-medicated topical therapy for treatment of AD without other active ingredients **(COMPARE and TEEN only)**		

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
Key exclusion criteria (full list presented in Appendix M)	• Presenting with active forms of other inflammatory skin diseases or had evidence of skin conditions at Day 1 that would interfere with evaluation of AD or response to treatment • Prior treatment with systemic JAK inhibitors (topical JAK inhibitors were not exclusionary) **(COMPARE and TEEN only);** Prior treatment with any JAK inhibitors **(MONO trials only)** • Any psychiatric condition including recent or active suicidal ideation or behaviour • Required treatment with prohibited concomitant medication within the specified time frame prior to first dose of study medication • Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results • Previous treatment with dupilumab and/or a history of hypersensitivity, intolerance, AE, or allergic reaction associated with prior exposure to dupilumab's excipients **(COMPARE only)**		
Settings and locations where the data were collected	Data were collected across 194 sites, globally (11 UK site)	Data were collected across 99 sites, globally (two UK sites)	**MONO-1:** Data were collected across 69 sites, globally (5 UK sites) **MONO-2:** Data were collected across 106 sites, globally (6 UK sites)
Trial drugs (the interventions for each group with sufficient details to allow replications, including how and when they were administered) Intervention(s), n; comparator(s), n	838 patients were randomised (2:2:2:1) to receive: • Abrocitinib 100 mg, oral administration, OD plus dupilumab-matched placebo injection Q2W for 16 weeks (N=238), followed by abrocitinib 100 mg OD until week 20 • Abrocitinib 200 mg, oral administration, OD plus dupilumab-matched placebo injection Q2W for 16 weeks (N=226), followed by abrocitinib 200 mg OD until week 20 • Dupilumab 300 mg, SC, Q2W following a 600 mg loading dose at baseline plus orally administered abrocitinib-matched placebo OD for 16 weeks (N=243), followed by	287 patients were randomised (1:1:1) to receive: • Abrocitinib 100 mg, oral administration, OD for 12 weeks (N=95) • Abrocitinib 200 mg, oral administration, OD for 12 weeks (N=94) • Placebo, oral administration, OD for 12 weeks (N=96)	**MONO-1:** 387 patients were randomised 2:2:1 to receive: • Abrocitinib 100 mg, oral administration, OD for 12 weeks (N=156) • Abrocitinib 200 mg, oral administration, OD for 12 weeks (N=154) • Placebo, oral administration, OD for 12 weeks (N=77). **MONO-2:** 391 patients were randomised 2:2:1 to receive: • Abrocitinib 100 mg, oral administration, OD for 12 weeks (N=158)

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
	abrocitinib-matched placebo OD until week 20 • Placebo, oral administration, OD for 16 weeks (N=131), followed by abrocitinib 100 mg or 200 mg OD until Week 20 One patient in the dupilumab treatment group did not receive treatment, so the FAS contained 837 patients (242 in the dupilumab treatment group) Rescue therapy was not permitted.		• Abrocitinib 200 mg, oral administration, OD for 12 weeks (N=155) • Placebo, oral administration, OD for 12 weeks (N=78).
Permitted and disallowed concomitant medication (full list presented in Appendix M)	**Permitted:** Participants in these trials were required to comply with standardised background medicated topical therapy guidance throughout the study: • Non-medicated topical emollient without other active ingredients indicated to treat AD, or other additives which could affect AD (e.g., hyaluronic acid, urea, ceramide or filaggrin degradation products): must be applied at least twice daily to all body areas affected with AD in the last 7 days prior to Day 1 and throughout the remainder of the study. • TCS must be applied once daily to areas with active lesions, starting on Day 1 (Baseline) and throughout the study (until 7 days after the lesions are under control [clear or almost clear]). • Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) or a phosphodiesterase type 4 (PDE4) inhibitor (e.g., crisaborole) may be used instead of corticosteroids in body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or if continued treatment with TCS of any potency is considered unsafe.		Background medicated topical therapy was not permitted in the MONO trials.
	Disallowed: • All medications and treatments that could affect AD must be discontinued except oral antihistamines • Prolonged exposure to the sun, use of tanning booths, sun lamps or other ultraviolet light sources		

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
	• Herbal medications with unknown properties or known beneficial effects for AD • Treatment with live or attenuated vaccinations • Treatment with CYP3A, CYP2C19 or CYP2C9 inhibitors/inducers Rescue therapies were not permitted.		
Primary outcomes (including scoring methods and timings of assessments)	**Co-primary endpoints** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12 **(powered for abrocitinib vs placebo comparison)** • Response based on EASI ≥75% improvement from baseline (EASI-75) at Week 12 **(powered for abrocitinib vs placebo comparison)**		
Other outcomes used in the economic model/specified in the scope	**Key secondary efficacy endpoints** • Response based on PP-NRS4 at Week 2 **(powered for abrocitinib vs dupilumab comparison)** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 **(powered for abrocitinib vs placebo comparison)** • Response based on EASI ≥75% improvement from baseline (EASI-75) at Week 16 **(powered for abrocitinib vs placebo comparison)** **Secondary efficacy endpoints:** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all other time points except Week 12 and Week 16	**Key secondary efficacy endpoints** • Response based on PP-NRS4 at Weeks 2, 4, and 12 **(powered for abrocitinib vs placebo comparison)** • CFB in PSAAD total score at Week 12 **(powered for abrocitinib vs placebo comparison)** **Secondary efficacy endpoints:** • Response based on PP-NRS4 at all scheduled time points other than Weeks 2, 4 and 12 • Time to achieve PP-NRS4 by Day 15	**Key secondary efficacy endpoints** • Response based on PP-NRS4 at Weeks 2, 4, and 12 **(powered for abrocitinib vs placebo comparison)** • CFB in PSAAD total score at Week 12 **(powered for abrocitinib vs placebo comparison)** **Secondary efficacy endpoints:** • Response based on PP-NRS4 at Week 8 • Time to achieve PP-NRS4 • Response based on EASI-75 at all scheduled time points except Week 12

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
	• Response based on EASI ≥75% improvement from baseline (EASI-75) at all other time points except Week 12 and Week 16 • Response based on achieving a ≥50%, ≥90% and 100% improvement in the EASI total score (EASI-50, EASI-90 and EASI-100) at all scheduled time points. • % CFB in total EASI score • Response based on achieving PP-NRS4 at all scheduled time points except Week 2 • Time from baseline to achieve PP-NRS4 • % CFB in severity of PP-NRS each day from Days 2-15, Weeks 4, 8, 2 and 16 • Steroid-free days by Week 16 • Response based on a ≥50% and ≥75% improvement in SCORAD from baseline at all scheduled time points • % CFB and CFB at all scheduled time points in SCORAD total score • % CFB and CFB at all scheduled time points in SCORAD subjective assessments of sleep loss **Other efficacy endpoints:** NA	• Response based on the EASI-75 at all scheduled time points except Week 12 • Response based on achieving the IGA of clear (0) or almost clear (1) and 2-point reduction from baseline at all scheduled time points except Week 12 **Other efficacy endpoints:** • Response based on a ≥50%, ≥90% and 100% improvement in the EASI total score (EASI-50, EASI-90 and EASI-100) at all scheduled time points	• Response based on achieving the IGA of clear (0) or almost clear (1) and ≥2-point reduction from baseline at all time points except Week 12 **Other efficacy endpoints:** • Response based on a ≥50% and ≥90% improvement in EASI (EASI-50, EASI-90) from baseline at all scheduled time points

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
		• CFB in the percentage BSA affected at all scheduled time points • Proportion of participants with affected BSA <5% at Week 12 • Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points • CFB at all scheduled time points in SCORAD subjective assessments of itch and sleep loss.	• Response based on ≥50% and ≥75% improvement in SCORAD (SCORAD-50. SCORAD-75) from baseline at all scheduled time points • CFB at all time points in the SCORAD subjective assessments of itch and sleep loss
	PROs • CFB of PtGA at all scheduled time points • CFB in DLQI at all scheduled time points • CFB in EQ-5D-5L at all scheduled time points • CFB in each HADS-Anxiety and HADS-Depression at all scheduled time points • CFB in POEM at all scheduled time points • CFB in PSAAD total score at all scheduled time points	**PROs** • CFB at Week 12 in CDLQI and at all other scheduled time points • CFB at Week 12 in HADS and at all other scheduled time points • CFB at Week 12 in POEM and at all other scheduled time points • CFB at Week 12 in DFI questionnaire • CFB of PtGA at Week 12 and at all other scheduled time points • CFB in EQ-5D-Y at Week 12 and at all other scheduled time points • CFB in Peds FACIT-F at Week 12 and at all other scheduled time points	**PROs** • CFB in DLQI or CDLQI at Week 12 or all other scheduled time points • CFB in HADS score at Week 12 and all other scheduled time points • CFB in POEM at Week 12 and all other scheduled time points • CFB of PtGA at Week 12 and all other scheduled time points • CFB of EQ-5D-5L or EQ-5D-Y at Week 12 and all other scheduled time points • CFB of FACIT-F or Peds-FACIT-F at Week 12 and all other scheduled time points • CFB in SF-36v2, acute, at Week 12 and all other scheduled time points • CFB of WPAI:AD AT Week 12 and all other scheduled time points (MONO-2 only) • Response based on PP-NRS4

Study	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) and MONO-2 (NCT03575871)
	Adverse events	**Adverse events**	• Time from baseline to achieve PP-NRS4 **Adverse events**
Pre-planned subgroups	• Sex • Race • Region of enrolment • Baseline disease severity: moderate, severe • Baseline EASI group: 16–25, >25 • Baseline % BSA group: 10–30, >30–50, >50 • Previous use of systemic immunosuppressant for AD: Yes, no • AD duration (years): <26, ≥26 **(COMPARE and MONO-1/-2 only)** • AD duration (years) group (less than or equal to the median value in FAS, above the median value) **(TEEN only)** • Age (years): <40, ≥40; <65, ≥65 **(COMPARE only)** • Age (years): <18, ≥18; <40, ≥40; <65, ≥65 **(MONO trials only)** • Weight **(COMPARE and MONO-2 only)**		

[†]Defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over the counter or prescribed product).
Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; CFB, change from baseline; DLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area Severity Index; EoS, end of study; EQ-5D-5L, European Quality of Life 5-Dimension 5-level scale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; POEM, Patient-Orientated Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PP-NRS4; Peak Pruritus Numerical Rating Scale ≥4-point improvement from baseline; PRO, patient-reported outcome; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; OD, once daily; Q2W, every 2 weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids; WPAI:AD, Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis.

Table 11: Summary of supporting trial methodology (EXTEND)

Trial number (acronym)	EXTEND (NCT03422822)
Location	International (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, China, Czech Republic, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Latvia, Mexico, Netherlands, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Taiwan, United Kingdom, United States) Future data collection is planned in additional countries and study sites.

Trial number (acronym)	EXTEND (NCT03422822)
Trial design	Phase 3, multicentre, long-term extension study
Key inclusion criteria (full list presented in Appendix M)	• Patients ≥12 years who completed the full treatment period of a qualifying parent study† OR must have completed the full rescue treatment period of a qualifying parent study† (if applicable) OR must have completed the full open-label run-in period in REGIMEN and did not meet the protocol-specified response criteria at Week 12
Key exclusion criteria (full list presented in Appendix M)	• Discontinued from treatment (or rescue treatment period/open-label run-in period, if applicable) early in a qualifying Parent study OR triggered a discontinuation criterion at any point during the qualifying Parent study which in the opinion of the investigator, or sponsor, is an ongoing safety concern.
Settings and locations where the data were collected	Data were collected across 465 sites, globally (17 UK sites)
Trial drugs (the interventions for each group with sufficient details to allow replications, including how and when they were administered) Intervention(s), n; comparator(s), n	Patients previously randomised to abrocitinib 100 mg or 200 mg OD in a Parent study† were allocated to the same dose in this long-term extension study (blind maintained throughout Treatment Period 1). Patients previously randomised to dupilumab or placebo only in a qualifying Parent study† were randomised to double-blind treatment; either abrocitinib 200 mg (N=190 [COMPARE]; N=74 [TEEN]; N=177 [MONO-1/-2]) or 100 mg (N=192 [COMPARE]; N=80 [TEEN]; N=181 [MONO-1/-2]) OD. Maximum total treatment duration differs between patients; patients may continue to receive treatment until availability of the commercial product in their country, or until the sponsor terminates the study in their country.
Permitted and disallowed concomitant medication (full list presented in Appendix M)	The following concomitant AD therapies were permitted during the study: • Oral antihistamines; • Non-medicated emollients and all topical medications for AD throughout the study at the discretion of the investigator and in accordance with their usual practice. All listed medications and treatments that could affect AD were to be discontinued except where expressly permitted. Due to the potential of effects to AD from ultraviolet light exposure, patients were to also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.
Primary outcomes (including scoring methods and timings of assessments)	• The incidence of treatment emergent adverse events. • The incidence of serious adverse events and adverse events leading to discontinuation. • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.
Other outcomes used in the economic	• Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points.

Trial number (acronym)	EXTEND (NCT03422822)
model/specified in the scope	• Response based on achieving ≥50%, ≥75% ≥90% and 100% improvement from baseline in the EASI total score (EASI-50, EASI-75, EASI-90) and EASI-100 at all scheduled time points. • Response based on achieving a PP-NRS4 all scheduled time points. • Change from baseline in the frequency of itching due to AD. • Change from baseline of PtGA at all scheduled time points. • Change from baseline in the percentage BSA affected at all scheduled time points. • Change from baseline in DLQI or CDLQI at all scheduled time points. • Change from baseline in POEM at all scheduled time points. • Change from baseline in HADS at all scheduled time points. • Change from baseline in EQ-5D-5L or EQ-5D-Y at all scheduled time points.
Pre-planned subgroups	There were no pre-planned subgroups.

†Qualifying parent studies were COMPARE, TEEN, MONO-1, MONO-2, REGIMEN and JADE MOA. Patients who received placebo or active comparator in the parent trial were randomised to receive either 100 mg or 200 mg abrocitinib.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, children's dermatology life quality index; DLQI, dermatology life quality index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; HADS, hospital anxiety and depression scale; IGA, Investigator's Global Assessment; OD, once daily; POEM, patient-oriented eczema measure; PP-NRS4, Peak Pruritus Numerical Rating Scale ≥4-point improvement from baseline; PtGA, patient global assessment.

Table 12: Summary of supporting trial methodology (REGIMEN)

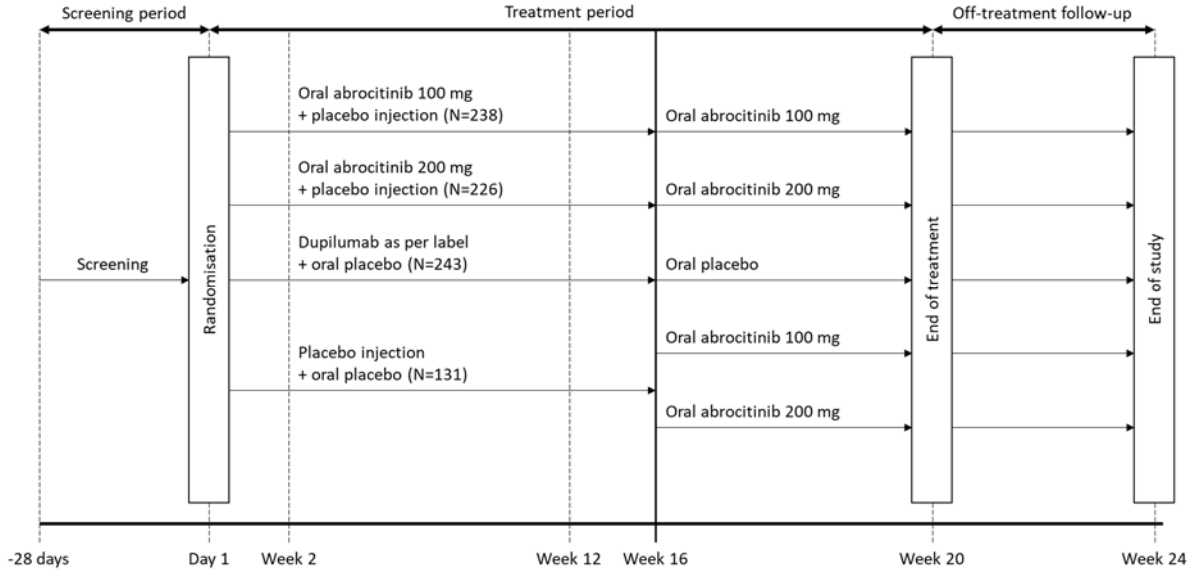
Trial number (acronym)	REGIMEN
Location	International (Canada, US, Belgium, Germany, Israel, Italy, Latvia, Netherlands, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, China, Taiwan, Argentina, Brazil, Chile, Mexico)
Trial design	Phase 3, randomised withdrawal, double-blind, placebo-controlled, multicentre study
Key inclusion criteria (full list presented in Appendix M)	≥12 years with moderate to severe AD and inadequate response to topical therapy†, or who have required systemic therapies, or are candidates for systemic therapy
Key exclusion criteria (full list presented in Appendix M)	• Recent or active suicidal ideation or behaviour • Prior treatment with any JAK inhibitors • Use of dupilumab within 6 weeks of first study dose
Settings and locations where the data were collected	Data were collected across 236 sites, globally (no UK sites).

Trial number (acronym)	REGIMEN
Trial drugs (the interventions for each group with sufficient details to allow replications, including how and when they were administered) Intervention(s), n; comparator(s), n	**<u>Open-label run-in period (12 weeks)</u>** • Abrocitinib (200 mg OD, oral) monotherapy (N=1233) **<u>Randomised, double-blind maintenance treatment period (40 weeks)</u>** • Abrocitinib (100 mg [n=265] or 200 mg [n=266] OD, oral) monotherapy • Placebo (OD) (n=267) Only responders from the open-label period were randomised. Response was defined as achieving an IGA of clear (0) or almost clear (1), a reduction from IGA baseline of ≥2 points, and reaching an EASI-75 response compared to baseline. If at any time during the maintenance period a flare was experienced (defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2) the patient began a 12-week rescue treatment period (open-label abrocitinib 200 mg with concomitant medicated topical therapy, including high or super-high potency, medium or low potency TCS, TCIs (e.g., tacrolimus, pimecrolimus) or PDE-4 inhibitor (e.g., crisaborole).
Permitted and disallowed concomitant medication (full list presented in Appendix M)	The following concomitant AD therapies were permitted during the study: • Oral antihistamines; • Topical non-medicated emollient. All medications and treatments that could affect AD were to be discontinued except oral antihistamines. Due to the potential to affect AD with ultraviolet light exposure, patients were to also avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
Primary outcomes (including scoring methods and timings of assessments)	Protocol-defined loss of response (defined as a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2) requiring rescue treatment was evaluated and compared among groups during the blinded treatment period.
Other outcomes used in the economic model/specified in the scope	**Key secondary endpoint** • Loss of response based on an IGA score of 2 or higher. **Clinical efficacy assessments:** • Response based on the IGA at all scheduled time points. • Response based on EASI total score at all scheduled time points. • Response based on achieving PP-NRS4 at all scheduled time points. • CFB in percent BSA affected at all scheduled time points. • CFB in SCORAD subjective assessments of itch and sleep loss at all scheduled time points. • Proportion of patients achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points. **<u>Clinical efficacy assessments at the end of the rescue period treatment:</u>**

Trial number (acronym)	REGIMEN
	• Response based on the IGA at the end of rescue therapy. • Response based on the EASI total score at the end of rescue therapy. • Response based on achieving PP-NRS4 at the end of rescue therapy relative to the start of rescue therapy baseline value. • Change in percent BSA at the end of rescue therapy relative to the start of rescue therapy baseline value. • Change in SCORAD subjective assessments of itch and sleep loss at the end of rescue therapy relative to the start of rescue therapy baseline value. • Proportion of patients achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) at the end of rescue therapy relative to the start of rescue therapy baseline value. **PROs in all patients:** • CFB in PtGA at all scheduled time points. • CFB in DLQI or CDLQI at all scheduled time points. • CFB in HADS at all scheduled time points. • CFB in POEM at all scheduled time points. • CFB in the PSAAD at all scheduled time points. • CFB in EQ-5D-5L or EQ-5D-Y, in select countries at all scheduled time points. • CFB in FACIT-F and Peds-FACIT-F at all scheduled time points. • CFB in SF-36, acute at all scheduled time points. **Safety Endpoints:** • Incidence of treatment emergent adverse events. • Incidence of SAEs and AEs leading to discontinuation. • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.
Pre-planned subgroups	• Patients who have received at least one dose of rescue treatment (following a protocol-defined flare during the randomised, double-blind period). • Patients participating in the open-label run-in period.

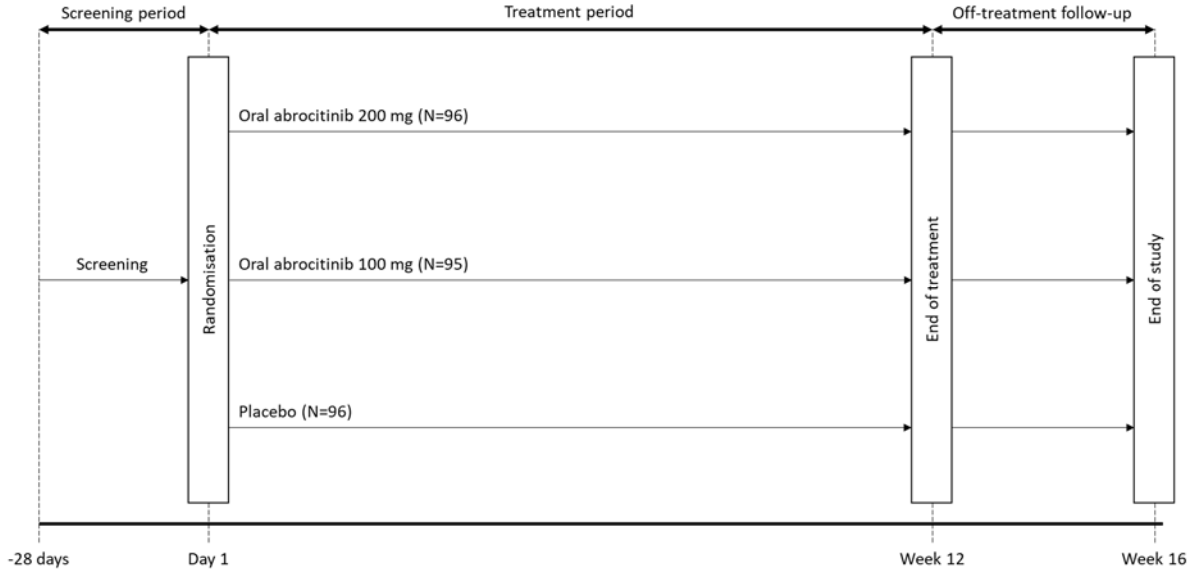
[†]Defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over the counter or prescribed product).
Abbreviations: AD, atopic dermatitis; AE, adverse event; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; CFB, change from baseline; DLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area Severity Index; EQ-5D-5L, European Quality of Life 5-Dimension 5-level scale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; POEM, Patient-Orientated Eczema Measure; PP-NRS4, Peak Pruritus Numerical Rating Scale ≥4-point improvement from baseline; PRO, patient-reported outcome; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; OD, once daily; SAE, serious adverse event; SCORAD, Scoring Atopic Dermatitis; SF-36, 36-item Short Form Health Survey.

Figure 6: COMPARE trial design (adults, combination therapy)



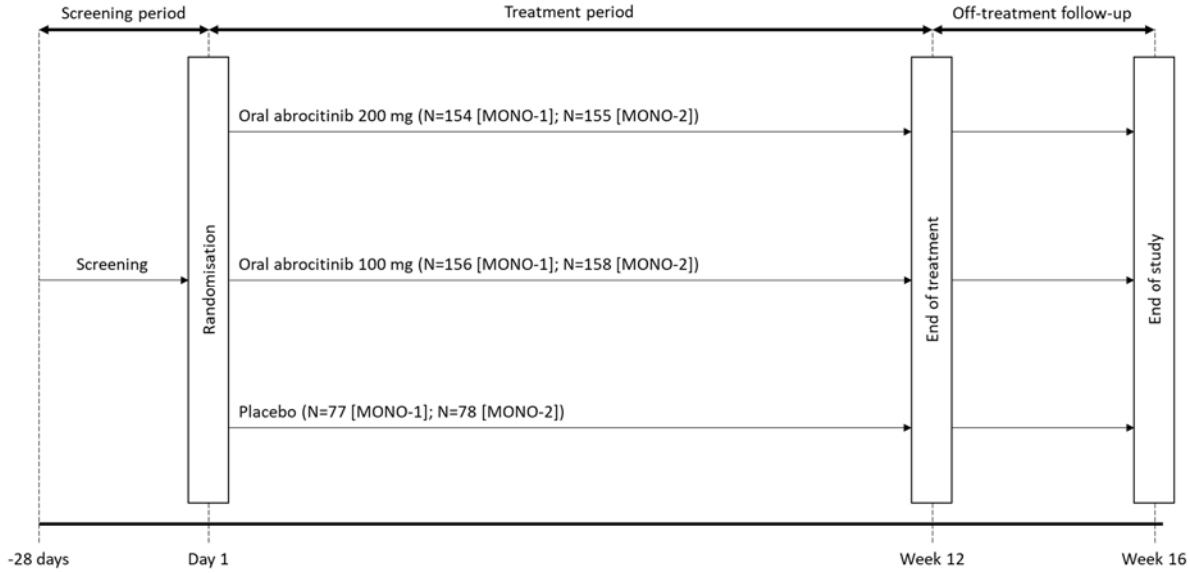
At Week 2 and Week 16, key secondary endpoints are measured; at Week 12, primary endpoints are measured; at Week 20, eligible patients will enter the EXTEND long-term extension study; ineligible patients will instead enter the 4-week off-treatment follow-up period.

Figure 7: TEEN trial design (adolescents, combination therapy)



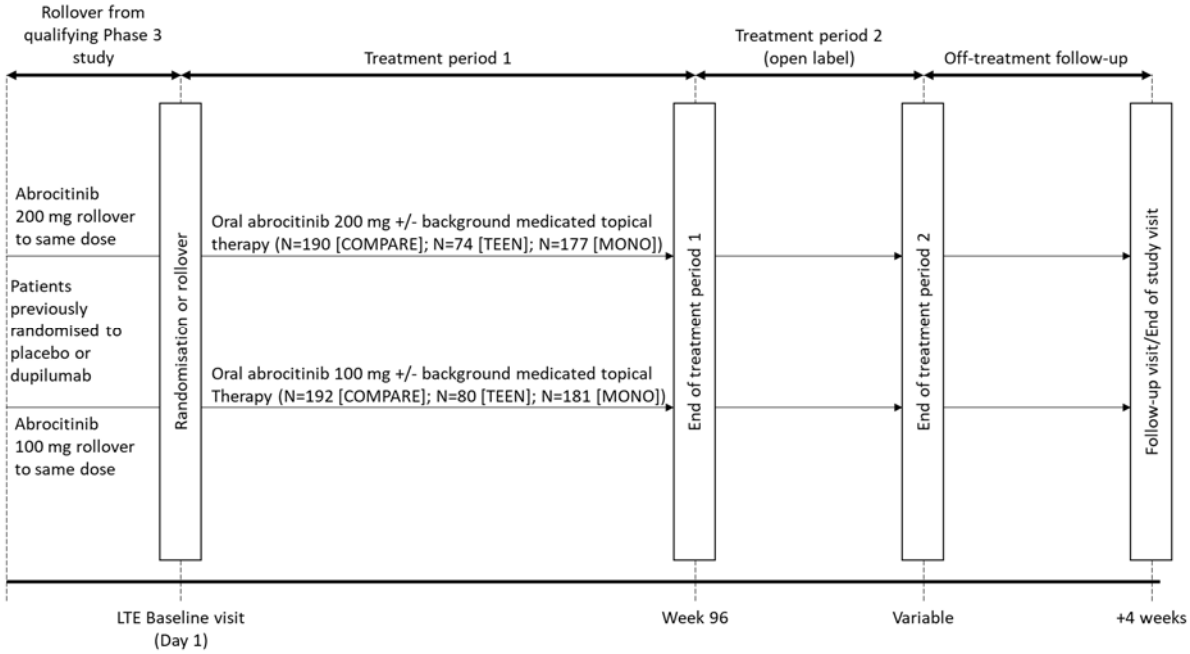
At Week 12, eligible patients may enter a long-term extension study (EXTEND); all other patients enter the 4-week follow-up period.

Figure 8: MONO-1 and MONO-2 trial design (adolescents and adults, monotherapy)



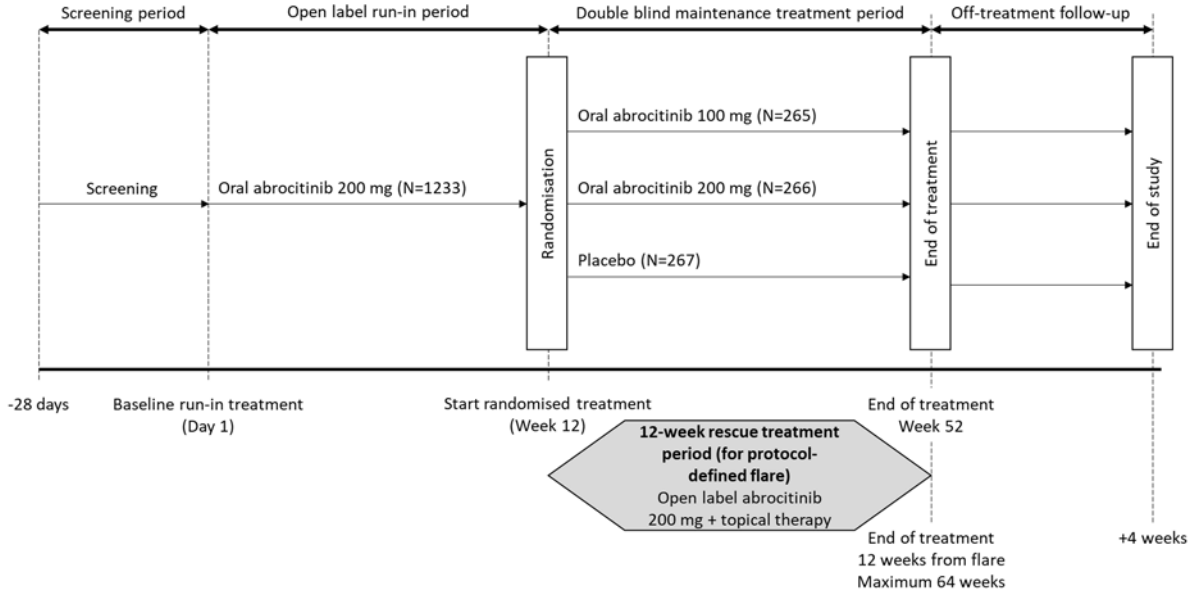
At Week 12, eligible patients may enter a long-term extension study (EXTEND); all other patients enter the 4-week follow-up period.

Figure 9: EXTEND trial design (adults and adolescents, monotherapy and combination therapy)



Abbreviations: LTE; long-term extension.

Figure 10: REGIMEN trial design (adults and adolescents, monotherapy with rescue therapy)



Protocol-defined flare is defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2.

B.2.3.2 Trial outcome definitions

The co-primary endpoints for each of the four pivotal studies were:

- Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12.
- Response based on EASI ≥75% improvement from baseline (EASI-75) at Week 12.

Importantly DLQI/CDLQI data were also collected, allowing the collection of DLQI/CDLQI data and post-hoc analysis on the composite outcome of EASI-50 and a greater than 4-point improvement in DLQI/CDLQI, which is the established outcome measure for NICE decision-making and in clinical practice (3, 61).

Other higher response thresholds for EASI that are captured include EASI-75/-90 and the composites EASI-75/-90 and DLQI/CDLQI ≥4-point improvement. Section B.1.3.5.2.2 highlights the importance of achieving higher thresholds of response given the impact on patient wellbeing and HRQL of the appearance of red and inflamed skin lesions.

Most of the other secondary and exploratory endpoints used are standard in clinical trials of AD. Outcome definitions are summarised in Appendix M.

B.2.3.3 Baseline characteristics

Full trial population baseline characteristics for COMPARE and TEEN are presented in Table 13; baseline characteristics for MONO-1 and MONO-2 are presented in Appendix M, together with generalisable population baseline characteristics for all trials.

Across both the full and generalisable populations, baseline characteristics were comparable between treatment groups and were broadly comparable between trials. The following differences are noted:

- **Between trials:** Differences in median age and disease duration reflected differences in trial eligibility criteria. In COMPARE (adult patients) median age at baseline was [redacted] years, with a median disease duration of [redacted] years. In TEEN (adolescent patients) median age at baseline was [redacted] years, with a median disease duration of [redacted] years.

  The proportion of patients who were White was similar in COMPARE and MONO-1 (72.4% and 72.1%, respectively), with lower proportions in TEEN and MONO-2 ([redacted] and 59.3%, respectively). The proportion of patients who were Black was similar between trials (ranging from 4.2% to 8.3%), while the proportion of patients who were Asian was highest in TEEN and MONO-2 ([redacted]) and lowest in COMPARE and MONO-1 (21.3% and 15%, respectively).

- [redacted]

A topic discussed during the TAs for dupilumab and baricitinib was the generalisability of trial EASI scores to patients with moderate to severe disease in UK clinical practice. The median EASI scores for the full trial populations were [redacted] (COMPARE), [redacted] (TEEN), [redacted] (MONO-1), and [redacted] (MONO-2). These were higher for the generalisable population as reported in Appendix M; however clinical experts confirmed that the generalisable population reflects the population who would likely receive abrocitinib in clinical practice based on the proposed place in therapy.

Table 13: Summary of baseline and disease characteristics, COMPARE and TEEN

	COMPARE					TEEN			
	Placebo (n=131)	**Abrocitinib 100 mg (n=238)**	**Abrocitinib 200 mg (n=226)**	**Dupilumab 300 mg (n=242)**	**Total population (N=837)**	**Placebo (N=96)**	**Abrocitinib 100 mg (N=95)**	**Abrocitinib 200 mg (N=94)**	**Total population (N=285)**
Age (years) <65, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	95 (99.0)†	95 (100.0)	94 (100.0)	284 (99.6)
Age (years), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14.0 (13.5, 16.5)	16.0 (14.0, 17.0)	15.0 (13.0, 16.0)	15.0 (13.0, 17.0)
Female, n (%)	54 (41.2)	118 (49.6)	22 (54.0)	134 (55.4)	428 (51.1)	52 (54.2)	50 (52.6)	38 (40.4)	140 (49.1)
Race									
White	87 (66.4)	182 (76.5)	161 (71.2)	176 (72.7)	606 (72.4)	56 (58.3)	52 (54.7)	52 (55.3)	160 (56.1)
Black or African American	6 (4.6)	6 (2.5)	9 (4.0)	14 (5.8)	35 (4.2)	3 (3.1)	9 (9.5)	5 (5.3)	17 (6.0)
Asian	31 (23.7)	48 (20.2)	53 (23.5)	46 (19.0)	178 (21.3)	32 (33.3)	31 (32.6)	31 (33.0)	94 (33.0)
Other	4 (3.1)	2 (0.8)	2 (0.8)	4 (1.6)	12 (1.0)	3 (3.0)	3 (3.2)	6 (6.5)	12 (4.2)
BMI (kg/m^2), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA, % moderate/severe	67.2/32.8	64.3/35.7	61.1/38.9	66.9/33.1	64.6/35.4	59.4/40.6	60.0/40.0	64.9/35.1	61.4/38.6
EASI, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSA (%), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS (severity), median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSAAD, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SCORAD, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI, Median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	COMPARE					TEEN			
	Placebo (n=131)	**Abrocitinib 100 mg (n=238)**	**Abrocitinib 200 mg (n=226)**	**Dupilumab 300 mg (n=242)**	**Total population (N=837)**	**Placebo (N=96)**	**Abrocitinib 100 mg (N=95)**	**Abrocitinib 200 mg (N=94)**	**Total population (N=285)**
HADS anxiety, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HADS depression, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POEM, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[†]One patient in TEEN was enrolled at the age of 18, which was a protocol deviation
N, total sample size; n (%), number of patients who met criteria, based on total sample size.
Abbreviations: BMI, body mass index; BSA, Body Surface Area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5 dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numeric Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; POEM, Patient Orientated Eczema Measure; SCORAD, Scoring Atopic Dermatitis.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

The primary analysis population for efficacy data in each pivotal RCT (COMPARE, TEEN, MONO-1 and MONO-2) was the full analysis set (FAS), defined as all randomised patients receiving at least one dose of study medication. The FAS would be expected to be identical to an intended-to-treat (ITT) population (randomised and dispensed study medication), because the first dose was administered in clinic. In TEEN, MONO-1 and MONO-2 this was the case and the FAS was identical to the ITT population; in COMPARE one patient in the dupilumab treatment group did not receive medication, so the FAS was equivalent to the ITT population minus this patient.

Data for the full, generalisable and restricted populations presented in this submission (Section B.2.2.3) are based on the FAS.

All patients who received investigational product were included in safety analyses, and thus considered in the safety population. Table 14 presents a summary of the analysis sets across the RCTs.

Table 14. Summary of analysis sets presented for MONO-1, MONO-2 and COMPARE

Analysis set	Description
Full analysis set (FAS)	Defined as all patients who were randomised and received ≥1 dose of treatment. Analyses were defined based on a threshold of change from baseline. For endpoints such as PP-NRS4 this requires the baseline value to be greater than or equal to that threshold (e.g., for PP-NRS4, the baseline value should be ≥4); the same applies for endpoints incorporating DLQI ≥4-point improvement (e.g., EASI-50 & DLQI ≥4).
Safety analysis set (SAS)	Defined as all patients who received at least one dose of study medication, classified according to actual study treatment received. This was the primary population for assessment of safety. A randomised, but not treated patient was excluded from the safety analyses.

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritis Numerical Rating Scale.

B.2.4.2 Statistical analysis

Summaries of the statistical analysis plans for the pivotal RCTs (COMPARE, TEEN, MONO-1 and MONO-2), EXTEND, and REGIMEN are presented in Table 15 and Table 16.

Table 15. Summary of the statistical methodology (pivotal RCTs)

Trial name (NCT)	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) MONO-2 (NCT03575871)
Hypothesis objective	To demonstrate superiority of 200 mg and 100 mg abrocitinib over placebo in adults (≥18 years) receiving background medicated topical therapy with moderate to severe AD. To demonstrate superiority of abrocitinib over dupilumab in attaining a clinically significant improvement in severity of pruritus for adults with moderate to severe AD receiving background medicated topical therapy.	To demonstrate superiority of 200 mg and 100 mg abrocitinib over placebo in adolescents (≥12 years to <18 years) receiving background medicated topical therapy with moderate to severe AD.	To demonstrate superiority of 100 mg abrocitinib and 200 mg abrocitinib over placebo in the treatment of patients ≥12 years with moderate to severe AD.
Multiple comparisons/ multiplicity	A sequential Bonferroni-based iterative multiple testing procedure to strongly control the familywise Type 1 error at 5% was used for assessing the primary and key secondary endpoints.		
Sample size, power calculation	Total of 700 patients, with 200 each randomised to 200 mg abrocitinib, 100 mg abrocitinib, 300 mg dupilumab, and 50 patients each randomised to two sequences of matching placebo for 16 weeks, followed by a switch to receive 100 mg abrocitinib and 200 mg abrocitinib was planned. A combination of the two placebo sequences for analyses at all visits resulted in a 2:2:2:1 randomisation ratio, which provided ≥96% power to detect a difference of ≥20% in IGA response rate between either dose of	Total sample of 225 participants, with 75 participants each randomised to abrocitinib 200 mg, abrocitinib 100 mg, or matching placebo (1:1:1 randomisation) was planned. This would provide at least 80% power to detect a difference of at least 20% in IGA response rate between either dose of abrocitinib and placebo, assuming the placebo response rate is 12% at Week 12. This would also provide at least 96% power to detect a difference of at least 30% in EASI-75 response rate between either dose of abrocitinib and placebo,	Total sample of 225 participants, with 150 each randomised to abrocitinib 200 mg and 100 mg, and 75 assigned to placebo was planned for each of MONO-1 and MONO-2. This provided ≥95% power to detect difference in IGA response of ≥20% between treatment groups, assuming placebo response rate was 6% at Week 12. This provided at least 99% power to detect a difference in EASI-75 response rate of ≥30% between treatment groups, assuming placebo response rate was 15% at Week 12.

Trial name (NCT)	COMPARE (NCT03720470)	TEEN (NCT03796676)	MONO-1 (NCT03349060) MONO-2 (NCT03575871)
	abrocitinib and placebo, assuming the placebo response rate was 12% at Week 12. This also provided ≥99% power to detect a difference of ≥30% in EASI-75 response between either dose of abrocitinib and placebo, assuming placebo response rate is 23% at Week 12. In addition, the sample size provided ≥92% power to detect a difference of ≥15% in the proportion of patients with ≥4-point improvement in severity of pruritus PP-NRS between abrocitinib and dupilumab, assuming the dupilumab response rate is 18% at Week 2.	assuming the placebo response rate is 23% at Week 12.	
Statistical analysis of primary endpoints	Efficacy analyses were performed using the FAS population. The coprimary efficacy endpoints were analysed using the Cochran–Mantel–Haenszel test, adjusted by baseline disease severity (moderate/severe) and (for MONO trial only) age and for a given dose, both endpoints must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of patients achieving IGA response (similarly for EASI-75), along with a 95% confidence interval (using the normal approximation for the difference in binomial proportions) was reported. Additional secondary analyses utilised missing-at-random and missing-not-at-random approaches.		
Statistical analysis of secondary and other endpoints	Key secondary endpoints and all other binary endpoints were also analysed using the CMH test. For continuous endpoints, a mixed-effects model with repeated measures was applied, including the factors (fixed effects) for treatment group, randomisation strata (age, disease severity), visit, treatment-by-visit interaction, and relative baseline value. Within the framework of MMRM, the treatment difference was tested at the pre-specified primary time point, Week 12, as well as other time points by time point-specific contrasts from the MMRM model.		
Data management, patient withdrawals	Data management was completed by the sponsor. The study used an external data monitoring committee, responsible for ongoing monitoring of the efficacy, safety, and PK of patients in the study. Patients were permitted to withdraw from the study at any time at their own request, or they were withdrawn at any time at the discretion of the investigator or sponsor for safety. Missing responses for patients who permanently discontinued the study were defined as non-responders at all visits after discontinuation.		

[†]Weight was considered as a subgroup in MONO-2 only.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; CFB, change from baseline; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; MI, multiple imputation; MMRM; mixed-effect repeated measures; NA, not applicable; NR, non-responder; Peds-FACIT, Paediatric Functional Assessment of Chronic Illness Therapy; PK,

pharmacokinetics; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; POEM, Patient Orientated Eczema Measure; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; SF-36, 36-item Short Form Health Survey.

Table 16. Summary of the statistical methodology (EXTEND and REGIMEN)

Trial name (NCT)	EXTEND (NCT03422822)	REGIMEN
Hypothesis objective	No formal hypothesis testing; efficacy analyses are descriptive in nature.	Evaluate and compare maintenance of effect of two doses of abrocitinib (200 mg and 100 mg) and placebo in patients aged 12 and above with moderate to severe AD who respond to initial open-label run-in treatment of 200 mg abrocitinib.
Multiple comparisons/ **multiplicity**	NA	Six key hypotheses were to be tested for each pairwise comparison between two abrocitinib doses (200 mg and 100 mg) and placebo, for the primary and key secondary endpoints. For these hypotheses, the familywise Type-I error rate was strongly controlled at 5% using a sequential, gatekeeping procedure.
Sample size, power calculation	Sample size was determined by the number of patients enrolling from the qualifying parent studies; it was estimated that at least 3,000 patients would enrol in the study	Total of 600 patients with 200 receiving abrocitinib 200 mg, 200 receiving abrocitinib 100 mg, and 200 receiving placebo (1:1:1 randomisation) provided 94% power to detect a ratio of median time to flare of at least 1.5 times between either dose of abrocitinib (200 mg or 100 mg) and placebo. The Type I error rate was set at 5% (2-sided). Assuming based on prior data, that about 44% of patients would meet the protocol-defined criteria to be a responder at Week 12, approximately 1,370 patients would need to enter the open label run-in period of the study to ensure that 600 patients are available for randomisation.
Statistical analysis of primary endpoints Statistical analysis of secondary and other endpoints	No formal hypothesis testing – descriptive statistics only	A combination of graphical and analytical methods will be used. The time (in weeks) to protocol-defined flare will be used to evaluate the primary endpoint while the time (in weeks) to achieve an IGA score of ≥2 will be used to evaluate the key secondary endpoint. Patients who do not report an event (i.e., protocol-defined flare or IGA ≥2) or discontinue the study during the double-blind randomised period will have their time to event censored at their last known visit in this period. Kaplan-Meier curves will be used to display the time to event and report the median time to event (and its 95% confidence interval) among the three randomised groups. The log-rank test will be used to compare these curves. Proportions of patients with an event and confidence intervals will also be reported by randomised group.
Data management, patient withdrawals	Data management was completed by the sponsor. The study used an E-DMC, responsible ongoing monitoring of the efficacy, safety and PK of patients in the study. Missing outcomes (post-discontinuation) from patient who discontinued from EXTEND were to be considered as non-	Data management was completed by the sponsor. The study used an E-DMC, responsible ongoing monitoring of the efficacy, safety and PK of patients in the study

Trial name (NCT)	EXTEND (NCT03422822)	REGIMEN
	responders (non-responder imputation).	

Abbreviations: E-DMC, external data monitoring committee; NA, not applicable; PK, pharmacokinetics.

B.2.4.3 Multiplicity-controlled comparisons

The co-primary and key secondary endpoints in each trial were multiplicity-controlled – hypotheses corresponding to other secondary and other endpoints were tested at the 5% level of significance without any adjustment for multiplicity.

Tables in this submission presenting non-multiplicity-controlled results have footnotes to indicate this, and p-values are not presented. Additionally, the wording ‘based on 95% CI’ is used in the grey summary boxes when describing the results. In these cases, ‘statistical significance’ means that the 95% CI for the difference between treatments excludes zero, supporting a true difference in treatment response.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment for each trial is presented in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

This section presents data from the full trial populations of abrocitinib studies for outcomes that are specified in the scope for this appraisal.

B.2.6.1 COMPARE (adults, combination therapy, full trial population)

- The COMPARE study met both co-primary endpoints; both abrocitinib treatment groups were superior to placebo for IGA and EASI-75 responses at Week 12.
- Analyses of key secondary endpoints demonstrated that at Week 2, abrocitinib 200 mg reduced itch more effectively (greater proportion of PP-NRS4 responders) than dupilumab, with statistical superiority. Abrocitinib 200 mg had a significantly greater proportion of responders for IGA and numerically higher proportion of EASI-75 responders than dupilumab at Week 16.
- Improved efficacy was observed for both abrocitinib groups compared with placebo in endpoints related to disease severity, symptom control, and HRQL. Both doses of abrocitinib consistently demonstrated an earlier onset of action than dupilumab. Over time, abrocitinib 200 mg appeared to be more effective than dupilumab across a range of endpoints, while abrocitinib 100 mg was comparable to dupilumab (based on 95% CI).

B.2.6.1.1 *Coprimary endpoints*

Abrocitinib vs placebo: IGA and EASI-75 response at Week 12

The co-primary endpoints in COMPARE were met. Both abrocitinib treatment groups were superior to placebo for IGA and EASI-75 response at Week 12 (p<0.001 for all comparisons; Table 17):

- IGA response (Week 12): statistically significantly higher proportions of patients achieved an IGA response of clear (0) or almost clear (1) with ≥2-point improvement from baseline for abrocitinib 200 mg (48.4%) and 100 mg (36.6%) compared with placebo (14.0%).
- EASI-75 response (Week 12): statistically significantly higher proportions of EASI-75 responders were observed for abrocitinib 200 mg (70.3%) and abrocitinib 100 mg (58.7%) compared with placebo (27.1%).

Abrocitinib vs dupilumab: IGA and EASI-75 response at Week 12

Although the primary objective for the co-primary endpoints was to compare abrocitinib doses with placebo, data is also presented in Table 17 for dupilumab for completeness. Significantly more patients receiving abrocitinib 200 mg than dupilumab achieved IGA and EASI-75 responses at Week 12. Response rates were similar between the abrocitinib 100 mg and dupilumab treatment groups (Table 17).

Table 17: Co-primary endpoints at Week 12, FAS, COMPARE (adults, combination therapy, full trial population)

	Abrocitinib 100 mg N=238	**Abrocitinib 200 mg N=226**	**Dupilumab 300 mg N=242**	**Placebo N=131**
IGA response				
IGA responders, n/N (%)	86/235 (36.6)	106/219 (48.4)	88/241 (36.5)	18/129 (14.0)
Difference from placebo, % (95% CI) p-value	23.1 (14.7, 31.4) p<0.001	34.8 (26.1, 43.5) p<0.001	22.5 (14.2, 30.9) NA†	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–
EASI-75 response				
EASI-75 responders, n/N (%)	138/235 (58.7)	154/219 (70.3)	140/241 (58.1)	35/12 (27.1)
Difference from placebo, % (95% CI) p-value	31.9 (22.2, 41.6) p<0.001	43.2 (33.7, 52.7) p<0.001	30.9 (21.2, 40.6) NA†	–

	Abrocitinib 100 mg N=238	Abrocitinib 200 mg N=226	Dupilumab 300 mg N=242	Placebo N=131
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–

†No formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib.
Abbreviations: CI, confidence interval; EASI, Eczema Area Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; NA, not applicable.

B.2.6.1.2 *Key secondary endpoints*

Abrocitinib vs placebo: PP-NRS4 at 2 weeks and IGA and EASI-75 response at Week 16

Both doses of abrocitinib were superior to placebo for all key secondary endpoints: PP-NRS4 at Week 2 and IGA/EASI-75 response at Week 16 ($p<0.001$ for all comparisons; Table 18 and Table 19).

[redacted]

Abrocitinib vs dupilumab: PP-NRS4 at 2 weeks

Abrocitinib 200 mg was superior to dupilumab in the first key secondary endpoint of PP-NRS4 response at Week 2 ($p<0.001$), indicating earlier onset of action in itch relief. Although not reaching statistical significance, the proportion of PP-NRS4 responders at Week 2 in the abrocitinib 100 mg treatment group was numerically higher vs dupilumab (31.8% vs 26.4%) (Table 18).

[redacted]

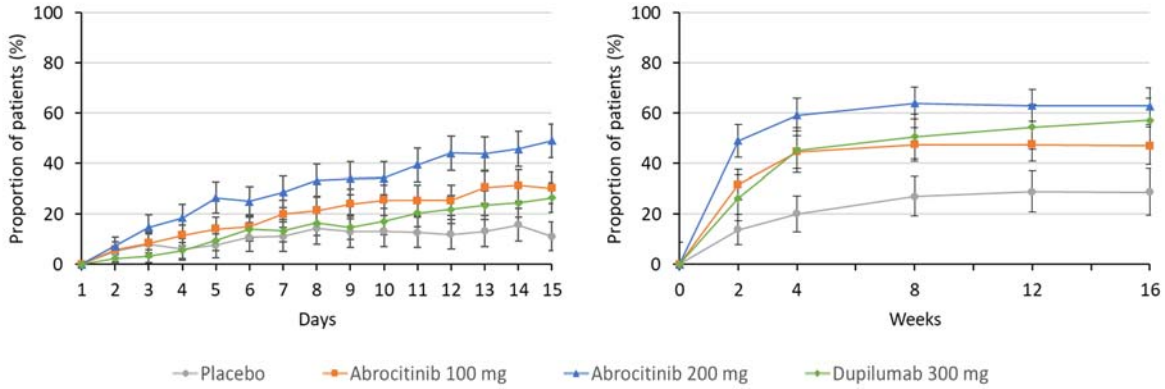
Table 18: PP-NRS4 response at Weeks 2 and 16, FAS, COMPARE (adults, combination therapy, full trial population)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
PP-NRS4 response at Week 2 (key secondary endpoint)				
PP-NRS4 responders†, n/N (%)	75/236 (31.8)	111/226 (49.1)	63/239 (26.4)	18/130 (13.8)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
Difference from placebo, % (95% CI) p-value	17.9 (9.5, 26.3) p<0.001	34.9 (26.0, 43.7) p<0.001	12.5 (4.4, 20.7) NA†	–
Difference between abrocitinib and dupilumab, % (95% CI)	5.2 (–2.9, 13.4) p=0.2	22.1 (13.5, 30.7) p<0.001	–	–
PP-NRS4 response at Week 16 (other secondary endpoint)				
PP-NRS4 responders, n/N (%)	79/168 (47.0)	108/172 (62.8)	108/189 (57.1)	27/94 (28.7)
Difference from placebo, % (95% CI) p-value	18.1 [redacted]	32.7 [redacted]	28.3 [redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	–10.2 [redacted]	5.2 [redacted]	–	–

†No formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib.
Abbreviations: CI, confidence interval; FAS, full analysis set; PP-NRS, Peak Pruritus Numerical Rating Scale.

Figure 11: Proportion of PP-NRS4 responders over Days 2–15 (left) and over the 16-week treatment period (right), FAS, COMPARE (adults, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: FAS, full analysis set; PP-NRS, Peak Pruritus Numerical Rating Scale.

Abrocitinib vs dupilumab: IGA and EASI-75 response at Week 16

At Week 16, a significantly higher proportion of patients in the abrocitinib 200 mg treatment group achieved an IGA response compared with those in the dupilumab treatment group (47.5% vs 38.8%). The proportion of EASI-75 responders was numerically greater for abrocitinib 200 mg compared with dupilumab, and numerically lower for abrocitinib 100 mg group compared with dupilumab; however no statistically significant differences were observed (Table 19).

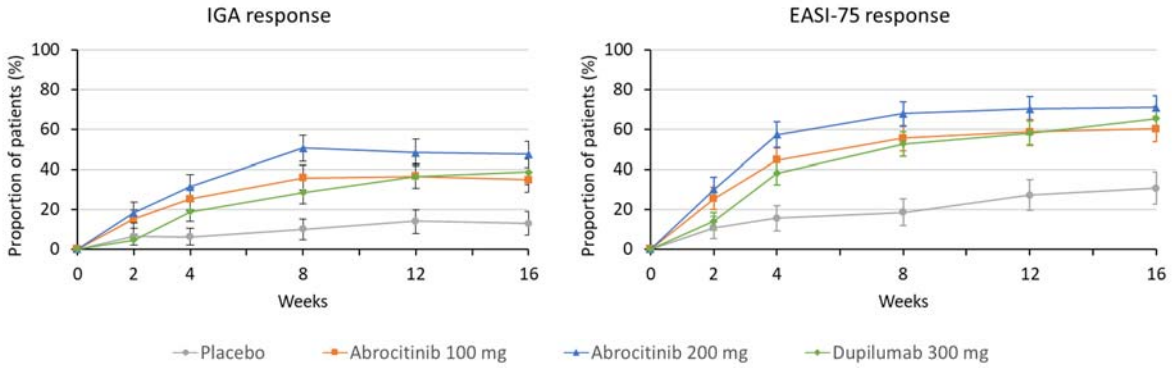
Table 19: IGA and EASI-75 response at Week 16, FAS, COMPARE (adults, combination therapy, full trial population)

	Abrocitinib 100 mg (N=238)	Abrocitinib 200 mg (N=226)	Dupilumab 300 mg† (N=242)	Placebo (N=131)
IGA response				
IGA responders, n/N (%)	80/230 (34.8)	105/221 (47.5)	90/232 (38.8)	16/124 (12.9)
Difference from placebo, % (95% CI) p-value	22.1 (13.7, 30.5) p<0.001	35.0 (26.3, 43.7) p<0.001	25.6 (17.1, 34.1) NA†	–
Difference between abrocitinib and dupilumab, % (95% CI)	–3.5 (–12.2, 5.2)	9.4 (0.4, 18.5)	–	–
EASI-75 response				
EASI-75 responders, n/N (%)	138/229 (60.3)	157/221 (71.0)	152/232 (65.5)	38/124 (30.6)
Difference from placebo, % (95% CI) p-value	29.7 (19.5, 39.9) p<0.001	40.4 (30.4, 50.4) p<0.001	34.7 (24.6,44.8) NA†	–
Difference between abrocitinib and dupilumab, % (95% CI)	–5.1 (–13.9, 3.7)	5.5 (–3.1, 14.1)	–	–

††No formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib.
Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritis Numerical Rating Scale.

Figure 12 presents the proportions of IGA and EASI-75 responders, respectively, over time up to Week 16. As per the PP-NRS4 results at Week 2, there was a general trend suggesting a faster onset of action for abrocitinib vs dupilumab, for the 100 mg dose of abrocitinib as well as the 200 mg dose.

Figure 12: Proportions of IGA and EASI-75 responders over time, FAS, COMPARE (adults, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: EASI- Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment.

B.2.6.1.3 *Other secondary endpoints and post-hoc analyses*

B.2.6.1.3.1 Improvement in disease severity

Outcomes related to disease severity and extent of skin clearance at Week 16, including additional EASI endpoints (EASI-50 and EASI-90), SCORAD and percentage change in BSA are summarised in Table 20, and time course profiles are presented in Figure 13.

Abrocitinib vs placebo

[redacted]

Abrocitinib vs dupilumab

[redacted]

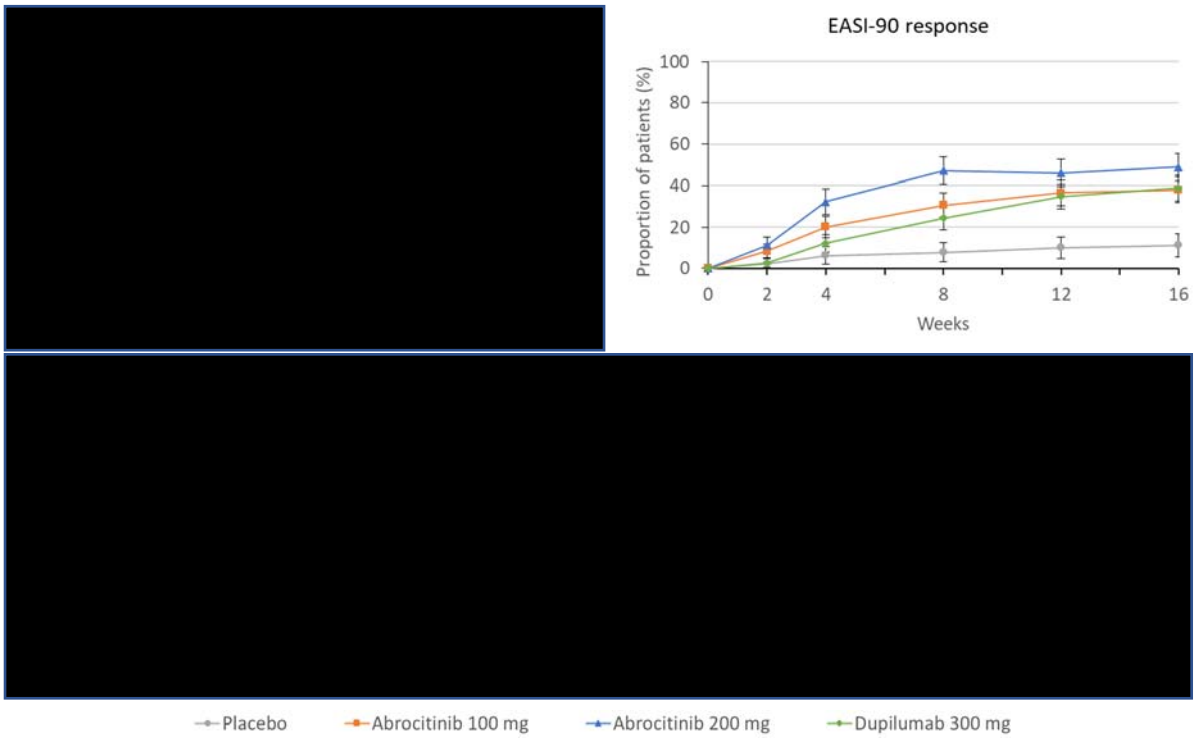
[redacted]

Table 20: Other disease severity endpoints at Week 16, FAS, COMPARE (adults, combination therapy, full trial population)†

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
EASI-50 response				
Responders, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–
EASI-90 response				
Responders, n/N (%)	87/229 (38.0)	108/221 (48.9)	90/232 (38.8)	14/124 (11.3)
Difference from placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–
SCORAD-75 response				
Responders, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–
LSM % CFB in % BSA affected				
LSM‡	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: BSA, body surface area; CFB, change from baseline; CI, confidence interval; EASI, Eczema Area and Severity Index; LSM, least squares mean; SCORAD, Scoring Atopic Dermatitis.

Figure 13: Other disease severity endpoints over time, FAS, COMPARE (adults, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: BSA, body surface area; EASI, eczema area and severity index; FAS, full analysis set; SCORAD, scoring atopic dermatitis.

B.2.6.1.3.2 Improvement in symptom control

The symptom control outcomes at Week 16, including achievement of PP-NRS score of 0 or 1 (PP-NRS 0/1) which represents being itch-free or virtually itch-free, POEM, PSAAD total score and PSAAD item 2 capturing skin pain are summarised in Table 21, with time course profiles presented in Figure 14.

Abrocitinib vs placebo

[redacted]

B.1.3.5.2.1

Abrocitinib vs dupilumab

[redacted]

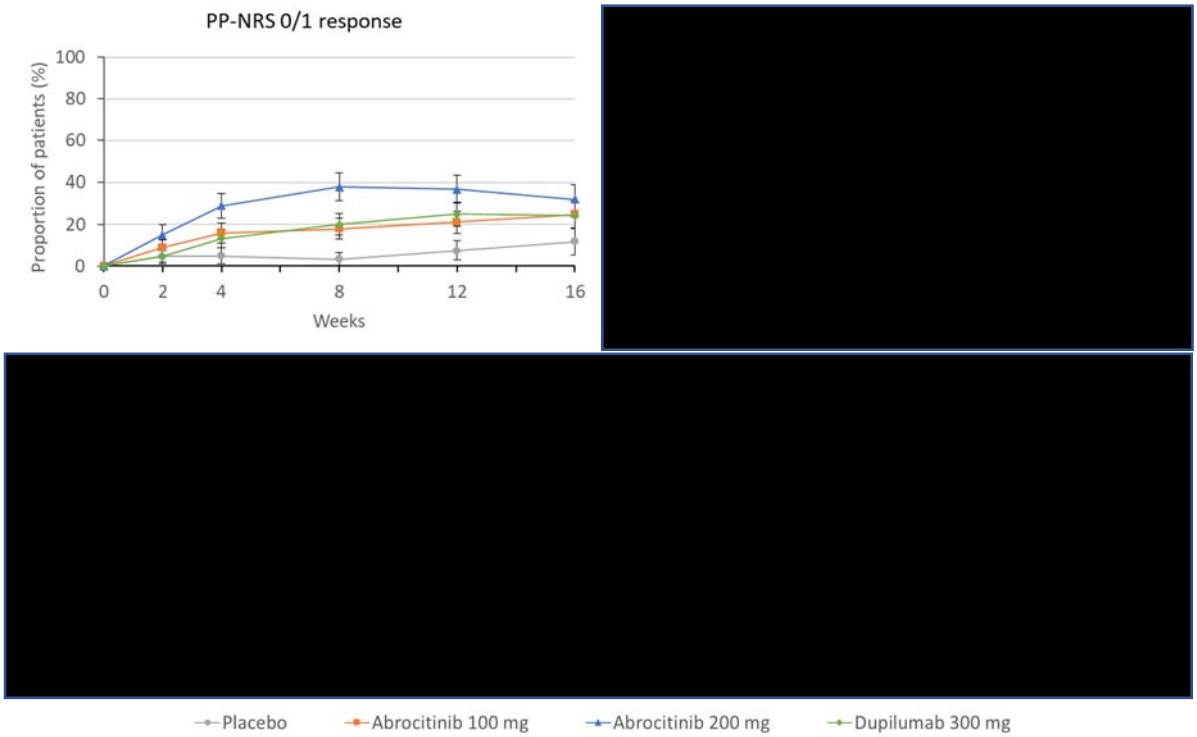
Table 21: Other symptom control endpoints at Week 16, FAS, COMPARE (adults, combination therapy, full trial population)†

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg†	Placebo
PP-NRS 0/1 response				
PP-NRS 0/1 responders, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference from placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–
LSM CFB in POEM				
LSM‡	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–
Abrocitinib–dupilumab estimate LSM (95% CI)	[redacted]	[redacted]	–	–
LSM CFB in PSAAD total score				
LSM‡	–2.8	–3.6	–3.4	–1.7
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–
Abrocitinib–dupilumab estimate LSM (95% CI)	[redacted]	[redacted]	–	–
LSM CFB in PSAAD item 2 (skin pain)				
LSM‡	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg†	Placebo
Abrocitinib–dupilumab estimate LSM (95% CI)	[redacted]	[redacted]	–	–

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: CFB, change from baseline; CI, confidence interval; LSM, least squares mean; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

Figure 14: Other symptom control endpoints over time, FAS, COMPARE (adults, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: CFB, change from baseline; FAS, full analysis set; LSM, least squares mean; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

B.2.6.1.3.3 Improvement in health-related quality of life

The HRQL outcomes at Week 16, including SCORAD VAS of sleep loss and DLQI are summarised in Table 22, with time course profiles presented in Figure 15. EQ-5D data are presented in Section B.3.4.5.

Abrocitinib vs placebo

[redacted]

[redacted]

Abrocitinib vs dupilumab

[redacted]

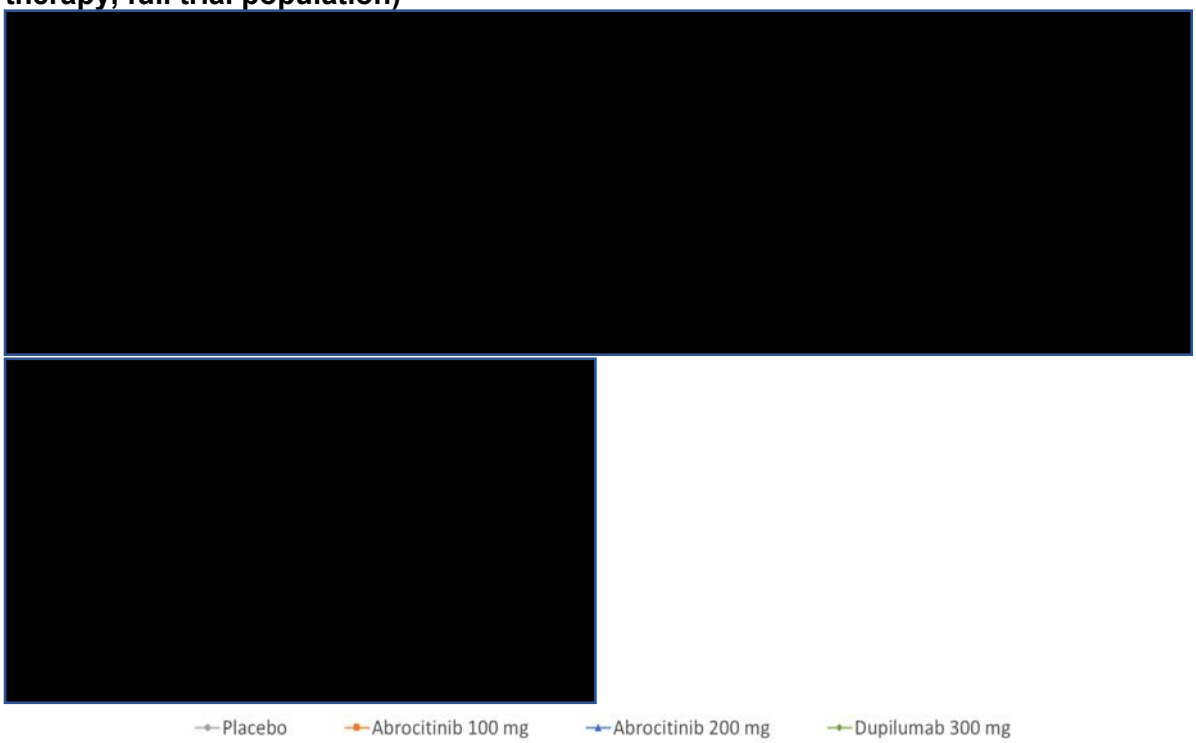
Table 22: Other HRQL endpoints at Week 16, FAS, COMPARE (adults, combination therapy, full trial population)†

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
LSM CFB in SCORAD VAS of sleep loss				
LSM‡	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–
Abrocitinib–dupilumab estimate LSM (95% CI)	[redacted]	[redacted]	–	–
LSM CFB in DLQI				
LSM‡	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]	–
Abrocitinib–dupilumab estimate LSM (95% CI)	[redacted]	[redacted]	–	–
DLQI ≥4 response				
Responders, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
Difference from placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: DLQI, Dermatology Life Quality Index; FAS, full analysis set; LSM, least squares mean; SCORAD, scoring atopic dermatitis; VAS, visual analogue scale.

Figure 15: Other HRQL endpoints over time, FAS, COMPARE (adults, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: DLQI, Dermatology Life Quality Index; FAS, full analysis set; LSM, least squares mean; SCORAD, scoring atopic dermatitis; VAS, visual analogue scale.

B.2.6.2 TEEN (adolescents, combination therapy, full trial population)

- The TEEN study met both co-primary endpoints; both abrocitinib treatment groups were superior to placebo for IGA and EASI-75 responses at Week 12.
- Among the key secondary endpoints, the abrocitinib 200 mg group had a significantly greater proportion of PP-NRS4 responders compared with the placebo group at Week 12 (and all earlier time points). The abrocitinib

200 mg group was also associated with a significantly greater reduction in PSAAD total scores compared with placebo.

- Improved efficacy was observed for both abrocitinib groups compared with placebo in endpoints related to disease severity, symptom control, and HRQL. Both abrocitinib treatment groups consistently demonstrated significantly greater proportions of patients with EASI-50, EASI-90, SCORAD-75, POEM and CDLQI responses vs placebo (based on 95% CI).

B.2.6.2.1 *Coprimary endpoints*

IGA and EASI-75 response at Week 12

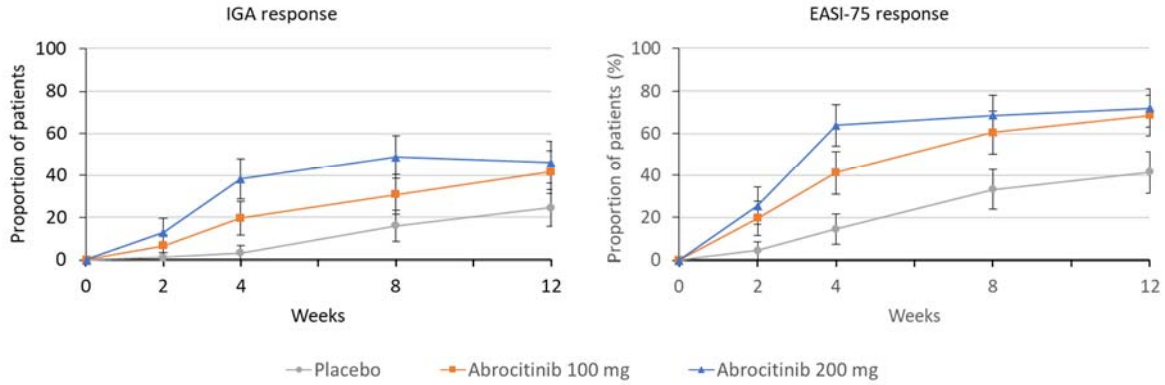
The study met both co-primary endpoints of IGA and EASI-75 responses at Week 12, demonstrating that both abrocitinib 200 mg and 100 mg treatment groups were superior to the placebo group (Table 23). Time course profiles are presented in Figure 16.

Table 23: Co-primary endpoints at Week 12, FAS, TEEN (adolescents, combination therapy, full trial population)

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
IGA response			
IGA responders, n/N (%)	23/94 (24.5)	37/89 (41.6)	43/93 (46.2)
Difference from placebo, % (95% CI) p-value	–	16.7 (3.5, 29.9) 0.0147	20.6 (7.3, 33.9) 0.0030
EASI-75 response			
EASI-75 responders, n/N (%)	39/94 (41.5)	61/89 (68.5)	67/93 (72.0)
Difference from placebo (%) (95% CI) p-value	–	26.5 (13.1, 39.8) 0.0002	29.4 (16.3, 42.5) <0.001

Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment.

Figure 16: Proportion of patients who achieved an IGA and EASI-75 response over the 12-week treatment period, FAS, TEEN (adolescents, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; FAS, full analysis set

B.2.6.2.2 *Key secondary endpoints*

PP-NRS4 and PSAAD total score at Week 12

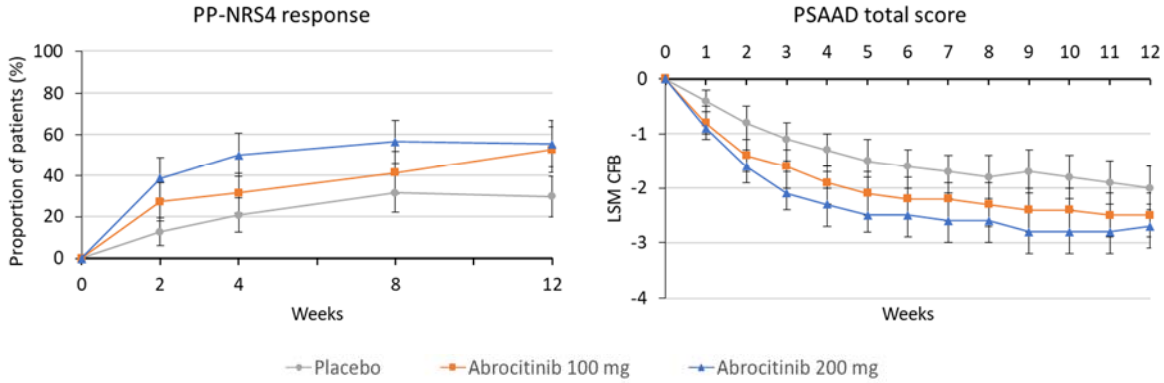
The abrocitinib 200 mg group had a significantly greater proportion of PP-NRS4 responders compared with the placebo group at all time points (Figure 17). The proportion of PP-NRS4 responders was significantly greater in the abrocitinib 100 mg group than the placebo group at Weeks 2 and 12, with numerical improvements at Weeks 4 and 8 (Figure 17, Table 24). The abrocitinib 200 mg group was also associated with a significantly greater reduction in PSAAD total scores compared with the placebo group, and the 100 mg group was associated with a numerical improvement (Table 24).

Table 24: Key secondary endpoints at Week 12, FAS, TEEN (adolescents, combination therapy, full trial population)

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
PP-NRS4 response			
Responders, n/N (%)	25/84 (29.8)	40/76 (52.6)	41/74 (55.4)
Difference from placebo, % (95% CI) p-value	–	22.8 (8.0, 37.7) [redacted]	25.6 (10.6, 40.6) 0.0013
LSM CFB in PSAAD total score			
LSM†	–2.0	–2.5	–2.7
Active–placebo estimate LSM (95% CI)	–	-0.5 (-1.1, 0.0) [redacted]	-0.7 (-1.3, -0.1) [redacted]

†Negative change indicates improvement.
Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LSM, least squares mean; PP-NRS, Peak Pruritis Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

Figure 17: Proportion of patients who achieved a PP-NRS-4 response, and PSAAD total score CFB over the 12-week treatment period, FAS, TEEN (adolescents, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: CFB, change from baseline; FAS, full analysis set; PP-NRS, Peak Pruritis Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

B.2.6.2.3 *Other secondary endpoints and post-hoc analyses*

B.2.6.2.3.1 Improvement in disease severity

Both abrocitinib treatment groups demonstrated significantly greater proportions of patients with EASI-50, EASI-90 and SCORAD-75 responses compared with the placebo group at all scheduled time points (Weeks 2, 4, 8, and 12; except for the abrocitinib 100 mg group SCORAD-75 at Week 8; based on 95% CI) (Figure 18).

[redacted]

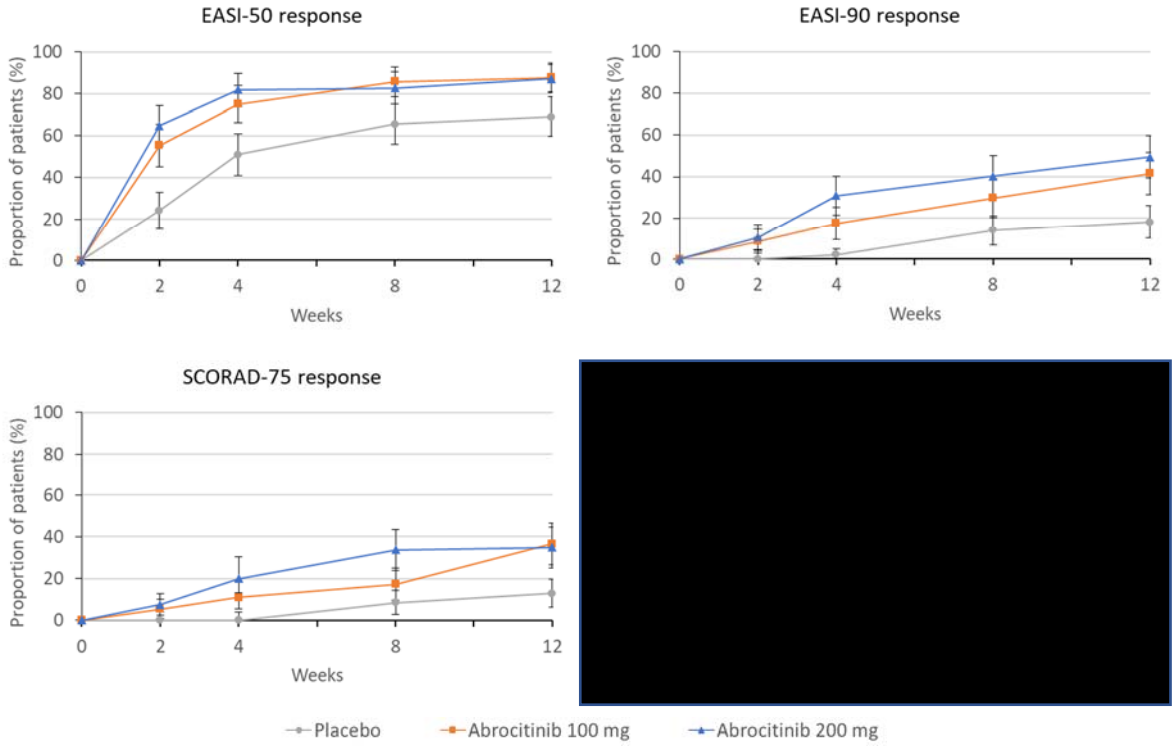
Table 25: Other secondary disease severity outcomes at Week 12, FAS, TEEN (adolescents, combination therapy, full trial population)†

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
EASI-50 response			
Responders, n/N (%)	65/94 (69.1)	78/89 (87.6)	81/93 (87.1)
Difference from placebo, % (95% CI)	–	18.2 (6.9, 29.4)	16.8 (5.6, 28.0)
EASI-90 response			
Responders, n/N (%)	17/94 (18.1)	37/89 (41.6)	46/93 (49.5)
Difference from placebo, % (95% CI)	–	23.4 (10.5, 36.2)	30.9 (18.0, 43.8)
SCORAD-75 response			
Responders, n/N (%)	12/93 (12.9)	33/90 (36.7)	32/92 (34.8)
Difference from placebo, % (95% CI)	–	23.7 (11.7, 35.8)	21.7 (9.7, 33.7)
LSM % CFB in %BSA affected			
LSM‡	[redacted]	[redacted]	[redacted]

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
Active–placebo estimate LSM (95% CI)	[redacted]	[redacted]	[redacted]

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: BSA, body surface area; CFB, change from baseline; CI, confidence interval; EASI, Eczema Area and Severity Index; LSM, least squares mean; SCORAD, Scoring Atopic Dermatitis

Figure 18: Disease severity endpoints over time, FAS, TEEN (adolescents, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: BSA, body surface area; FAS, full analysis set; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis.

B.2.6.2.3.2 Improvement in symptom control

[redacted]

The LSM of change from baseline in POEM scores was significantly improved (lower) in both abrocitinib treatment groups compared with the placebo group at Weeks 2, 4, 8, and 12 (Figure 19).

[redacted]

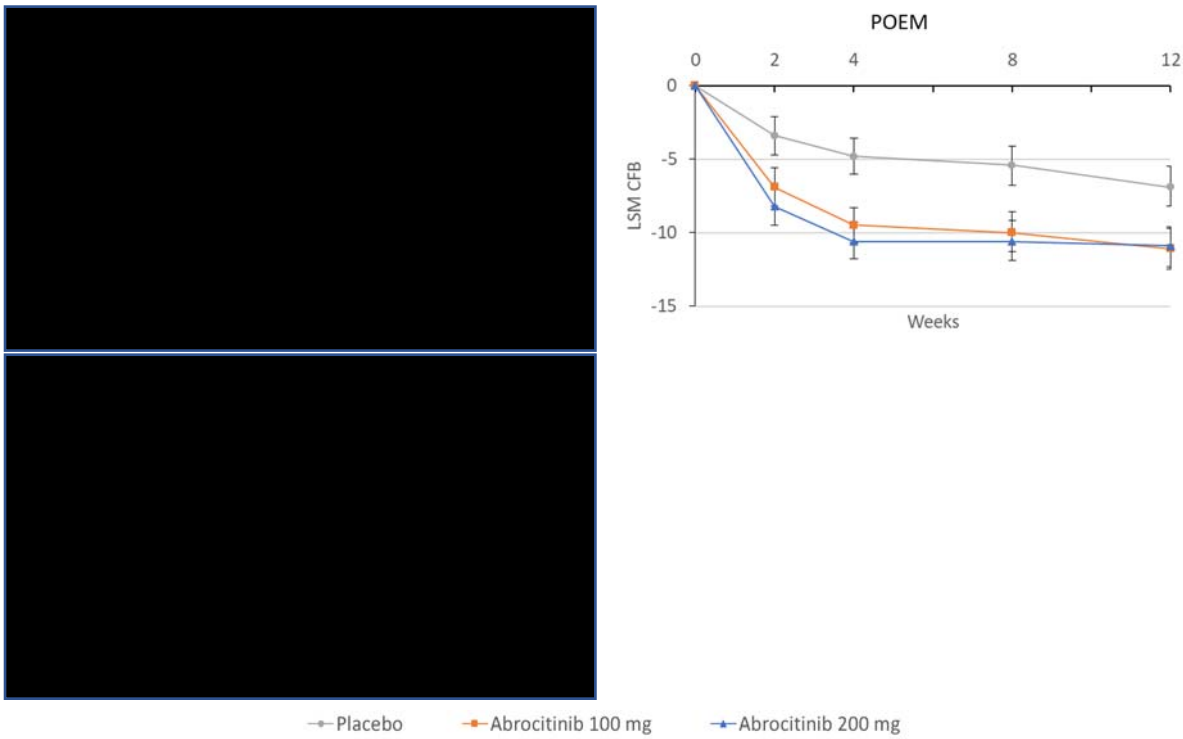
[redacted]

Table 26: Other secondary symptom control outcomes at Week 12, FAS, TEEN (adolescents, combination therapy, full trial population)†

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
PP-NRS 0/1 response			
PP-NRS 0/1 responders, n/N (%)	[redacted]	[redacted]	[redacted]
Difference from placebo, % (95% CI)			
LSM CFB in POEM			
LSM‡	–6.9	–11.1	–10.9
Active–placebo estimate LSM (95% CI)	–	–4.1 (–6.1, –2.2)	–3.9 (–5.9, –2.0)
LSM CFB in PSAAD item 2 (skin pain)			
LSM‡	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)			

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LSM, least squares mean; POEM, Patient Orientated Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

Figure 19: Other symptom control endpoints over time, FAS, TEEN (adolescents, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: CFB, change from baseline; FAS, full analysis set; LSM, least squares mean; POEM, Patient Orientated Eczema Measure

B.2.6.2.3.3 Improvement in health-related quality of life

[redacted]

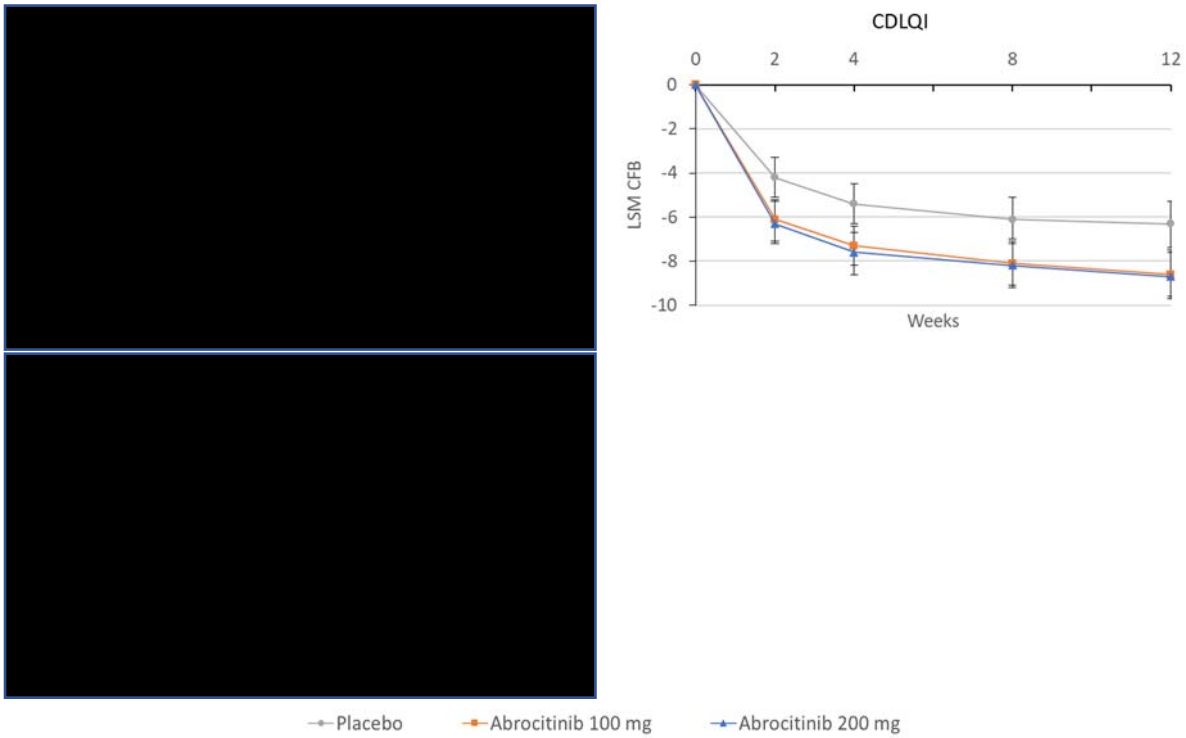
[redacted]

Table 27: Other HRQL outcomes at Week 12, FAS, TEEN (adolescents, combination therapy, full trial population)†

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
LSM CFB in SCORAD VAS of sleep loss			
LSM‡	[redacted]	[redacted]	[redacted]
Active–placebo estimate LSM (95% CI)			
LSM CFB in CDLQI			
LSM‡	–6.3	–8.6	–8.7
Active–placebo estimate LSM (95% CI)	–	–2.3 (–3.7, –0.8)	–2.3 (–3.8, –0.9)
CDLQI ≥4 response			
Responders, n/N (%)	[redacted]	[redacted]	[redacted]
Difference from placebo, % (95% CI)			

†No formal multiplicity-adjusted comparisons were made; ‡Negative change indicates improvement.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LSM, least squares mean.

Figure 20: Other HRQL endpoints over time, FAS, TEEN (adolescents, combination therapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; FAS, full analysis set; LSM, least squares mean

B.2.6.3 MONO-1 and MONO-2 (adolescents and adults, monotherapy)

- These identically designed monotherapy trials both met their co-primary efficacy endpoints: both doses of abrocitinib were superior to placebo for IGA and EASI-75 responses at Week 12.
- In the key secondary endpoint of PP-NRS at Week 12, both abrocitinib doses resulted in significant improvements in the relief of itch (and at Weeks 2 and 4). Significantly greater reductions (improvements) vs placebo were also observed for both abrocitinib doses for the other key secondary endpoint, PSAAD total scores at Week 12.
- Improved efficacy was observed for both abrocitinib doses compared with placebo in endpoints related to disease severity, symptom control, and HRQL (Appendix M).

B.2.6.3.1 *Coprimary endpoints*

IGA and EASI-75 response at Week 12

In both trials, the proportion of patients who achieved IGA and EASI-75 responses was significantly higher for abrocitinib 200 mg and 100 mg compared with placebo (Table 28). Time course profiles are presented in

Figure **21** and Figure 22.

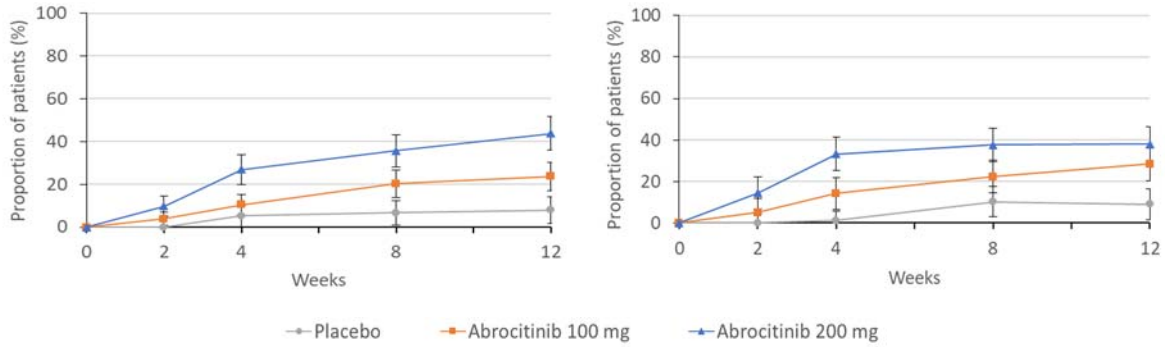
Table 28: Co-primary endpoints at Week 12, FAS, MONO-1 and MONO-2 (adults and adolescents, monotherapy, full trial population)

	MONO-1			MONO-2		
	Placebo	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**Placebo**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**
IGA response						
Responders, n/N (%)	6/76 (7.9)	37/156 (23.7)	67/153 (43.8)	7/77 (9.1)	44/155 (28.4)	59/155 (38.1)
Difference from placebo, % (95% CI) p-value	–	15.8 (6.8, 24.8) p=0.0037	36.0 (26.2, 45.7) p<0.0001	–	19.3 (9.6, 29.0) p<0.001	28.7 (18.6, 38.8) p<0.001
EASI-75 response						
Responders, n/N (%)	9/76 (11.8)	62/156 (39.7)	96/153 (62.7)	8/77 (10.4)	69/155 (44.5)	94/154 (61.0)
Difference from placebo, % (95% CI)	–	27.9 (17.4, 38.3) p<0.0001	51.0 (40.5, 61.5) p<0.0001	–	33.9 (23.3, 44.4) p<0.001	50.5 (40.0, 60.9) p<0.001

	MONO-1			MONO-2		
	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
p-value						

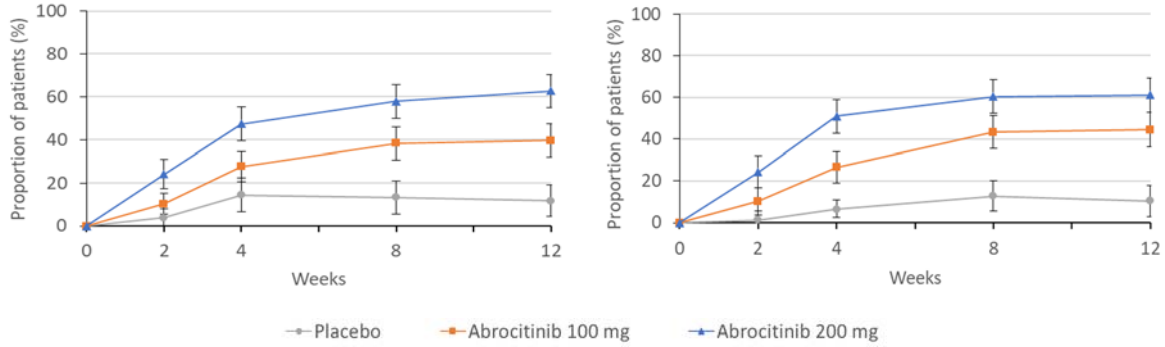
Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment

Figure 21. Proportion of patients who achieved an IGA response over the 12-week treatment period, FAS, MONO-1 (left) and MONO-2 (right) (adults and adolescents, monotherapy, full trial population)



Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment.

Figure 22. Proportion of patients who achieved an EASI-75 response over the 12-week treatment period 12, FAS, MONO-1 (left) and MONO-2 (right) (adults and adolescents, monotherapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: EASI, Eczema Area Severity Index; FAS, full analysis set.

B.2.6.3.2 *Key secondary endpoints*

PP-NRS4 response and PSAAD total score to Week 12

In MONO-1 and MONO-2, the proportion of patients achieving a PP-NRS4 response increased between Week 2 and Week 12, with significant differences observed between both abrocitinib doses and placebo at Weeks 2, 4, and 12 (Table 29 and Figure 23).

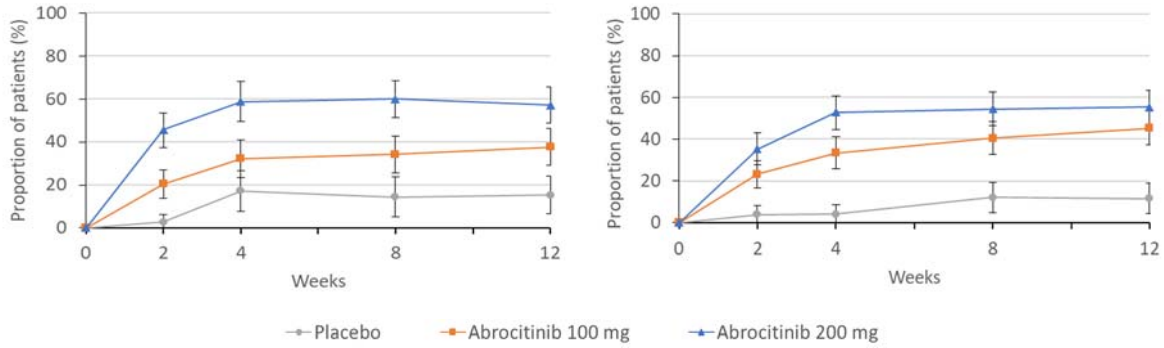
In both trials, at Week 12, significantly greater reductions (improvement) from baseline in PSAAD total scores were observed for both abrocitinib doses compared with placebo (Table 29 and Figure 24).

Table 29: PP-NRS response and PSAAD total score at Week 12, FAS, MONO-1 and MONO-2 (adults and adolescents, monotherapy, full trial population)

	MONO-1			MONO-2		
	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
PP-NRS4 response at Week 12						
Responders, n/N (%)	11/74 (15.3)	55/147 (37.7)	84/147 (57.2)	9/76 (11.5)	71/156 (45.2)	85/153 (55.3)
Difference from placebo, % (95% CI) p-value	–	22.5 (10.3, 34.8) p=0.0003	41.7 (29.6, 53.9) p<0.0001	–	33.7 (22.8, 44.7) p<0.0001	43.9 (32.9, 55.0) p<0.0001
LSM CFB in PSAAD total score at Week 12						
LSM†	–1.1	–2.2	–3.2	–0.8	–2.4	–3.0
Difference from placebo, % (95% CI) p-value	–	–1.1 (–1.7, –0.4) p=0.0010	–2.1 (–2.7, –1.4) p<0.0001	–	–1.7 (–2.3, –1.1) p<0.0001	–2.2 (–2.8, –1.6) p<0.0001

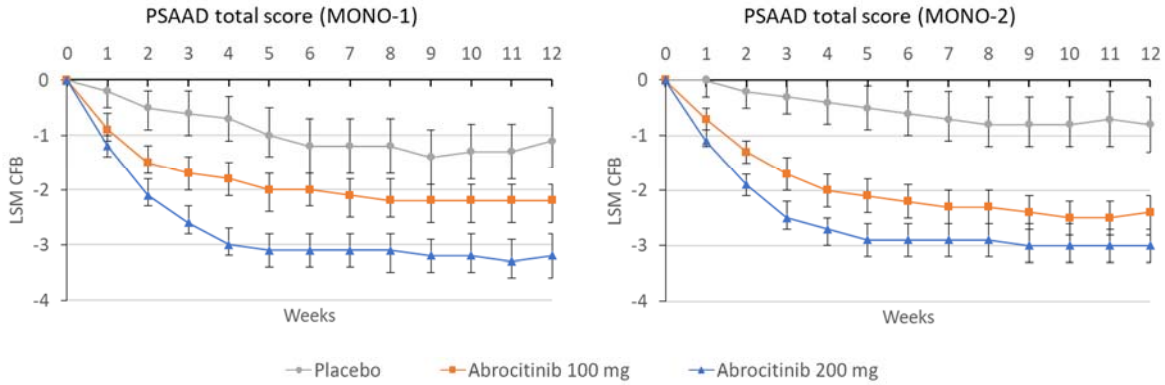
†Negative change indicates improvement.
Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; LSM, least squares mean; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

Figure 23. PP-NRS4 response over the 12-week treatment period, FAS, MONO-1 (left) and MONO-2 (right) (adults and adolescents, monotherapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: FAS, full analysis set; PP-NRS, Peak Pruritus Numerical Rating Scale.

Figure 24: PSAAD total score CFB to Week 12, FAS, MONO-1 (left) and MONO-2 (right) (adults and adolescents, monotherapy, full trial population)



Error bars represent 95% confidence interval.
Abbreviations: CFB, change from baseline; FAS, full analysis set; LSM, least squares mean; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis.

B.2.6.3.3 *Other secondary endpoints and post-hoc analyses*

Other secondary endpoints and post-hoc analyses from MONO-1/-2 are presented in Appendix M.

B.2.6.4 EXTEND (adults combination therapy and monotherapy)

This section presents data for patients who responded at either Week 16 in COMPARE or Week 12 in MONO1/2 (adults only) and who maintained their response in long-term follow-up during EXTEND. Please note the following:

- These data are for patients who remained on the same dose of abrocitinib in EXTEND as they received in the parent trials.
- For patients from the MONO trials, only those remaining on monotherapy in EXTEND were included in the analysis (to represent the efficacy of abrocitinib without the confounding effect of medicated topical treatments), whereas all patients entering EXTEND from COMPARE were included regardless of concomitant therapy use (to represent how abrocitinib is likely to be used in clinical practice).
- Given data availability based on the schedule of response measurements in EXTEND, the data represents the Week 44 timepoint for patients from COMPARE (20 weeks from COMPARE and 24 weeks from EXTEND), and the Week 48 timepoint for patients from the MONO-1 and MONO-2 trials (12 weeks from MONO-1/-2 and 36 weeks from EXTEND).

Data for adolescents in EXTEND who were previously treated with abrocitinib in MONO-1/2 (adolescents monotherapy data) were not included as the sample size was too small to draw any conclusions (N=35, 26 and 16 for EASI-50/-75/-90, respectively). Similarly, data for adolescents in EXTEND who were previously treated with abrocitinib in TEEN (adolescent combination data) were immature (only 12–14% and 6–17% of patients had reached Week 48 and 52 respectively for EASI-50/-75/-90 for both abrocitinib treatment groups) and have not been included.

B.2.6.4.1 *EXTEND results for patients from COMPARE*

[redacted]

Table 30: Proportion of EASI-50/-75/-90 responders at Week 44 (FAS, Week 16 responders from COMPARE)

	Abrocitinib 100 mg	Abrocitinib 200 mg
EASI-50		
Responders, n/N (%)	[redacted]	[redacted]
EASI-75		
Responders, n/N (%)	[redacted]	[redacted]
EASI-90		
Responders, n/N (%)	[redacted]	[redacted]

If a patient withdrew from the study, then this patient was counted as non-responder after withdrawal.
Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set.

B.2.6.4.2 *EXTEND results for patients from MONO-1/2*

[redacted]

Table 31: Proportion of EASI-50/-75/-90 responders at Week 48 (FAS, Week 12 adult responders from MONO-1/-2)

	Abrocitinib 100 mg	Abrocitinib 200 mg
EASI-50		
Responders, n/N (%)	[redacted]	[redacted]
EASI-75		
Responders, n/N (%)	[redacted]	[redacted]
EASI-90		
Responders, n/N (%)	[redacted]	[redacted]

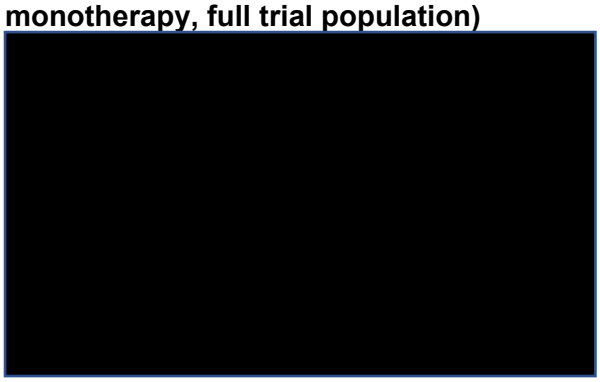
If a patient withdrew from the study, then this patient was counted as non-responder after withdrawal.
Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set.

B.2.6.5 REGIMEN (adults and adolescents, monotherapy with optional rescue treatment for flares)

B.2.6.5.1 *Open-label run-in period*

In REGIMEN, all enrolled patients initiated the 12-week, open-label induction treatment with abrocitinib 200 mg. At Week 12, 64.7% of patients had achieved the protocol-defined responder criteria (achieving both IGA 0/1 and EASI-75) (Figure 25).

Figure 25: Proportion of patients achieving both IGA and EASI-75 response during the initial 12-week open-label run-in period, FAS, REGIMEN (adults and adolescents, monotherapy, full trial population)



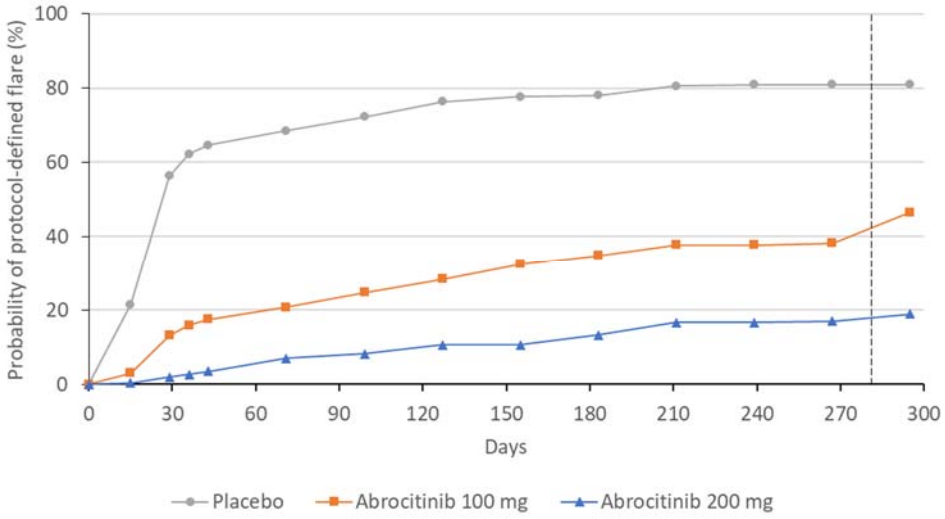
Abbreviations: EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment.

B.2.6.5.2 *Primary endpoint (randomisation period)*

Responders at the end of the open-label run-in period entered the 40 week, double-blinded, maintenance treatment period in which they were randomised to abrocitinib 200 mg, 100 mg, or placebo. Following randomisation, patients who remained on abrocitinib 200 mg and those who switched to the 100 mg dose were significantly

less likely to experience a protocol-defined flare* (p<0.0001) than those switched to placebo (Figure 26). At the end of the 40-week randomisation period, 81.1% and 57.4% of patients on abrocitinib 200 mg and 100 mg, respectively, did not experience a flare requiring rescue treatment as compared to 19.1% in the placebo group.

Figure 26: Time to protocol-defined flare†, FAS, REGIMEN (adults and adolescents, monotherapy, full trial population)



†A flare was defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2.
Vertical line at Day 281 indicates end of treatment period.
Abbreviations: FAS, full analysis set.

B.2.6.5.3 *Rescue treatment period*

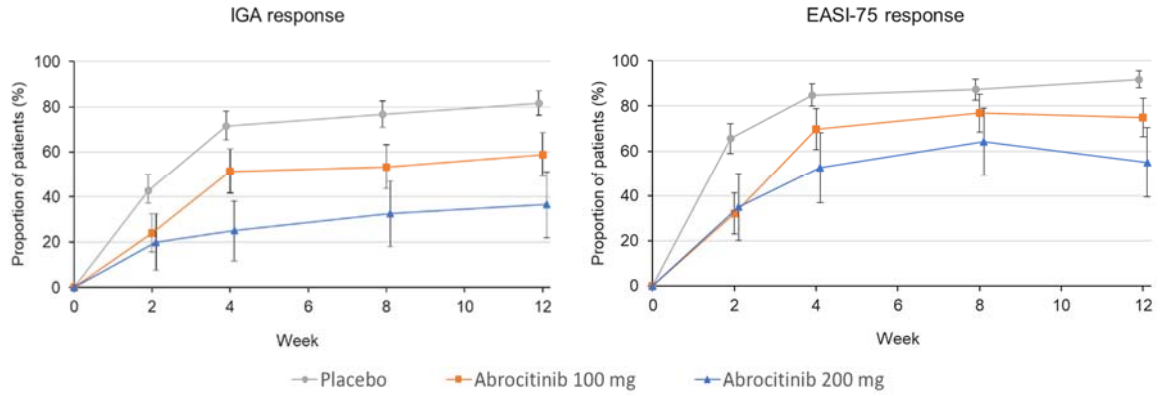
Recapture of IGA and EASI-75 responses

During the blinded treatment period, when patients experienced a protocol-defined flare, they entered a 12-week rescue phase in which they received abrocitinib 200 mg with concomitant medicated topical therapy. Figure 29 and Figure 30 show the proportions of patients recapturing IGA and EASI-75 responses during the rescue period. At the end of the 12-week rescue therapy, 81.6% and 91.8% of patients previously randomised to placebo recaptured IGA 0/1 and EASI-75 responses, respectively, as compared to abrocitinib 100 mg (59.0%, 75.0%) and 200 mg (36.6%, 55.9%). Notably, since patients already on abrocitinib 200 mg only

*Defined as a loss of response associated with a decrease of at least 50% of the EASI response at Week 12 and an IGA score ≥2 (Table 12)

received adds-on topical treatments if they flared, it could be expected that fewer patients would recapture response in this group vs those who received 100 mg or placebo prior to flaring, as these patients would have their treatment escalated and received abrocitinib 200 mg alongside topical medications as rescue treatment for flares.

Figure 27: Proportion of patients recapturing IGA and EASI-75 response when treated with abrocitinib 200 mg and concomitant medicated topical therapy in the rescue treatment period, FAS, REGIMEN



Abbreviations: EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment.

B.2.7 Subgroup analysis

B.2.7.1 Prespecified trial subgroups

Forest plots for subgroups that were pre-specified in the trials are presented in Appendix E. [redacted]

B.2.7.2 Subgroup analyses relevant to the population of interest

As described in Section B.2.2.3, this section presents results for the generalisable population. The generalisable population includes all patients who received at least one systemic treatment for AD (excluding patients who only received oral corticosteroids previously) and who discontinued the prior treatment(s) for any reason. Patient demographics and baseline characteristics are presented in Appendix M.

Data are presented for endpoints captured in the economic model (Section B.3.2.2): EASI-50 in combination with ≥4-point improvement in CDLQI/DLQI from baseline, EASI-75 and EASI 90. Further for COMPARE data a broader set of endpoints has been captured to illustrate benefits of abrocitinib 200 mg compared with dupilumab. Results are presented for the higher threshold of responses, including EASI-75/EASI-90 & CDLQI/DLQI ≥4 and EASI-90 & CDLQI/DLQI 0/1 and PP-NRS4 (which represents a clinically meaningful improvement in itch).

B.2.7.2.1 *COMPARE (adults, combination therapy, generalisable population)*

[redacted]

Table 32: Generalisable population subgroup results, Week 16, COMPARE (adults, combination therapy)

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg
EASI-50 & DLQI ≥4 improvement from baseline				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	–	[redacted]	[redacted]	–
EASI-75				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	–	[redacted]	[redacted]	–
EASI-90				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	–	[redacted]	[redacted]	–
EASI-75 & DLQI ≥4 improvement from baseline				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	_	[redacted]	[redacted]	_
EASI-90 & DLQI ≥4 improvement from baseline				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	_	[redacted]	[redacted]	_
EASI-90 & DLQI 0/1				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	_	[redacted]	[redacted]	_
PP-NRS4				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]	[redacted]
Abrocitinib–dupilumab estimate (%) (95% CI)	_	[redacted]	[redacted]	_

Key: **Bold** = abrocitinib statistically significantly better than dupilumab based on 95% CI.
If a patient withdrew from the study, then this patient was counted as a non-responder after withdrawal.
Abbreviations: AD, atopic dermatitis; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritis Numerical Rating Scale.

B.2.7.2.2 *TEEN (adolescents, combination therapy, generalisable population)*

[redacted]

Table 33: Generalisable population subgroup results, Week 12, TEEN (adolescents, combination therapy)

	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
EASI-50 & CDLQI ≥4 improvement from baseline			
n/N (%)	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]
EASI-75			
n/N (%)	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]
EASI-90			
n/N (%)	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	_	[redacted]	[redacted]

If a patient withdrew from the study, then this patient was counted as non-responder after withdrawal.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index ; CI, confidence interval; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritis Numerical Rating Scale.

B.2.7.2.3 *MONO-1/-2 (adolescents and adults, monotherapy, generalisable population)*

[redacted]

Table 34: Generalisable population subgroup results, Week 12, MONO-1/-2 (adults and adolescents, monotherapy)

	Adults			Adolescents		
	Placebo	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**Placebo**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**
EASI-50						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
EASI-75						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
EASI-90						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
EASI-50 & C/DLQI ≥4 improvement from baseline						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
EASI-75 & C/DLQI ≥4 improvement from baseline						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo	–	[redacted]	[redacted]	–	[redacted]	[redacted]

	Adults			Adolescents		
	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg
estimate (%) (95% CI)						
EASI-90 & C/DLQI ≥4 improvement from baseline						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
PP-NRS4						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
EASI-90 & C/DLQI 0/1						
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Active–placebo estimate (%) (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]

Key: **Bold** = abrocitinib statistically significantly better than placebo based on 95% CI.
If a patient withdrew from the study, then this patient was counted as non-responder after withdrawal.
Abbreviations: CI, confidence interval; IDLQI, (Children's) Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritis Numerical Rating Scale.

B.2.8 Meta-analysis

A network meta-analysis (NMA) is a frequently used method for comparing multiple interventions. Results from an NMA comparing abrocitinib 200 mg and 100 mg doses with dupilumab and baricitinib is presented in Section B.2.9.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Objective

A NMA was conducted to compare abrocitinib 200 mg and 100 mg with dupilumab 300 mg (adults and adolescents), and baricitinib 4 mg and 2 mg (adults only) for patients with moderate to severe AD who have been previously exposed to systemic therapies.

As per Table 1 in Section B.1.1, consideration was given separately to adult combination, adolescent combination, adult monotherapy and adolescent monotherapy analyses, although the combination comparisons are deemed most relevant as this is how abrocitinib is likely to be used in clinical practice. No dupilumab combination therapy data were identified for adolescents so an

adolescent combination analyses was not feasible, and TEEN was not used in the NMA: only COMPARE for an adult combination comparison, and MONO-1/2 for adult and adolescent monotherapy comparisons.

Generalisable, restricted, and full populations (defined in Section B.2.2.3) were analysed for all outcomes where feasible and not redundant (e.g., if EASI-50/-75/-90 was analysed, EASI-50/-75 was not). A summary of how the abrocitinib generalisable and restricted populations compare with dupilumab and baricitinib populations is provided in Table 35.

Table 35: Subgroups considered in the submission and their comparability with data captured for dupilumab and baricitinib

	Generalisable population (Section B.2.9)	Restricted population (Section B.2.9)	Dupilumab and baricitinib populations
Prior exposure to systemic treatment(s)†			
Ciclosporin	✓	✓¶	✓††
Other non-biologics (e.g. mycophenolate mofetil, methotrexate, azathioprine)	✓	✗	✗
Biologics (e.g. dupilumab‡)	✓	✗	✗
Oral corticosteroids only (without prior exposure to any other systemic treatments)	✗	✗	✗

†Patients may have received one or multiple prior systemic treatments; ‡[redacted] patients received prior treatment with dupilumab in MONO-1/-2 and TEEN; ¶In the restricted population, only patients who previously failed or did not tolerate ciclosporin were included. Contraindication was not captured within the clinical trial programme for abrocitinib; ††Dupilumab and baricitinib populations included patients who had previously failed or were contraindicated or intolerant to ciclosporin.

Data for the generalisable population was used for abrocitinib as the primary analysis for interpretation with the restricted population used as a secondary analysis. Although the restricted population represents more of a like-for-like comparison with available dupilumab and baricitinib data, the generalisable population is larger and has greater relevance to clinical practice. Further, outcomes between the generalisable and restricted populations are similar within JADE studies. If generalisable and restricted population comparisons were not feasible due to lack of comparator data, the full trial populations were used as the base case for interpretation instead.

The primary outcomes for the NMA comparison were the ordered multinomial composite outcome EASI-50/-75/-90 with ≥4-point improvement in (C)DLQI from

baseline (EASI-50/-75/-90 & (C)DLQI ≥4) and the ordered multinomial outcome EASI-50/-75/-90 alone.

These outcomes were analysed at the duration of the included trials: Week 16 for all baricitinib and dupilumab data and for the COMPARE trial for abrocitinib, and Week 12 for the MONO1/2 trial. Where comparisons incorporated 12-week data for abrocitinib and 16-week data for comparators this is hereafter referred to as a 12/16-week comparison. Given abrocitinib has a fast onset of action, no notable differences in efficacy would be expected between Week 12 and 16, as was illustrated in COMPARE. The Week 12/16 comparison might be expected to bias against abrocitinib given that dupilumab shows relatively slower response in COMPARE and improvements in outcomes from Week 12 to Week 16.

Key secondary outcomes were PP-NRS CFB and (C)DLQI CFB at Week 12/16, as well as PP-NRS4 at 2 weeks to explore the rapidity of itch relief. The tertiary outcome of IGA response is reported in Appendix D.

Although analyses exploring EASI-75 & DLQI ≥4 and EASI-90 & DLQI ≥4 were planned, these composites were not reported for any comparator, so it was only feasible to analyse the binomial composite EASI-50 & DLQI ≥4. Full details of feasibility are provided in Appendix D.

The key indirect comparisons were the NMAs. [redacted]

B.2.9.2 Evidence networks for NMA

Trials informing each of the generalisable and restricted evidence networks are presented in Table 36, and trials informing the full population networks are presented in Table 37.

Table 36: Trials included in NMA for the generalisable and restricted populations for adults combination and adult monotherapy comparisons

Trial (NCT no.)	Treatments	Reference
Adults combination therapy		
LIBERTY AD CAFÉ & CHRONOS pooled (NCT02755649, NCT02260986)	Placebo, dupilumab 300 mg Q2W	Dupilumab NICE submission (1)
COMPARE (NCT03720470)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg, dupilumab, 300 mg Q2WPlacebo, abrocitinib 100 mg, abrocitinib 200 mg, dupilumab 300 mg Q2W	Data on file (77)
BREEZE-AD4 (NCT03428100)	Placebo, baricitinib 2 mg, baricitinib 4 mg, Placebo, baricitinib 2 mg, baricitinib 4 mg	Bieber et al, 2020 (78)
Adults monotherapy		
Gooderham, 2019a (NCT02780167)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Gooderham et al, 2019 (80)
MONO-1 & 2 pooled (NCT03349060, NCT03575871)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Data on file (80, 81)
LIBERTY AD SOLO 1 & 2 pooled (NCT02277743, NCT02277769)	Placebo, dupilumab 300 mg Q2W	Dupilumab NICE submission (1)

Abbreviations: NMA, network meta-analysis; TCS, topical corticosteroids; Q2W, every other week.

Table 37 Trials included in NMA for the full trial population analyses for adults combination therapy, adults monotherapy and adolescents monotherapy comparisons

Trial (NCT)	Treatments	Reference
Adults combination therapy		
LIBERTY AD CAFÉ (NCT02755649)	Placebo, dupilumab 300 mg Q2W	(66)
LIBERTY AD CHRONOS (NCT02260986)	Placebo, dupilumab 300 mg Q2W	(63)
COMPARE (NCT03720470)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg, dupilumab, 300 mg Q2W	Data on file (77)
BREEZE-AD 7 (NCT03733301)	Placebo, baricitinib 2 mg, baricitinib 4 mg	(83)
Guttman-Yassky, 2019a (NCT02576938)	Placebo, baricitinib 2 mg, baricitinib 4 mg	(84)

Trial (NCT)	Treatments	Reference
Adults monotherapy		
Gooderham, 2019a (NCT02780167)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	(80)
MONO-1 (NCT03349060)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Data on file (80)
MONO-2 (NCT03575871)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Data on file (81)
LIBERTY AD SOLO 1 (NCT02277743)	Placebo, dupilumab 300 mg Q2W	(64)
LIBERTY AD SOLO 2 (NCT02277769)	Placebo, dupilumab 300 mg Q2W	(64)
BREEZE-AD1 (NCT03334396)	Placebo, baricitinib 2 mg, baricitinib 4 mg	(85)
BREEZE-AD2 (NCT03334422)	Placebo, baricitinib 2 mg, baricitinib 4 mg	(85)
Thaci, 2016 (NCT01859988)	Placebo, dupilumab 300 mg Q2W	(86)
Adolescents monotherapy		
MONO-1 (NCT03349060)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Data on file (80)
MONO-2 (NCT03575871)	Placebo, abrocitinib 100 mg, abrocitinib 200 mg	Data on file (81)
LIBERTY AD ADOL (NCT03054428)	Placebo, dupilumab 300 mg Q2W	(65)

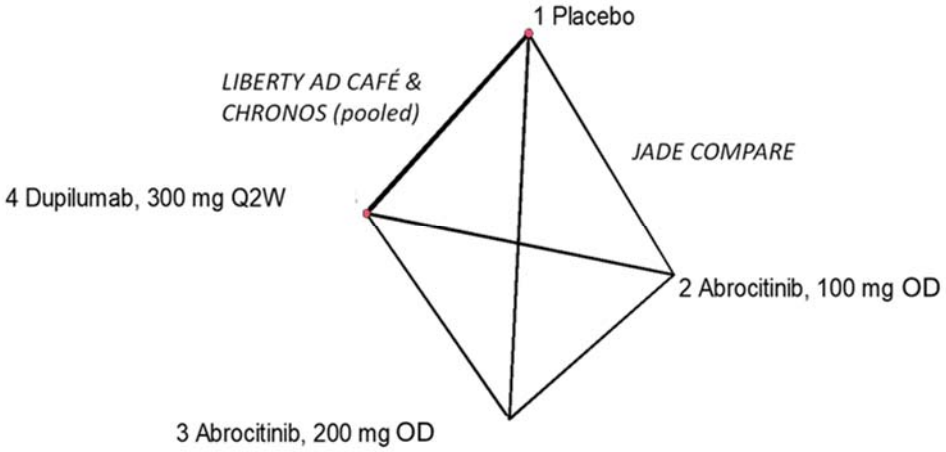
Abbreviations: NMA, network meta-analysis; TCS, topical corticosteroids; Q2W, every other week.

A summary of studies identified in the SLR but excluded from the NMAs, along with reasons for exclusion, is provided in Appendix D. The primary reason was that they capture efficacy for unlicensed treatments or did not add indirect evidence to comparisons of interest.

Feasible comparisons by endpoint and population for the comparison with dupilumab and baricitinib are summarised in Table 38 and Table 39 and are described below. Evidence networks in the key outcome of EASI-50 & DLQI ≥4 in the generalisable population for adults combination therapy and adults monotherapy are presented in

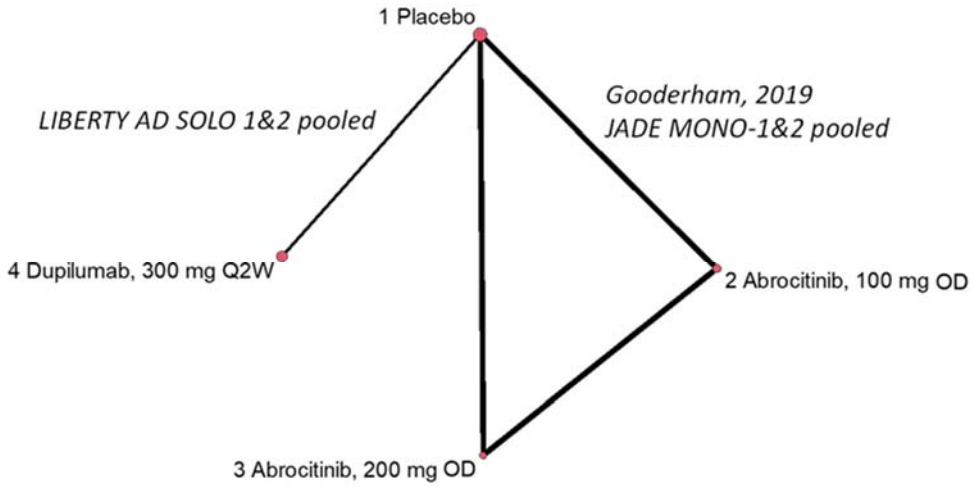
Figure 28 and Figure 29, respectively. Diagrams of all feasible evidence networks are provided in Appendix D.

Figure 28: Evidence network for the adult combination comparison: generalisable population



Edge thickness proportional to number of studies on comparison, node size proportional to number of studies on treatment. Trials included: COMPARE (placebo [N=24], abrocitinib 100 mg [N=40], abrocitinib 200 mg [N=42], dupilumab 300 mg Q2W [N=55]); LIBERTY AD CAFÉ and CHRONOS pooled (placebo [N=169], dupilumab 300 mg Q2W [N=130]).
Abbreviations: OD, every day; Q2W, every other week

Figure 29: Evidence network for the adult monotherapy comparison: generalisable population



Edge thickness proportional to number of studies on comparison, node size proportional to number of studies on treatment. Trials included: MONO-1 and 2 pooled (placebo [N=35], abrocitinib 100 mg [N=77], abrocitinib 200 mg [N=63]); Gooderham, 2019a (placebo [N=10], abrocitinib 100 mg [N=10], abrocitinib 200 mg [N=13]); LIBERTY AD SOLO 1 and 2 pooled (Placebo, dupilumab 300 mg Q2W).
Abbreviations: OD, every day; Q2W, every other week.

Abrocitinib vs dupilumab

Comparisons of the different efficacy endpoints between abrocitinib 200 mg, abrocitinib 100 mg and dupilumab that were feasible based on available data are presented in Table 38.

Table 38: NMA analyses – abrocitinib vs dupilumab (all network diagrams in Appendix D)

Endpoint	Timepoint (weeks)	Generalisable population	Restricted population	Full population
EASI-50 & DLQI ≥4	12/16	✓ Adults combo & mono only	✓ Adults combo & mono only	✗
EASI-75 & DLQI ≥4	12/16	✗	✗	✗
EASI-90 & DLQI ≥4	12/16	✗	✗	✗
EASI-50/-75	12/16	✓ Adults mono only Not conducted in combo as EASI-50/-75/-90 available	✓ Adults mono only Not conducted in combo as EASI-50/-75/-90 available	Not conducted as EASI-50/-75/-90 available
EASI-50/-75/-90	12/16	✓ Adults combo only	✓ Adults combo only	✓ Adults combo/ mono & adolescents mono
PP-NRS4	12/16	✗ Adolescents mono only	✗ Adolescents mono only	✓ Adults combo/ mono & adolescents mono
PP-NRS4	2	✗	✗	✓ Adults combo/ mono & adolescents mono
PP-NRS CFB	12/16	✓ Adults combo & mono only	✓ Adults combo & mono only	✓ Adults combo/ mono & adolescents mono
(C)DLQI CFB	12/16	✗	✗	✓ Adults combo/ mono & adolescents mono

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NMA, network meta-analysis; PP-NRS, Peak Pruritus Numerical Rating Scale.

Abrocitinib vs baricitinib

Comparisons of the different efficacy endpoints between abrocitinib 200 mg, abrocitinib 100 mg and baricitinib 4 mg and 2 mg that were feasible based on available data are presented in Table 39.

Table 39: NMA analyses – abrocitinib vs baricitinib (adults only; all network diagrams in Appendix D)

Endpoint	Timepoint (weeks)	Generalisable population	Restricted population	Full population
EASI-50/-75	12/16	Not conducted as EASI-50/-75/-90 available		
EASI-50/-75/-90	12/16	✓ Adults combo only	✓ Adults combo only	✓ Adult combo & mono
EASI-50 & DLQI ≥4	12/16	✗	✗	✗
EASI-75 & DLQI ≥4	12/16	✗	✗	✗
EASI-90 & DLQI ≥4	12/16	✗	✗	✗
PP-NRS4	12/16	✗	✗	✓ Adult combo & mono
PP-NRS4	2	✗	✗	✓ Adult combo & mono
DLQI CFB	12/16	✗	✗	✓ Adults combo only

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NMA, network meta-analysis; PP-NRS, Peak Pruritus Numerical Rating Scale.

B.2.9.3 Heterogeneity

B.2.9.3.1 *Comparison of baseline characteristics*

Patient characteristics compared were key demographics age, % male and % white; whereas for baseline disease characteristics consideration was given to duration of AD, EASI score, PP-NRS, % BSA, (C)DLQI, SCORAD and % IGA4 (severe), which were identified by clinical experts as being the most important prognostic factors or effect modifiers (Appendix D). We also compared HADS total score where available as JADE trials excluded patients with any psychiatric condition (e.g., clinically significant depression) that meet the protocol-defined exclusion criteria (Appendix M). Patient and disease characteristics were compared for the adult combination and adult monotherapy generalisable comparisons and for the adolescent monotherapy comparison in the full trial population in Table 40–Table 42; restricted and full populations for the adult analyses are compared in Appendix D.

[redacted]

[redacted]

Table 40: Baseline characteristics of trials included in NMA for adults combination therapy generalisable population

Trial	Treatment	N	Age, mean (SD)	Duration of AD (years), mean (SD)	Male (%)	White (%)	EASI score, mean (SD)	% BSA, mean (SD)	DLQI, mean (SD)	IGA 4 (severe) %	HADS total score, mean (SD)	SCORAD, mean (SD)	PP-NRS, mean (SD)
[redacted]													

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NMA, network meta-analysis; NR, not reported; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroids.

Table 41: Baseline characteristics of trials included in NMA for adults monotherapy generalisable population.

Trial	Treatment	N	Age, mean (SD)	Duration of AD (years), mean (SD)	Male (%)	White (%)	EASI score, mean (SD)	% BSA, mean (SD)	DLQI, mean (SD)	IGA 4 (severe) %	HADS total score, mean (SD)	SCORAD, mean (SD)	PP-NRS, mean (SD)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NMA, network meta-analysis; NR, not reported; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroids.

Table 42: Baseline characteristics of trials included in NMA for adolescents monotherapy full trial populations.

Trial Name	Treatment	Age, mean (SD)	Duration of AD (years)	Male (%)	White (%), mean (SD)	EASI score, mean (SD)	% BSA, mean (SD)	CDLQI, mean (SD)	IGA4 (severe) %	HADS total score, mean (SD)	SCORAD, mean (SD)	PP-NRS, mean (SD)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NMA, network meta-analysis; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroids.

B.2.9.3.2 *Comparison of rescue medications*

There were differences in the handling of rescue medications across the trials for abrocitinib, dupilumab, and baricitinib.

In the NICE submission for dupilumab, a primary analysis was defined where patients receiving rescue medications were “censored and set to non-responders” (1). Missing data was inputted thereafter using a range of methods including last observation carried forward and multiple imputation. An “all observed” analysis includes all patients regardless of rescue treatment. [redacted]

In the baricitinib NICE submission, similarly a primary censoring analysis was defined where patients receiving rescue medications were “censored as missing or non-responder imputation” (2). A secondary censoring analysis was also defined where patients receiving rescue medications were “censored as missing or non-responder imputation after initiation of systemic rescue therapies, but patients were not considered as missing after rescue with TCS.” [redacted]

B.2.9.3.3 *Comparison of washout procedures*

The wash-out/wash-in procedures and conditions for prior treatment for each trial included in the adult combination therapy, adult monotherapy or adolescent monotherapy networks are detailed in Appendix D. [redacted]

[redacted]

Table 43: Comparison of washout periods for studies considered in the NMA

Study	Intervention/comparators	Washout/Wash-in period for medicated topical treatments
Combination studies		
COMPARE	Abrocitinib, Placebo, Dupilumab	1 week washout
LIBERTY AD CHRONOS	Dupilumab, Placebo	1 week washout
LIBERTY AD CAFÉ	Dupilumab, Placebo	TCS standardisation wash-in period for 14 days prior to baseline but excluded patients who used TCI within 1 week
BREEZE-AD4	Baricitinib, Placebo	2 weeks washout
BREEZE-AD7	Baricitinib, Placebo	2 weeks washout
Guttman-Yassky, 2019a	Baricitinib, Placebo	TCS standardisation wash-in period for 4 weeks before randomisation
Monotherapy studies		
Gooderham, 2019a	Abrocitinib, Placebo	1 week washout
MONO-1 & MONO-2	Abrocitinib, Placebo	3 days washout
LIBERTY AD SOLO 1 & 2	Dupilumab, Placebo	1 week washout
LIBERTY AD ADOL	Dupilumab, Placebo	2 weeks washout
Thaci, 2016	Dupilumab, Placebo	1 week washout
BREEZE-AD1 & AD2	Baricitinib, Placebo	2 weeks washout

B.2.9.3.4 *Comparison of background medicated therapies (adult combination only)*

[redacted] In COMPARE, most patients received TCS alongside abrocitinib; far fewer patients received TCI or a PDE4 inhibitor (crisaborole), primarily in body areas of thin skin (e.g., face, neck) or if TCS were considered unsafe (full details of concomitant therapies summarised in Appendix D). In comparison, the dupilumab and baricitinib trials LIBERTY CAFÉ and Guttman Yassky 2019, respectively, allowed TCS only as background medicated therapy (84). LIBERTY CHRONOS allowed the use of TCI, and BREEZE-AD7 allowed TCI and/or crisaborole in body locations considered inadvisable for TCS.

There were also subtle differences in the schedule of TCS use between abrocitinib, dupilumab and baricitinib trials (as described in Appendix D) which are considered insignificant and would not be expected to have an impact on the results of the NMA.

B.2.9.4 Methods of NMA

The methods of the NMA are fully described in Appendix D and are fully aligned with those of the NICE DSU TSD (86). All analyses were conducted in the Bayesian paradigm using the OpenBUGS Markov Chain Monte Carlo (MCMC) software (87). Simulations used two chains, 50,000 burn-in iterations, and 10,000 iterations for posterior sampling; chains were assessed for convergence both visually and using the Gelman-Brooks-Rubin Rhat statistic.

The ordered multinomial outcomes EASI-50/-75/-90 and EASI-50/-75 were analysed using a multinomial likelihood and probit link function. Treatment effects are on the probit scale and represent differences in probability of not achieving the EASI outcome. Binary outcomes (i.e., EASI-50 & DLQI ≥4, PP-NRS4) were analysed using a binomial likelihood and logistic link function, with treatment effects on the odds ratio scale. As there were at most two or three trials for each treatment comparison (e.g., JADE MONO-1, MONO-2, and Gooderham for abrocitinib vs placebo for the adult monotherapy comparison), random effects models were not expected to converge as there was too little data to estimate the heterogeneity standard deviation; this was confirmed by initial exploratory analyses. Fixed effects with vague prior distributions was used as the base case. Random effects with informative priors on the heterogeneity standard deviation was conducted as sensitivity analysis (88). Also due to limited numbers of studies on dupilumab and baricitinib, particularly in the generalisable population, sensitivity analyses excluding studies were not feasible.

Results are presented as mean effects with 95% credible intervals (CrI). Bayesian probabilities that abrocitinib 200 mg or 100 mg are better than the comparator are also presented; these are labelled “p-best”. These are probabilities that the relative treatment effect is greater than 1 (for odds ratios) or less than 0 (for probit or CFB differences). These probabilities are interpreted in line with frequentist p-values, so a value of 0.05 or 0.95 represents statistically significant evidence, against or in favour of abrocitinib, respectively.

B.2.9.4.1 *Methods for meta-regression*

Meta-regressions in generalisable and restricted populations were not feasible given there is at most one baricitinib study, only pooled data available for the multiple dupilumab studies, and in adult combination therapy there is only one abrocitinib study. A meta-regression for the adult monotherapy generalisable or restricted populations could have been conducted based on the abrocitinib studies, Gooderham 2019 and MONO-1 and 2, but this would have to assume the same covariate effects for dupilumab as for abrocitinib, and this would be untestable. We therefore did not conduct this analysis.

In the full trial populations, meta-regressions were feasible as there are multiple abrocitinib, baricitinib, and dupilumab studies for each treatment comparison. Meta-regression was used with a common fixed covariate effect across non-placebo treatments on age, gender, % White, and on baseline AD duration, PP-NRS, IGA4, SCORAD, % BSA and EASI, and HADS to explore the impact of heterogeneity. All covariates were centred at their average value across trials. We also conducted meta-regression on placebo response, as an attempt to account for multiple potential effect modifiers (90). Placebo response was a probit score for EASI-50 on placebo, and we centred placebo response at the average across all trials. These were conducted for the only primary outcome that was feasible in the full trial populations (i.e., EASI-50/-75/-90). Further details on the meta-regression are presented in Appendix D.

B.2.9.4.2 *Methods for model comparison*

All models (fixed effects, random effects with informative priors, fixed effects with meta-regressions) were compared to each other using the Deviance Information Criterion (DIC) and total residual deviance (90). DIC differences less than 5 were not considered important and the fixed effect model with no regression was taken as the default (87). Total residual deviance was compared to the total number of datapoints (e.g., number of arms across all trials in binomial-logistic, number of EASI categories reported across arms across trials in multinomial-probit) to assess overall goodness of fit. Covariate effects were judged by considering whether the 95% CrI were crossing the point of no effect (i.e., 0 for multinomial-probit models).

B.2.9.5 NMA results for comparisons with dupilumab

The mean effects, 95% CrI, and Bayesian probabilities (p-best) that abrocitinib has greater effect are presented. The interpretation is focused on the generalisable population; unless otherwise stated, the restricted population results are consistent in direction of effect but with lower precision.

The DIC and residual deviance presented in Appendix D did not favour any model and fixed effects are therefore presented in the base case. Random effects with informative prior were consistent in direction but differences were largely not statistically significant. Meta-regressions found no statistically significant covariate effects. Results for random effects and meta-regressions are in Appendix D.

B.2.9.5.1 *Adult combination therapy comparisons with dupilumab*

Results for adult combination therapy are presented in Table 44.

[redacted]

[redacted]

Table 44: NMA Results for abrocitinib comparisons vs dupilumab 300 mg Q2W in adults combination therapy

	Abrocitinib 200 mg vs dupilumab			Abrocitinib 100 mg vs dupilumab		
	Generalisable	**Restricted**	**Full**	**Generalisable**	**Restricted**	**Full**
EASI-50 & DLQI ≥4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI-50/-75/-90 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 week 2 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unless otherwise stated, all comparisons at Week 16; NA=Not applicable due to lack of comparator data; NC=Full population not conducted as generalisable or restricted feasible; Significantly in favour (p-best>0.95) of abrocitinib are **bold**, significantly against (p-best<0.05) are *italic*.
Abbreviations: CFB, change from baseline; CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; p-best: Bayesian probability that abrocitinib is better than dupilumab; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week.

B.2.9.5.2 *Adult monotherapy comparisons with dupilumab*

Adult monotherapy comparisons with dupilumab are presented in Table 45.

[redacted]

Table 45: NMA results for abrocitinib comparisons vs dupilumab 300 mg Q2W in adults monotherapy

	Abrocitinib 200 mg vs dupilumab			Abrocitinib 100 mg vs dupilumab		
	Generalisable	**Restricted**	**Full**	**Generalisable**	**Restricted**	**Full**
EASI-50 & DLQI ≥4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI-50/-75 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EASI-50/-75/-90 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 week 2 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unless otherwise stated, all outcomes at Week 12 for abrocitinib and Week 16 for dupilumab; NA=Not applicable due to lack of comparator data; NC=Full population not conducted as generalisable or restricted feasible. Significantly in favour (p-best>0.95) of abrocitinib are **bold**, significantly against (p-best<0.05) are *italic*.

Abbreviations: CFB, change from baseline; CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; p-best: Bayesian probability that abrocitinib is better than dupilumab; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week.

B.2.9.5.3 *Adolescent monotherapy comparisons with dupilumab*

Results for adolescent monotherapy analyses are presented in Table 46.

[redacted]

Table 46: NMA Results for abrocitinib comparisons vs dupilumab 200 mg or 300 mg Q2W in adolescents monotherapy

	Abrocitinib 200 mg vs dupilumab			Abrocitinib 100 mg vs dupilumab		
	Generalisable	**Restricted**	**Full**	**Generalisable**	**Restricted**	**Full**
EASI-50/-75/-90 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CDLQI CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All outcomes at Week 12 for abrocitinib and Week 16 for dupilumab; NA=Not applicable due to lack of comparator data. Significantly in favour (p-best>0.95) of abrocitinib are **bold**, significantly against (p-best<0.05) are *italic*.
Abbreviations: CFB, change from baseline; CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; p-best: Bayesian probability that abrocitinib is better than dupilumab; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week.

B.2.9.6 NMA results for comparisons with baricitinib 4 mg and 2 mg

In the public committee slides for the baricitinib appraisal the NICE technical team commented that the impact on the incremental cost-effectiveness ratio (ICER) of not modelling the 2 mg dose is likely to be small, given use is expected to be limited (2). We therefore present only baricitinib 4 mg results in detail here and provide results for baricitinib 2 mg are provided in Appendix D.

As noted in the dupilumab comparison, fixed effects was chosen as the base case given the limited differences in DIC and residual deviance with other models. Random effects with informative priors were consistent in direction but differences were largely not statistically significant (Appendix D). Meta-regressions found no statistically significant effects.

B.2.9.6.1 *Adult combination therapy comparisons with baricitinib*

The results of the NMA comparisons with baricitinib 4 mg in adults combination therapy are presented in Table 47. [redacted]

Table 47 NMA Results for abrocitinib comparisons vs baricitinib 4 mg in adults combination therapy

	Abrocitinib 200 mg vs baricitinib 4 mg			Abrocitinib 100 mg vs baricitinib 4 mg		
	Generalisable	**Restricted**	**Full**	**Generalisable**	**Restricted**	**Full**
EASI-50/-75/-90 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PP-NRS4 week 2 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI CFB Mean difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Unless otherwise stated, all outcomes at Week 16; NA=Not applicable due to lack of comparator data; NC=Full population not conducted as generalisable or restricted feasible. Significantly in favour (p-best>0.95) of abrocitinib are **bold**, significantly against (p-best<0.05) are *italic*.
Abbreviations: CFB, change from baseline; CrI, credible interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; p-best: Bayesian probability that abrocitinib is better than baricitinib; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every other week.

B.2.9.6.2 *Adult monotherapy comparisons with baricitinib*

The results of the NMA comparisons with 4 mg in adults monotherapy are presented in Table 48. [redacted]

Table 48 NMA Results for abrocitinib comparisons vs baricitinib 4 mg in adults monotherapy in the full trial populations

Outcome Effect measure	Abrocitinib 200 mg vs baricitinib 4 mg	Abrocitinib 100 mg vs baricitinib 4 mg
EASI-50/-75/-90 Probit difference (95% CrI), values less than zero favour abrocitinib	[redacted]	[redacted]
PP-NRS4 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]
PP-NRS4 week 2 Odds ratio (95% CrI), values greater than one favour abrocitinib	[redacted]	[redacted]

No comparisons feasible in the generalisable or restricted populations. Unless otherwise stated, all outcomes at Week 12 for abrocitinib and Week 16 for baricitinib. Significantly in favour (p-best>0.95) of abrocitinib are **bold**, significantly against (p-best<0.05) are *italic*.
Abbreviations: CrI, credible interval; EASI, Eczema Area and Severity Index; NMA, network meta-analysis; PP-NRS, Peak Pruritus Numerical Rating Scale.

[redacted]

[redacted]

30 [redacted]

[redacted]

49 [redacted]

49 [redacted]

	EASI-50		EASI-75		PP-NRS4	
	Abrocitinib 200 mg	Abrocitinib 100 mg	Abrocitinib 200 mg	Abrocitinib 100 mg	Abrocitinib 200 mg	Abrocitinib 100 mg
Base case (based on clinical opinion)	[redacted]					
AIC selection†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	EASI-50		EASI-75		PP-NRS4	
	Abrocitinib 200 mg	Abrocitinib 100 mg	Abrocitinib 200 mg	Abrocitinib 100 mg	Abrocitinib 200 mg	Abrocitinib 100 mg
All covariates			[redacted]			

†The AIC of all possible covariate combination models were compared and that with minimal AIC selected.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, SCoring Atopic Dermatitis; STC, simulated treatment comparison.

[redacted]

50 [redacted]

50 [redacted]

	EASI-50 conditional on EASI-50 at week 12/16		EASI-75 conditional on EASI-75 at week 12/16		[redacted]	
	Population with either EASI-75 or IGA 0/1 at Week 12/16					
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	EASI-50 conditional on EASI-50 at week 12/16		EASI-75 conditional on EASI-75 at week 12/16		[redacted]	
	Population with either EASI-75 or IGA 0/1 at Week 12/16					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

B.2.9.8 Uncertainties in the indirect and mixed treatment comparisons

B.2.9.8.1 *Limitations of the NMA arising from data availability*

The primary limitation of the NMA comparisons was related to data availability.

- No adolescent combination therapy analysis was feasible given no dupilumab combination therapy data were identified for adolescents
- Outcomes were limited in the generalisable and restricted populations across analyses but particularly for:
    - The adolescent monotherapy comparison vs dupilumab in adolescents where no generalisable or restricted comparisons could be conducted. Data to support a generalisable/restricted population comparison was identified for EASI-75 and PP-NRS4. However, few events took place in the placebo arms of MONO 1/2 (for adolescents) and the dupilumab study (LIBERTY AD ADOL) so the NMA results were not useable, even with continuity corrections.

    - Comparisons vs baricitinib, where the only feasible outcome was for EASI-50/-75/-90 for adult combination analysis.

- Comparisons were not feasible on the primary endpoints of EASI-75 & DLQI ≥4 and EASI-90 & DLQI ≥4 for either comparisons with dupilumab or baricitinib given these composite outcomes were not identified in comparator data.

Further, in the adult and adolescent monotherapy comparisons, outcomes were analysed at the duration of the included trials: Week 12 for abrocitinib trials compared with Week 16 results from dupilumab and baricitinib trials. Given abrocitinib has a fast onset of action, no notable differences in efficacy would be expected between Week 12 and 16, as was illustrated in COMPARE. The Week 12/16 comparison might be expected to bias against abrocitinib given that dupilumab shows relatively slower response in COMPARE and improvements in outcomes from Week 12 to Week 16.

B.2.9.8.2 *Heterogeneity*

As discussed in Section B.2.9.3, there were minor differences in patient and disease characteristics, washout periods, and concomitant medications across abrocitinib, dupilumab, and baricitinib trials, although no significant impact of the differences on the treatment effects is expected. There were also differences across trials in use of rescue medications which were permitted in dupilumab and baricitinib trials but not for abrocitinib, however clinical expert guidance was followed on the appropriate data to use for comparators within the NMA.

The conclusions from the NMA for abrocitinib 200mg vs dupilumab are largely consistent with trial data from COMPARE for the adult combination analysis.

Although the generalisable population is of most interest for abrocitinib given this is how the treatment is anticipated to be used in clinical practice, the population for which dupilumab and baricitinib data is available is more similar to the restricted population. Results in the generalisable and restricted population were similar for all outcomes, with a reduction in precision going from generalisable to restricted being

the main change. Further, the outputs from the full trial comparisons were also similar.

B.2.9.8.3 *Methodological issues with the NMA*

Random effects models, which impose weaker assumptions about heterogeneity than fixed effects models, with informative priors did not converge in most cases (Appendix D) and those with non-informative priors did not converge in any case. However, in cases where random effects converged directions of results were consistent with the base case fixed effects analysis and DIC and deviance did not favour one model over the other. Meta-regressions also found no evidence of covariate effect for any outcome.

As all evidence networks were “star” networks, with no loops of evidence constructed from more than one trial, inconsistency could not be tested using either node splitting or independent means models. Consistency has been assumed for NMA comparisons between abrocitinib, dupilumab, and baricitinib. However, the JADE COMPARE study provides a direct comparison, not relying on a consistency assumption, of abrocitinib and dupilumab in the adults combination therapy group for full trial (Section B.2.6) and generalisable populations (Section B.2.7.2).

B.2.9.8.4 *Uncertainties in the STCs*

[redacted]

B.2.9.9 Conclusions

[redacted]

[redacted].

[redacted].

B.2.10 Adverse reactions

Results of a safety assessment based on pooled analyses of the Phase 2b and Phase 3 trials for abrocitinib, including the long-term extension study EXTEND, support the followings findings:

- Short-and long-term use of abrocitinib (in monotherapy and in combination with background medicated topical therapy) was well tolerated.
- Most adverse events were mild, self-limited, and seldom required interruption or permanent discontinuation of therapy. The most common dose-related adverse reactions associated with abrocitinib were nausea, headache, and acne.
- The incidence of serious adverse events (SAE) was low[redacted]

- Adverse events of special interest were those that have been identified from abrocitinib clinical studies and the broader JAK class.

- Platelet count was reduced transiently in a dose-dependent manner. Overall, there were no changes over time in lymphocytes, neutrophils and haemoglobin associated with abrocitinib treatment. The adverse event and laboratory profiles suggest that there are no risks unique to the adolescent population.

B.2.10.1 Safety Pooling Strategy

The evaluation of the abrocitinib tolerability and safety profile is primarily drawn from safety assessments in six studies in the AD clinical development program. These data were included in two pre-specified pools to address specific goals:

- **Primary Safety Pool ("Primary Pool"):**

  The Primary Pool is used to assess abrocitinib safety relative to placebo, dose–response relationships for frequent adverse drug reactions, and laboratory changes. It comprised the initial placebo-controlled 12 to 16 weeks of exposure including patients who participated in the Phase 2b dose ranging study (B7451006; 12-week), the two pivotal Phase 3 monotherapy studies (MONO-1, MONO-2; 12-week) and the adult combination therapy study (COMPARE; 16-week).

- **All Exposure Pool:**

  The All Exposure Pool is a comprehensive review of the safety data from all patients who received at least one dose of abrocitinib 200 mg or 100 mg [redacted]). Day 1 of exposure in this pool was the first day of abrocitinib exposure. Patients included from EXTEND who received abrocitinib in the parent studies continued to receive the same dose over the long-term extension study. Patients initially randomised to placebo or dupilumab contributed exposure to this pool starting at the time they were randomised to either dose of abrocitinib at Week 16 (in COMPARE) or in the long-term extension study. This cohort enabled assessment of incidence rates (IRs; rate of occurrence of an AE during a given period), changes in laboratory parameters, and, where possible, risk factors for AEs.

AE data from the individual studies, including COMPARE, TEEN, MONO-1, and MONO-2, are provided in Appendix F.

B.2.10.2 Adverse events definitions

Treatment emergent adverse events (TEAE), referred to as AEs in the following section, are defined as any untoward medical occurrence which emerged or worsened during the treatment period but these were not necessarily causally related to treatment unless classified as treatment-related.

A serious adverse event (SAE) is any untoward medical occurrence at any dose that results in death, is life-threatening (immediate risk of death), requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), results in congenital anomaly/birth defect, and is an important medical event based on investigator's judgment.

The investigators assessment of AE intensity is classified as mild, moderate or severe. A mild AE does not interfere with patient's usual function whereas a moderate AE interferes to some extent. A severe AE is one that interferes significantly with a patient's usual function although it is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs.

B.2.10.3 Patient exposure

The Primary Pool included a total of 1,540 patients (124 [8.1%] adolescents), 608 exposed to abrocitinib 100 mg, 590 exposed to 200 mg, and 342 exposed to placebo. The median duration of exposure was [redacted] days. Among patients in the Primary Pool, [redacted] were randomised in a monotherapy study (B7451006, MONO-1, MONO-2) and [redacted] were randomised in a study including background medicated topical therapy (COMPARE).

The All Exposure Pool included 3,128 patients ([redacted] adolescents), representing 2088.8 person-years of exposure to abrocitinib. Among these patients, [redacted] were adolescents, representing [redacted] of exposure. There were 994 patients exposed for at least 48 weeks and [redacted] exposed for at least 72 weeks.

B.2.10.4 Short-term safety and tolerability

As summarised in Table 51 in the Primary Pool, TEAEs occurred in 68.3% of patients receiving abrocitinib 200 mg, 61.0% receiving 100 mg, and 55.0% receiving placebo; proportions of SAEs and severe AEs were similar across groups (Table 50). The most common TEAEs with a dose response and excess over placebo, which drove the difference overall, were nausea, headache, and acne. Most patients (94.2%) had events that were mild or moderate in severity. Most AEs were generally self-limited and seldom required interruption or permanent discontinuation of

treatment. A full list of AEs occurring in ≥2% of patients in any treatment group in the Primary Pool is provided in Appendix F.

Table 51: Overall safety summary and frequent TEAEs (all causalities) in the placebo-controlled cohorts (Primary Pool)

	Placebo N=342 n (%)	Abrocitinib 100 mg N=608 n (%)	Abrocitinib 200 mg N=590 n (%)
Patients evaluable for AEs	342	608	590
Number of AEs	360	816	921
Patients with AEs	188 (55.0)	371 (61.0)	403 (68.3)
Patients with SAEs	11 (3.2)	19 (3.1)	11 (1.9)
Patients with severe AEs	20 (5.8)	29 (4.8)	19 (3.2)
Patients discontinued from study due to AEs	31 (9.1)	33 (5.4)	32 (5.4)
Most frequent adverse events			
Nausea	7 (2.0)	37 (6.1)	86 (14.6)
Nasopharyngitis	27 (7.9)	75 (12.3)	51 (8.6)
Headache	12 (3.5)	36 (5.9)	46 (7.8)
Upper respiratory tract infection	19 (5.6)	40 (6.6)	30 (5.1)
Acne	0	10 (1.6)	28 (4.7)
AD (worsening of the AD condition)	37 (10.8)	45 (7.4)	24 (4.1)
Vomiting	3 (0.9)	9 (1.5)	19 (3.2)
Blood creatine phosphokinase increased	5 (1.5)	14 (2.3)	17 (2.9)
Dizziness	3 (0.9)	11 (1.8)	17 (2.9)
Herpes simplex	3 (0.9)	10 (1.6)	17 (2.9)
Diarrhoea	10 (2.9)	10 (1.6)	16 (2.7)
Urinary tract infection	4 (1.2)	10 (1.6)	13 (2.2)
Folliculitis	7 (2.0)	6 (1.0)	10 (1.7)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Nausea

Nausea was the most frequently reported AE in the abrocitinib 200 mg group occurring in 14.6% of patients, compared with 6.1% for the abrocitinib 100 mg group (Table 51). Across all treatment groups, no nausea events were serious although one event (0.2%) in the 200 mg group was severe. Most resolved with no change or interruption to treatment: 4 events of nausea (2 from each abrocitinib treatment group) led to discontinuation. Across all abrocitinib-treated patients, most nausea events occurred in the first week of treatment (63.5% of events with 200 mg and 72.3% of events with 100 mg). The median time to resolution of nausea was 15 days (17 days for patients treatment with the 200 mg dose and 8 days for the 100 mg dose). Female patients had a higher frequency of nausea compared with male patients (18.1% vs 7.6%).

Headache

A dose-related increase in the proportion of patients with headache was observed in abrocitinib-treated patients (Table 51). No headache events were categorised as serious or severe. Three abrocitinib-treated patients overall (0.3%) had headache events leading to study discontinuation (two in the 200 mg and one in the 100 mg group); no placebo-treated patients discontinued due to headache. Among patients who experienced headache, the initial event, in >40%, occurred within the first week of treatment (47.6% with 200 mg; 39.6% with 100 mg). Median time to resolution of headache was 4 days (5 days in the 200 mg and 3.5 days in the 100 mg group).

Acne

There was a dose-related increase in acne events (4.7%, 1.6%, and 0% for 200 mg, 100 mg, and placebo groups, respectively; Table 51). There were no serious or severe AEs, or AEs that led to discontinuation. The median time to resolution was 247 days. There was no clustering of acne events early or late in treatment, and approximately one-third (33.0%) of the events occurred by Day 84.

B.2.10.5 Longer term safety and adverse events of special interest

The two dose groups in the All Exposure Pool had similar proportions of AEs, SAEs, severe AEs and AEs leading to discontinuation (Table 52). SAEs occurred most frequently [redacted] The most frequent SAEs, occurring in 4 or more patients across all abrocitinib-treated patients (denoted below as “all abrocitinib”) were [redacted]. A safety summary from the All Exposure pool is provided in Table 51. Full lists of SAEs and AEs leading to permanent discontinuation that occurred in ≥2 patients in abrocitinib 100 mg or 200 mg treatment group in the All Exposure Pool are provided in Appendix F.

Table 52: Overall safety summary and frequent SAEs (all causalities) in all abrocitinib-treated patients (All Exposure Pool)

	Abrocitinib 100 mg, n (%)	Abrocitinib 200 mg, n (%)	All Abrocitinib, n (%)
Patients evaluable for AEs	[redacted]	[redacted]	[redacted]
Number of AEs			
Patients with AEs			
Patients with SAEs			
Patients with severe AEs			
Patients discontinued from study due to AEs			
Deaths			
Most frequent SAEs			
[redacted]			

Abbreviations: AE, adverse event; SAE, serious adverse event.

The selected events of interest derived from review of the nonclinical and clinical experience with abrocitinib and other JAK inhibitors are discussed in this section.

Serious infections

An increased incidence of serious infections has been observed during treatment with other JAK inhibitors (95). In the abrocitinib studies, the data do not suggest a meaningful increase in the incidence of serious infections overall compared to placebo nor exhibit a dose response (Table 53). The most frequent serious infections [redacted] in abrocitinib-treated patients were herpes zoster, herpes simplex, pneumonia and eczema herpeticum. [redacted].

Table 53: Summary of infection events in the Primary and All Exposure Pool

	Primary Pool			All Exposure Pool		
	Placebo ***N*** **= 342**	**Abrocitinib 100 mg** ***N*** **= 608**	**Abrocitinib 200 mg** ***N*** **= 590**	**Abrocitinib 100 mg** ***N*** **= 1023**	**Abrocitinib 200 mg** ***N*** **= 2105**	**All Abrocitinib**
Serious infections						
[redacted]						
				2.18	2.11	

	Primary Pool			All Exposure Pool		
	Placebo *N* = 342	Abrocitinib 100 mg *N* = 608	Abrocitinib 200 mg *N* = 590	Abrocitinib 100 mg *N* = 1023	Abrocitinib 200 mg *N* = 2105	All Abrocitinib
Herpes zoster						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Herpes simplex†						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eczema herpeticum						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Includes events of genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, oral herpes.
Abbreviations: CI, confidence interval; IR incidence rate, NMSC nonmelanoma skin cancer.

Herpes zoster

Herpes zoster is an identified risk of treatment with JAK inhibitors (95). [redacted] A multivariate analysis has found that abrocitinib 200 mg, age ≥65 years, and severe disease at baseline was associated with a higher risk of herpes zoster.

Herpes simplex and eczema herpeticum

[redacted]

[redacted]

Malignancies

The immune system is thought to function a tumor suppressor through the effect of cytokines or cell types (e.g., NK cells) that may be affected by JAK inhibitors and other immunomodulators

(95)[redacted]

Cardiovascular safety

Dose dependent increases in total cholesterol, LDL-c, and HDL-c have been seen with other JAK inhibitors and IL-6 antagonists in rheumatoid arthritis (97), although no association between these changes in lipid parameters and major adverse cardiovascular events (MACE) events has been established so far (98). Other JAK

inhibitors have also been associated with venous thromboembolism (VTE) events, particularly at higher doses and in populations that are at risks for CV disease.

[redacted]

Laboratory abnormalities

There was a dose–dependent decrease in platelets with median values reaching the lowest point at week 4. Median platelet counts subsequently increased and plateaued at week 12 with values remaining below baseline. [redacted]

In the Primary Pool, there were no changes over time in median absolute lymphocyte count (ALC), absolute neutrophil count (ANC), or haemoglobin values.

[redacted]

B.2.10.6 Safety in adolescents

In the All Exposure Pool, the proportions of adolescent patients having AEs, SAEs, severe AEs and AEs leading to study discontinuation were [redacted]

respectively [redacted]

[redacted]

B.2.11 Ongoing studies

JADE DARE (NCT04345367) is a randomised, double-blind, double-dummy, active-controlled, multi-centre study designed to assess the efficacy and safety of abrocitinib 200 mg vs dupilumab 300 mg administered in adult participants on background medicated topical therapy, with moderate to severe AD. The primary objective of the study is to compare the efficacy of abrocitinib 200 mg vs dupilumab for adults on medicated topical therapy, measured by PP-NRS4 at Week 2 and EASI-90 at Week 4. The study is currently recruiting patients.

JADE MOA (NCT03915496) is a randomised, double-blind, placebo-controlled, parallel-group, Phase 2a study to investigate the mechanism of action of abrocitinib by correlating efficacy outcomes with changes from baseline in key skin and blood biomarkers in adult participants at least 18 years of age with moderate to severe AD. The study is currently recruiting patients.

Early Access to Medicines Scheme (EAMS)

Abrocitinib was granted Promising Innovative Medicine (PIM) designation by the MHRA on 21 July 2020. Positive scientific opinion for EAMS was received on 28 January 2021 for the following indication.

Abrocitinib is being made available to adult and adolescent patients with severe atopic dermatitis requiring treatment with systemic therapy and have had inadequate response or have lost response to approved systemic therapies, or those who are ineligible or intolerant of approved systemic therapies.

[redacted]

B.2.12 Innovation

Abrocitinib has been recognised as a Promising Innovative Medicine by the MHRA

Abrocitinib has been granted a Promising Innovative Medicine (PIM) designation and a positive scientific opinion for Early Access to Medicine Scheme (EAMS) by the MHRA for the treatment of severe AD. This indicates that severe AD is a seriously debilitating condition and that abrocitinib (200 mg and 100 mg once daily) offers major advantages over existing systemic therapies (100).

Abrocitinib offers a novel mode of action, and the selective inhibition of JAK1 spares the undesirable side effects of JAK2 inhibition.

Abrocitinib is a potent orally-administered JAK1-selective inhibitor that targets several cytokine pathways implicated in AD beyond those targeted by dupilumab (Section B.1.3.2) (101). Unlike dupilumab which is a biologic, abrocitinib is a small molecule and there is no anticipated immunogenicity, and so it is unlikely to generate antidrug antibodies which may potentially result in loss of efficacy over time.

Abrocitinib has been demonstrated to rapidly reduce itch, which is the key symptom driving reduced HRQL in patients with AD (Section B.1.3.5.2). Although the anti-pruritic effects of JAK inhibitors are likely due, in part, to their anti-inflammatory properties, neuronal JAK1 signalling has been shown to critically mediate itch, thus JAK1 inhibition may represent a broader anti-itch therapeutic strategy (103).

Baricitinib targets JAK1 and JAK2 whereas abrocitinib selectively blocks JAK1 and is less potent against other JAK isoforms (103). Selective inhibition of JAK1 is a desirable target to modulate a broad range of cytokines involved in the pathogenesis of AD while reducing the risk for undesirable effects of JAK2 inhibition, such as neutropenia and anaemia.

Abrocitinib allows flexibility in dosing, with 200 mg and 100 mg doses.

In clinical trials treatment with once-daily oral abrocitinib, both 200 mg and 100 mg doses were effective and well tolerated in adolescents and adults with moderate to severe AD (Section B.2.6). The licensed posology for abrocitinib is expected to permit flexible dosing regimens such that treatment can be tailored based on a patients individual goal and condition (104).

The recommended dose is either 200 mg or 100 mg once daily. For most patients, particularly those with severe disease, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions. During treatment, the dose may be decreased or increased based on tolerability and efficacy.

The oral route of administration for abrocitinib is preferable for some patients.

Given that dupilumab is a subcutaneous injection, and baricitinib is the only advanced oral treatment available there remains an unmet need for oral treatments with good efficacy and acceptable safety profile for patients with moderate to severe AD. In a discrete choice experiment to analyse patient preferences in moderate to severe AD, oral pills taken once daily were strongly preferred over fortnightly injections (required for dupilumab treatment). (33).

B.2.13 Interpretation of clinical effectiveness and safety evidence

Abrocitinib is a new treatment option for patients aged 12 years and older with moderate to severe AD who have not responded to, or have lost response to, at

least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated (Section B.1.2).

Figure 31 illustrates the impact of abrocitinib treatment on skin appearance in a patient treated within the clinical trial programme.

Figure 31: Skin appearance before and during treatment with abrocitinib

Shared with patient consent.

The 200 mg dose of abrocitinib represents an alternative to dupilumab, which may not be suitable for all patients given the association with injection site reactions, eye complications and face and neck erythema which can cause burning and itching (Section B.1.3.7). Clinical evidence demonstrates that 200 mg abrocitinib appears to be more effective than dupilumab in rapidly reducing itch and achieving more complete skin clearance (Section B.2.6.1), which are the two major drivers of disease burden in AD (Section B.1.3.5.2). This may explain the improvement in HRQL observed for abrocitinib 200 mg dose compared with dupilumab in COMPARE, as measured using DLQI (B.2.6.1.3.3). [redacted]

The availability also of a lower 100 mg dose of abrocitinib enables tailoring of treatment regimens based on individual tolerability and efficacy (Section B.2.12). For most patients, particularly those with severe disease, 200 mg is the recommended starting dose given the higher efficacy. However, a starting dose of 100 mg is recommended for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for

those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions (Section B.2.12).

[redacted] B.2.6.1 B.2.9 [redacted]

Baricitinib represents a newer treatment option for patients previously treated with immunosuppressants but as the NICE committee recognised within TA681 it is less effective than dupilumab(4). [redacted] (Section B.2.9).

[redacted]

Strengths and limitations of the clinical evidence

The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD was assessed in an extensive clinical trial programme, comprising four pivotal trials (COMPARE, TEEN, MONO-1, and MONO-2). All four trials were randomised, double-blind, and placebo controlled, representing the gold standard for evaluating treatment effectiveness (105).

Importantly, COMPARE provides a comparison between abrocitinib 200 mg and 100 mg and dupilumab, which is a key comparator for abrocitinib. [redacted]

The full trial populations for the pivotal RCTs included patients who had and had not received prior systemic therapies, which is broader than the proposed positioning. Therefore, data are presented in Section B.2.7.2 for the 'generalisable' population are representative of patients who would be treated with abrocitinib in clinical practice, namely patients who were previously treated with at least one systemic treatment for AD. Across both the full and generalisable populations, baseline

characteristics were comparable between treatment arms and were broadly comparable between trials.

[redacted]

Data are also presented for the long-term extension study (EXTEND), and a ‘dosing down’ study (REGIMEN). EXTEND provides long-term follow-up data for patients receiving abrocitinib 200 mg and 100 mg, but data are not yet fully mature.

The primary limitation of the NMA was related to data availability. No adolescent combination therapy analysis was feasible vs dupilumab given the lack of a trial where background medicated therapies were permitted. Outcomes were limited in the generalisable/restricted comparisons. Further, comparisons were not feasible for endpoints measuring higher thresholds of response (EASI-75 & DLQI ≥4; EASI-90 & DLQI ≥4) for either comparisons with dupilumab or baricitinib given the composite outcomes were not identified in comparator data.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A broad systematic literature review (SLR) was conducted in June 2020 to identify cost-effectiveness studies from the published literature. The SLR was updated with the searches re-run in January 2021. The scope for the original and update SLRs was broader than that required for the submission as additional interventions not relevant to the NICE decision problem were included. Only studies focusing on abrocitinib, baricitinib, and dupilumab are considered relevant to the NICE decision problem. A complete description of the search strategies is presented in Appendix G.

B.3.1.1 Description of identified studies

No previously published cost-effectiveness studies of abrocitinib for AD were identified.

The broad SLR identified nine studies that met the pre-defined inclusion criteria, of which seven were deemed relevant to the NICE decision problem. Three of these studies were UK-based which were HTAs for NICE and SMC. Two were conducted for dupilumab, one by the NICE and one by the Scottish Medicines Consortium (SMC). In addition, one was conducted for baricitinib by NICE. These provide information about the modelling of comparator products for HTA, which has been utilised to inform the modelling approach for abrocitinib. Each of the UK HTA appraisals are summarised in Table 54.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the overall flow of studies across the review is shown in Appendix G, together with a complete list of studies excluded after the full-text review stage.

Table 54: Summary of included studies

Study, Country	Intervention/comparator	Summary of model	Patient population	Base case costs (currency, year)	Base case health outcomes	Base case ICER
NICE TA534 STA, dupilumab(1) UK	• Dupilumab: initial dose of 600 mg (administered in two 300 mg injections consecutively in different injection sites), followed by 300 mg every other week administered as subcutaneous injection • BSC: a combination of emollients, low-to-mid potency TCS and rescue therapy (such as higher potency topical or oral corticosteroids or TCIs)	• Markov model and decision tree • Health states: maintenance treatment with dupilumab plus SOC, SOC treatment, death • Time horizon: lifetime (100 years of age) • Perspective: payer (NHS) • Cycle length: annual • Discounting: 3.5% per year for costs and benefits	Adult patients with moderate or severe AD	• Total costs: NR	Incremental QALYs: ranging from 1.4 to 1.8; greater than 1.0 in all scenarios. •	• Manufacturer's submission: • ICER: £28,874 (dupilumab with TCS) £24,703 (dupilumab monotherapy) • ERG revised base case: • ICER: £25,749 (dupilumab monotherapy) £30,419 (dupilumab with TCS) • ICERs from final guidance document: • Company: ranging from £27,410 to £28,495 (based on plausible sensitivity analyses) for dupilumab with TCS
SMC dupilumab (SMC2011)(106) UK	• Dupilumab: initial dose of 600 mg (two 300 mg injections), followed by 300 mg administered every other week by subcutaneous injection • BSC: assumed to be comprised of treatments as used in the placebo arms of the clinical study	• Markov model and decision tree • Health states: maintenance treatment with dupilumab plus SOC, BSC treatment and death	Adult patients with moderate or severe AD	Incremental cost (GBP, 2018) • Dupilumab with TCS £63,911 • Dupilumab monotherapy £41,532	Incremental QALYs • Dupilumab with TCS 1.81 • Dupilumab monotherapy 1.41	ICER vs BSC • Dupilumab with TCS £35,351/QALY gained • Dupilumab monotherapy £29,504/QALY gained

Study, Country	Intervention/comparator	Summary of model	Patient population	Base case costs (currency, year)	Base case health outcomes	Base case ICER
	programme (e.g., emollients, low to mid-potency TCS and rescue medication with higher potency TCS, oral corticosteroids or TCI)	• Time horizon: lifetime • Perspective: payer (NHS) • Cycle length: annual • Discounting: NR				
NICE TA681, Baricitinib(107) UK	• Baricitinib: 4 mg administered orally once a day in combination with TCS • Dupilumab: an initial dose of 600 mg (administered in two 300 mg injections consecutively in different injection sites), followed by 300 mg every other week administered as subcutaneous injection • BSC: emollients, low-to-mid potency TCS, phototherapy, psychological support, and rescue therapy including higher potency topical or oral corticosteroids or TCI	• Markov state transition model • Health states: induction, maintenance, non-response, death • Time horizon: lifetime (max 100 years) • Perspective: payer (NHS and PSS) • Cycle length: 4 weeks • Discounting: 3.5% per year for costs and benefits	Adult patients with moderate or severe AD	• Total costs: NR	• Incremental QALYs: NR	Manufacturer's submission: • ICER: £17,941 baricitinib vs. BSC) • ICER: £203,525 saved per QALY foregone for baricitinib vs. dupilumab (PAS applied for baricitinib only) ERG critique: • ICER: £64,710 baricitinib vs. BSC) • ICER: NR for baricitinib vs dupilumab ICERs from final guidance document: • Company: £27,037– • £28,396/QALY for baricitinib vs BSC dependent on waning assumptions.

Study, Country	Intervention/comparator	Summary of model	Patient population	Base case costs (currency, year)	Base case health outcomes	Base case ICER
						• ERG: £70,825 without QoL waning on BSC; £26,987 baricitinib vs. BSC with QoL waning on BSC • ICER: NR for baricitinib vs. dupilumab (was withing range NICE considers an acceptable use of NHS resources)

Abbreviations: AD, atopic dermatitis; BSA, body surface area; BSC, best supportive care; EASI, Eczema area and severity index; ERG, Evidence review group; GBP, British pound; ICER, incremental cost-effectiveness ratio; ICUR, Incremental cost-utility ratio; IGA, Investigators global assessment; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PSS, Personal Social Services; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; SOC, standard-of-care; STA, single technology appraisal; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

B.3.2 Economic analysis

Here we present a de-novo cost-effectiveness model comparing abrocitinib with dupilumab (adults and adolescents), and baricitinib (adults only) for patients with moderate to severe AD who had been previously exposed to systemic therapies.

As per Table 1 in Section B.1.1, consideration was given separately to adult combination, adolescent combination, adult monotherapy and adolescent monotherapy analyses, although the combination comparisons are deemed most relevant as this is how abrocitinib is expected to be used in practice.

The economic evaluations submitted in previous NICE appraisals for moderate to severe AD for dupilumab (TA534) and baricitinib (TA681) (Section B.3.1), as well as the committees' comments, were used to inform model structure, assumptions, and data sources (1-4).

B.3.2.1 Patient population

The economic model for abrocitinib incorporates clinical data from the JADE trial programme for abrocitinib from the generalisable and restricted patient populations. These abrocitinib populations, and how they have been compared to the population for which we have data for dupilumab and baricitinib within an NMA, are fully described in Section B.2.2.3 and Section B.2.9.

The generalisable population has been considered in the base case analysis with the restricted population explored as a scenario for adults. Although the restricted population represents more of a like-for-like comparison with available dupilumab and baricitinib data, the generalisable population is larger and has greater relevance to clinical practice. Further, outcomes between the generalisable and restricted populations are similar within JADE studies.

If generalisable and restricted population comparisons were not feasible due to lack of comparator data, the full trial populations were used although this was for a small number of analyses and is fully described in Section B.3.3.1.

In addition to using the data from the NMA within the model, we have also included a scenario where COMPARE trial data is used directly for combination comparisons with dupilumab.

Table 55: Clinical trial summaries

	COMPARE	TEEN	MONO-1	MONO-2
Reference	Adult combination	Adolescent combination	Adult and adolescents, monotherapy	
Mean weight (kg)	73.0	57.2	Adults: 77.7 Adolescents: 65.3	
Mean BSA (%)	45.6	45.5	Adults: 45.6 Adolescents: 45.5	
Mean age (years)	34.0	15.0	Adults: 37.4 Adolescents: 15.2	
Female %	51.1	49.1	Adults: 41.8 Adolescents: 46.4	
Population	Adults (≥18 years) with moderate/severe AD who have experienced inadequate response to treatment with topical medications, or who have required systemic therapies for control of their disease	Adolescents (≥12 and ≤18 years) with moderate/severe AD who have experienced inadequate response to treatment with topical medications, or who have required systemic therapies for control of their disease or who are candidates for systemic therapies	Adults and adolescents (≥12 years) with moderate/severe AD who have experienced inadequate response to treatment with topical medications, or for whom topical medications are medically inadvisable, or who have required systemic therapies for control of their disease	
N, total, FAS	837	287	387	391
N, subgroup (generalisable)†	161	36	Adults: 172 Adolescents: 23	
N, subgroup (restricted)‡	85	13	94	

	COMPARE	TEEN	MONO-1	MONO-2
Arms (n, generalisable)	Abrocitinib 100 mg (40)	Abrocitinib 100 mg (13)	Abrocitinib 100 mg adults (77) Abrocitinib 100 mg adolescents (10)	
	Abrocitinib 200 mg (42)	Abrocitinib 200 mg (10)	Abrocitinib 200 mg adults (63) Abrocitinib 200 mg adolescents (9)	
	Dupilumab 300 mg (55)	Placebo (13)	Placebo adults (35) Placebo adolescents (8)	
	Placebo (24)	-	-	

†Subgroup of patients who have received immunosuppressant therapies (Section B.2.2.3); ‡Subgroup of patients who have failed or did not tolerate ciclosporin (Section B.2.2.3).
Abbreviations: AD, atopic dermatitis; BSA, body surface area; FAS, full analysis set.

B.3.2.2 Intervention technology and comparators

Separate analyses were performed to model abrocitinib as a 100 mg or 200 mg dose. In a scenario, clinical opinion was used to inform the uptake of each dose in clinical practice, which was then used to weight the results of each analysis to produce an overall result for both doses. It has been assumed that [redacted] of patients would receive abrocitinib 200mg and [redacted] would receive abrocitinib 100mg.

Although efficacy data for patients moving from 200 mg to 100 mg doses of abrocitinib exists in REGIMEN (Section B.2.6.5), patients were not permitted to change dose of abrocitinib in the model, either “dosing-up” from 100 mg to 200 mg, or “dosing-down” from 200 mg to 100 mg. [redacted]

Abrocitinib was compared against all available second-line systemic therapies for patients with moderate to severe AD in the UK. These are dupilumab (adults and adolescents) and baricitinib (adults). The licensed dose of dupilumab (300 mg Q2W) was considered and only the 4 mg dose for baricitinib given the recognition from the NICE technical team that the impact on the ICER of not modelling the 2 mg dose in the baricitinib appraisal would likely be small given use is expected to be limited (2). Presented ICERs vs baricitinib are thus conservative given that a proportion of patients, albeit small would be treated with baricitinib 2mg which is has been shown to be less efficacious.

B.3.2.3 Model structure

The model is structured as a one-year decision-tree, followed by a three-state Markov model, and was developed in Microsoft Excel®. Costs and outcomes are measured over a lifetime time horizon, assuming a one-year cycle length. A scenario has been considered in which the time horizon for adolescents is limited to model only patients up to 18 years of age.

The perspective on costs is that of the National Health Service (NHS) England and personal social services (PSS), however PSS costs do not have a significant impact on results.

Atopic dermatitis is a complex and dynamic disease and patients experience natural variation in disease severity over time. Different model structures were considered including a state transition model with defined states depicting disease severity. This would allow patients to move more naturally between disease severity health states defined by IGA (for example clear, almost clear, mild, moderate and severe disease). However, building this model with the clinical data available would add a significant amount of uncertainty to the results. Primary endpoints were assessed at Week 12 or 16 and disease flares were not captured in the pivotal trial outcomes. However, as EQ-5D was captured in the JADE trials, the impact on utility of disease flares were captured in the utility analysis (Section B.3.4). The model structure used and described fully below captures the short-term treatment decisions made in clinical practice while also capturing the long-term chronic nature of AD for many patients.

This model approach has been accepted by NICE in previous TAs in AD (3, 4). The model is based primarily on the model used in TA534 for dupilumab, accounting for comments made by the ERG/NICE committee for both TAs. The model for TA681 omits the decision tree portion of the model and opts instead for a 4-week cycle length incorporating an induction period for starting treatment. However, this is primarily a difference in implementation of data and the model follows the same structure seen in TA534 (1, 2). A one-year cycle length has been selected for this model as this best aligns with the available data on resource use and discontinuation used in the Markov portion of the model.

B.3.2.3.1 *Year 1, decision tree*

The first year of the model was structured as a one-year decision tree reflecting the short-term treatment decisions made in UK clinical practice based on initial response to treatment. Patients enter the model and receive either abrocitinib or a comparator treatment before response is assessed.

The time point for response assessment in the model was selected to align with the time at which patients on dupilumab and baricitinib are currently assessed for response in clinical practice which is Week 16; clinical experts confirmed this was also an appropriate timepoint to assess response for abrocitinib. Patients are assessed for EASI-50 & DLQI ≥4 response in adults or EASI-50 & CDLQI ≥4 in adolescents in the base case, to align with the committees' preferred response measure for decision-making in previous appraisals (3, 4). Further detail on the time point at which response is assessed and additional exploratory measures of response used in the model is presented in Section B.3.3.1.

In the model, patients who are non-responders at Week 16 discontinue treatment and subsequently received BSC. Patients who achieve response continue to receive maintenance therapy. At Week 52, patients discontinue or continue treatment in the Markov phase of the model. Patients who continue treatment at Week 52 transition to the "maintenance therapy" state, while patients who discontinue treatment at Week 52 transition to the "BSC" health state.

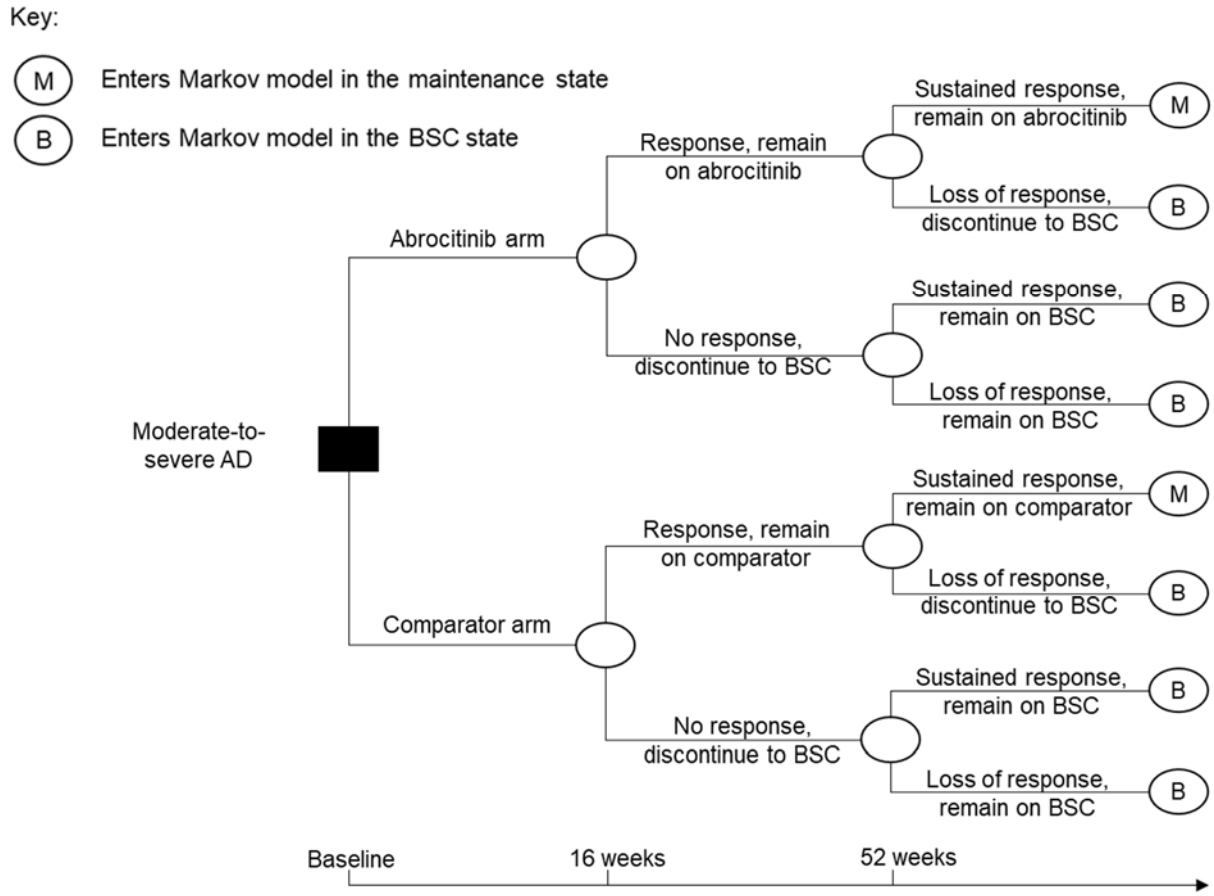
In TA534, transitions to BSC at Week 52 were informed by Week 52 response conditional on patients having responded at Week 16 (i.e., conditional response data) (1). In the baricitinib NICE appraisal, the ERG and committee's preference was to use discontinuation rates at Week 52 conditional on response at Week 16 (i.e., conditional discontinuation data) to model the transition to maintenance therapy at the end of the decision-tree (2, 4). Therefore, conditional discontinuation data are used to model treatment continuation at the end of the decision tree, although conditional response data are also considered in an alternative scenario.

In the decision-tree phase of the model, patients accrue costs and QALYs depending on whether they are a “responder” or “non-responder” to treatment; although patients who do not respond and discontinue treatment are assumed to have:

- the average utility for a non-responder on treatment and BSC utility regardless of response between Weeks 16 – 52 (Section B.3.4.5.2)
- costs associated with BSC (Section B.3.5).

It is assumed that the average time to response for “responders” is 8 weeks, i.e., halfway between treatment initiation and response assessment at Week 16. This approach is in line with the dupilumab model used for TA534 (1) although it is considered conservative for abrocitinib, as EQ-5D improvements are observed from Week 2 in JADE clinical trials (Section B.3.4.1). Further, abrocitinib 200mg has demonstrated significant improvements over dupilumab in outcomes related to itch relief and skin clearance at Week 2 (Section B.2.6.1). A decision-tree schematic is presented in Figure 32.

Figure 32: Decision-tree



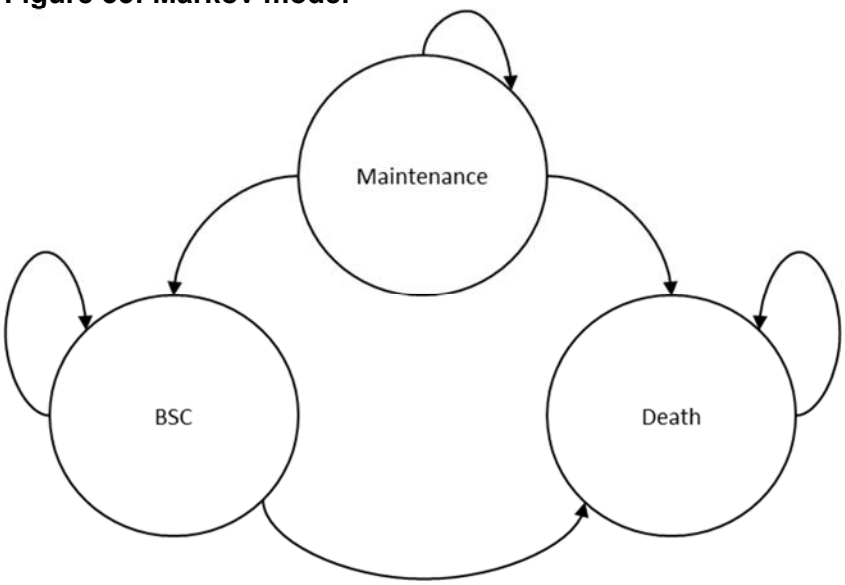
Abbreviations: AD, atopic dermatitis; BSC, best supportive care.

B.3.2.3.2 *Year 2 +, maintenance therapy*

Following the decision-tree phase of the model, and the assessment of response at Week 52, patients enter the Markov model and either transition to the “maintenance

therapy" health state or transitioned to the "BSC" health state. A model schematic is presented in Figure 33.

Figure 33: Markov model



Abbreviations: BSC, best supportive care.

Transitions to the BSC health state from the maintenance health state are modelled as a constant rate in each cycle and reflect conditional discontinuation data at Week 52, converted to annual probabilities. A half-cycle correction is applied.

Maintenance therapy responders accrue costs and QALYs associated with response to maintenance treatment. If response is lost and patients transition to BSC then the costs and QALYs associated with BSC are accrued as fully described below in Section B.3.2.3.2.1. The waning of treatment effect in the maintenance state and on BSC can be applied in the model through loss of utility benefit. Treatment waning assumptions for abrocitinib were as per TA534 and TA681 for dupilumab and baricitinib where the utility benefit is largely maintained (1, 2). Waning assumptions for BSC align with clinical advice that few patients would maintain any benefit achieved in the long term (Section B.3.4.5.4).

Patients can move into the death state at any time in the model.

B.3.2.3.2.1 Modelling BSC

If response is lost and patients transition to BSC the waxing and waning nature of AD is captured through the accrual of costs and QALYs equal to the weighted average of responders and non-responders in the base-case, aligning with the ERG and committees preferred assumption in the baricitinib appraisal in AD (TA681) (2, 4).

Clinical experts have confirmed that where response to BSC is lost overtime patients will be kept on treatment (given the absence of any alternatives) and that they may recapture response at varying time points throughout the model time-horizon (depending on the potency of steroids and other “BSC” treatments being given). However, they have commented that only a minority of patients on BSC are likely to retain disease control in the long-term.

Several waning assumptions have been considered for BSC as explored in Section B.3.4.5. In the base case utility waning assumptions are aligned to a scenario considered within TA534 based on data from CHRONOS, where a small percentage of the utility benefit remained from 5 years onwards. These assumptions were also applied in TA681 and are deemed the most plausible based on clinical discussions.

In a scenario, assumptions that model a utility benefit for BSC that is between the company and ERG assumptions from the baricitinib appraisal have been incorporated to align with the committee’s preferred position. In their updated base case post-technical engagement, the company had applied waning assumptions from CHRONOS as per the dupilumab appraisal whereas the ERG preferred no application of treatment waning and highlighted that applying waning separates utilities from costs within the model. The committee concluded that the proportion of patients on BSC losing the quality-of-life benefit over time was likely to be somewhere between the base cases of the company and ERG.

The model is flexible to test alternative assumptions relating to BSC utility in scenario analysis given the varying opinion on the most appropriate method from previous TAs (TA534 and TA681 (3, 4)).

- Modelling BSC patients separately by response both with and without waning (ICERs presented within the submission).

- Modelling patients on BSC using the average baseline utility value (model only scenario)

B.3.2.3.2.2 Treatment sequencing

According to clinical opinion, patients with AD may receive another line of systemic therapy upon discontinuing either abrocitinib, dupilumab or baricitinib, before receiving BSC. The assumption that patients transition to BSC after treatment is a simplification of the model in line with TA534 and TA681 given there is little clinical data to inform this.

Exploratory analysis which allowed for treatment sequencing has therefore been presented acknowledging comments from the NICE committee for baricitinib (TA681) that cost effectiveness analysis considering sequencing is relevant for decision-making (4). There is some uncertainty in the outputs of treatment sequencing modelling given the lack of clinical data on sequencing treatments so this analysis should be considered supportive. To limit the complexity of the modelling we have made assumptions about how treatments are most likely to be used in clinical practice based on clinical expert opinion. In clinical practice treatment decisions are very individualised and there is no “standard” sequence that is appropriate for all patients. The exploratory treatment sequencing analysis is presented in Section B.3.10.

Table 56 summarises the settings applied in the model.

Table 56: Model settings

	Previous appraisals		Current appraisal	
Factor	**TA534 (dupilumab) (1, 3)**	**TA681 (baricitinib) (2, 4)**	**Chosen values**	**Justification**
Time horizon	Lifetime (100 years)	Lifetime (100 years)	Lifetime (100 years) A scenario will be considered modelling adolescents up until age 18 only	AD is associated with a lifelong impact on costs and quality of life Consistent with previous models in AD
Perspective	NHS and Personal Social Services (PSS), a scenario was included with a broader societal perspective	NHS and PSS	NHS and PSS, a scenario was included with a broader societal perspective	An NHS and PSS perspective is consistent with NICE methods guidance. A broader societal perspective is considered as a scenario given that a NHS and PSS perspective alone undervalues the benefits of many technologies within society (Section B.3.5.8).
Model structure	One-year decision tree followed by Markov model with annual cycles, half-cycle correction applied	Markov state transition model with 4-week cycles, no half-cycle correction	One-year decision tree followed by Markov model with annual cycles, half-cycle correction applied	Able to capture the short-term treatment decisions in clinical practice and the long-term waxing and waning of AD Consistent with previous models in AD
Response criteria	EASI-50 & DLQI ≥4	EASI-50 & DLQI ≥4	EASI-50 & (C)DLQI ≥4	Clinical input found EASI-50 & DLQI ≥4 to be the most clinically relevant measure of response for adults and adolescents Consistent with previous models in AD
Discontinuation rate	Constant annual rate, conditional on response at Week 16	Constant annual rate, conditional on response at Week 16	Constant annual rate, conditional on response at Week 12/16	Consistent with previous models in AD
Source of utilities	Utility values from responders and non-responders were estimated from a mixed effects regression model. Utilities are adjusted for age multiplicatively.	EQ-5D-5L data from the JAIN clinical trials was mapped to the EQ-5D-3L using the van Hout et al. 2012 algorithm. Utility values for responders and non-responders were then assessed using a mixed effects	EQ-5D-5L data from adults in the JADE clinical trials was mapped to the EQ-5D-3L using the van Hout et al 2012 algorithm. EQ-5D-Y utility values in adolescents were assessed directly. Utility values for responders and	This approach is consistent with previous models in AD and the NICE reference case.

	Previous appraisals		Current appraisal	
Factor	**TA534 (dupilumab) (1, 3)**	**TA681 (baricitinib) (2, 4)**	**Chosen values**	**Justification**
		regression model. Utilities are adjusted for age multiplicatively. Dupilumab utility values were preferred by the ERG.	non-responders were then assessed using a mixed effects regression model. Utilities are adjusted for age multiplicatively.	
Costs included	Drug acquisition, administration and monitoring Disease management Adverse events	Drug acquisition, administration and monitoring Disease management Adverse events	Drug acquisition, administration and monitoring Disease management Adverse events	All costs expected to differ between the compared technologies included

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.3 Clinical parameters and variables

Clinical parameters which were included in the model include:

- Response rates
- Discontinuation and long-term response
- Disease flares
- Disease resolution
- Adverse events
- Mortality.

B.3.3.1 Response

In the model, response assessment determines which patients continue on maintenance therapy at Week 16. Response rates are derived from the NMA, which is fully described in Section B.2.9.

Outcomes were analysed in the NMA at the duration of the included trials: Week 16 for all baricitinib and dupilumab data and for the COMPARE trial for abrocitinib, and Week 12 for the MONO1/2 trial. Where comparisons incorporated 12-week data for abrocitinib and 16-week data for comparators this referred to as a 12/16-week comparison. Response data for TEEN applied in the model (but not used within the NMA) was also for Week 12.

Given abrocitinib has a fast onset of action, no notable differences in efficacy would be expected between Week 12 and 16, as was illustrated in COMPARE. The Week 12/16 comparison might be expected to bias against abrocitinib given that dupilumab shows relatively slower response in COMPARE and improvements in outcomes from Week 12 to Week 16.

In the base-case, response was assessed based on patients achieving EASI-50 & (C)DLQI ≥4 response. This response measure was used in the model to align with the approved response assessment for dupilumab and baricitinib (3, 4). Notably, clinician feedback suggested that although the composite of EASI-50 & (C)DLQI ≥4 is the most appropriate measure for decision making, higher thresholds of response (EASI 75 or EASI 90) which demonstrate more complete skin clearance are also

clinically important (Section B.1.3.5.2.2). Therefore, scenario analyses were conducted for combination analyses which measured response using each of the following definitions:

- EASI-75 (primary endpoint in pivotal studies)
- EASI-90

Other definitions of response were also considered, including EASI-50 alone, EASI-75 & (C)DLQI ≥4 and EASI-90 & (C)DLQI ≥4. EASI-50 alone was not deemed clinically relevant as it represents a lower threshold for response than is currently applied. EASI-75 & (C)DLQI ≥4 and EASI-90 & (C)DLQI ≥4 were excluded as comparisons were not feasible within the NMA given the lack of comparator data for dupilumab and baricitinib.

B.3.3.1.1 *Base case*

Response data used in the model base-case for EASI-50 & (C)DLQI ≥4 are presented in Table 57. These data are mostly from the NMA although this was not a feasible outcome for comparisons with dupilumab and baricitinib 4 mg across all analyses; various assumptions were made for modelling as described below.

The restricted population is explored as a scenario for adults given fewer assumptions have been made.

Data for other response endpoints is summarised in Appendix N.

Table 57: EASI-50 & (C)DLQI ≥4 response rates based on NMA data unless otherwise specified (base case)

	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC
	Generalisable population (base case)					Restricted population (scenario)				
Adults, combination therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescents, combination therapy	[redacted]	[redacted]	[redacted]	-	[redacted]	-	-	-	-	-
Adults, monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescents, monotherapy	[redacted]	[redacted]	[redacted]	-	[redacted]	-	-	-	-	-

Adult combination: NMA response data was applied for abrocitinib and dupilumab; the OR for baricitinib 4mg vs BSC for EASI-50 from the generalisable or restricted population comparisons in the NMA was applied to BSC data to generate an estimate of EASI 50 & DLQI ≥4 response for baricitinib 4mg.
Adolescent combination: Rates from the NMA for the adult combination comparison are assumed to hold for the adolescent combination comparison given no dupilumab combination data was identified for adolescents.
Adult monotherapy: NMA response data was applied for abrocitinib and dupilumab; the OR for baricitinib 4mg vs BSC for EASI-50 from the full population comparison in the NMA was applied to abrocitinib data to generate an estimate of EASI 50 & DLQI ≥4 response for baricitinib 4mg.
Adolescent monotherapy: Trial data was applied for abrocitinib; the OR for dupilumab vs BSC for EASI-50 from the full population comparison in the NMA was applied to BSC trial data for abrocitinib to generate an estimate of EASI 50 & DLQI ≥4 response for dupilumab.
Abbreviations: BSC, best supportive care; CDLQI, children's disease quality of life index; DLQI, disease quality of life index; EASI, Eczema Area Severity Index; NMA, network meta-analysis.

Adult combination

For EASI outcomes, only EASI-50/-75/-90 comparisons were feasible in the NMA for the adult combination comparison with baricitinib 4mg; generalisable, restricted and full trial comparisons were conducted. Response rates for EASI 50 & DLQI ≥4 for abrocitinib and dupilumab are based on the NMA. Baricitinib 4mg data for EASI 50 & DLQI ≥4 was generated by applying the OR for EASI-50 response for baricitinib vs BSC for the relevant population (generalisable or restricted) to EASI 50 & DLQI ≥4 NMA data for BSC.

Table 58: Baricitinib 4 mg EASI-50 odds ratios vs BSC for the adult combination analyses (base case)

	Baricitinib 4 mg EASI-50 response %	BSC EASI-50 response %	Odds ratio
Adult combination therapy, generalisable	[redacted]	[redacted]	[redacted]
Adult combination therapy, restricted	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index.

Adolescent combination

The NMA did not include an adolescent combination analysis because no combination data was identified for dupilumab in adolescents. For the adolescent combination comparison in the base-case the adult combination response rates from the NMA are assumed to hold for the adolescent population.

Adult monotherapy comparisons

For EASI outcomes, only EASI-50/-75/-90 full trial population comparisons were feasible in the NMA for the adult monotherapy comparison with baricitinib 4mg. Response rates for EASI 50 & DLQI ≥4 for abrocitinib and dupilumab are based on the NMA. Baricitinib 4mg data for EASI 50 & DLQI ≥4 was generated by applying the OR for EASI-50 response for baricitinib vs BSC in the full population to EASI 50 & DLQI ≥4 NMA data for BSC.

The ORs for baricitinib vs BSC are summarised in Table 59

Table 59: Baricitinib 4 mg EASI-50 odds ratios vs BSC for the adult monotherapy analyses (base case)

	Baricitinib 4 mg EASI-50 response %	BSC EASI-50 response %	Odds ratio
Adult monotherapy, full population	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index.

Adolescent monotherapy

For EASI outcomes, only EASI-50/-75/-90 full trial population comparisons were feasible in the NMA for the adolescent monotherapy analysis comparison with dupilumab. Response rates for EASI 50 & CDLQI ≥4 for abrocitinib have therefore been taken directly from the adolescent population in MONO-1/2. Dupilumab data for EASI 50 & CDLQI ≥4 was generated by applying the OR for EASI-50 response for dupilumab vs BSC in the full population to EASI 50 & CDLQI ≥4 trial data for BSC from MONO-1/2 (Table 60).

Table 60: Dupilumab odds ratios (adolescent monotherapy)

	Dupilumab response %	BSC response %	Odds ratio
EASI 50 adolescent monotherapy, full population	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.

B.3.3.1.2 *Trial data*

For the adult combination comparison, trial data from COMPARE in the generalisable population has been applied in a scenario for the comparison with dupilumab. These data are summarised in Table 61.

Table 61: EASI-50 & DLQI ≥4 response rates based on trial data (scenario)

	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC
Response rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.

An alternative scenario was considered for the adolescent combination comparison where response rates for abrocitinib and BSC in the full population of TEEN are used (given the small number of patients in the generalisable population); the EASI 50 & DLQI ≥4 OR for dupilumab vs BSC from the adult combination NMA is then applied

(Table 62) to generate response data for dupilumab. Data for this scenario is summarised in Table 63.

Table 62: Dupilumab odds ratios (adolescent combination therapy)

	Dupilumab response %	BSC response %	Odds ratio
EASI 50 & DLQI ≥4 adult combination therapy, generalisable population	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.

Table 63: EASI-50 & DLQI ≥4 response rates based on trial data (scenario)

	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC
Response rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index.

B.3.3.2 Discontinuation and long-term response

To align with the committee's preferred assumptions in TA681 for baricitinib,(4) the health state that a patient transitions to at the end of the decision-tree phase was modelled using conditional discontinuation data in the base case. This is the proportion of patients discontinuing treatment at Week 52 from those who achieved response at Week 12/16.

Conditional discontinuation data for abrocitinib was from EXTEND for patients responding to treatment at Week 12 for MONO-1/2 and Week 16 for COMPARE. Adult combination therapy data was assumed to apply for the adolescent combination analyses as the number of adolescent patients completing Week 52 in the EXTEND trial who were previously in TEEN was low. For the other parent studies, the large majority of patients had reached Week 48 in EXTEND ([redacted] for abrocitinib 200mg and [redacted] for abrocitinib 100mg for patients from COMPARE).

To align with previous submissions in AD, discontinuation data in the JADE trials were restricted to discontinuation by either lack of efficacy, adverse event or withdrawal by patient (1, 2). Death has been excluded as a reason for discontinuation, as this is already accounted for in the model.

Discontinuation rates are for the full trial population for abrocitinib as those for the generalisable population are unreliable given that the sample size for the subgroup of patients who have been exposed to a previous systemic therapy, achieved a response at Week 12/16 and entered EXTEND, is relatively small (n=[redacted] for abrocitinib 100 mg/200 mg from COMPARE). Further, as described in Section B.2.6.4, data from EXTEND is for patients who remained on the same dose of abrocitinib. For patients who entered EXTEND from MONO-1/2, only those who remained on monotherapy were considered.

Discontinuation rates for dupilumab and baricitinib are taken from TA534 and TA681 respectively (1, 2). For dupilumab, discontinuation rates for adults are assumed to hold for adolescents. Baricitinib 4 mg discontinuation rates were conservatively set equal to those presented by the ERG in TA681, rather than the higher discontinuation rates applied in the companies updated base-case.

Conditional discontinuation data were converted to annual probabilities to inform transitions to BSC at the end of each cycle in the Markov model from Year 2 onwards. No longer-term data on conditional discontinuation was identified for dupilumab and baricitinib. For abrocitinib, although EXTEND follows patients for up to 96 weeks, data beyond Week 52 is immature.

Discontinuation rates used in the model at Week 52 and Year 2 onwards are presented in Table 64. A scenario is also included which models long term response using conditional response as per TA534 as presented in Appendix O. These data were handled in a similar way to the conditional discontinuation data as described above.

Table 64: Conditional discontinuation data used in the model base-case

Population	Discontinuation week 16 – 52				Annual discontinuation in year 2+			
	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg
Adults, combination therapy	[redacted]	[redacted]	3.70%	[redacted]	[redacted]	[redacted]	5.30%	[redacted]
Adolescents, combination therapy	[redacted]	[redacted]	3.70%	-	[redacted]	[redacted]	5.30%	-
Adults, monotherapy	[redacted]	[redacted]	6.30%	[redacted]	[redacted]	[redacted]	8.97%	[redacted]
Adolescents, monotherapy	[redacted]	[redacted]	6.30%	-	[redacted]	[redacted]	8.97%	-

B.3.3.3 Disease flares

The cost of treating a disease flare was also captured within the model. Periods of acute worsening (exacerbation of signs and symptoms, or flares with intense erythema with oozing, and crusting) occur frequently in patients with moderate to severe AD (108). A study by Thomas et al. demonstrated that 'use of topical anti-inflammatory medications' and periods of treatment escalation were good proxies for estimating disease flares in AD patients (109). Rates of flares applied in the model were based on those presented in TA534 calculated from rescue therapy use (1).

The annual rate of flares for abrocitinib 200 mg was assumed to be equal to dupilumab (0.18) as data from REGIMEN showed that 81.1% of patients did not experience a protocol-defined flare during the 40-week treatment period. The rate of flare for abrocitinib 100 mg was assumed to be 0.426 as 57.4% of patients did not experience a flare in REGIMEN and baricitinib was assumed to be equivalent to abrocitinib 100 mg. This is considered conservative given [redacted] Further, the assumption applied by the ERG in TA681 was that the baricitinib flare rate should be equivalent to BSC. The flare rate for BSC (0.78) has been taken from TA534 (1).

Further information on REGIMEN data can be found in Section B.2.6.5 and the flare rates used in the model are presented in Table 65.

Table 65: Annual rate of flares

Treatment	Rate of flare	Source
Abrocitinib 200 mg	0.18	TA534 (1)
Abrocitinib 100 mg	0.43	REGIMEN
Dupilumab	0.18	TA534 (1)
Baricitinib	0.43	Assumed equal to abrocitinib 100 mg
BSC	0.78	TA534 (1)

B.3.3.4 Adverse events

The adverse events considered in the analysis were treatment emergent adverse events occurring in greater than 5% of patients in either arm in the full trial populations in COMPARE, TEEN and pooled MONO trials. In addition, any adverse events that did not occur in greater than 5% of patients in the JADE trials but were

included in the analysis in TA534 for dupilumab and TA681 for baricitinib were also included in the model (1, 2).

Adverse events were modelled as a yearly probability as per TA681 (2). Adverse event probabilities from Week 12 or Week 16 trial data were converted into annual rates, which were then used to calculate annual probabilities to be used in the model. Injection site reaction was also modelled in this way, rather than as a one-off cost, as per the committee's preferred assumption in TA534 that injection site reactions could occur more than once during a patient's treatment (3).

Adverse event data for abrocitinib and BSC given in combination with background medicated topical therapies were taken from COMPARE and TEEN for adults and adolescents, respectively. Data included in the model for abrocitinib and BSC for the monotherapy comparisons are taken from MONO-1 and -2 for adults. For adolescent monotherapy, adverse event data were assumed to be equivalent to the adolescent combination therapy population as sub-group membership was low (n=23) for the adolescent patients in MONO1/2, and no marked differences were seen between patients who received combination therapy compared with those who received monotherapy.

COMPARE data were used to inform the dupilumab adult combination therapy arm, while dupilumab adult monotherapy data were obtained from TA534 (1). As no AE data were available for dupilumab in adolescents, the AE rates for dupilumab in adults were assumed to be the same for adolescents.

In TA534, conjunctivitis rates were modelled separately for allergic and infectious conjunctivitis (1), however data from the JADE trials was not available on the rates of different types of conjunctivitis. Therefore, the rate of conjunctivitis modelled for abrocitinib and BSC was assumed to be infectious conjunctivitis, and conjunctivitis was split for dupilumab.

Adverse event data were redacted in the baricitinib submission; therefore AE rates were taken from the safety publication by Bieber et al (110).

The risk of adverse events is assumed to be constant over the modelled time horizon which is a simplifying assumption given the lack of longer-term data.

Table 66: Adverse event rates per person per year, combination therapy (adults and adolescents)

Adverse event	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg†	BSC
Adults					
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]	-	[redacted]
Infectious conjunctivitis	0.04	0.03	0.26	0.05	0.07
Headache	0.20	0.13	0.16	0.11	0.14
Injection site reaction	[redacted]	[redacted]	[redacted]	0.00	[redacted]
Nasopharyngitis	0.20	0.27	0.28	0.34	0.21
Nausea	0.32	0.13	0.09	0.02	0.05
Upper respiratory tract infection	0.12	0.15	0.12	0.08	0.14
Folliculitis	[redacted]	[redacted]	[redacted]	0.03	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	0.00	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	0.07	[redacted]
Adolescents					
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]	-	[redacted]
Infectious conjunctivitis	[redacted]	[redacted]	0.26	0.00	[redacted]
Headache	[redacted]	[redacted]	0.16	0.00	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]	0.00	[redacted]
Nasopharyngitis	[redacted]	[redacted]	0.28	0.00	[redacted]
Nausea	[redacted]	[redacted]	0.09	0.00	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	0.12	0.00	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	0.00	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	0.00	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	0.00	[redacted]

†Only applicable to adult populations.
Abbreviations: BSC, best supportive care.

Table 67: Adverse event rates per person per year, monotherapy (adults)

Adverse event	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC
Allergic conjunctivitis	[redacted]	[redacted]	0.11	-	[redacted]
Infectious conjunctivitis	[redacted]	[redacted]	0.16	0.05	[redacted]
Headache	[redacted]	[redacted]	0.00	0.11	[redacted]
Injection site reaction	[redacted]	[redacted]	0.09	0.00	[redacted]

Adverse event	Abrocitinib 200 mg	Abrocitinib 100 mg	Dupilumab	Baricitinib 4 mg	BSC
Nasopharyngitis	[redacted]	[redacted]	0.00	0.34	[redacted]
Nausea	[redacted]	[redacted]	0.00	0.02	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	0.00	0.08	[redacted]
Folliculitis	[redacted]	[redacted]	0.00	0.03	[redacted]
Pharyngitis	[redacted]	[redacted]	0.00	0.00	[redacted]
Oral herpes	[redacted]	[redacted]	0.14	0.07	[redacted]

Abbreviations: BSC, best supportive care.

B.3.3.5 Mortality

All-cause mortality was estimated using National life Tables for England and Wales with no adjustment made for AD-specific mortality (111).

Although patients with moderate to severe AD report higher levels of suicide ideation and depression, there is limited evidence of a direct link between AD and increased mortality (113-115). Through better management of AD, abrocitinib may result in lower rates of depression although the conservative approach will be made to apply no specific adjustment to mortality.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

The JADE clinical trial programme collected HRQL data via the EQ-5D-5L and EQ-5D-Y instruments.

EQ-5D-5L was collected at:

- Weeks 0, 2, 4, 8, 12 and 16 in MONO-1 and -2
- Weeks 0, 12, 16, 20 and 24 in COMPARE

EQ-5D-Y was collected at:

- Weeks 0, 2, 4, 8, 12 and 16 in TEEN.

Consistent with the reference case, EQ-5D (/Y) data from the JADE trial programme has been used to generate utilities.

Figure 34 presents the EQ-5D scores over time for COMPARE, TEEN and MONO-1/2 combined, mapped to the EQ-5D-3L (Section B.3.4.2). All three analyses show a similar pattern, with larger changes from baseline in EQ-5D for abrocitinib and dupilumab than are observed in the placebo arm. The figures from MONO-1/2 and TEEN show that the EQ-5D response is rapid, with most of the benefit occurring by Week 2. This pattern is not seen in the COMPARE data; however, this is due to the collection schedule given EQ-5D was not collected between baseline and Week 12. These findings are consistent with those observed using CDLQI/DLQI, a dermatology-specific questionnaire (Section B.2.3.2).

Figure 34: EQ-5D scores over time in JADE clinical trials

B.3.4.2 Mapping

While a UK value set does exist for the EQ-5D-5L, NICE's position statement published in October 2019 states that the 3L value set should be used for reference-case analyses. Therefore EQ-5D-5L for the JADE clinical trials has been mapped to the EQ-5D-3L using the algorithm published by van Hout et al. (115) and utility values generated using the UK valuation set by Dolan et al. (116) . There is no mapping algorithm for EQ-5D-Y and the questionnaire uses three levels, thus utility

values for the EQ-5D-Y have been generated directly using the Dolan et al. valuation set (116).

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify health state utility value (HSUV) studies relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix H.

B.3.4.3.1 *Description of identified studies*

The SLR identified 39 studies that met the pre-defined inclusion criteria. Of these, two of the studies met the NICE reference case in terms of requirements for HSUV evidence, i.e., health states should be described by patients and valued using UK societal values. The two published studies reported utility values derived using either the standard gamble (117) or time to trade off methods (118). Additionally, three HTA appraisals were included, which reported relevant EQ-5D data for health states in comparator evaluations (dupilumab and baricitinib) (107, 108, 120).

A PRISMA diagram showing the overall flow of studies across the review is shown in Appendix H, together with a complete list of studies excluded after the full-text review stage.

Of the identified papers meeting the reference case, only the previous submissions for dupilumab and baricitinib included relevant health state utility values for the economic analysis (107, 108, 120). These studies do not report utility values for adolescents as the submissions solely considered adults and no studies were identified reporting utility values for abrocitinib, thus use of JADE trial data was preferred in the base-case.

A scenario was also considered where utility values from TA534 were utilised, where the dupilumab responder utility value is also applied for abrocitinib and baricitinib responders (1). Baricitinib utility data was criticised as the utility data for non-responders was assumed to be equal to the trial baseline, hence this has not been considered in a scenario.

B.3.4.4 Adverse reactions

Adverse event disutilities were not included in the model. EQ-5D was collected at regular time points in the JADE trials and therefore, any disutility attributable to adverse events would be implicitly captured in these values. The inclusion of AE disutilities alongside this method would have resulted in double-counting. This approach is in line with the dupilumab (TA534) and baricitinib (TA681) submissions(1, 2).

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

B.3.4.5.1 *Regression modelling*

Mixed model repeated measures (MMRM) were fitted to patient-level trial data to generate health state utility values. The models were fit for the full trial population, to make best use of all available data although predicted values for use in the model have been generated using the characteristics of the generalisable population.

The parameters used within the models include age (for all trials except TEEN), baseline EQ-5D (/Y), parameters for response (EASI 50, (C)DLQI ≥4) and treatment arm (abrocitinib 100 mg, abrocitinib 200 mg and for COMPARE dupilumab).

Baseline EQ-5D (/Y) as well as EASI-50 and (C)DLQI ≥4 response measures were incorporated into the models regardless of significance. Age was also considered in COMPARE and MONO 1 and 2 analyses regardless of significance, but not in TEEN analyses, as the spread across age groups was more limited.

The following additional variables were also tested and a backward selection process was used with a significance level of 0.1 for determining whether or not to retain a variable.

- Interaction between EASI-50 response and (C)DLQI ≥4
- Gender
- Baseline severity of itch
- Baseline EASI

- Baseline IGA
- Prior use of immunosuppressants
- Treatment arm.

Only parameters relating to treatment arm were retained in the models for MONO-1/2 or COMPARE as being significant. Baseline IGA (severe) as well as parameters relating to treatment arm were found to be significant in the analysis for TEEN and incorporated in the model for the adolescent combination analyses. Prior use of immunosuppressants was not a significant factor in any of the models, however these patients do have lower EQ-5D at baseline and this has been included in all models.

Table 68: MONO-1 & -2 EQ-5D analysis

	Coefficient	Standard error	LCI	UCI
Age				
Baseline EQ-5D				
EASI-50				
(C)DLQI ≥4				
Abrocitinib 100 mg				
Abrocitinib 200 mg				
Constant				

Abbreviations: DLQI, disease quality of life index; EASI-50, 50% reduction in eczema area and severity index; LCI, lower confidence interval; UCI, upper confidence interval.

Table 69: COMPARE EQ-5D analysis

	Coefficient	Standard error	LCI	UCI
Age				
Baseline EQ-5D				
EASI-50				
DLQI ≥4				
Abrocitinib 100 mg				
Abrocitinib 200 mg				
Dupilumab				
Constant				

Abbreviations: DLQI, disease quality of life index; EASI-50, 50% reduction in eczema area and severity index; LCI, lower confidence interval; UCI, upper confidence interval.

Table 70: TEEN EQ-5D analysis

	Coefficient	Standard error	LCI	UCI
Baseline EQ-5D				
Baseline IGA severe				
EASI-50				
CDLQI ≥4				
Abrocitinib 100 mg				
Abrocitinib 200 mg				
Constant				

Abbreviations: DLQI, disease quality of life index; EASI-50, 50% reduction in eczema area and severity index; LCI, lower confidence interval; UCI, upper confidence interval.

Utility values were separated into responders and non-responders for each treatment in the model where response is defined as EASI-50 & (C)DLQI ≥4 in the base case. All models show a significant improvement in utility scores for EASI-50 & (C)DLQI ≥4 responders, though no interaction term was included given that it was not significant with EASI-50 and (C)DLQI ≥4 already independently in the model. In all cases, the benefit associated with a (C)DLQI ≥4 was larger than the benefit associated with EASI-50 response. The utility benefit for EASI-50 and DLQI ≥4 response (equal to the sum of the individual coefficients) was largest in the TEEN analysis, where response is associated with a [redacted] increase in utility, compared to [redacted] in the MONO-1/2 analysis and [redacted] in the COMPARE analysis. A scenario using a single coefficient for EASI-50 & (C)DLQI ≥4 response has been included.

[redacted]

Utility scores are adjusted by response measure in scenarios using EASI-75 and EASI-90 response (Appendix N). [redacted].

Table 71 presents the results of an analysis of the EQ-5D data from COMPARE, including disaggregated, mutually exclusive EASI response categories (i.e., 50–74%, 75–89%, or ≥90% reduction in EASI score). This analysis shows that higher levels of EASI response are associated with greater improvements in HRQL.

Table 71: COMPARE EQ-5D analysis including EASI-75 and EASI-90 response

	Coefficient	Standard error	LCI	UCI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]
DLQI ≥4	[redacted]	[redacted]	[redacted]	[redacted]
EASI-50 to -74	[redacted]	[redacted]	[redacted]	[redacted]
EASI-75 to -89	[redacted]	[redacted]	[redacted]	[redacted]
EASI-90	[redacted]	[redacted]	[redacted]	[redacted]

Abrocitinib 100 mg		[redacted]			[redacted]			[redacted]			[redacted]	
Abrocitinib 200 mg		[redacted]			[redacted]			[redacted]			[redacted]	
Dupilumab		[redacted]			[redacted]			[redacted]			[redacted]	
Constant		[redacted]			[redacted]			[redacted]			[redacted]	

Abbreviations: DLQI, disease quality of life index; EASI0, Eczema Area and Severity Index; LCI, lower confidence; UCI, upper confidence interval.

B.3.4.5.2 *Implementation of utility data within the model*

Utility values are applied in the model as per Table 72, aligning with the committee's preferred assumptions in TA534 (3).

Table 72: Application of utility values in the model

Time	Abrocitinib/comparator		BSC health state†
0 – 8 weeks	Baseline utility regardless of treatment or response		NA
8 –16 weeks	Utility of all patients on abrocitinib/comparator at Week 16 regardless of response		NA
16-week response	*Responder*	*Non-responder*	
16 – 52 weeks	Utility from abrocitinib/comparator responders at Week 16	Average utility of abrocitinib/comparator non-responders and BSC regardless of response at Week 16	Weighted average utility of BSC responders and non-responders
52-week response	*Responder*	*Non-responder*	
Year 2+	Utility from abrocitinib/comparator responders at week 16	Average utility of all BSC patients at Week 16 regardless of response	Weighted average utility of BSC responders and non-responders

†Patients who are being treated with BSC having previously received an initial treatment strategy such as abrocitinib/dupilumab/baricitinib. Abbreviations: BSC, best supportive care; NA, not applicable

In the model, response was assumed to occur at the halfway point from baseline until Week 16 (i.e., 8 weeks) hence the utility weights are tailored for 0–8 and 8–16 weeks. From 0–8 weeks, all patients in the model have baseline utility weights from all patients regardless of treatment or response. From 8–16 weeks, patients receive utility weights specific to their treatment regardless of response. Given the schedule for utility data collection from COMPARE, utility data could not be generated at an earlier timepoint than Week 12 or 16, however the assumptions around utility benefit at 0–8 and 8–16 weeks are deemed conservative given the rapidity of response associated with abrocitinib 200mg vs dupilumab as described in Section B.2.6.

From 16–52 weeks, patients who achieved an EASI-50 & DLQI ≥4 response at Week 16 were assigned the utility weight for being a responder on treatment. Patients who

did not maintain response on maintenance therapy received the mean utility weight of abrocitinib/comparator and BSC. This is as per the preferred assumptions from the ERG and committee in the appraisal for dupilumab TA534 (1, 3). Including the utility of abrocitinib/comparator non-responders was deemed appropriate given that the utility for BSC after active treatment may not be comparable to utility associated with having BSC from the outset in the model.

From Week 52 onwards, patients who continued to respond to maintenance therapy received the utility weight of responders. Non-responders moving to the BSC health state are assigned the average utility of all BSC patients to reflect the waxing and waning nature of AD (see Section B.3.2.3.2.1)

B.3.4.5.3 *Utility data*

The utility values for the base-case model are summarised in Table 73, Table 74, Table 75 and Table 76. In the adolescent combination and monotherapy analyses no coefficient is available for dupilumab given this was not a treatment within TEEN and MONO-1/2 trials. In these analyses the utility benefit for dupilumab has been set to the same proportional benefit as was seen in the COMPARE analysis vs abrocitinib 200mg. Thus, in the adolescent combination and monotherapy analyses dupilumab is associated with [redacted] ([redacted] [Table 69]) of the benefit seen with abrocitinib 200 mg. [redacted]

Table 73: Week 16 utility values: adult combination analyses (COMPARE)

Treatment	Response†	From 0 to 8 weeks	From 8 to 16 weeks	From 16-52 weeks	Markov model
Abrocitinib 200 mg	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Abrocitinib 100 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Dupilumab	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Baricitinib 4 mg	Responder		[redacted]	[redacted]	[redacted]

Treatment	Response†	From 0 to 8 weeks	From 8 to 16 weeks	From 16-52 weeks	Markov model
	Non-responder			[redacted]	[redacted]
BSC	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]

†Response is defined as EASI-50 & DLQI ≥4. Non responder values also inform utility waning within the model. Abbreviations: BSC, best supportive care.

Table 74: Week 16 utility values: adolescent combination analyses (TEEN)

Treatment	Response†	From 0 to 8 weeks	From 8 to 16 weeks	From 16-52 weeks	Markov model
Abrocitinib 200 mg	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Abrocitinib 100 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Dupilumab	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Baricitinib 4 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
BSC	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]

†Response is defined as EASI-50 & CDLQI ≥4. Non responder values also inform utility waning within the model. Abbreviations: BSC, best supportive care.

Table 75: Week 16 utility values: adult monotherapy analyses (MONO-1/2)

Treatment	Response†	From 0 to 8 weeks	From 8 to 16 weeks	From 16-52 weeks	Markov model
Abrocitinib 200 mg	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Abrocitinib 100 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Dupilumab	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Baricitinib 4 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
BSC	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]

†Response is defined as EASI-50 & DLQI ≥4. Non responder values also inform utility waning within the model. Abbreviations: BSC, best supportive care.

Table 76: Week 16 utility values: adolescent monotherapy analyses (MONO-1/2)

Treatment	Response†	From 0 to 8 weeks	From 8 to 16 weeks	From 16-52 weeks	Markov model
Abrocitinib 200 mg	Responder	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Abrocitinib 100 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
Dupilumab	Responder		[redacted]	[redacted]	[redacted]

	Non-responder			[redacted]	[redacted]
Baricitinib 4 mg	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]
BSC	Responder		[redacted]	[redacted]	[redacted]
	Non-responder			[redacted]	[redacted]

†Response is defined as EASI-50 & CDLQI ≥4. Non responder values also inform utility waning within the model. Abbreviations: BSC, best supportive care.

The utility values from the dupilumab appraisal (TA534) for adults have been summarised in Table 77 and are applied in a scenario analysis for both adults and adolescents (1).

Table 77: Utility values used in the dupilumab model

Patient population (baseline utility)	Parameter	Dupilumab utility	BSC utility
Combination treatment (CAFÉ and CHRONOS-like) (0.66)	All patients week 16	0.891	0.797
	Week 16 responder	0.898	-
Monotherapy (SOLO-like) (0.55)	All patients week 16	0.817	0.699
	Week 16 responder	0.845	-

Abbreviations: BSC, best supportive care.

Baseline utility values were adjusted for age using general population values. Using the multiplicative method for age adjustment as per NICE DSU guidance (120), the age coefficient was replaced by a general population age adjustment using the general population utility values published by Ara and Brazier (121).

B.3.4.5.4 *Waning of utility benefit*

To estimate the long-term utility benefit associated with treatment beyond the first year of the model, a probability of sustained response informed from TA534, TA681 and clinical opinion was applied in the Markov phase of the model to represent the waning of treatment benefit over time (1, 2).

The probability of sustained response for patients being treated with abrocitinib was set as equal to dupilumab in TA534 and baricitinib in TA681 where the utility benefit is largely maintained (Table 70) (1, 2). Clinical expert discussion confirmed this was appropriate in the absence of any specific data.

For BSC, scenario 2 in Table 78 was used in the base case to align with clinical advice to the company that utility benefit on BSC would wane quickly overtime. This

scenario represents one of the preferred scenarios from the dupilumab appraisal based on long-term CHRONOS data.

Additional scenarios were explored for BSC waning.

- Scenario 1 is additional scenario from the dupilumab appraisal based on CHRONOS that was preferred by the committee

- Scenario 3 reflects assumptions that are between the company and ERG base cases in the baricitinib appraisal. As described in Section B.3.2.3.2.1, in this appraisal in the revised base case the company applied waning assumptions from CHRONOS as per the dupilumab appraisal whereas the ERG preferred no application of treatment waning (2). The committee commented that the true value was likely somewhere between the company and ERG assumptions. Scenario 3 matches the base case (scenario 2), however there is assumed to be no further waning beyond year 3.

Table 78: Sustained utility benefit in the Markov model phase

Year	Abrocitinib, dupilumab and baricitinib	BSC – scenario 1	BSC – scenario 2	BSC – scenario 3
2	98%	43%	18%	18%
3	95%	18%	10%	10%
4	93%	8%	6%	10%
5	92%	3%	4%	10%

Abbreviations: BSC, best supportive care.

B.3.4.5.5 *Carer HRQL*

The NICE reference case states that the perspective on outcomes should encompass all direct health effects, whether for patients or, when relevant, carers (122). AD is known to have a substantial impact on families and carers, and therefore a disutility for carers was included in scenario analyses (123). There is limited data on disutility for carers in AD, however a recent review of the literature identified disutilities ranging from −0.04 to −0.14 in a variety of chronic conditions including AD (124). In TA534, carer utility benefits of 0.01 – 0.1 were tested in scenario analysis (1). The abrocitinib model applies carer disutility to non-responders in the base-case for adolescents, assuming a disutility of 0.05. More information on the humanistic burden of AD is presented in Section B.1.3.5.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify cost and resource use data relevant to the decision problem from the published literature as summarised in Appendix I. In total 58 studies were identified that met the pre-defined inclusion criteria. Of these, six studies include data from UK patients, one full text publication, one conference abstract and four HTA appraisals: two conducted by NICE (for dupilumab and baricitinib) and two by the SMC (for dupilumab and tacrolimus). The inputs and approach for modelling costs and healthcare resource use from TA534 and TA681 was largely followed, as described in the following sections(3, 4).

B.3.5.1 Intervention and comparators' costs

Drug acquisition costs for dupilumab and baricitinib were obtained from the British National Formulary (BNF) (125, 126). Drug acquisition costs are presented in Table 79. For dupilumab, adults as well as adolescents weighing over 60kg receive a loading dose of 600 mg followed by 300 mg Q2W; adolescents weighing under 60 kg receive a loading dose of 400 mg followed by a dose of 200 mg Q2W. Baricitinib patients receive a dose of 4 mg per day.

Table 79: Drug acquisition costs (List price)

Treatment	Dose	Cost per pack	Pack size	Dose per unit	Cost per dose
Abrocitinib	100 mg	[redacted]	28	100 mg	[redacted]
Abrocitinib	200 mg	[redacted]	28	200 mg	[redacted]
Dupilumab†	300 mg	£1264.89	2	300 mg	£632.45
Dupilumab	200 mg	£1264.89	2	200 mg	£632.45
Baricitinib	4 mg	£805.56	28	4 mg	£28.77

†Adults and adolescents weighing > 60kg: 300mg; adolescents weighing < 60kg: 200mg

A patient-access scheme has been submitted for abrocitinib, as summarised in Table 80. Confidential patient access schemes are also in place for dupilumab and baricitinib.

Table 80: Abrocitinib PAS cost

Treatment	Dose	Cost per pack	Pack size	Dose per unit	Cost per dose
Abrocitinib	100 mg	[redacted]	28	100 mg	[redacted]

Treatment	Dose	Cost per pack	Pack size	Dose per unit	Cost per dose
Abrocitinib	200 mg	[redacted]	28	200 mg	[redacted]

Abbreviations: PAS, patient access scheme.

B.3.5.2 Background medicated therapies

In the combination therapy analysis, the costs of background medicated therapies were also included for patients being treated with abrocitinib, dupilumab or baricitinib. The costs of emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs) were applied. Since the publication of TA534, there has been a significant decrease in the use of bathing products in routine clinical practice following the results of the BATHE randomised controlled trial (62). As per the ERG's preferred assumption in the baricitinib NICE appraisal, bathing products were not included in the model. Clinical opinion validated the most used treatments and the percentage of patients who would use them.

Emollients

The same method for identifying the most commonly used emollients from NHS prescribing data that was used in TA534 and TA681 was applied (1, 2). However, the most recent data from 2018 (127) has been used as summarised in Table 81. In TA534, clinical opinion was that 500g of emollients is a plausible amount per week for patients unresponsive to treatment and that there would be between a 50% to 80% reduction in emollients use in responders (1). In the base-case, the conservative assumption of a 50% reduction in emollient use was used, assuming 1g of product is equivalent to 1ml as per TA534 and TA681 (1, 2). There are some marked differences in the proportion of each emollient prescribed and so a weighted average has been taken to calculate the total costs per year for a non-responder and responder.

Table 81: Emollients use by response status

Drug	Proportion prescribed	Pack size	Cost per pack†	Number of packs per week: non-responder	Cost per year: non responder	Cost per year: responder
Dermol 500 lotion	25%	500ml	£6.04	1	£315.16	£157.58
Doublebase gel	19%	1000g	£10.98	0.5	£286.46	£143.23

Drug	Proportion prescribed	Pack size	Cost per pack†	Number of packs per week: non-responder	Cost per year: non responder	Cost per year: responder
Aveeno cream	16%	500ml	£6.47	1	£337.60	£168.80
Diprobase ointment	14%	500g	£5.99	1	£312.55	£156.27
E45 cream	12%	500g	£5.99	1	£312.55	£156.27
Dermol cream	8%	500g	£6.63	1	£345.94	£172.97
Oilatum cream	4%	500ml	£5.28	0.5	£137.75	£68.88
White soft paraffin 50%/ liquid paraffin 50% ointment	3%	500g	£2.01	1	£104.74	£52.73
Total cost					£301.18	£150.59

†Prices as per the BNF and eMIT where available.

TCS

Mometasone 0.1% ointment was modelled as the most frequently prescribed TCS to align with TA534 and TA681 (Table 82) (1, 2). The number of grams used per week is calculated based on the median BSA involvement from all treatment arms at baseline in the COMPARE study [redacted] and the TEEN study [redacted]. The BNF recommend that 500 mg of product from a tube with a standard 5 mm diameter nozzle is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers) (128). One hand-print was calculated to be 0.87% of the area of an adult (129). For simplicity, the same assumptions were assumed to be apply for adolescents. Assuming a twice daily application, non-responding patients would require 183.03g per week for adults and 182.63g per week for adolescents.

In TA534 for dupilumab, a 49% reduction in cost of TCS was applied to responding patients to reflect the 49% drop in the observed TCS dose in the CAFÉ trial (1). The same assumption was applied in the abrocitinib model. According to clinical opinion provided in TA534, a 49% reduction was a conservative assumption as most patients do not wish to be on TCS if they do not need to through fear of the side-effects.

Table 82: TCS costs

				Non-responder		Responder (49% reduction)	
TCS	**Grams per tube**	**Cost per tube**	**Cost per gram**	**Grams per week**	**Cost per year**	**Grams per week**	**Cost per year**
Adults							
Mometasone 0.1% ointment	100	£2.58	£0.03	183.03	£246.41	93.34	£125.67
Adolescents							
Mometasone 0.1% ointment	100	£2.58	£0.03	182.63	£245.87	93.14	£125.40

†Prices as per eMIT (130). Abbreviations: TCS, topical corticosteroids.

TCI

Clinical opinion in TA534 suggested that TCIs were more appropriate for facial use than TCS, and that protopic 0.1% ointment is the most commonly used TCI in clinical practice (1). As per TA534, protopic 0.1% ointment is assumed to apply thinly twice weekly with an interval of 2–3 days between applications (i.e., assumed 2 applications per week) (131). To align with TA534, an estimate of 1.75 g per week for adult non-responders was applied and this was assumed to hold for adolescents (Table 83). It was assumed that upon treatment response, TCI use was discontinued.

Table 83: TCI costs

				Non-responder		Responder	
TCI	**Grams per tube**	**Cost per tube**	**Cost per gram**	**Grams per week**	**Cost per year**	**Grams per week**	**Cost per year**
Adults							
Protopic 0.1% ointment, tacrolimus	60	£47.28	£0.79	1.75	£71.95	0	£0
Adolescents							
Protopic 0.1% ointment, tacrolimus	60	£47.28	£0.79	1.75	£71.95	0	£0

†Prices as per the BNF (132) Abbreviations: TCI, topical calcineurin inhibitor.

B.3.5.3 BSC costs

BSC was costed based on the calculations described previously for background medicated therapies for emollients, TCSs and TCIs. Other components of best practice for treating patients are captured within healthcare resource use estimates:

for example, the cost of bandages within day-case costs as well as psychological support and phototherapy. Education was not included in the model as there is no reliable data. This was acceptable to the NICE committee in TA534 and TA681 (3, 4).

B.3.5.4 Rescue treatment for disease flares

The cost of treating a disease flare is also applied within the model according to the likelihood of a patient having a flare dependent on the treatment they are receiving. A disease flare was costed as the proportion of patients receiving potent TCS, very potent TCS, systemic steroids and TCIs. The most commonly used therapies in clinical practice and associated costs are summarised in Table 84. These are as per TA534 for dupilumab and TA681, except for the dose of TCIs (1, 2). Previously this was assumed to be applied twice weekly, however the SmPC states twice daily application for flare management (131). It was assumed that maximum treatment for a flare was 4 weeks as per previous appraisals.

Table 84: Disease flare treatments, adults and adolescents

Resource	Product	Indication	Grams per tube	Cost per tube	Cost per gram	Grams per week	Cost per week	Cost for flare
Potent TCS	Betamethasone valerate cream	Apply 1–2 times a day, to be applied thinly (to be conservative have assumed twice daily)	100	£2.71	£0.03	25	£0.68	£2.71
Potent TCS	Cutivate 0.05% cream	Apply 1–2 times a day, to be applied thinly (to be conservative have assumed twice daily)	30	£4.24	£0.14	25	£3.53	£14.13
Very potent TCS	Eumovate 0.05% ointment	Max 50g per week up to 4 weeks	100	£5.44	£0.05	25	£1.36	£5.44
Very potent TCS	Dermovate 0.05% cream	Max 50g per week up to 4 weeks	100	£7.90	£0.08	25	£1.98	£7.90
Systemic steroid	Predisolone 5mg	10mg per day for 2 weeks	28	£0.40	£0.01	7	£0.10	£0.40
TCI	Protopic 0.1% ointment	5.7g/dose twice daily over 4 weeks	60	£47.28	£0.79	80	£10.48	£41.92

Sources: BNF (133), eMIT (130).
Abbreviations: TCI, topical calcineurin inhibitor; TCS, topical corticosteroids.

The proportion of use of each treatment from TA534 and TA681 is summarised in Table 85. The total cost of treatment for a disease flare for BSC patients was modelled as £37.41. The cost of treating a disease flare for abrocitinib, dupilumab and baricitinib patients was modelled as £29.81. The costs of disease flares are applied to the annual rate of flares (Section B.3.3.3) in the model.

Table 85: Cost of treatment of disease flares

Resource	Proportion from TA534		Cost	
	BSC	Abrocitinib/ Dupilumab/ Baricitinib	BSC	Abrocitinib/ Dupilumab/ Baricitinib
Potent TCS	0.54	0.42	£33.22	£25.83
Very potent TCS	0.27	0.23	£3.60	£3.07
Systemic steroid	0.13	0.29	£0.26	£0.58
TCI	0.06	0.00	£0.33	£0.33
Total			£37.41	£29.81

Abbreviations: BSC, best supportive care; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids.

B.3.5.5 Administration costs

The cost of administration for dupilumab was assumed as a one-time cost of a training session on self-administration as per TA534 for dupilumab (1). This cost was obtained from the Personal Social Services Research Unit (PSSRU) Unit costs of Health and Social Care 2019 as the cost of 30 minutes of patient contact time of a Band 6 Nurse specialist/team leader with qualifications' (134). There was no cost for the administration for abrocitinib or baricitinib they are oral therapies. Administration costs are presented in Table 86.

Table 86: Administration costs

Drug	Assumption	Cost of administration	Source
Abrocitinib	No cost	£0	-
Dupilumab	30-minute training session with a nurse	£56.50	PSSRU 2019 Band 6 Nurse specialist/team leader with qualifications (£113 per hour of patient contact)
Baricitinib	No cost	£0	-

Source: PSSRU 2020 (134).
Abbreviations: PSSRU, Personal Social Services Research Unit.

B.3.5.6 Health-state unit costs and resource use

Health care resource use captured within the model aligns with TA534 and TA681(1, 2). Costs incurred are specific to the treatment a patient is on and is separated for responders and non-responders and applied to the model health states accordingly. All costs for resource use in the BSC health state were the weighted average of responders and non-responders using the Week 16 response measure for BSC.

Patients who respond to abrocitinib and baricitinib treatment were assumed to have the same resource use as dupilumab patients from TA534 (Table 87) (1). According to clinical opinion, responders would still be tested regularly while on treatment, therefore abrocitinib and baricitinib patients are assumed to have 4 blood tests per year. Monitoring requirements are lower for dupilumab and 2 tests per year has been assumed based on clinical discussion. The cost of phototherapy was aligned with the revised base-case in TA534, assuming 22 sessions per treatment although phototherapy was only applied to patients receiving BSC given clinicians confirmed it would not be used for patients already on abrocitinib, dupilumab or baricitinib (1). All resource use assumptions were validated by clinical opinion. Patients that do not respond to treatment will discontinue and are assumed to have the same resource use as BSC patients.

Table 87: Resource use per patient

Resource	Abrocitinib/dupilumab/ baricitinib	BSC
Dermatologist outpatient consultation (per patient per year)		
Responder	4 in first year, 2 thereafter	4 in first year, 2 thereafter
Non-responder	-	6.09
Dermatology related GP consultation (per patients per year)		
Responder	2	2
Non-responder	-	12.8
Dermatology nurse visit (per patient per year)		
Responder	0.42	0.42
Non-responder	-	0.55
A&E visit (per patient per year)		
Responder	0.02	0.02
Non-responder	-	0.09
Hospitalisation		
Responder	0.02	0.02
Non-responder	-	0.12
Tests and investigation (per patient per year)		
Responder	4/2[†]	0
Non-responder	-	0
Day-case		
Responder	0	0
Non-responder	-	0.21
Phototherapy course (per patient per year)		
Responder	0	0.06
Non-responder	-	0.06

Resource	Abrocitinib/dupilumab/ baricitinib	BSC
Psychological support (per patient per year)		
Responder	0	0.07
Non-responder	0.07	0.07

†Abrocitinib and baricitinib patients are assumed to receive four tests and investigation per year, dupilumab patients two.
Abbreviations: A&E, accident and emergency; BSC, best supportive care.

The unit cost applied to each resource use in the model is presented in Table 88.

Table 88: Resource unit costs

Resource	Cost	Source
Dermatologist outpatient consultation	£114.57	NHS reference costs 2018/2019 weighted average of WF01A-WF02D
Dermatology related GP consultation	£39.23	PSSRU 2020, surgery consultation lasting 9.22 minutes
Dermatology nurse visit	£10.50	PSSRU 2020, 15 minutes of GP practice nurse @ £42 per hour
A&E visit	£182.58	Weighted average of VB01Z-VB09Z NHS ref costs 2018/2019
Hospitalisation	£1,854.72	Weighted average presented in TA534 (£1,795 in the 2018 cost year) adjusted for inflation to 2020 cost year. As per TA681.
Tests and investigations	£2.79	NHS reference costs 2018/2019 code: DAPS05
Day-case	£433.69	Weighted average of day-case JD07A-JD07K NHS ref costs 2018/2019
Phototherapy	£102.95	NHS reference costs 2018/2019 code: JC47A
Psychological support	£289.46	Clinical psychology, NHS ref costs 2018/2019 service code 656

Sources: PSSRU 2020, NHS reference costs 2018/19.
Abbreviations: GP, general practitioner; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.7 Adverse reaction unit costs and resource use

The cost of each adverse event in the model (Section B.3.3.4) were informed by TA534 and clinical opinion (1). All costs were taken from the 2020 PSSRU Unit Costs of Health and Social Care and 2018/19 NHS reference costs (134, 135). The assumptions and costs of each adverse event are presented in Table 89.

Table 89: Adverse event costs

Adverse event	Cost	Source
Infectious conjunctivitis	£55.34	Ophthalmologist consultation: assumed to be £101.46, derived as weighted average of NHS Reference Costs (2018–19) WF01A–D and WF02A–C.

Adverse event	Cost	Source
		Infectious conjunctivitis: weighted average of ophthalmologist consultation (20%) and GP consultation (£39.23, PSSRU; 80%) with unit cost of 1% prednisolone eye drops (£3.66, MIMS)
Allergic conjunctivitis	£39.23	Cost of 1 GP visit (9.22 minutes of patient contact with qualifications, PSSRU 2020) NHS reference costs 2018/2019)
Headache	£39.23	
Injection site reaction	£112.12	NHS reference costs 2018/19 WF01A
Nasopharyngitis	£39.23	Cost of 1 GP visit (9.22 minutes of patient contact with qualifications, PSSRU 2020) NHS reference costs 2018/2019)
Nausea	£39.23	
Upper respiratory tract infection	£39.23	
Folliculitis	£39.23	
Pharyngitis	£39.23	
Oral herpes	£41.72	Cost of 1 GP visit £39.23, PSSRU 2020, plus 1 Aciclovir 5% cream 10 gram @ £2.49 (eMIT)

Sources: eMIT; MIMS; PSSRU 2020; NHS reference costs 2018/19.
Abbreviations: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool; GP, general practitioner; NHS, National Health Service; MIMS, Monthly Index of Medical Specialities; PSSRU, Personal Social Services Research Unit.

B.3.5.8 Miscellaneous unit costs and resource use

The model also included an option to consider work productivity loss for adults. The effect of productivity loss is presented as a scenario analysis. The same method was used as in TA534, with productivity loss modelled as days lost through sickness (1).

Responders were assumed to have the same rate of absenteeism as the general population, according to the Office of National Statistics (ONS); 4.4 days per year (Table 90) (136). According to a 2013 National Health and Wellness Survey (NHWS) for patients with moderate to severe AD, absenteeism was three times larger than the general population, therefore 13.2 sick days per year was modelled for non-responders (48). The same rate of employment was modelled as in TA534 (78.5%) (1). Average wages and working hours was calculated as a weighted average of part-time and full-time work from the ONS (Table 91) (136).

Table 90: Productivity loss by response

Productivity loss	Responder (days per year)	Non-responder (days per year)
Sick days	4.4	13.2

Table 91: Productivity loss inputs

Parameter	Input
Value of productivity loss per hour	£15.12 (137)
Percentage employed	78.5% (137)
Working hours per day	6.67 (137)

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 92 summarises the variables applied in the economic model and Table 93 summarises the assumptions made.

Table 92: Summary of variables applied in the economic model

Variable	Source	Measurement of uncertainty and distribution	Reference to section in submission
Population settings			
Baseline age, % female, weight, BSA, adults combination therapy	COMPARE	DSA: varied within 95% CI interval PSA: Log-normal distribution (age, weight) Beta distribution (BSA, female %)	Section B.3.2.1 Table 55: Clinical trial summaries
Baseline age, % female, weight, BSA, adults monotherapy	MONO-1 &-2	DSA: varied within 95% CI interval PSA: Log-normal distribution (age, weight) Beta distribution (BSA, female %)	Section B.3.2.1 Table 55: Clinical trial summaries
Baseline age, % female, weight, BSA, adolescents combination therapy	TEEN	DSA: varied within 95% CI interval PSA: Log-normal distribution (age, weight) Beta distribution (BSA, female %)	Section B.3.2.1 Table 55: Clinical trial summaries
Baseline age, % female, weight, BSA, adolescents monotherapy	MONO-1 &-2	DSA: varied within 95% CI interval PSA: Log-normal distribution (age, weight) Beta distribution (BSA, female %)	Section B.3.2.1 Table 55: Clinical trial summaries
Discount rate, costs	3.5%	Not varied	Section B.3.2.3
Discount rate, outcomes	3.5%	Not varied	Section B.3.2.3
Clinical inputs			
Response rates	NMA, JADE clinical trials	Varied using CODA output	Section B.3.3.1

Variable	Source	Measurement of uncertainty and distribution	Reference to section in submission
Discontinuation rates, abrocitinib	EXTEND	DSA: varied within 95% CI interval PSA: Beta distribution	Section B.3.3.2
Discontinuation rates, dupilumab, baricitinib and BSC	TA534, TA681	DSA: varied within 95% CI interval PSA: Beta distribution	Section B.3.3.2
Disease flares	REGIMEN and TA534	DSA: varied within 95% CI interval PSA: Log-normal distribution	Section B.3.3.3
Adverse events	JADE clinical trials, TA534, Bieber et al	DSA: varied within 95% CI interval PSA: Beta distribution	Section B.3.3.4
Mortality	England and Wales life tables	Not varied	Section B.3.3.5
Utilities			
Health state utility values	JADE clinical trials; TA534 (scenario)	DSA: varied within 95% CI interval PSA: Multivariate normal distribution	Section B.3.4.5
Costs and resource use			
Drug acquisition costs	Abrocitinib: Anticipated dosing schedule and price provided by Pfizer Dupilumab and baricitinib: BNF	Not varied	Section B.3.5.1
Background medicated therapies	Resource use based on TA534 and TA681 Costs from BNF and eMIT	Not varied	Section B.3.5.2
Disease flares	Based on assumptions from TA534	Not varied	Section B.3.5.4
Administration costs	Based on assumptions from TA534	Not varied	Section B.3.5.5
Health state costs	Based on assumptions from TA534	DSA Varied with the 95% CI PSA: Gamma distribution	Section B.3.5.6
Adverse events	Based on assumptions from TA534 Costs from PSSRU 2020	Not varied	Section B.3.5.7

Abbreviations: BNF, British National Formulary; BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; PSSRU, Personal Social Services Research Unit; PSA, probabilistic sensitivity analysis.

Table 93: Summary of assumptions used in the economic model

Base-case assumptions	Justification
Response is based on EASI-50 & (C)DLQI ≥4	To align with TA534 and TA681 and the approved stopping rule of dupilumab and baricitinib. Alternative response definitions (EASI 75, EASI 90) are tested as scenarios for the combination analyses.
Response is assessed at Week 16; Week 12 response rates from MONO-1, MONO-2 and TEEN can be generalised to Week 16	Given abrocitinib has a fast onset of action, no notable differences in efficacy would be expected between Week 12 and 16, as was illustrated in COMPARE. The Week 12/16 comparison would be expected to bias against abrocitinib given that dupilumab shows relatively slower response in COMPARE and improvements in outcomes from Week 12 to Week 16.
For the adolescent combination comparison in the base-case the adult combination response rates from the NMA are assumed to hold for the adolescent population	No data was available for dupilumab in the adolescent combination therapy population and subgroups in the TEEN trial were small. Data from clinical trials for abrocitinib suggests comparable response rates for adults and adolescents.
Odds ratios for EASI 50 were applied for EASI 50 & DLQI ≥4 for several comparisons; the full population was also used as a proxy for the generalisable population where comparisons were not feasible	Limitations of available data for dupilumab and baricitinib; scenario analyses using alternative endpoints have also been presented.
Patients losing response to treatment move to BSC in all treatment arms	This is a simplifying assumption in line with TA534 and TA681. While in practice patients may receive further treatment prior to moving to BSC, there is little clinical data to inform this. A scenario considering treatment sequences is presented.
BSC can be modelled as a single health state with a weighted average utility value based on responders and non-responders.	This approach is in line with the ERG and committee's preferences from TA534 and TA681. Scenarios are considered that model BSC as separate health states by response
Discontinuation rates at Week 52 conditional on achieving response at Week 12/16 ("conditional discontinuation" data) inform the probability of transitioning to BSC at Week 52 and at the end of each cycle in the Markov model	Using conditional discontinuation data to inform Week 52 transitions was preferred by the committee for TA681 (4). Conditional response (i.e., response at week 52 conditional on response at week 12/15) is tested in scenario analysis Conditional discontinuation data informs transitions at the end of each cycle in the Markov model given that longer term data are unavailable
Data from EXTEND for adolescents previously in TEEN are immature so conditional discontinuation data from COMPARE were applied to the adolescent combination comparison.	This was deemed reasonable by clinical experts given the absence of data.
Baricitinib is assumed to have the same disease flare rates as abrocitinib 100 mg dose (REGIMEN data) in the absence of data	This is considered conservative given the [redacted]. Further, the assumption applied by the ERG in TA681 was that the baricitinib flare rate should be equivalent to BSC.
The risk of adverse events is assumed to be constant over the modelled time horizon	This is a simplifying assumption given the lack of longer-term data

Base-case assumptions	Justification
For the adolescent combination, and monotherapy comparisons, the utility benefit for dupilumab vs abrocitinib 200mg has been set to the same proportional benefit as was seen in the COMPARE adult combination analysis	Differential utility values reflect differences in the rates of adverse events and changes in other symptoms, such as itch and sleep loss. [redacted]
It was assumed that baricitinib 4mg has the same utility weight as abrocitinib 100 mg	It was not possible to include baricitinib 4mg in any of the utility analyses. The assumption that baricitinib 4mg is equivalent to abrocitinib 100mg is expected to be conservative given the [redacted]
Patients who do not maintain response at Week 16 and transition to BSC receive the average of abrocitinib/comparator non-responder utility and BSC utility regardless of response between Weeks 16 – 52.	As per the preferred assumptions from the ERG and committee in the appraisal for dupilumab TA534. Including the utility of abrocitinib/comparator non-responders was deemed appropriate given that the utility for BSC after active treatment may not be comparable to utility associated with having BSC from the outset in the model.
Utility waning for abrocitinib and baricitinib is assumed to be the same as dupilumab in TA534. BSC utility waning is assumed to be as per the analysis from CHRONOS presented in TA534.	There are no long-term data to support utility waning assumption for patients receiving abrocitinib or baricitinib, therefore it is assumed that patients receiving abrocitinib, dupilumab and baricitinib experience equal waning effects. The BSC waning effect is aligned with clinical advice that utility benefit would quickly wane for patients on BSC.

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, evidence review group, NMA, network meta-analysis

B.3.7 Base-case results

All results presented are calculated using the PAS price for abrocitinib, with list prices applied for dupilumab and baricitinib. In all analysis, abrocitinib 200 mg and 100 mg doses are cost-effective when compared with dupilumab and baricitinib in adults, and dupilumab in adolescents. Base case ICERs for all analyses are presented although only sensitivity analyses for combination analyses are presented given this is most relevant for decision making.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

In the adult combination therapy analysis (Table 94), abrocitinib 200 mg and abrocitinib 100 mg are associated with ICERs of [redacted] vs dupilumab. The ICERs [redacted].

Compared with baricitinib (4mg dose), abrocitinib 200 mg and abrocitinib 100mg are associated with ICERs of [redacted] and [redacted]

Table 94: Base-case results: adults, combination therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs dupilumab (£)	Incremental QALYs vs dupilumab	Pairwise ICER vs dupilumab (£/QALY)	Incremental costs vs baricitinib (£)	Incremental QALYs vs baricitinib	Pairwise ICER vs baricitinib (£/QALY)
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results presented are calculated using the PAS price for abrocitinib, with list prices applied for dupilumab and baricitinib.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not relevant to decision problem; QALYs, quality-adjusted life years.

In the adolescent combination therapy analysis (Table 95), abrocitinib 200 mg and abrocitinib 100 mg are associated with ICERs of [redacted] vs dupilumab. [redacted]

Table 95: Base-case results: adolescents, combination therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs dupilumab (£)	Incremental QALYs vs dupilumab	Pairwise ICER vs dupilumab (£/QALY)
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results presented are calculated using the PAS price for abrocitinib, with list prices applied for dupilumab.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Base case ICERs for the monotherapy analysis are presented in Table 96 and Table 97. Both doses of abrocitinib remain cost-effective when compared with dupilumab and baricitinib. ICERs for abrocitinib 200 mg and 100 mg [redacted]

[redacted]

Table 96 Base-case results: adults, monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs dupilumab (£)	Incremental QALYs vs dupilumab	Pairwise ICER vs dupilumab (£/QALY)	Incremental costs vs baricitinib (£)	Incremental QALYs vs baricitinib	Pairwise ICER vs baricitinib (£/QALY)
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results presented are calculated using the PAS price for abrocitinib, with list prices applied for dupilumab and baricitinib.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not relevant to the decision problem; QALYs, quality-adjusted life years.

Table 97 Base-case results: adolescents, monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs dupilumab (£)	Incremental QALYs vs dupilumab	Pairwise ICER vs dupilumab (£/QALY)
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results presented are calculated using the PAS price for abrocitinib, with list prices applied for dupilumab.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through probabilistic sensitivity analysis, in which all parameters are assigned distributions and varied jointly. 10,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. The PSA shows a small increase in both costs and QALYs across all arms in the adult and adolescent analyses; full tables of probabilistic results are presented in Appendix Q. Results were also plotted on a cost-effectiveness plane and cost-effectiveness acceptability curves (CEAC) generated.

Abrocitinib vs dupilumab

Cost-effectiveness planes and CEACs for abrocitinib 200mg vs dupilumab for the adult combination and adolescent combination analyses are presented in Figure 35.

[redacted]

Figure 35: Cost-effectiveness plane and CEAC, abrocitinib 200 mg vs. dupilumab

A: Cost-effectiveness plane, abrocitinib 200 mg vs dupilumab, adults.
B: CEAC, abrocitinib 200 mg vs dupilumab, adults.
C: Cost-effectiveness plane, abrocitinib 200 mg vs dupilumab, adolescents.
D: CEAC, abrocitinib 200 mg vs dupilumab, adolescents.
Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life-year.

Similar results were obtained for abrocitinib 100mg vs dupilumab as illustrated in Figure 36;

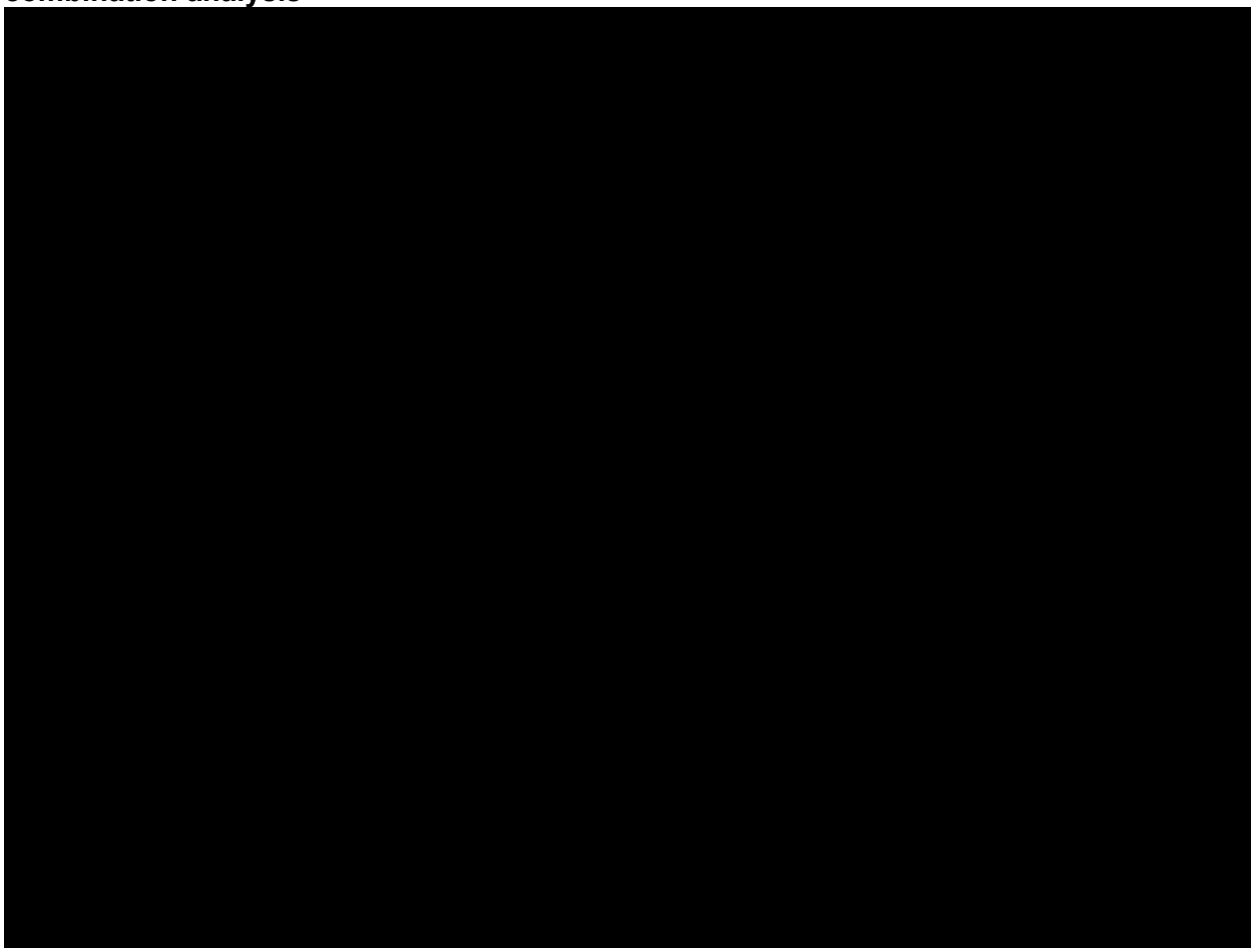
Figure 36 Cost-effectiveness plane and CEAC, abrocitinib 100 mg vs dupilumab

A: Cost-effectiveness plane, abrocitinib 100 mg vs dupilumab, adults.
B: CEAC, abrocitinib 100 mg vs dupilumab, adults.
C: Cost-effectiveness plane, abrocitinib 100 mg vs dupilumab, adolescents.
D: CEAC, abrocitinib 100 mg vs dupilumab, adolescents.
Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life-year.

Abrocitinib vs baricitinib

Cost-effectiveness planes and CEACs for abrocitinib 200mg and abrocitinib 100mg vs dupilumab in the adult combination analyses are presented in Figure 37. Abrocitinib 200mg and abrocitinib 100mg were considered cost-effective in [redacted] and [redacted] of simulations respectively vs baricitinib at a threshold of £30,000 per QALY for the adult combination analysis.

Figure 37: Cost-effectiveness plane and CEAC abrocitinib vs baricitinib, adult combination analysis



A: Cost-effectiveness plane, abrocitinib 200 mg vs baricitinib, adults.
B: CEAC, abrocitinib 200 mg vs baricitinib, adults.
C: Cost-effectiveness plane, abrocitinib 100 mg vs baricitinib, adults.
D: CEAC, abrocitinib 100 mg vs baricitinib, adults.
Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life-year.

B.3.8.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using one-way sensitivity analysis (OWSA), in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±15% where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

Results for the ten most influential parameters are reported for each analysis. The most influential parameters were the probability of response, the probability of discontinuation for each arm, coefficients of the utility models and utility waning in Year 5. None of the varied parameters led to a change in the conclusions of the analysis, with the ICERs for abrocitinib vs dupilumab [redacted] in all analyses and ICERs for abrocitinib vs baricitinib [redacted]

Abrocitinib vs dupilumab

OWSA results for the adult and adolescent combination comparison for abrocitinib 200 mg and abrocitinib 100mg vs dupilumab are presented in Figure 38.

Figure 38: Tornado diagram, abrocitinib vs. dupilumab

A: Abrocitinib 200 mg vs dupilumab, adults *
B: Abrocitinib 100 mg vs dupilumab, adults *resized for readability,)
C: Abrocitinib 200 mg vs dupilumab, adolescents *
D: Abrocitinib 100 mg vs dupilumab, adolescents *)

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis

Abrocitinib vs baricitinib

The OWSA results for the adult combination comparison abrocitinib 200 mg and abrocitinib 100 mg in combination with background topical therapies vs baricitinib in adults are presented in Figure 39.

Figure 39: Tornado diagram, abrocitinib vs. baricitinib

A: Abrocitinib 200 mg vs baricitinib, adults
B: Abrocitinib 100 mg vs baricitinib, adolescents
Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis

B.3.8.3 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied. In all scenarios, the resultant ICERs were still cost-effective, and the conclusions of the analysis did not change. In comparisons vs dupilumab, the resultant ICERs were [redacted] while in all analysis vs baricitinib [redacted]

Abrocitinib vs dupilumab

Scenario analyses for the adult and adolescent combination comparison of abrocitinib 200 mg vs dupilumab are presented in Table 98 and Table 99. The scenarios with the biggest impact on the ICER were excluding utility waning for all interventions, switching to using EASI-75 or EASI-90 as a measure of response and for the adolescent comparison, modelling until adulthood. Excluding utility waning and switching to EASI-75 [redacted] Switching to an EASI-90 as measure of response or modelling until adulthood (for adolescents) [redacted].

Table 98: Scenario analysis: adult combination therapy analysis, abrocitinib 200 mg vs dupilumab

Scenario	Inc. costs	Inc. QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90†	[redacted]	[redacted]	[redacted]	[redacted]
NMA, restricted trial data, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Trial data, generalisable population, EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

† [redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year.

Table 99: Scenario analysis: adolescent combination therapy analysis, abrocitinib 200 mg vs dupilumab

Scenario	Inc. costs	Inc. QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90†	[redacted]	[redacted]	[redacted]	[redacted]
Trial data, full population, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Model until adulthood†	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

† [redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Scenario analysis for the adult and adolescent combination comparison of abrocitinib 100 mg vs dupilumab are presented in in Table 100 and Table 101 respectively. The scenario with the biggest impact on the ICER is using EASI-90 trial data as the measure of response [redacted].

Table 100: Scenario analysis: adult combination therapy analysis, abrocitinib 100 mg vs dupilumab

Scenario	Inc. costs	Inc. QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90	[redacted]	[redacted]	[redacted]	[redacted]
NMA, restricted trial data, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Trial data, generalisable population, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Inc. costs	Inc. QALYs	ICER	% change
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year.

Table 101: Scenario analysis: adolescent combination therapy analysis, abrocitinib 100 mg vs dupilumab

Scenario	Inc. costs	Inc. QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90†	[redacted]	[redacted]	[redacted]	[redacted]
Trial data, full population, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Model until adulthood	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc. incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Abrocitinib vs baricitinib

The scenario analysis results for the adult combination comparison of abrocitinib 200 mg and abrocitinib 100 mg vs baricitinib are presented in Table 102 and Table 103. For both the 200 mg and 100 mg doses of abrocitinib, the scenario with the greatest impact on the ICER was excluding utility waning for all interventions. [redacted]

[redacted] Including societal costs within the analysis reduces the ICER vs baricitinib by [redacted] for the abrocitinib 200 mg comparison and [redacted] for the abrocitinib 100 mg comparison.

Table 102: Scenario analysis: adult combination therapy analysis, abrocitinib 200 mg vs baricitinib

Scenario	Inc costs	Inc QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90	[redacted]	[redacted]	[redacted]	[redacted]
NMA, restricted trial data, EASI-50 & DLQI response measure	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc., incremental; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year.

Table 103: Scenario analysis: adult combination therapy analysis, abrocitinib 100 mg vs baricitinib

Scenario	Inc costs	Inc QALYs	ICER	% change
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Utility data from TA534 for dupilumab for all comparators	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-75	[redacted]	[redacted]	[redacted]	[redacted]
Measure of response: EASI-90	[redacted]	[redacted]	[redacted]	[redacted]
Societal costs included	[redacted]	[redacted]	[redacted]	[redacted]
Utility waning excluded	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 1	[redacted]	[redacted]	[redacted]	[redacted]
BSC waning scenario 3	[redacted]	[redacted]	[redacted]	[redacted]
BSC modelling split by response	[redacted]	[redacted]	[redacted]	[redacted]
Conditional response data at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D analysis: combined EASI-50 & DLQI ≥4 response measure	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Inc. incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

An additional scenario considers the results for a mixed dose of abrocitinib where [redacted] of patients receive the 200 mg dose and [redacted] receive the 100 mg dose. Results for these scenarios are generated by weighting costs and QALYs for the abrocitinib arms and as such results fall in between those for abrocitinib 200mg and 100mg separately. Table 104 present the ICERs vs dupilumab and baricitinib in the adult and adolescent combination populations.

Table 104: Results for the mixed dose scenario

Population	ICER vs dupilumab	ICER vs baricitinib
Adult combination therapy	[redacted]	[redacted]
Adolescent combination analysis	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable.

B.3.8.4 Summary of sensitivity analyses results

Many sensitivity analyses have been undertaken, assessing the impact of variation in all parameters and assumptions applied within the model.

Results of the PSA were congruent with the deterministic base-case. [redacted] Similar findings were seen for the abrocitinib 100mg comparisons.

In one-way sensitivity analysis the most influential parameters across comparisons were the probability of response, the probability of discontinuation for each arm, coefficients of the utility models and utility waning in Year 5. None of the varied parameters led to a change in the conclusions of the analysis, with ICERs for abrocitinib vs dupilumab remaining [redacted] in all analyses and ICERs for abrocitinib vs baricitinib remaining [redacted]

In scenario analysis the impact of switching to trial data, applying EASI 75 & EASI 90 or restricted population NMA data, removing utility waning and applying dupilumab utility data (TA534) were explored. In all cases abrocitinib 200 mg and 100 mg doses are a cost-effective use of NHS resources vs dupilumab and baricitinib. Including societal costs within the analysis reduces the ICER vs baricitinib by [redacted] for the adult combination comparison and [redacted] for abrocitinib 200 mg and abrocitinib 100 mg respectively in the adult combination therapy comparison.

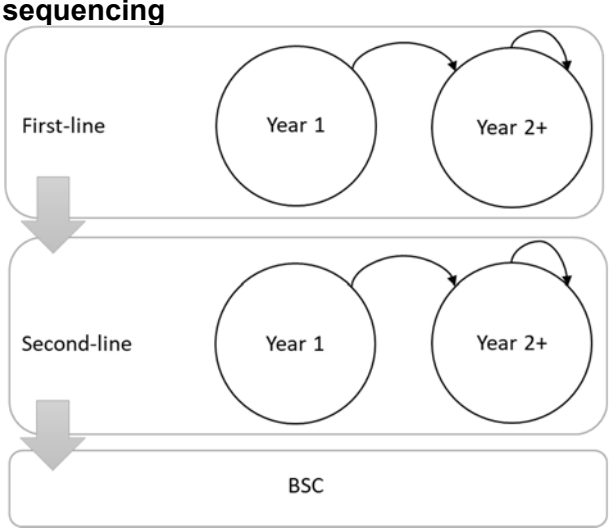
B.3.9 Subgroup analysis

No subgroup analyses were considered in the analysis.

B.3.10 Treatment sequencing

Figure 40 summarises the structure for the exploratory treatment sequencing analysis.

Figure 40: Treatment sequencing



Abbreviations: BSC, best supportive care

In the analysis patients receiving abrocitinib in line with the proposed positioning (in first line after one systemic immunosuppressant therapy), move to dupilumab (in "second line") if they discontinue. This is based on clinical advice to the company that it is unlikely that patients would receive two JAK inhibitors (abrocitinib and baricitinib) in sequence without considering dupilumab as a treatment option.

This sequence is compared with dupilumab followed by baricitinib. Clinical experts have confirmed that based on NICE recommendations this would be an appropriate standard-of-care comparator, although baricitinib has recently been recommended and is not yet widely established.

We have also considered in the model the sequence of dupilumab followed by abrocitinib to explore the cost-effectiveness of sequencing dupilumab before and after a JAK treatment, where abrocitinib represents a JAK. Clinical opinion has suggested that in the longer term the sequence of dupilumab following by abrocitinib may be more likely than dupilumab followed by baricitinib given the profiles of

abrocitinib and baricitinib. For simplicity, the sequencing analysis is presented for the adult combination analysis. Only the 200 mg dose of abrocitinib is considered.

The sequencing analysis followed the same structure as the base-case analysis; however, patients can re-enter the assessment phase and receive a second-line therapy, if they do not respond to first-line therapy, prior to transitioning to the BSC health state.

After receiving first-line therapy, patients may experience a loss of response at the assessment phase of the decision-tree period at Week 16, before Week 52, or at any point from Year 2 onwards.

- If a patient loses response to a first-line therapy at Week 16, they move onto a second line of therapy and re-enter the assessment phase of the decision-tree period at Week 16 of the model. As a simplifying assumption it is assumed that patients continue second-line treatment until Week 52, and those maintaining response enter the maintenance health-state; otherwise they enter the BSC health state. The percentage of patients responding is the proportion that would respond at Week 16 and would not have discontinued by Week 52 of treatment.

- If a patient loses response to first-line therapy after Week 16, but before 52-weeks, it is assumed that they will not start their second-line therapy until the beginning of the first Markov-cycle where they re-enter the assessment phase.

- If a patient discontinues first-line therapy at any point from Year 2 onwards, they start second-line therapy at the next Markov cycle. Response rates at Week 16 and Week 52 are assessed as per the model base-case (without sequencing).

If a patient discontinues second-line treatment at any point in the model, they transitioned to the BSC health state until death or the end of the model time horizon.

B.3.10.1 Clinical inputs and assumptions

There is a lack of clinical data on sequencing regimens. In the abrocitinib clinical trial programme the only available data is for the efficacy of abrocitinib following discontinuation of dupilumab available from patients entering EXTEND from COMPARE. However, this subgroup only contained 51 patients and therefore was not considered informative for modelling treatment sequencing. Furthermore, there were no data available on patients who have discontinued abrocitinib and received dupilumab, therefore a comparison of sequencing efficacy between dupilumab and abrocitinib could not be made. Thus, in the scenario that includes treatment sequencing, efficacy data for patients who received their second systemic therapy was assumed as equal to the base-case model data with no adjustment made. For all other inputs/assumptions the sequencing model followed the base-case model described previously.

B.3.10.2 Results

As for other results presented in this submission calculations use the PAS price for abrocitinib, with list prices applied for dupilumab and baricitinib.

Abrocitinib 200mg → Dupilumab vs Dupilumab → Baricitinib

[redacted]

Abrocitinib 200mg → Dupilumab vs Dupilumab → Abrocitinib 200mg

[redacted] When comparing these sequences patients spend a similar amount of time on treatment and the difference in costs and

QALYs is primarily due to patients spending more time on a therapy when it is used in first-line and the impact of discounting applied within the model.

[redacted] where abrocitinib is used first in sequence.

A summary of result in the sequencing analysis are presented in Table 105.

B.3.11 Validation of cost-effectiveness analysis

Quality control of the electronic model was performed both internally by the model developers, and externally by an independent health economist. Validation of the model by both internal and external health economists involved review of:

- Formulae
- Consistency with the model decision problem
- VBA implementation
- Inputs
- Model functionality

Furthermore, model inputs and assumptions were validated with two UK clinical experts in a series of teleconference discussions. Their biographies are provided in Appendix R.

Table 105: Treatment sequencing analysis results, adults, combination therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) vs dupi → bari	Incremental QALYs vs dupi → bari	Pairwise ICER vs dupi → bari	Incremental costs (£) vs dupi → abro	Incremental QALYs vs dupi → abro	Pairwise ICER vs dupi → abro
Abrocitinib → Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab → Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab → Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not relevant to decision problem; QALYs, quality-adjusted life years

B.3.12 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis shows that abrocitinib 200 mg and 100 mg are a cost-effective use of NHS resources vs dupilumab and baricitinib for combination and monotherapy analyses.

For the adult combination analysis, abrocitinib 200 mg and abrocitinib 100 mg are associated with ICERs of [redacted] vs dupilumab which [redacted]; ICERs are similarly [redacted] for the adolescent combination comparison.

[redacted] conditional discontinuation data which is reliant on data between Weeks 12/16 and Week 52 has a disproportionate impact on the ICER given that it is applied over the lifetime of the model. [redacted] There is uncertainty associated with rates of discontinuation in the longer term in the absence of data beyond 52 weeks across treatments.

Sequencing modelling explores the costs and QALYs associated with abrocitinib 200mg when used in sequence with another treatment. [redacted]

Compared with baricitinib 4mg, ICERs for the 200 mg and 100 mg doses of abrocitinib are [redacted] and [redacted] respectively for the adult combination comparison. [redacted]

The key strengths of the analysis are:

- The model closely aligns with the committees preferred assumptions in previous NICE TAs in AD.
- Key components of the analysis were validated by clinical experts
- Multiple scenario and sensitivity analyses were conducted. In OWSA and scenario analysis the conclusions of the economic analysis remain consistent, with the ICERs for abrocitinib vs dupilumab [redacted]
- A key active comparator was included in the COMPARE trial, giving randomised data for the comparison of abrocitinib 200 mg and 100 mg doses vs dupilumab. ICERs based on trial data, that do not rely on NMA outputs, show that abrocitinib represents a cost-effective use of NHS resources.

The key limitations of the analysis are:

- Key active comparator trial data were not available vs dupilumab and baricitinib for every analysis however extensive NMAs were performed to inform the comparative efficacy of abrocitinib with comparators, so this limitation was minimised.
- Long term discontinuation data were not available to inform the model beyond Week 52 although conditional discontinuation data has a disproportionate impact on the ICER given it is applied over the lifetime of the model. This is also a limitation of the models presented for TA534 and TA681. Conditional response data has also been explored as a scenario for informing transitions to BSC within the model.

There is a substantial unmet need in moderate to severe AD for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. Dupilumab may not be appropriate for all patients due to its side effect profile and route of administration and abrocitinib 200 mg and abrocitinib 100 mg both represent [redacted] Further, the 200 mg dose has been shown to be

more effective than dupilumab at rapidly reducing itch and improving skin clearance, which are two major drivers of disease burden in AD.

[redacted]. Further, they are associated with [redacted].

Given that both doses of abrocitinib are clinically and cost-effective compared with existing treatments, and with a flexible oral administration, they are attractive treatment options for the NHS in an area where substantial unmet need remains.

References

1. National Institute for Health and Care Excellence. TA534: Dupilumab for treating moderate to severe atopic dermatitis (committee papers). Available at: https://www.nice.org.uk/guidance/ta534/documents/committee-papers (last accessed 23 Sept 2020). 2018.
2. National Institute for Health and Care Excellence. TA681: Baricitinib for treating moderate to severe atopic dermatitis (committee papers). Available at: https://www.nice.org.uk/guidance/gid-ta10562/documents/committee-papers (last accessed 24th February 2021). 2020.
3. National Institute for Health and Care Excellence. TA534: Dupilumab for treating moderate to severe atopic dermatitis (final appraisal determination). Available at: https://www.nice.org.uk/guidance/ta534/documents/final-appraisal-determination-document (last accessed 29 Jul 2020). 2018.
4. National Institute for Health and Care Excellence. TA681: Baricitinib for treating moderate to severe atopic dermatitis (final appraisal document). Available at: https://www.nice.org.uk/guidance/ta681/documents/final-appraisal-determination-document (last accessed 8th April 2021). 2020.
5. Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. Journal of the American Academy of Dermatology. 2017;77(4):623-33.
6. Rodenbeck DL, Silverberg JI, Silverberg NB. Phototherapy for atopic dermatitis. Clinics in Dermatology. 2016;34(5):607-13.
7. National Institute for Health and Care Excellence. TA177: Alitretinoin for the treatment of severe chronic hand eczema. Available at: https://www.nice.org.uk/guidance/ta177 (last accessed 20 Jan 2021). 2009.
8. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J, et al. Guidelines for diagnosis, prevention and treatment of hand eczema--short version. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG. 2015;13(1):77-85.
9. English J, Aldridge R, Gawkrodger DJ, Kownacki S, Statham B, White JML, et al. Consensus statement on the management of chronic hand eczema. Clinical and Experimental Dermatology. 2009;34(7):761-9.
10. Ruff SMD, Engebretsen KA, Zachariae C, Johansen JD, Silverberg JI, Egeberg A, et al. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. British Journal of Dermatology. 2018;178(4):879-88.
11. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunological Reviews. 2009;228(1):273-87.
12. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of Chronic Pruritus in Atopic Dermatitis: Getting the Itch Out? Clinical Reviews in Allergy & Immunology. 2016;51(3):263-92.
13. Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. JAK-STAT. 2013;2(3):e24137.
14. Howell MD, Kuo FI, Smith PA. Targeting the Janus Kinase Family in Autoimmune Skin Diseases. Frontiers in Immunology. 2019;10:2342.

15. Crowley EL, Nezamololama N, Papp K, Gooderham MJ. Abrocitinib for the treatment of atopic dermatitis. Expert Rev Clin Immunol. 2020;16(10):955-62.
16. Cork MJ, Danby SG, Ogg GS. Atopic dermatitis epidemiology and unmet need in the United Kingdom. The Journal of Dermatological Treatment. 2019:1-9.
17. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-22.
18. National Health Service. Overview: atopic eczema. Available at: https://www.nhs.uk/conditions/atopic-eczema/ (last accessed 29 Jul 2020). 2019.
19. Silverberg JI. Adult-Onset Atopic Dermatitis. J Allergy Clin Immunol Pract. 2019;7(1):28-33.
20. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. The Lancet. 2020;396(10247):345-60.
21. Zuberbier T, Orlow SJ, Paller AS, Taieb A, Allen R, Hernanz-Hermosa JM, et al. Patient perspectives on the management of atopic dermatitis. J Allergy Clin Immunol. 2006;118(1):226-32.
22. Pfizer. Data on file - Talk Health itch study.
23. He H, Guttman-Yassky E. JAK Inhibitors for Atopic Dermatitis: An Update. Am J Clin Dermatol. 2019;20(2):181-92.
24. Nguyen HL, Anderson KR, Tollefson MM. New and Emerging Therapies for Pediatric Atopic Dermatitis. Paediatr Drugs. 2019;21(4):239-60.
25. National Institute for Health and Care Excellence. CG57: Atopic eczema in under 12s: diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg57 (last accessed 28 Jul 2020). 2007.
26. Gooderham MJ, Bissonnette R, Grewal P, Lansang P, Papp KA, Hong C-H. Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document. Section II: Tools for Assessing the Severity of Atopic Dermatitis. Journal of Cutaneous Medicine and Surgery. 2018;22(1_suppl):10S-6S.
27. Lusignan Sd, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. The epidemiology of eczema in children and adults in England: A population-based study using primary care data. Clinical & Experimental Allergy. 2020.
28. AllergyUK, Sanofi Genzyme. Seeing Red. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiGr-vl1ffqAhWhURUIHdzrD74QFjAAegQIBRAB&url=https%3A%2F%2Fwww.allergyuk.org%2Fassets%2F000%2F001%2F411%2FSeeing_Red_Report_FINAL_25.04.17_original.pdf%3F1508228476&usg=AOvVaw0pk1xvk_BimCRJ8S5QR0k6 (last accessed 31 Jul 2020). 2017.
29. More Than Skin Deep. Understanding the lived experience of eczema. Available at: http://www.morethanskindeep-eczema.org/uploads/1/2/5/3/125377765/mtsd_report_-_digital_file_1.pdf (last accessed 31 Jul 2020). 2020.
30. European Federation of Allergy and Airways Diseases Patients' Associations. Itching for life - Quality of Life and costs for people with severe atopic eczema in Europe. Available at: https://www.efanet.org/news/3373-european-report-itching-for-life-quality-of-life-and-costs-for-people-with-severe-atopic-eczema-in-europe#:~:text=EFA%27s%202018%20European%20report%20Itching,lives%20with%20a%20severe%20condition (last accessed 20 Jan 2021). 2018.
31. Girolomoni G, Luger T, Nosbaum A, Gruben D, Romero W, Llamado LJ, et al. The Economic and Psychosocial Comorbidity Burden Among Adults with Moderate-

to-Severe Atopic Dermatitis in Europe: Analysis of a Cross-Sectional Survey. Dermatology and Therapy. 2020.
32. Egeberg A, Andeson P, Piercy J, Massey L, Cappelleri JC, Encinas GA, et al. Symptom burden of patients with moderate-to-severe atopic dermatitis. Manuscript in development. 2021.
33. Boeri M, Sutphin J, Hauber B, Cappelleri JC, Romero W, Di Bonaventura M. Quantifying patient preferences for systemic atopic dermatitis treatments using a discrete-choice experiment. The Journal of Dermatological Treatment. 2020:1-10.
34. Grant L, Seiding Larsen L, Trennery C, Silverberg JI, Abramovits W, Simpson EL, et al. Conceptual Model to Illustrate the Symptom Experience and Humanistic Burden Associated With Atopic Dermatitis in Adults and Adolescents. Dermatitis. 2019;30(4):247-54.
35. National Institute for Health and Care Excellence. NICE's response to comments on the draft scope and provisional stakeholder list. Available from: https://www.nice.org.uk/guidance/gid-ta10764/documents/scope-consultation-comments-and-responses (last accessed 9th April 2021).
36. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340-7.
37. DiBonaventura M, Anderson P, De Villarreal J, Bell D, Milligan G, Cappelleri JC, et al. The relationship between pruritus, sleep disruption, and quality of life among patients with moderate-to-severe atopic dermatitis. Presented at 10th World Congress on Itch. 17-19 Nov 2019, Sydney, Australia. Abstract number OP28. Available at: https://journals.lww.com/itch/Fulltext/2019/11001/Abstracts.2.aspx. 2019.
38. Vakharia PP, Chopra R, Sacotte R, Patel KR, Singam V, Patel N, et al. Burden of skin pain in atopic dermatitis. Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology. 2017;119(6):548-52.e3.
39. Sinclair R, Eisman S, Murrell DF, Yosipovitch G, Su JC, Feeney C, et al. The relationship between pruritus and sleep improvement: Post hoc analysis of a randomized, double-blind, phase 3 clinical trial of abrocitinib. Presented at 10th World Congress on Itch. 17-19 Nov 2019, Sydney, Australia. Abstract number OP20. Available at: https://journals.lww.com/itch/Fulltext/2019/11001/Abstracts.2.aspx. 2019.
40. Hinkley SB, Holub SC, Menter A. The Validity of Cutaneous Body Image as a Construct and as a Mediator of the Relationship Between Cutaneous Disease and Mental Health. Dermatology and Therapy. 2020;10(1):203-11.
41. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA Dermatol. 2017;153(5):406-12.
42. Birdi G, Cooke R, Knibb RC. Impact of atopic dermatitis on quality of life in adults: a systematic review and meta-analysis. International Journal of Dermatology. 2020;59(4):e75-e91.
43. Capucci S, Hahn-Pedersen J, Vilsbøll A, Kragh N. Impact of Atopic Dermatitis and Chronic Hand Eczema on Quality of Life Compared With Other Chronic Diseases. Dermatitis. 2020;31(3):178–84.

44. Amaral CSFd, March MdFBP, Sant'Anna CC. Quality of life in children and teenagers with atopic dermatitis. Anais Brasileiros de Dermatologia. 2012;87(5):717-23.
45. Campos ALB, de Araújo FM, dos Santos MAL, dos Santos AdAS, Pires CAA. Impact of atopic dermatitis on the quality of life of pediatric patients and their guardians. Revista Paulista de Pediatria. 2017;35(1):5-10.
46. Herd RM, Tidman MJ, Prescott RJ, Hunter JA. The cost of atopic eczema. Br J Dermatol. 1996;135(1):20-3.
47. Tsakok T, Woolf R, Smith CH, Weidinger S, Flohr C. Atopic dermatitis: the skin barrier and beyond. Br J Dermatol. 2019;180(3):464-74.
48. Whiteley J, Emir B, Seitzman R, Makinson G. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. Current medical research and opinion. 2016;32(10):1645-51.
49. National Institute for Health and Care Excellence. QS44: Atopic eczema in under 12s. Available at: https://www.nice.org.uk/guidance/qs44 (last accessed 24th February 2021). 2013.
50. National Institute for Health and Care Excellence. TA82: Tacrolimus and pimecrolimus for atopic eczema. Available at: https://www.nice.org.uk/guidance/ta82/resources/tacrolimus-and-pimecrolimus-for-atopic-eczema-pdf-2294815625413 (last accessed 31 Jul 2020). 2004.
51. National Institute for Health and Care Excellence. Clinical knowledge summary: Eczema - atopic. Available at: https://cks.nice.org.uk/eczema-atopic#!topicSummary (last accessed 31 Jul 2020). 2018.
52. Arkwright PD, Motala C, Subramanian H, Spergel J, Schneider LC, Wollenberg A, et al. Management of difficult-to-treat atopic dermatitis. The Journal of Allergy and Clinical Immunology In Practice. 2013;1(2):142-51.
53. Bieber T. Atopic dermatitis. Annals of Dermatology. 2010;22(2):125-37.
54. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. The British Journal of Dermatology. 2017;177(5):1316-21.
55. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology (Basel, Switzerland). 1997;195(1):10-9.
56. National Institute for Health and Care Excellence. Oral corticosteroids. Available at: https://cks.nice.org.uk/topics/eczema-atopic/prescribing-information/oral-corticosteroids/ (last accessed 20 Jan 2021). 2018.
57. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. The British Journal of Dermatology. 2015;172(5):1353-7.
58. Eichenfield LF, Ahluwalia J, Waldman A, Borok J, Udkoff J, Boguniewicz M. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. The Journal of Allergy and Clinical Immunology. 2017;139(4S):S49-S57.
59. European Medicines Agency. Dupilumab summary of product characteristics. Available at: https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_en.pdf (last accessed 23rd April 2021).

60. National Institute for Health and Care Excellence. ID3768: Final scope. Available at: https://www.nice.org.uk/guidance/gid-ta10764/documents/final-scope (last accessed 27th April 2021). 2021.
61. National Institute for Health and Care Excellence. ID1622: Baricitinib for treating moderate to severe atopic dermatitis (final appraisal document). Available at: https://www.nice.org.uk/guidance/gid-ta10562/documents/final-appraisal-determination-document (last accessed 24th February 2021). 2020.
62. Santer M, Ridd MJ, Francis NA, Stuart B, Rumsby K, Chorozoglou M, et al. Emollient bath additives for the treatment of childhood eczema (BATHE): multicentre pragmatic parallel group randomised controlled trial of clinical and cost effectiveness. BMJ. 2018;361:k1332.
63. Blauvelt A, Bruin-Weller Md, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. The Lancet. 2017;389(10086):2287-303.
64. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. New England Journal of Medicine. 2016;375(24):2335-48.
65. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA dermatology. 2020;156(1):44-56.
66. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). Br J Dermatol. 2018;178(5):1083-101.
67. Gardette E, Ramyead S, Smola A, Jones J, Ameen M. Real-world experience of dupilumab for the treatment of severe recalcitrant atopic dermatitis in a tertiary centre. Abstract presented at British Association of Dermatologists Annual Meeting, 02-04 Jul 2019, Liverpool, UK. Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjd.17749 (last accessed 23 Sept 2020). 2019.
68. Worm M, Simpson EL, Thaçi D, Bissonnette R, Lacour J-P, Beissert S, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. JAMA dermatology. 2020;156(2):131-43.
69. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol. 2019;181(3):459-73.
70. Olesen CM, Holm JG, Norreslet LB. Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre. 2019;33(8):1562-8.
71. Ariens LFM, van der Schaft J, Bakker DS, Balak D, Romeijn MLE, Kouwenhoven T, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry. 2020;75(1):116-26.

72. Wang C, Kraus CN, Patel KG, Ganesan AK, Grando SA. Real-world experience of dupilumab treatment for atopic dermatitis in adults: a retrospective analysis of patients' records. Int J Dermatol. 2019.
73. Ariëns LF, van der Schaft J, Spekhorst LS, Bakker DS, Romeijn GLE, Kouwenhoven TA, et al. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-weeks results from the Dutch BioDay registry. Journal of the American Academy of Dermatology. 2020.
74. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz J-D, Reguiai Z, et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. Journal of the American Academy of Dermatology. 2019;81(1):143-51.
75. Stewart KD, Johnston JA, Matza LS, Curtis SE, Havel HA, Sweetana SA, et al. Preference for pharmaceutical formulation and treatment process attributes. Patient Prefer Adherence. 2016;10:1385-99.
76. Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. Annals of Allergy, Asthma & Immunology. 2020;124(1):28-35.
77. Pfizer. Data on file - JADE COMPARE Clinical Study Report.
78. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP, et al. Efficacy and Safety of Baricitinib in Combination With Topical Coticosteroids in Patients With Moderate-to-Severe Atopic Dermatitis Who Failed, Are Intolerant to, or Have Contraindication to Cyclosporine: Results from a Randomized, Placebo-Controlled, Phase 3 Clinical Trial (BREEZE-AD4). EADV Conference. 2020;P0183-854.
79. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol. 2019;155(12):1371-9.
80. Pfizer. Data on file - JADE MONO-1 Clinical Study Report.
81. Pfizer. Data on file - JADE MONO-2 Clinical Study Report.
82. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T, et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020.
83. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol. 2019;80(4):913-21 e9.
84. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020.
85. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet. 2016;387(10013):40-52.
86. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network Meta-Analysis for Decision-Making: John Wiley & Sons; 2018 2018-01-08. 470 p.

87. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. The BUGS Book: A Practical Introduction to Bayesian Analysis: CRC Press; 2012 2012-10-02. 402 p.
88. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol. 2012;41(3):818-27.
89. Achana FA, Cooper NJ, Dias S, Lu G, Rice SJ, Kendrick D, et al. Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. Stat Med. 2013;32(5):752-71.
90. Spiegelhalter DJ, Best NG, Carlin BP, Linde AVD. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002;64(4):583-639.
91. Phillippo D, Ades A, Dias S, Palmer S, Abrams K, Welton N. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. Report by the Decision Support Unit. 2016.
92. Phillippo DM, Dias S, Ades AE, Welton NJ. Assessing the performance of population adjustment methods for anchored indirect comparisons: A simulation study. Stat Med. 2020.
93. Cork MJ, Thaci D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85-96.
94. Deleuran M, Thaci D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020;82(2):377-88.
95. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nature Reviews Rheumatology. 2017;13(4):234-43.
96. Pfizer. Data on file - B7451045 Study Report.
97. Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, Boy M, Geier J, Luo Z, et al. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. Seminars in Arthritis and Rheumatism. 2016;46(1):71-80.
98. Charles-Schoeman C, DeMasi R, Valdez H, Soma K, Hwang LJ, Boy MG, et al. Risk Factors for Major Adverse Cardiovascular Events in Phase III and Long-Term Extension Studies of Tofacitinib in Patients With Rheumatoid Arthritis. Arthritis & Rheumatology (Hoboken, Nj). 2019;71(9):1450-9.
99. Pfizer. Data on file - B7451044 Study Report.
100. Medicines & Healthcare products Regulatory Agency (MHRA). Abrocitinib: Information for NHS Medical Directors. Available at: https://www.gov.uk/government/publications/abrocitinib-in-the-treatment-of-severe-atopic-dermatitis/abrocitinib-information-for-nhs-medical-directors. 2021.
101. Ferreira S, Guttman-Yassky E, Torres T. Selective JAK1 Inhibitors for the Treatment of Atopic Dermatitis: Focus on Upadacitinib and Abrocitinib. American Journal of Clinical Dermatology. 2020;21(6):783-98.
102. Wang F, Kim BS. Itch: A Paradigm of Neuroimmune Crosstalk. Immunity. 2020;52(5):753-66.
103. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. The Biochemical Journal. 2014;462(1):1-13.

104. Weidinger S, Schreiber S. Abrocitinib for atopic dermatitis: a step forward. The Lancet. 2020;396(10246):215-7.
105. Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005;90(8):840-4.
106. SMC. dupilumab 300mg solution for injection in pre-filled syringe (Dupixent®). SMC2011. 2018;https://www.scottishmedicines.org.uk/medicines-advice/dupilumab-dupixent-fullsubmission-smc2011/.
107. NICE. Baricitinib for treating moderate to severe atopic dermatitis [ID1622]. https://wwwniceorguk/guidance/indevelopment/gid-ta10562. 2021.
108. Zuberbier T, Orlow SJ, Paller AS, Taïeb A, Allen R, Hernanz-Hermosa JM, et al. Patient perspectives on the management of atopic dermatitis. Journal of Allergy and Clinical Immunology. 2006;118(1):226-32.
109. Thomas KS, Stuart B, O'Leary CJ, Schmitt J, Paul C, Williams HC, et al. Validation of treatment escalation as a definition of atopic eczema flares. PLoS One. 2015;10(4):e0124770.
110. Bieber T, Thyssen JP, Reich K, Simpson EL, Katoh N, Torrelo A, et al. Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials. Journal of the European Academy of Dermatology and Venereology. 2021;35(2):476-85.
111. Office for National S. National life tables: UK. 2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables (last accessed 25 June 2020).
112. Thyssen JP, Hamann CR, Linneberg A, Dantoft TM, Skov L, Gislason GH, et al. Atopic dermatitis is associated with anxiety, depression, and suicidal ideation, but not with psychiatric hospitalization or suicide. Allergy. 2018;73(1):214-20.
113. Dieris-Hirche A, Gieler U, Petrak F, Milch W, Te Wildt B, Dieris B, et al. Suicidal ideation in adult patients with atopic dermatitis: a German cross-sectional study. Acta Dermato-Venereologica. 2017;97(8-9):1189-95.
114. Kimata H. Prevalence of suicidal ideation in patients with atopic dermatitis. Suicide and Life-Threatening Behavior. 2006;36(1):120-4.
115. Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health. 2012;15(5):708-15.
116. Dolan P. Modeling valuations for EuroQol health states. Medical Care. 1997;35(11):1095-108.
117. Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, et al. The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2005;9(29):iii-230.
118. Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: Twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Ser. British Journal of Dermatology. 2011;164(2):387-95.
119. NICE. Dupilumab for treating moderate to severe atopic dermatitis. Technology appraisal guidance [TA534]. 2018;https://www.nice.org.uk/guidance/TA534.

120. The National Institute for Health and Care Excellence. NICE DSU technical support document 12: The use of health state utility values in decision models. Available at: http://nicedsuorguk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINALpdf (last accessed 25 June 2020). 2011.
121. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.
122. The National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available at https://wwwniceorguk/process/pmg9/chapter/foreword (last accessed 25 June 2020). 2013.
123. Misery L, Finlay AY, Martin N, Boussetta S, Nguyen C, Myon E, et al. Atopic dermatitis: impact on the quality of life of patients and their partners. Dermatology. 2007;215(2):123-9.
124. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics. 2013;31(6):489-500.
125. National Institute for Health and Care Excellence. British National Formulary - dupilumab. Available at: https://bnf.nice.org.uk/medicinal-forms/dupilumab.html (last accessed 19th May 2021).
126. National Institute for Health and Care Excellence. British National Formulary - baricitinib. Available at: https://bnf.nice.org.uk/medicinal-forms/baricitinib.html (last accessed 19th May 2021).
127. National Health Service (NHS). National Health Service. Prescription cost analysis. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis. 2018.
128. National Institute for Health and Care Excellence. British National Formulary - mometasone furoate. Available at: https://bnf.nice.org.uk/drug/mometasone-furoate.html (last accessed 19th May 2021).
129. Rhodes J, Clay C, Phillips M. The surface area of the hand and the palm for estimating percentage of total body surface area: results of a meta-analysis. British Journal of Dermatology. 2013;169(1):76-84.
130. GOV.UK. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (last accessed 23rd April 2021).
131. Electronic Medicines Compendium. Protopic 0.1% ointment. Available at: https://www.medicines.org.uk/emc/product/1608/smpc (last accessed 13th May 2021).
132. National Institute for Health and Care Excellence. British National Formulary - tacrolimus. Available at: https://bnf.nice.org.uk/medicinal-forms/tacrolimus.html (last accessed 19th May 2021).
133. National Institute for Health and Care Excellence. British National Formulary. Available at: https://bnf.nice.org.uk/ (last accessed 23rd April 2021).
134. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2020. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/ (last accessed 2nd March 2021). 2020.
135. National Health Service. 2018/19 National Cost Collection data. Available at: https://www.england.nhs.uk/national-cost-collection/#ncc1819 (last accessed 10th May 2021). 2019.
136. The Office for National Statistics. Sickness absence in the UK labour market: 2018. Available at

https://wwwonsgovuk/employmentandlabourmarket/peopleinwork/labourproductivity/articles/sicknessabsenceinthelabourmarket/2018 (last accessed 25 June 2020). 2018.
137. Office for National Statistics. Annual Survey of Hours and Earnings: 2016 provisional results. Available at: https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2016provisionalresults (last accessed 2nd March 2021). 2016.

Appendices

The following appendices are provided as a separate document:

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Pfizer disease burden studies

Appendix M: Supplementary data from abrocitinib clinical trial programme

Appendix N: Data used in the EASI-75 and EASI-90 response scenarios

Appendix O: Conditional response data

Appendix P: List price results

Appendix Q: PSA results tables

Appendix R: Clinician biographies

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

August, 2021

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A; second-line systemic treatment).

Based on the company submission (CS) for upadacitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning upadacitinib as a treatment option at both first- and second- line in the management of AD for adolescents and adults. The EAG's systematic literature review has identified the key studies evaluating updacitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which updacitinib, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating upadacitinib and, therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA, or were intolerant of or experienced a medical complication of CsA.

The EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England (the "all observed" analysis in the CS). However, the EAG might carry out sensitivity analyses for a population from which those who receive rescue therapy are censored regardless of treatment discontinuation, referred to as the primary analysis in the CS.

Where possible, the EAG has sourced relevant data from the CS, specifying the time point for reporting of results. Please confirm that the extracted data are correct. If data are available for additional time points of clinical assessment, please complete separate clinical effectiveness tables for the time points for the outcomes requested.

Data on clinical effectiveness

A1. Please complete the tables below for individual studies to provide data on the outcomes specified in the protocol for population of interest, together with baseline characteristics of the patients from which data on clinical effectiveness are derived.

a) AD UP (results yet to be published)

a1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib plus background TCS as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

M16-047 Adult systemic naïve			**First line**			**Second line**			
			Upa 30 mg QD +TCS	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	**Upa 30 mg QD +TCS**	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	**Reference**
			(N=198)	**(N=195)**	**(N=203)**	**(N=56)**	**(N=57)**	**(N=53)**	
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
		Non respond	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3

		er at week 16							
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.1_3
Proportion of people achieving EASI 75									
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3

	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
	Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
Proportion of people achieving EASI 75									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3

		Non responder at week 16							UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 52								UK_NICE_HTA_M16047 Table 1.1.2_3
		Responder at week 16							UK_NICE_HTA_M16047 Table 1.1.2_3
		Non responder at week 16							UK_NICE_HTA_M16047 Table 1.1.2_3
Change in EQ-5D score from baseline									
Primary analysis	Week 16								
All observed analysis	Week 16								
Proportion of people who discontinue treatment for any reason after achieving EASI 50 + ΔDLQI ≥4 (conditional discontinuation)									
			(N=198)	**(N=195)**		**(N=56)**	**(N=57)**		
Primary analysis	Responder at week 16	Week 16 - 24							UK_NICE_HTA_M16047 Table 2.2.1_3
		Week 16 - 52							UK_NICE_HTA_M16047 Table 2.2.1_3
	Non responder at week 16	Week 16 - 24							UK_NICE_HTA_M16047 Table 2.2.1_3
		Week 16 - 52							UK_NICE_HTA_M16047 Table 2.2.1_3

Commented [MK1]: This will be provided in final response

All observed analysis	Responder at week 16	Week 16-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.1.3
		Week 16-52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.1.3
	Non responder at week 16	Week 16-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.1.3
		Week 16-52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.1.3
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)									
			(N=203)	**(N=203)**		**(N=57)**	**(N=58)**		
Primary analysis	Responder at week 16	Week 16-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.2_3
		Week 16 - 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.2_3
	Non responder at week 16	Week 16-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.2_3
		Week 16-52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.2_3
All observed analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.2_3
		Week 16-52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.2_3
	Non responder at	Week 16 - 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.2_3

	week 16	Week 16-52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.2_3
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)									
Primary analysis	Week 16								
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Other Topical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3

		Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
	Baseline to Week 24								
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Non-biologic systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3

	Baseline to Week 52								
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Non-biologic systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Other systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
		Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.1_3
Number of days free from TCS during treatment									
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	

Primary analysis	Week 16 (Mean [CI])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA _M16047 Table 4.2.1_3
All observed analysis	Week 16 (Mean [CI])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA _M16047 Table 4.1.1_3

Baseline characteristics

	First line			Second line			
Characteristic	**Upa 30 mg QD +TCS (N=260)**	**Upa 15 mg QD +TCS (N=261)**	**Placebo plus TCS (N=264)**	**Upa 30 mg QD +TCS (N=260)**	**Upa 15 mg QD +TCS (N=261)**	**Placebo plus TCS (N=264)**	
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Gender, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Race							
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3

Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean baseline EQ-5D Score (SD)							
Prior treatment							
OCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.							

Commented [MK2]: This will be provided in final response

a2) Adolescents

Subgroup of adolescents (aged ≥12 years to <18 years) who received upadacitinib plus background TCS as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

M16-047 Adolescent		**Upa 30 mg QD +TCS**	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	**References**
		(N=37)	**(N=39)**	**(N=40)**	
Proportion of people achieving EASI 75					
Primary analysis	Week 8	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 24	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3

		Responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 52		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
All observed analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 24		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 52		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
		Responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
		Non responder at week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
Change in EQ-5D score from baseline						
Primary analysis	Week 16					
All observed analysis	Week 16					
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)						
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.3_3
		Week 16 - 52	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.3_3
		Week 16 - 24	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.3_3

Commented [MK3]: This will be provided in final response

	Non responder at week 16	Week 16 - 52	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.2.3_3
All observed analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.3_3
		Week 16 - 52	[redacted]	[redacted]		
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 2.1.3_3
		Week 16 - 52	[redacted]	[redacted]		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis	Week 16	Any rescue	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Other Topical	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
	Baseline to Week 24					
		Any rescue	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3

		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Topical	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
	Baseline to Week 52					
		Any rescue	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Topical	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3

		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.2.2_3
Number of days free from TCS during treatment						
Primary analysis	Week 16 (Mean [CI])		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 4.2.2_3
All observed analysis	Week 16 (Mean [CI])		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 4.1.2_3

Baseline characteristics

Characteristic	Upa 30 mg QD +TCS (N=37)	Upa 15 mg QD +TCS (N=39)	Placebo plus TCS (N=40)	Reference
Mean age, years	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx	
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	
Race				
White, n (%)	[redacted]	[redacted]	[redacted]	
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	
Asian, n (%)	[redacted]	[redacted]	[redacted]	
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	

Mean baseline EQ-5D Score (SD)				
Prior treatment				
OCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
TCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
TCI, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3

Commented [MK4]: This will be provided in final response

b) RISING UP (results yet to be published)

b1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib plus background TCS as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	First line			**Second line**		
	Upa 30 mg QD +TCS (N=)	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						
Primary analysis						
All observed analysis						
Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						

All observed analysis						
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						
All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			**Second line**		
Characteristic	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Mean age, years						
Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						

Black or African American, n (%)						
Asian, n (%)						
Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						
Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.						

b2) Adolescents

Subgroups of adolescents (aged ≥12 years to <18 years) who received upadacitinib plus background TCS as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	Upa 30 mg QD +TCS (N=)	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4			
Primary analysis			
All observed analysis			
Proportion of people achieving EASI 75			
Primary analysis			
All observed analysis			
Change in EQ-5D score from baseline			
Primary analysis			
All observed analysis			
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)			
Primary analysis			
All observed analysis			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)			
Primary analysis			
All observed analysis			
Number of days free from TCS during treatment			
Primary analysis			
All observed analysis			

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.

Baseline characteristics

Characteristic	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Mean age, years			
Gender, n (%)			
Male			
Mean duration of AD, years (SD)			
Race			
White, n (%)			
Black or African American, n (%)			
Asian, n (%)			
Mean EASI score (SD)			
Baseline IGA score of 4			
Mean DLQI score (SD)			
Mean SCORAD score (SD)			
Mean peak pruritus NRS score (SD)			
Mean % BSA affected (SD)			
Mean baseline EQ-5D Score (SD)			
Prior treatment			
OCS, n (%)			
Immunosuppressant, n (%)			
TCS, n (%)			
TCI, n (%)			
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-			

Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.

c) MEASURE UP 1 (results yet to be published)

c1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	First line			**Second line**		
	Upa 30 mg QD (N=)	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						
Primary analysis						
All observed analysis						
Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						

All observed analysis						
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						
All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			**Second line**		
Characteristic	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Mean age, years						
Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						
Black or African American, n (%)						

Asian, n (%)						
Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						
Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.						

c2) Adolescents

Subgroup adolescents (aged ≥12 years to <18 years) who received upadacitinib as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	Upa 30 mg QD (N=42)	**Upa 15 mg QD (N=42)**	**Placebo (N=40)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4			
Primary analysis			
All observed analysis			
Proportion of people achieving EASI 75			
Primary analysis			
All observed analysis	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline			
Primary analysis			
All observed analysis			
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)			
Primary analysis			
All observed analysis			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)			
Primary analysis			
All observed analysis			
Number of days free from TCS during treatment			
Primary analysis			
All observed analysis			
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.			

Baseline characteristics

Characteristic	Upa 30 mg QD (N=42)	Upa 15 mg QD (N=42)	Placebo (N=40)
Mean age, years	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]
Race			
White, n (%)	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]
Weekly mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)			
Prior treatment			
OCS, n (%)			
Immunosuppressant, n (%)			
TCS, n (%)			
TCI, n (%)			

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.

d) MEASURE UP 2 (results yet to be published)

d1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	First line			**Second line**		
	Upa 30 mg QD (N=)	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						
Primary analysis						
All observed analysis						
Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						
All observed analysis						

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						
All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			**Second line**		
Characteristic	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Mean age, years						
Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						
Black or African American, n (%)						
Asian, n (%)						

Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						
Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.						

d2) Adolescents

Subgroup of adolescents (aged ≥12 years to <18 years) who received upadacitinib as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	Upa 30 mg QD (N=35)	**Upa 15 mg QD (N=33)**	**Placebo (N=36)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4			
Primary analysis			
All observed analysis			
Proportion of people achieving EASI 75			
Primary analysis			
All observed analysis	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline			
Primary analysis			
All observed analysis			
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)			
Primary analysis			
All observed analysis			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)			
Primary analysis			
All observed analysis			
Number of days free from TCS during treatment			
Primary analysis			
All observed analysis			
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.			

Baseline characteristics

Characteristic	Upa 30 mg QD (N=35)	Upa 15 mg QD (N=33)	Placebo (N=36)
Mean age, years	[redacted]	[redacted]	[redacted]
Gender, n (%)			
Male	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]
Race			
White, n (%)	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]
Weekly mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)			
Prior treatment			
OCS, n (%)			
Immunosuppressant, n (%)			
TCS, n (%)			
TCI, n (%)			

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.

e) HEADS UP (results yet to be published)

e1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	First line	**Second line**	
	Upa 30 mg QD (N=)	**Upa 30 mg QD (N=)**	**Dupilumab 300 mg Q2W (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4			
Primary analysis			
All observed analysis			
Proportion of people achieving EASI 75			
Primary analysis			
All observed analysis			
Change in EQ-5D score from baseline			
Primary analysis			
All observed analysis			

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)			
Primary analysis			
All observed analysis			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)			
Primary analysis			
All observed analysis			
Number of days free from TCS during treatment			
Primary analysis			
All observed analysis			
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.			

Baseline characteristics

	First line	**Second line**	
Characteristic	**Upa 30 mg QD (N=)**	**Upa 30 mg QD (N=)**	**Dupilumab 300 mg Q2W (N=)**
Mean age, years			
Gender, n (%)			
Male			
Mean duration of AD, years (SD)			
Race			
White, n (%)			
Black or African American, n (%)			
Asian, n (%)			

Mean EASI score (SD)			
Baseline IGA score of 4			
Mean DLQI score (SD)			
Mean SCORAD score (SD)			
Mean peak pruritus NRS score (SD)			
Mean % BSA affected (SD)			
Mean baseline EQ-5D Score (SD)			
Prior treatment			
OCS, n (%)			
Immunosuppressant, n (%)			
TCS, n (%)			
TCI, n (%)			
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.			

f) Phase II dose finding study

f1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Clinical effectiveness at week 16

	First line			**Second line**		
	Upa 30 mg QD (N=)	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						
Primary analysis						
All observed analysis						
Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						
All observed analysis						
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						

All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			Second line		
Characteristic	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Mean age, years						
Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						
Black or African American, n (%)						
Asian, n (%)						
Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						

Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.						

A2. Please clarify the discrepancy in the number of adolescents included in the clinical effectiveness analysis of upadacitinib 30 mg plus TCS ([redacted]) in AD UP versus the number of adolescents for whom baseline characteristics are reported ([redacted]; tables presented in a2).

[Company: please enter your answer to this question here]

A3. The CS states the choice of dose of upadacitinib , either 15 mg or 30 mg QD for adults, would be decided [redacted]. Please could the company expand on [redacted] they anticipate would influence choice of dose. For example,

[redacted]

[redacted]?

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

[Add subheadings as needed]

B1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

[Add subheadings as needed]

C1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section D. References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

10 September, 2021

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic dermatitis EAG CQs Upadacitinib SD 170821 ACiC v2 Final 10Sep21	V1.0	Yes	10th September 2021

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);
and
those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A; second-line systemic treatment).

Based on the company submission (CS) for upadacitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning upadacitinib as a treatment option at both first- and second- line in the management of AD for adolescents and adults. The EAG's systematic literature review has identified the key studies evaluating updacitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which updacitinib, either in combination with topical corticosteroids or as a

monotherapy, was given as both a first- and a second-line systemic treatment. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating upadacitinib and, therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA, or were intolerant of or experienced a medical complication of CsA.

The EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England (the "all observed" analysis in the CS). However, the EAG might carry out sensitivity analyses for a population from which those who receive rescue therapy are censored regardless of treatment discontinuation, referred to as the primary analysis in the CS.

Where possible, the EAG has sourced relevant data from the CS, specifying the time point for reporting of results. Please confirm that the extracted data are correct. If data are available for additional time points of clinical assessment, please complete separate clinical effectiveness tables for the time points for the outcomes requested.

Data on clinical effectiveness

A1. Please complete the tables below for individual studies to provide data on the outcomes specified in the protocol for population of interest, together with baseline characteristics of the patients from which data on clinical effectiveness are derived.

a) AD UP (results yet to be published)

a1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib plus background TCS as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 1 and 2.

Table 1: AD UP (M16-047) - Clinical effectiveness at week 16 (Adult population)

AD UP (M16-047) Adult systemic naïve		**First line**			**Second line**			**Reference**
		Upa 30 mg QD +TCS	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	**Upa 30 mg QD +TCS**	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	
		(N=198)	**(N=195)**	**(N=203)**	**(N=56)**	**(N=57)**	**(N=53)**	
Proportion of people achieving EASI 50 + ΔDLQI ≥4								
Primary analysis	Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 24	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.2.1.3

		Responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.2.1.3
		Non responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.2.1.3
	Week 52				N/A				UK_NICE_HTA_M16047 Table 1.2.1.3
		Responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.2.1.3
		Non responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.2.1.3
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Observed analysis	Week 8								UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 16								UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 24				N/A			N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
		Responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
		Non responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
	Week 52				N/A			N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
		Responder at week 16						N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
		Non responder at week 16			N/A			N/A	UK_NICE_HTA_M16047 Table 1.1.1_3
Proportion of people achieving EASI 75									
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	
Primary analysis	Week 8								UK_NICE_HTA_M16047 Table 1.2.2_3
	Week 16								UK_NICE_HTA_M16047 Table 1.2.2_3
	Week 24							N/A	UK_NICE_HTA_M16047 Table 1.2.2_3

		Responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.2.2_3
		Non responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.2.2_3
	Week 52		[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.2_3
		Responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.2.2_3
		Non responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.2.2_3
Proportion of people achieving EASI 75									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 24		[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
		Responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
		Non responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
	Week 52		[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
		Responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
		Non responder at week 16	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 1.1.2_3
Change in EQ-5D score from baseline									
Primary analysis	EQ-5D at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Proportion of people who discontinue treatment for any reason after achieving EASI 50 + ΔDLQI ≥4 (conditional discontinuation)									
			(N=198)	**(N=195)**		**(N=56)**	**(N=57)**		
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	N/A	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 2.2.1_3

		Week 16 - 52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.1_3
	Non responder at week 16	Week 16 - 24			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.1_3
		Week 16 - 52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.1_3
All observed analysis	Responder at week 16	Week 16-24						N/A	UK_NICE_HTA_M16047 Table 2.1.1.3
		Week 16-52						N/A	UK_NICE_HTA_M16047 Table 2.1.1.3
	Non responder at week 16	Week 16-24						N/A	UK_NICE_HTA_M16047 Table 2.1.1.3
		Week 16-52						N/A	UK_NICE_HTA_M16047 Table 2.1.1.3
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)									
			(N=203)	**(N=203)**		**(N=57)**	**(N=58)**		
Primary analysis	Responder at week 16	Week 16-24			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.2_3
		Week 16 - 52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.2_3
	Non responder at week 16	Week 16-24			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.2_3
		Week 16-52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.2.2_3
All observed analysis	Responder at week 16	Week 16 - 24			N/A			N/A	UK_NICE_HTA_M16047 Table 2.1.2_3
		Week 16-52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.1.2_3
	Non responder at week 16	Week 16 - 24			N/A			N/A	UK_NICE_HTA_M16047 Table 2.1.2_3
		Week 16-52			N/A			N/A	UK_NICE_HTA_M16047 Table 2.1.2_3
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)									
Primary analysis	Week 16								
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	

		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
		Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.1_3
	Baseline to Week 24								
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		Non-biologic systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	UK_NICE_HTA_M16047 Table 3.2.1_3

		Other systemic therapy						N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
		Phototherapy						N/A	UK_NICE_HTA_M16047 Table 3.2.1_3
	Baseline to Week 52								
		Any Rescue Medication							UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS High Potency							UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Medium Potency							UK_NICE_HTA_M16047 Table 3.2.1_3
		TCS Low Potency							UK_NICE_HTA_M16047 Table 3.2.1_3
		TCI							UK_NICE_HTA_M16047 Table 3.2.1_3
		Other Topical Therapy							UK_NICE_HTA_M16047 Table 3.2.1_3
		Biologic systemic							UK_NICE_HTA_M16047 Table 3.2.1_3
		Non-biologic systemics							UK_NICE_HTA_M16047 Table 3.2.1_3
		Other systemic therapy							UK_NICE_HTA_M16047 Table 3.2.1_3
		Phototherapy							UK_NICE_HTA_M16047 Table 3.2.1_3
Number of days free from TCS during treatment									
			(N=203)	**(N=203)**	**(N=209)**	**(N=57)**	**(N=58)**	**(N=55)**	
Primary analysis	Week 16 (Mean [CI])								UK_NICE_HTA_M16047 Table 4.2.1_3
All observed analysis	Week 16 (Mean [CI])								UK_NICE_HTA_M16047 Table 4.1.1_3

Abbreviations: CI: Confidence interval, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib	

Table 2: AD UP (M16-047) - Baseline characteristics (Adult population)

	First line			Second line			Reference
Characteristic	**Upa 30 mg QD +TCS (N=203)**	**Upa 15 mg QD +TCS (N=203)**	**Placebo plus TCS (N=209)**	**Upa 30 mg QD +TCS (N=57)**	**Upa 15 mg QD +TCS (N=58)**	**Placebo plus TCS (N=55)**	
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Gender, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Race							
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3

Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.3
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment							
OCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.1._3
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib							

a2) Adolescents

Subgroup of adolescents (aged ≥12 years to <18 years) who received upadacitinib plus background TCS as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 3 and 4.

Table 3: AD UP (M16-047) - Clinical effectiveness at week 16 (Adolescent)

AD UP (M16-047) Adolescent		**Upa 30 mg QD +TCS**	**Upa 15 mg QD +TCS**	**Placebo plus TCS**	**References**
		(N=37)	**(N=39)**	**(N=40)**	
Proportion of people achieving EASI 75					
Primary analysis	Week 8	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 16	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 24	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3

		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.2.3_3
All observed analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 24		[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 1.1.3_3
Change in EQ-5D score from baseline						
Primary analysis	EQ-5D at Week 16		[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)						
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.2.3_3
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.2.3_3
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.2.3_3
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.2.3_3

All observed analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.1.3_3
		Week 16 -52	[redacted]	[redacted]		
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 2.1.3_3
		Week 16 -52	[redacted]	[redacted]		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis	Week 16					
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 3.1.2_3
	Baseline to Week 24					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047

						Table 3.2.2_3
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
	Baseline to Week 52					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_M16047 Table 3.2.2_3
Number of days free from TCS during treatment						

Primary analysis	Week 16 (Mean [CI])	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 4.2.2_3
All observed analysis	Week 16 (Mean [CI])	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 4.1.2_3
Abbreviations: CI: Confidence interval, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib					

Table 4: AD UP (M16-047) - Baseline characteristics (Adolescent)

Characteristic	Upa 30 mg QD +TCS (N=37)	Upa 15 mg QD +TCS (N=39)	Placebo plus TCS (N=40)	Reference
Mean age, years	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Race				
White, n (%)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Asian, n (%)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2

Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	UK request/M16-047 Table 14.1_2.8.2
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment				
OCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
TCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3
TCI, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_M16047 Table 5.2_3

AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib

b) RISING UP (results yet to be published)

b1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib plus background TCS as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Results from the AD Up, Measure Up 1, Measure Up 2 and Heads Up were prioritised for this response

Clinical effectiveness at week 16

	First line			Second line		
	Upa 30 mg QD +TCS (N=)	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						

Primary analysis						
All observed analysis						
Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						
All observed analysis						
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						
All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			Second line		
Characteristic	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**	**Upa 30 mg QD +TCS (N=)**	**Upa 15 mg QD +TCS (N=)**	**Placebo plus TCS (N=)**
Mean age, years						
Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						
Black or African American, n (%)						
Asian, n (%)						
Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						
Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.

b2) Adolescents

Subgroups of adolescents (aged ≥12 years to <18 years) who received upadacitinib plus background TCS as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Results from the AD Up, Measure Up 1, Measure Up 2 and Heads Up were prioritised for this response

Clinical effectiveness at week 16

	Upa 30 mg QD +TCS (N=)	Upa 15 mg QD +TCS (N=)	Placebo plus TCS (N=)
Proportion of people achieving EASI 50 + ΔDLQI ≥4			
Primary analysis			
All observed analysis			
Proportion of people achieving EASI 75			
Primary analysis			
All observed analysis			
Change in EQ-5D score from baseline			
Primary analysis			
All observed analysis			
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)			
Primary analysis			
All observed analysis			
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)			
Primary analysis			
All observed analysis			
Number of days free from TCS during treatment			
Primary analysis			
All observed analysis			
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.			

Baseline characteristics

Characteristic	Upa 30 mg QD +TCS (N=)	Upa 15 mg QD +TCS (N=)	Placebo plus TCS (N=)
Mean age, years			
Gender, n (%)			
Male			
Mean duration of AD, years (SD)			
Race			
White, n (%)			
Black or African American, n (%)			
Asian, n (%)			
Mean EASI score (SD)			
Baseline IGA score of 4			
Mean DLQI score (SD)			
Mean SCORAD score (SD)			
Mean peak pruritus NRS score (SD)			
Mean % BSA affected (SD)			
Mean baseline EQ-5D Score (SD)			
Prior treatment			
OCS, n (%)			
Immunosuppressant, n (%)			
TCS, n (%)			
TCI, n (%)			

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.

c) MEASURE UP 1 (results yet to be published)

c1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 5 and 6.

Table 5: Measure UP 1 (M16-045) - Clinical effectiveness at week 16 (Adult population)

	First line	Second line	Reference

Measure UP 1 (M16-045) Adult systemic naïve			**Upa 30 mg QD**	**Upa 15 mg QD**	**Placebo**	**Upa 30 mg QD**	**Upa 15 mg QD**	**Placebo**	
			(N=204)	**(N=195)**	**(N=196)**	**(N=31)**	**(N=39)**	**(N=40)**	
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Primary analysis	Week 8								UK-NICE-HTA-045_891_047 Table 1.2.1_1
	Week 16								UK-NICE-HTA-045_891_047 Table 1.2.1_1
	Week 24				NA			NA	UK-NICE-HTA-045_891_047 Table 1.2.1_1
		Responder at week 16			NA			NA	UK-NICE-HTA-045_891_047 Table 1.2.1_1
		Non responder at week 16			NA			NA	UK-NICE-HTA-045_891_047 Table 1.2.1_1
	Week 52				NA			N/A	UK-NICE-HTA-045_891_047 Table 1.2.1_1
		Responder at week 16			NA			NA	UK-NICE-HTA-045_891_047 Table 1.2.1_1
		Non responder at week 16			NA			NA	UK-NICE-HTA-045_891_047 Table 1.2.1_1
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Observed analysis	Week 8								UK-NICE-HTA-045_891_047 Table 1.1.1_1
	Week 16								UK-NICE-HTA-045_891_047 Table 1.1.1_1

	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.1_1
Proportion of people achieving EASI 75									
			(N=211)	**(N=200)**	**(N=201)**	**(N=32)**	**(N=39)**	**(N=40)**	
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 1.2.2.1
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 1.2.2.1
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1

	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.2.2.1
Proportion of people achieving EASI 75									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 1.1.2_1
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 1.1.2_1
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 1.1.2_1
Change in EQ-5D score from baseline									

Primary analysis	EQ-5D at Week 16		[redacted]						NICE_MTA_CLQ _SectionA
Proportion of people who discontinue treatment for any reason after achieving EASI 50 + ΔDLQI ≥4 (conditional discontinuation)									
			(N=204)	**(N=195)**		**(N=31)**	**(N=39)**		
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.2.1_1
		Week 16 - 52	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.2.1_1
	Non responder at week 16	Week 16 - 24	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.2.1_1
		Week 16 - 52	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.2.1_1
All observed analysis	Responder at week 16	Week 16-24	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.1.1_1
		Week 16-52	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.1.1_1
	Non responder at week 16	Week 16-24	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.1.1_1
		Week 16-52	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.1.1_1
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)									
			(N=211)	**(N=200)**		**(N=32)**	**(N=39)**		
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]		NA			NA	UK-NICE-HTA-045_891_047 Table 2.2.2_1

		Week 16 - 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.2.2_1
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.2.2_1
		Week 16 - 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.2.2_1
All observed analysis	Responder at week 16	Week 16-24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.1.2_1
		Week 16-52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.1.2_1
	Non responder at week 16	Week 16-24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.1.2_1
		Week 16-52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 2.1.2_1
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)									
Primary analysis	Week 16								
			(N=211)	**(N=200)**	**(N=201)**	**(N=32)**	**(N=39)**	**(N=40)**	
		Any Rescue Medication	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		TCS High Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1

		TCS Low Potency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		TCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		Biologic systemic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
		Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 3.1.1_1
	Baseline to week 24								
		Any Rescue Medication	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS High Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS Medium Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS Low Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCI	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1

		Other Topical Therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Biologic systemic	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Non-biologic Systemics	[redacted]	[redacted]	N/A	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Other Systemic therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Phototherapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
	Baseline to week 52								
		Any Rescue Medication	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS High Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS Medium Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCS Low Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		TCI	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Other Topical Therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Biologic systemic	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1

		Non-biologic Systemics	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Other Systemic therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
		Phototherapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK-NICE-HTA-045_891_047 Table 3.2.1_1
Abbreviations: DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib									

Table 6: Measure UP 1(M16-045) - Baseline characteristics (Adult population)

	First line			Second line			Reference
Characteristic	**Upa 30 mg QD (N=211)**	**Upa 15 mg QD (N=200)**	**Placebo (N=201)**	**Upa 30 mg QD (N=32)**	**Upa 15 mg QD (N=39)**	**Placebo (N=40)**	
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Gender, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Race							
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1

Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK request/M16-045 Table_14.1_2.8.1
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment							
OCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA 045_891_047 Table 5.1._1
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 5.1._1
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 5.1._1

TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA-045_891_047 Table 5.1._1
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib							

c2) Adolescents

Subgroup adolescents (aged ≥12 years to <18 years) who received upadacitinib as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 7 and 8.

Table 7: Measure UP 1 (M16-045) - Clinical effectiveness at week 16 (Adolescent)

Measure UP 1 (M16-045) Adolescent			**Upa 30 mg QD**	**Upa 15 mg QD**	**Placebo**	**References**
			(N=42)	**(N=42)**	**(N=40)**	
Proportion of people achieving EASI 75						
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.2.3.1_
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.2.3.1_
	Week 24		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.1
All observed analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.1.3.1
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.1.3.1
	Week 24		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1

		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.1
Change in EQ-5D score from baseline						
Primary analysis	EQ-5D at Week 16		[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)						
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.1
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.1
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.1
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.1
All observed analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.1.3.1
		Week 16 -52	[redacted]	[redacted]		
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.1.3.1
		Week 16 -52	[redacted]	[redacted]		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis	Week 16	Any Rescue Medication	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1

		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2_1
	Baseline to Week 24					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
	Baseline to Week 52					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1

		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2_1
Abbreviations: DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib						

Table 8: Measure UP 1 (M16-045)- Baseline characteristics (Adolescent)

Characteristic	Upa 30 mg QD (N=42)	Upa 15 mg QD (N=42)	Placebo (N=40)	Reference
Mean age, years	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Race				
White, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Asian, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2

Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment				
OCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_1
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_1
TCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_1
TCI, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_1
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib				

d) MEASURE UP 2 (results yet to be published)

d1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 24 and 52, and later time points if available, please provide data on:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %);

Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);

Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 9 and 10.

Table 9: Measure UP 2 (M18-891) - Clinical effectiveness at week 16 (Adult population)

Measure UP 2 (M18-891) Adult systemic naïve			**First line**			**Second line**			**Reference**
			Upa 30 mg QD	**Upa 15 mg QD**	**Placebo**	**Upa 30 mg QD**	**Upa 15 mg QD**	**Placebo**	
			(N=178)	**(N=164)**	**(N=169)**	**(N=56)**	**(N=73)**	**(N=60)**	
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.2.1.2
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.2.1.2
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2

		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.1.2
Proportion of people achieving EASI 50 + ΔDLQI ≥4									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.1.1.2
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.1.1.2
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.1.2

Proportion of people achieving EASI 75								
			(N=189)	(N=168)	(N=178)	(N=58)	(N=75)	(N=64)	
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.2.2.2
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.2.2.2
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.2.2.2
Proportion of people achieving EASI 75									
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.1.2.2
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891_047 Table 1.1.2.2
	Week 24		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2

		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2
	Week 52		[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2
		Responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2
		Non responder at week 16	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 1.1.2.2
Change in EQ-5D score from baseline									
Primary analysis	EQ-5D at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_Section A
Proportion of people who discontinue treatment for any reason after achieving EASI 50 + ΔDLQI ≥4 (conditional discontinuation)									
			(N=178)	**(N=164)**		**(N=56)**	**(N=73)**		
Primary analysis	Responder at week 16	Week 16 – 24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.1.2
		Week 16 – 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.1.2
	Non responder at week 16	Week 16 – 24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.1.2
		Week 16 – 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.1.2
All observed analysis	Responder at week 16	Week 16 – 24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.1.2

		Week 16 – 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.1.2
	Non responder at week 16	Week 16 – 24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.1.2
		Week 16 – 52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.1.2
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)									
			(N=189)	**(N=168)**		**(N=58)**	**(N=75)**		
Primary analysis	Responder at week 16	Week 16 –24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.2.2
		Week 16 –52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.2.2
	Non-responder at week 16	Week 16 –24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.2.2
		Week 16 –52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.2.2.2
All observed analysis	Responder at week 16	Week 16 –24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.2.2
		Week 16 –52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.2.2
	Non-responder at week 16	Week 16 –24	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.2.2
		Week 16 –52	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 2.1.2.2

Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)									
Primary Analysis			**(N=189)**	**(N=168)**	**(N=178)**	**(N=58)**	**(N=75)**	**(N=64)**	
	Week 16								
		Any Rescue Medication							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		TCS High Potency							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		TCS Medium Potency							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		TCS Low Potency							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		TCI							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		Other Topical Therapy							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		Biologic systemic							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		Non-biologic Systemics							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		Other Systemic therapy							UK_NICE_HTA_045_891_047 Table 3.1.1.2
		Phototherapy							UK_NICE_HTA_045_891_047 Table 3.1.1.2
	Baseline to Week 24								
		Any Rescue Medication			NA			NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS High Potency			NA			NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS Medium Potency			NA			NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS Low Potency			NA			NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCI			NA			NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2

		Other Topical Therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Biologic systemic	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Non-biologic Systemics	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Other Systematic therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Phototherapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
	Baseline to week 52								
		Any Rescue Medication	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS High Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS Medium Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCS Low Potency	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		TCI	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Other Topical Therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Biologic systemic	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Non-biologic Systemics	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Other Systematic therapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
		Phototherapy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA	UK_NICE_HTA_045_891_047 Table 3.2.1.2
Abbreviations: DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib									

Table 10: Measure UP 2 (M18-891) - Baseline characteristics (Adult population)

	First line			Second line			Reference
Characteristic	**Upa 30 mg QD (N=189)**	**Upa 15 mg QD (N=168)**	**Placebo (N=178)**	**Upa 30 mg QD (N=58)**	**Upa 15 mg QD (N=75)**	**Placebo (N=64)**	
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Gender, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Race							
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2

Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK/request M18-891 Table 14.1_2.8.2
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment							
OCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891 Table 5.1_2
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891 Table 5.1_2
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891 Table 5.1_2
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045_891 Table 5.1_2
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib							

d2) Adolescents

Subgroup of adolescents (aged ≥12 years to <18 years) who received upadacitinib as a systemic treatment. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 11 and 12.

Table 11: Measure UP 2 (M18-891)- Clinical effectiveness at week 16 (Adolescent)

Measure UP 2 (M18-891) Adolescent			**Upa 30 mg QD**	**Upa 15 mg QD**	**Placebo plus TCS**	**References**
			(N=35)	**(N=33)**	**(N=36)**	
Proportion of people achieving EASI 75						
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.2.3.2
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.2.3.2
	Week 24		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2

		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.2.3.2
All observed analysis	Week 8		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.1.3.2
	Week 16		[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 1.1.3.2
	Week 24		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
	Week 52		[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
		Responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
		Non responder at week 16	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 1.1.3.2
Change in EQ-5D score from baseline						
Primary analysis	EQ-5D at Week 16		[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Proportion of people who discontinue treatment for any reason after achieving EASI 75 (conditional discontinuation)						
Primary analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.2
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.2
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.2
		Week 16 -52	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.2.3.2
All observed analysis	Responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.1.3.2
		Week 16 -52	[redacted]	[redacted]		
	Non responder at week 16	Week 16 - 24	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 2.1.3.2
		Week 16 -52	[redacted]	[redacted]		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						

Primary analysis	Week 16	Any Rescue Medication	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		TCS High Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		TCS Medium Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		TCS Low Potency	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		TCI	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		Other Topical Therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		Biologic systemic	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		Non-biologic Systemics	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		Other Systemic therapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
		Phototherapy	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 3.1.2.2
	Baseline to Week 24					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2

		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
	Baseline to Week 52					
		Any Rescue Medication	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS High Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS Medium Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCS Low Potency	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		TCI	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Other Topical Therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Biologic systemic	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Non-biologic Systemics	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Other Systemic therapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
		Phototherapy	[redacted]	[redacted]	NA	UK_NICE_HTA_045-891-047 Table 3.2.2.2
Abbreviations: DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib						

Table 12: Measure UP 2 (M18-891) - Baseline characteristics (Adolescent)

Characteristic	Upa 30 mg QD (N=35)	Upa 15 mg QD (N=33)	Placebo (N=36)	Reference
Mean age, years	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Race				
White, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Asian, n (%)	[redacted]	[redacted]	[redacted]	T_14.1_4.2
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	T_14.1_5.2
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	NICE_MTA_CLQ_SectionA
Prior treatment				
OCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_2
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_2
TCS, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_2

TCI, n (%)	[redacted]	[redacted]	[redacted]	UK_NICE_HTA_045-891-047 Table 5.2_2
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib				

e) HEADS UP (results yet to be published)

e1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Answer: Data for these questions can be found in Tables 13 and 14.

Table 13: Heads UP (M16-046) - Clinical effectiveness at week 16 (Adult population)

Heads UP (M16-046) Adult systemic naïve			**First line**		**Second line**		**Reference**
			DUPI 300mg Q2W (N=288)	**Upa 30 mg QD (N=298)**	**DUPI 300mg Q2W (N=56)**	**Upa 30 mg QD (N=50)**	
Proportion of people achieving EASI 75							
Primary analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.2
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.2
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.2
		Response at Week 16	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.2
		Non-responder at Week 16	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.2
Proportion of people achieving EASI 75							
Observed analysis	Week 8		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.1
	Week 16		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.1
	Week 24		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.1
		Response at Week 16	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.1
		Non-responder at Week 16	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 1.1
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)							
Primary analysis	Baseline to Week 16						
	Any Rescue Medication		[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 3

	TCS High Potency					UK-NICE-HTA_M16046 Table 3
	TCS Medium Potency					UK-NICE-HTA_M16046 Table 3
	TCS Low Potency					UK-NICE-HTA_M16046 Table 3
	TCI					UK-NICE-HTA_M16046 Table 3
	Other Topical Therapy					UK-NICE-HTA_M16046 Table 3
	Biologic systemic					UK-NICE-HTA_M16046 Table 3
	Non-biologic Systemics					UK-NICE-HTA_M16046 Table 3
	Other Systemic therapy					UK-NICE-HTA_M16046 Table 3
	Phototherapy					UK-NICE-HTA_M16046 Table 3
	Baseline to Week 24					
	Any Rescue Medication					UK-NICE-HTA_M16046 Table 3
	TCS High Potency					UK-NICE-HTA_M16046 Table 3
	TCS Medium Potency					UK-NICE-HTA_M16046 Table 3
	TCS Low Potency					UK-NICE-HTA_M16046 Table 3
	TCI					UK-NICE-HTA_M16046 Table 3
	Other Topical Therapy					UK-NICE-HTA_M16046 Table 3
	Biologic systemic					UK-NICE-HTA_M16046 Table 3
	Non-biologic Systemics					UK-NICE-HTA_M16046 Table 3
	Other Systemic therapy					UK-NICE-HTA_M16046 Table 3

	Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 3
Abbreviations: DUPI: Dupilumab, EASI: Eczema area and severity, Q2W: Once every 2 weeks, QD: Once daily, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid						

Table 14: Heads UP (M16-046) - Baseline characteristics (Adult population)

	First line		Second line		Reference
Characteristic	**DUPI 300mg Q2W (N=288)**	**Upa 30 mg QD (N=298)**	**DUPI 300mg Q2W (N=56)**	**Upa 30 mg QD (N=50)**	
Mean age, years	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Gender, n (%)					
Male	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Race					
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31

Baseline IGA score of 4	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	M16046-MAAP-UK Table 31
Prior treatment					
OCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 5
Immunosuppressant, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 5
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 5
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	UK-NICE-HTA_M16046 Table 5
AD: Atopic dermatitis, BSA: Body surface area, DLQI: Dermatology life quality index, DUPI: Dupilumab, EASI: Eczema area and severity, EQ-5D: European quality of life five dimension, IGA: Investigator global assessment, NRS: Numerical rating scale, OCS: Oral corticosteroid, PEOM: Patient-oriented eczema measure, Q2W: Once every 2 weeks, QD: Once daily, SCORAD: SCORing atopic dermatitis, SD: Standard deviation, TCI: Topical calcineurin inhibitor, TCS: Topical corticosteroid, UPA: Upadacitinib					

f) Phase II dose finding study

f1) Adults

Subgroups of adults (aged ≥18 years) who received upadacitinib as a first-line systemic treatment or after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders for both the primary analysis and the all observed analysis:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

Answer: Results from the AD Up, Measure Up 1, Measure Up 2 and Heads Up were prioritised for this response

Clinical effectiveness at week 16

	First line			Second line		
	Upa 30 mg QD (N=)	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4						
Primary analysis						
All observed analysis						

Proportion of people achieving EASI 75						
Primary analysis						
All observed analysis						
Change in EQ-5D score from baseline						
Primary analysis						
All observed analysis						
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)						
Primary analysis						
All observed analysis						
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)						
Primary analysis						
All observed analysis						
Number of days free from TCS during treatment						
Primary analysis						
All observed analysis						
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCS, topical corticosteroid; Upa, upadacitinib.						

Baseline characteristics

	First line			Second line		
Characteristic	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**	**Upa 30 mg QD (N=)**	**Upa 15 mg QD (N=)**	**Placebo (N=)**
Mean age, years						

Gender, n (%)						
Male						
Mean duration of AD, years (SD)						
Race						
White, n (%)						
Black or African American, n (%)						
Asian, n (%)						
Mean EASI score (SD)						
Baseline IGA score of 4						
Mean DLQI score (SD)						
Mean SCORAD score (SD)						
Mean peak pruritus NRS score (SD)						
Mean % BSA affected (SD)						
Mean baseline EQ-5D Score (SD)						
Prior treatment						
OCS, n (%)						
Immunosuppressant, n (%)						
TCS, n (%)						
TCI, n (%)						
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Upa, upadacitinib.						

A2. Please clarify the discrepancy in the number of adolescents included in the clinical effectiveness analysis of upadacitinib 30 mg plus TCS ([redacted]) in AD UP versus the number of adolescents for whom baseline characteristics are reported ([redacted]; tables presented in a2).

Answer: Apologies, this is a typographical error. This should read [redacted] throughout. This has been corrected in the table above

A3. The CS states the choice of dose of upadacitinib , either 15 mg or 30 mg QD for adults, would be decided [redacted]. Please could the company expand on [redacted] they anticipate would influence choice of dose. For example, [redacted]?

Answer: Upadacitinib has recently received marketing authorisation for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

In adults the recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation.

- A dose of 30 mg once daily may be appropriate for patients with high disease burden.
- A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily.
- The lowest effective dose for maintenance should be considered.

For patients ≥ 65 years of age, the recommended dose is 15 mg once daily.

Adolescents (from 12 to 17 years of age)

The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

(Latest SmPC can be accessed here: https://www.medicines.org.uk/emc/search?q=rinvoq)

Section B: Clarification on cost-effectiveness data

[Add subheadings as needed]

B1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

[Add subheadings as needed]

C1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section D. References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

10 September, 2021

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic dermatitis HE EAG CQs upadacitinib (ACIC) Final 10Sep21	V1.0	Yes	10/09/21

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A; second-line systemic treatment).

Based on the company submission (CS) for upadacitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning upadacitinib as a treatment option at both first- and second- line in the management of AD for adolescents and adults. The EAG's systematic literature review has identified the key studies evaluating upadacitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which upadacitinib, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating upadacitinib and, therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA, or were intolerant of or experienced a medical complication of CsA.

The EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England (the "all observed" analysis in the CS).

Health related quality of life data

For all utility analyses requested below, please provide the data and utility calculations in a separate excel file.

B1. Please provide the following requested data from Measure UP 1 & 2 (all-observed) for monotherapy patients on upadacitinib and placebo:

a) **Adults second-line systemic treatment (adult-exposed)** – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52. If data are available for timepoints after week 52, please provide these data.

b) **Adolescents** – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52. If data are available for timepoints after week 52, please provide these data.

Answer: Data for these questions can be found in the accompanying spreadsheet Tab MTA_B1_2_Tables. The Question B1 tab of the spreadsheet provides the data in Tables 1 and 2 in Excel format

CsA exposure status can be found in the header row whereby Y= CsA exposed.

The data for Table 1 is in column N/O for 15 mg dose, R/S for 30 mg dose and V/W for placebo in the accompanying spreadsheet and marked in yellow. Please note that placebo data was not collected beyond week 16 and data for upadacitinib is not available beyond week 52.

Table 1: Adult second-line monotherapy – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52

Visit	Upadacitinib 15 mg		Upadacitinib 30 mg		Placebo	
	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]		
Week 52	[redacted]	[redacted]	[redacted]	[redacted]		

Data for question b) can be found in Table 2, data can be found in columns F to K and are marked in yellow.

Table 2: Adolescent monotherapy – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52

Visit	Upadacitinib 15 mg		Placebo	
	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility
Baseline (0)	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]		
Week 52	[redacted]	[redacted]		

B2. Please provide the following requested data from AD UP for *combination* patients on upadacitinib and placebo:

a) **Adults second-line systemic treatment (adult-exposed)** – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52. If data are available for timepoints after week 52, please provide these data.

b) **Adolescents** – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52. If data are available for timepoints after week 52, please provide these data.

c) **Adults first-line systemic treatment (adult-eligible)** – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52. Please provide results for both the full and restricted populations separately. If data are available for timepoints after week 52, please provide these data.

Answer: Data for these questions can be found in the accompanying spreadsheet Tab MTA_B1_2_Tables. The Question B2 tab of the spreadsheet provides the data in Tables 3 to 5 below in Excel format

CsA exposure status can be found in the header row whereby Y= CsA exposed and N= CsA naïve.

The data for Table 3 is in column N/O for 15 mg dose, R/S for 30 mg dose and V/W for placebo in the accompanying spreadsheet and marked in yellow. Please note that placebo data was not collected beyond week 16 and data for upadacitinib is not available beyond week 52.

Table 3: Adult second-line combination therapy – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52

Visit	Upadacitinib 15 mg		Upadacitinib 30 mg		Placebo	
	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility
Baseline (0)	[redacted]					
Week 4	[redacted]					
Week 16	[redacted]					
Week 32	[redacted]					
Week 52	[redacted]					

Data for question b) can be found in Table 4, data can be found in columns F to K and are marked in yellow.

Table 4: Adolescent combination therapy – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52

Visit	Upadacitinib 15 mg		Upadacitinib 30 mg		Placebo	
	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility
Baseline (0)	[redacted]					
Week 4						
Week 16						
Week 32						
Week 52						

The data for Table 5 is in column L/M for 15 mg dose, P/Q for 30 mg dose and T/U for placebo in the accompanying spreadsheet and marked in yellow.

Table 5: Adult first-line combination therapy – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 4, 16, 32, and 52

Visit	Upadacitinib 15 mg		Upadacitinib 30 mg		Placebo	
	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility	No of patients	mean ED-5D utility
Baseline (0)	[redacted]					
Week 4						
Week 16						
Week 32						
Week 52						

B4. Please clarify if the utility equation on page 165 of the CS is used to estimate utility values and provide an example of how it is used. If this utility equation is not used, please provide the equation that is.

The utility equation on page 165 of the upadacitinib submission was outdated and was not used to derive the health state utility values (HSUVs), however, the approach described below was used in the economic model.

Health-related quality of life

The EQ-5D-5L was used to capture health related quality of life (HRQoL) data in Measure UP 1, Measure UP 2 and AD UP trials at baseline, week 4, week 16, week 32, week 52 and every 24 weeks post the week 52 visit. The Heads UP trial did not collect HRQoL data. In line with NICE guidance, we have mapped the EQ-5D-5L responses onto the EQ-5D-3L value set using the van Hout *et al.* 2012 algorithm[1].

Health state utility data were then derived for each population (adult systemic-eligible, adult systemic-exposed and adolescent systemic-eligible) and response

outcome (Eczema Area and Severity Index [EASI] 50 + DLQI [Dermatology Life Quality Index] ≥4, EASI 75 and EASI 50).

The trial data was used directly to inform the baseline utility values and the utility value at the week 16 assessment point. Utility values beyond the week 16 assessment point in the decision were derived through regression analysis. A description of the regression analysis and the utility values applied in the short-term decision tree and long-term Markov model are given in the following subsections.

B5. The EAG has found it difficult to interpret the company's description of identifying the regression model and covariates best-fit to predict utility. The EAG is of the opinion that the regression model is identified first, then covariates are identified which have a significant effect on the estimates from the regression model, and not the reverse as suggested by the company.

a) In order to fully understand what the company has done, please provide a step-by-step guide

Answer: Model selection was performed using backward selection in line with Section B, question B6, in the NICE Multiple Technology Appraisal Clarification Questions.

Utility at baseline or week 16 was analysed using a linear regression model. In line with the original company submission, covariates included in the model selected procedure included age (AGE), baseline IGA (BLVIGA), baseline EASI (BLEASI), gender (SEX), TCI/TCS intolerance (PIGRP) and treatment (TRT01P) where applicable. Baseline utility (CW_UK_BASE) was also included when analysing week 16 values. In addition, week 16 response status according to EASI 75 (EASI75_AO_Week16) or EASI 50 +DLQI4 (EASI50DLQI_AO_Week16Y) was included where relevant. Model selection was performed based on the significance of model coefficients at a pre-specified threshold of $p<0.1$.

Covariates reaching the level of pre-specified significance following model selection were summarised. When reporting results by treatment and/or response status, respective covariates were added to the model if not retained by the backward

selection process. For this final model, coefficient estimates and associated standard errors and p values were reported.

The least squared means approach using equal weights for covariates across groups was used to estimate the mean utility and associated standard error as requested in question B6 Table 9 and Table 10.

Analyses were conducted in R version 3.6.0. The ‘fastbw’ function (‘rms’ package) was used to perform backward selection. ‘Glm’ and ‘lm’ functions were used to perform linear regression models. ‘lsmeans’ (‘rms’ package) and ‘predict’ functions were used to generate least squared means. The full analysis code is presented below in Figure 1.

Figure 1: Full analysis code for linear regression model

```
#DEFINE FUNCTION
utilitymodel<-function(datain=NULL,depvar=NULL,forcevars=NULL,selectvars=NULL,lsby=NULL,totalcolname=NULL,lsout=NULL){
  model<-Glm(as.formula(paste(depvar,"~",paste(c(forcevars,selectvars),collapse="+"),sep= "")),family=gaussian,datain)
  selectedModel<-fastbw(fit=model, rule="p", sls=0.10)
  modelvars<-c(forcevars,selectedModel$names.kept[!selectedModel$names.kept %in% forcevars])
  finalModel<-lm(paste(depvar,"~",paste(modelvars, collapse="+"),sep = ""),datain)
  if (length(lsby)>0) {
    if (length(totalcolname)>0){
      outModel<-cbind("Total", summary(lsmeans(finalModel,lsby,weight="equal"))[1:(length(lsby)+2)],
                      paste(noquote(selectedModel$names.kept), collapse=", "),paste(noquote(modelvars), collapse=", "))
      colnames(outModel)=c(totalcolname,lsby,"Mean","SE","Significant variables (p<0.1)","Included in model")
      outModelDetail<-cbind("Total",rownames(summary(finalModel)$coefficients),summary(finalModel)$coefficients)
      colnames(outModelDetail)=c(totalcolname,"Parameter",colnames(summary(finalModel)$coefficients))
    } else {
      outModel<-cbind(summary(lsmeans(finalModel,lsby,weight="equal"))[1:(length(lsby)+2)],
                      paste(noquote(selectedModel$names.kept), collapse=", "),paste(noquote(modelvars), collapse=", "))
      colnames(outModel)=c(lsby,"Mean","SE","Significant variables (p<0.1)","Included in model")
      outModelDetail<-cbind(lsby[1],rownames(summary(finalModel)$coefficients),summary(finalModel)$coefficients)
      colnames(outModelDetail)=c(lsby[1],"Parameter",colnames(summary(finalModel)$coefficients))}
  }else {
    finalModel_pred<-(predict(finalModel,se.fit=TRUE,interval="confidence"))
    outModel<-cbind("Total",mean(finalModel_pred$fit),mean(finalModel_pred$se.fit),
                    paste(noquote(selectedModel$names.kept), collapse=", "),paste(noquote(modelvars), collapse=", "))
    colnames(outModel)=c(totalcolname,"Mean","SE","Significant variables (p<0.1)","Included in model")
    outModelDetail<-cbind("Total",rownames(summary(finalModel)$coefficients),summary(finalModel)$coefficients)
    colnames(outModelDetail)=c(totalcolname,"Parameter",colnames(summary(finalModel)$coefficients))
  }

  D<-list(a=outModel,b=outModelDetail)
  names(D) <- c(lsout,paste0(lsout,"_detail"))
  list2env(D, envir = .GlobalEnv)
}
```

b) Please consider only including statistically significant coefficients in the regression models to estimate utility values (or provide the rationale for including non-statistically significant coefficients).

Answer: We can confirm in the revised regression analyses only statistically significant coefficients were considered in the regression models to estimate utility values.

B6. Please complete Table 9 and Table 10 below by running the following regression models:

a) Regression models according to TCS use:

   i. One which represents monotherapy treatment (including data from Measure UP 1 and Measure UP 2 for the all-observed population).

   ii. One which represents combination treatment (including data from AD UP for the all-observed population).

b) Regression models which include treatment arm as an additional covariate (regardless of statistical significance);

c) For each regression model, please provide the coefficient, standard error and p value for each covariate. Additionally, please consider only including

statistically significant coefficients in the regression models (except for the request to include treatment arm) to estimate utility values for these patients (or provide the rationale for including non-statistically significant coefficients);

d) If 52-week EQ-5D data from AD UP, Measure UP 1 and Measure UP 2 has become available, please incorporate this data in your response.

Answer: No EQ-5D data is collected for the placebo arm past the 16-week timepoint. Therefore, to maintain consistency and comparability between utility values estimates, analyses were conducted using 16-week data for all treatment arms.

Data for Table 6 and Table 7 is taken from the accompanying spreadsheet Tab MTA_B6_Tables.

Table 6: Mean utility values (standard error), adults

Adults	Monotherapy				Combination therapy			
	Upa 15 mg	Upa 30 mg	Placebo	All patients	Upa 15 mg	Upa 30 mg	Placebo	All patients
First line population (as defined at the beginning of this letter)								
Baseline	[redacted]							
Week 16	[redacted]							
Responder (EASI 75)	[redacted]							
Non responder (EASI 75)	[redacted]							
Second line population (as defined at the beginning of this letter)								
Baseline	[redacted]							
Week 16	[redacted]							
Responder (EASI 75)	[redacted]							
Non responder (EASI 75)	[redacted]							
Responder (EASI 50 + DLQI 4)	[redacted]							
Non responder (EASI 50 + DLQI 4)	[redacted]							

EASI: Eczema Area and Severity Index, DLQI: Dermatology Life Quality Index

Table 7. Mean utility values (standard error), adolescents

Adolescents	Monotherapy		
	Upa 15 mg	Placebo	All patients
Baseline	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]

EASI: Eczema Area and Severity Index

The tables below provide information for question B6c. Data can be found on the accompanying spreadsheet Tab MTA_B6-details.

A key for the codes used in the Tables is provided below:

- TRT01P = 15 mg as treatment covariate
- TRT01PABT-494 30 MG QD = 30 mg as treatment covariate
- TRT01PPLACEBO = Placebo as treatment covariate
- BLVIGASevere = Baseline IGA severe
- BLEASI = Baseline EASI
- SEXM= Male
- AGE=Age
- CW_UK_BASE = Crosswalk UK baseline
- EASI75_AO_Week16Y = EASI 75 response at week 16
- EASI50DLQI_AO_Week16Y = EASI 50 + DLQI>4 at week 16

Table 8: First-line adult monotherapy – coefficient, standard error and p value for each covariate

TimePoint	Treatment	Parameter	Estimate	Std. Error	t value	Pr(>|t|)
Baseline	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLVIGASevere	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	SEXM	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLVIGASevere	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	SEXM	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]

Baseline	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLVIGASevere	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	EASI50DLQI_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]

EASI 50 + DLQI 4	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	Total	EASI50DLQI_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: First-line adult combination therapy – coefficient, standard error and p value for each covariate

Baseline	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLVIGASevere	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]

EASI 75	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Second-line adult combination therapy – coefficient, standard error and p value for each covariate

Baseline	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]

EASI 50 + DLQI 4	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	EASI50DLQI_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	Total	EASI50DLQI_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 50 + DLQI 4	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Total population adolescent monotherapy – coefficient, standard error and p value for each covariate

Baseline	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	TRT01P	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	AGE	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	Total	BLEASI	[redacted]	[redacted]	[redacted]	[redacted]

EASI 75	TRT01P	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PABT-494 30 MG QD	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	TRT01PPLACEBO	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	TRT01P	AGE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	EASI75_AO_Week16Y	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	CW_UK_BASE	[redacted]	[redacted]	[redacted]	[redacted]
EASI 75	Total	AGE	[redacted]	[redacted]	[redacted]	[redacted]

Section C: Textual clarification and additional points

C2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

References

1. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15**(5): 708-15.

2. Furnival GM, Wilson RW. Regressions by Leaps and Bounds. *Technometrics* 1974; **16**(4): 499-511.

3. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**(5): 509-18.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

August, 2021

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to severe-atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A; second-line systemic treatment).

Based on the company submission (CS) for tralokinumab, the Evidence Assessment Group (EAG) has assumed that the company is positioning tralokinumab as a treatment option at second line in the management of AD for adults. The EAG's systematic literature review has identified the key studies evaluating tralokinumab in the treatment of moderate-to-severe AD, some of which present results for a population in which tralokinumab, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment.

The EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. However, the EAG might carry out sensitivity analyses for a population from which those who receive rescue therapy are censored regardless of treatment discontinuation, referred to as the composite estimand in the CS.

Where possible, the EAG has sourced relevant data from the CS for the relevant population (ECZTRA 7 and ECZTRA 7-like), specifying the time point for reporting of results. Please confirm that the extracted data are correct. If data are available for additional time points of clinical assessment, please complete separate clinical effectiveness tables for the time points.

Data on clinical effectiveness

A1. Please complete the tables below for individual studies to provide data on the outcomes specified in the protocol for population of interest, together with baseline characteristics of the patients from which data on clinical effectiveness are derived.

LEO response:

As the EAG amass a common data set across comparators for the purposes of synthesis, we wish to reiterate the sources of potential heterogeneity in the evidence base that we flagged in our original STA submission.

The results of any NMA based on the available phase 2 and phase 3 trials of the included comparators should be interpreted while considering several sources of potential heterogeneity (section B.2.9.4 [page 93] of our original STA submission). Although the baseline characteristics of the patients are broadly similar across the included trials, important differences concerning study design have been highlighted. These include the eligibility criteria of the trials, the requirement for and duration of TCS washout, the type and administration of concomitant TCS used, the timing and frequency of follow-up and rules around rescue therapy, all of which could have a substantial impact on trial outcomes, with varying effects on active and control treatments. The impact of observed and unobserved differences is apparent, as variation in placebo response rates across the included studies was found to constitute an important source of heterogeneity and uncertainty. We submitted the results of a sensitivity analysis of the combination therapy network using a baseline-risk adjusted meta-regression model and although this cannot compensate for all

heterogeneity and uncertainty, we would strongly encourage the EAG to consider exploring such methods as part of their own evaluation.

We have provided data at all the timepoints requested in the tables below. We would like to reaffirm that week 8 was not an endpoint in any of the trials contained within the tralokinumab trial program, or in the tralokinumab NICE submission. It is proposed that patients' response to tralokinumab is assessed at week 16, in line with its license and the guidance for comparator treatments dupilumab and baricitinib.

We have grouped rescue therapy slightly differently than requested in this document, using the following categories: TCS, other topical, systemic steroid, systemic immunosuppressants. As discussed during the clarification meeting, this is in line with the way in which these data were reported for the clinical trials and ensures that all forms of rescue therapy are captured within the tables. The breakdown has only been provided at week 16, not at other timepoints.

ECZTRA 7[1] (results yet to be published in a journal)

a1) Adults

Trial population was adults (aged ≥18 years) who received tralokinumab plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For week 8, and later time points if available (data for week 16 and 26 are reported in the tables below), please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N; %)]).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

LEO response:

Due to time constraints and the volume of additional data requested, the requested data points at week 8 were not generated for the proportion of people achieving EASI 50 + ΔDLQI ≥4 or EASI 75 for the requested estimand (i.e. no censoring for receipt of rescue medication). Instead, we refer the EAG to Panel 26 of the ECZTRA

7 clinical study report (CSR) for the proportion of people achieving EASI 75 by visit, including week 8 using the composite estimand. We also refer the EAG to Figure 2.10 of the ECZTRA 7 CSR for the proportion of people discontinuing treatment by visit, including week 8.

Please note that TCS free days are only quoted for Week 0 to Week 26.

Clinical effectiveness at week 16

	Composite estimand		No censoring for receipt of rescue medication	
	Tralokinumab Q2W plus TCS (N=138)	**Placebo plus TCS (N=137)**	**Tralokinumab Q2W plus TCS (N=138)**	**Placebo plus TCS (N=137)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	[redacted]	[redacted]	[redacted]	[redacted]
TCS	[redacted]	[redacted]	[redacted]	[redacted]
Topical other	[redacted]	[redacted]	[redacted]	[redacted]
Systemic corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressants	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Please note that the proportion of patients who achieved an EASI 75 at week 26 in ECZTRA 7 was subject to a minor data input error. This was an error in the tralokinumab STA submission that were copied over into the clarification questions document. There were [redacted] patients who achieved an EASI 75 in the tralokinumab arm using the treatment policy estimand at week 26, not the [redacted] that was previously reported in the submission. This was a typographical error that did not affect any of the analyses.

Due to time constraints, some week 26 datapoints were only generated for the preferred estimand (i.e. no censoring for receipt of rescue medication). These include change in EQ-5D from baseline, proportion discontinuing treatment, proportion receiving rescue medication and number of TCS free days. For the proportion discontinuing treatment, the proportion receiving rescue medication and the number of TCS free days the figures quoted are not conditional on response at Week 16 (i.e. they are from Week 0 to Week 26)

Clinical effectiveness at week 26

	Composite estimand		**No censoring for receipt of rescue medication**	
	Tralokinumab Q2W plus TCS (N=138)	**Placebo plus TCS (N=137)**	**Tralokinumab Q2W plus TCS (N=138)**	**Placebo plus TCS (N=137)**
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD) among **EASI 75** responders at W16	-	-	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD) among **EASI 50 + ΔDLQI ≥4** responders at W16	-	-	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) – not conditional on response, data is from Week 0 to Week 26	-	-	[redacted]	[redacted]

(%)				
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) – not conditional on response, data is from Week 0 to Week 26 (%)	-	-	[redacted]	[redacted]
Number of days free from TCS during treatment – not conditional on response, data is from Week 0 to Week 26 (SD)	-	-	[redacted]	[redacted]
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.				

Baseline characteristics

Characteristic	**Tralokinumab Q2W plus TCS (N=140)**	**Placebo plus TCS (N=137)**
Median age, years (IQR)	[redacted]	[redacted]
Gender, n (%)		
Male	[redacted]	[redacted]
Median duration of AD, years (IQR)	[redacted]	[redacted]
Race		
White, n (%)	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]
Median EASI score (IQR)	[redacted]	[redacted]
Baseline IGA score of 4	[redacted][a]	[redacted]
Median DLQI score (IQR)	[redacted][b]	[redacted]
Median SCORAD score (IQR)	[redacted][a]	[redacted]
Median weekly average worst peak pruritus NRS score (IQR)	[redacted][b]	[redacted][c]
Median % BSA affected (IQR)	[redacted]	[redacted]
Mean baseline EQ-5D-3L score (SD) [N]	[redacted]	[redacted]
Prior treatment		

OCS, n (%)	[redacted]	[redacted]
Immunosuppressant, n (%)		
CsA (%)	[redacted]	[redacted]
Methotrexate (%)	[redacted]	[redacted]
Azathioprine (%)	[redacted]	[redacted]
Mycophenolate (%)	[redacted]	[redacted]
Other immunosuppressant (%)	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]

[a] Data missing for two patients.

[b] Data missing for three patients.

[c] Data missing for one patient.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

b) ECZTRA 3[2]

b1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For week 8, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N; %)]).

For time points beyond week 16, after which responders were re-randomised to tralokinumab Q2W plus TCS, tralokinumab Q4W plus TCS or placebo plus TCS, please complete separate clinical effectiveness table(s) reporting outcomes for the ECZTRA 7-like population, for the three treatment groups at week 24 and later time points and for both the composite estimand and the no censoring for receipt of rescue medication.

LEO response:

We have provided data at all the timepoints requested in the table below. We would like to reaffirm that week 8 and week 24 were not endpoints in ECZTRA 3, or in the tralokinumab STA submission. It is proposed that patients' response to tralokinumab is assessed at week 16, in line with its license and the guidance for comparator treatments dupilumab and baricitinib.

Due to time constraints, the requested datapoints at week 8 were not generated for the proportion of people achieving EASI 50 + ΔDLQI ≥4 or EASI 75 for the requested estimand (i.e., no censoring for receipt of rescue medication). Instead, we refer the EAG to Figure 2A and Figure S6 in the Silverberg 2021 publication of the ECZTRA 3 trial for the proportion of people achieving EASI 75 and EASI 50 by visit, respectively including week 8 using the composite estimand. We also refer the EAG to Figure 2.13 of the ECZTRA 3 CSR for the proportion of people discontinuing treatment by visit, including week 8.

Data for the EASI 50 + ΔDLQI ≥4 endpoint have been updated and are now slightly different from the data that were submitted as part of the STA. In the data previously submitted, the post-hoc analysis only included patients if they had a DLQI strictly greater than 4 at baseline. This has been subsequently amended to include patients who had a DLQI equal to 4 at baseline, increasing the sample of eligible patients. This brings the outcome in line with the analysis of the secondary endpoint ΔDLQI ≥4 which included only patients with baseline DLQI ≥4.

Data for the EASI 50 and DLQI≥4-pt change response definition are not available at week 24, as DLQI was not recorded at this timepoint within the trial. The same is true for EQ-5D. We have therefore provided data at the week 28 timepoint for these outcomes instead. All other outcomes are presented at week 24 as requested.

Due to time constraints, only outcomes assuming no censoring for receipt of rescue medication are presented at weeks 24 and 32 (trial endpoint).

Efficacy data were requested for the ECZTRA 7-like subgroup, including for the maintenance phase. Whilst we have provided these data, we caution using them in any formal analysis because they are underpowered. Further, we are not aware of any evidence or argumentation to suggest that the probability of maintaining a response within the ECZTRA 7-like subgroup differs from the all-patient population. For these reasons, we have provided the all-patient data alongside the ECZTRA 7-like data in maintenance and recommend using the former.

Due to time constraints, we have not been able to present discontinuation, days from free TCS or receipt of rescue medication at week 24, conditional on response at week 16. Neither is recorded as a time to event outcome, making it challenging and time consuming to report at interim timepoints. Outcomes have been reported for Week 16 and the end of the study for the proportion discontinuing treatment and days free from TCS. For the proportion requiring use of rescue therapy during treatment only Week 16 is reported.

Clinical effectiveness at week 16 – ECZTRA-7 like

	Composite estimand		No censoring for receipt of rescue medication	
	Tralokinumab Q2W plus TCS [redacted]	**Placebo plus TCS** [redacted]	**Tralokinumab Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	[redacted]	[redacted]	[redacted]	[redacted]
TCS (%)	[redacted]	[redacted]	[redacted]	[redacted]
Other topical (%)	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid (%)	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressant (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 24 – E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W plus TCS [redacted]	**Tralokinumab Q4W plus TCS** [redacted]	**Placebo plus TCS** [redacted]	**Tralokinumab Q2W plus TCS, EASI 75 responder at Week 16** [redacted]	**Tralokinumab Q4W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 **(WEEK 28) (%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD) **(WEEK 28)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	NR	NR	NR	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	NR	NR	NR	NR	NR	NR

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 32 – E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W plus TCS [redacted]	**Tralokinumab Q4W plus TCS** [redacted]	**Placebo plus TCS** [redacted]	**Tralokinumab Q2W plus TCS** [redacted]	**Tralokinumab Q4W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Baseline characteristics E7-like population

Characteristic	Tralokinumab Q2W plus TCS	Placebo plus TCS
Median age, years (IQR)		
Gender, n (%)		
Male		
Median duration of AD, years (IQR)		
Race		
White, n (%)		
Black or African American, n (%)		
Asian, n (%)		
Median EASI score (IQR)		
Baseline IGA score of 4		
Median DLQI score (IQR)		
Median SCORAD score (IQR)		
Median peak pruritus NRS score (IQR)		
Median % BSA affected (IQR)		
Mean baseline EQ-5D-3L score (SD) [N]		
Prior treatment		
OCS, n (%)		
Immunosuppressant, n (%)		
CsA (%)		
Methotrexate (%)		
Mycophenolate (%)		
Other immunosuppressant (%)		
TCI, n (%)		

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

c) ECZTRA 8[3] (results yet to be published in a journal)

c1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 26, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N; %)]).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %).

LEO response:

ECZTRA 8 is due to be completed in August 2021 and as such data are not yet available. Information on the ECZTRA 8 trial can be accessed using the link below.

https://clinicaltrials.gov/ct2/show/NCT04587453

d) ECZTRA 1[4]

d1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab monotherapy after inadequate response to, inability to tolerate, or contraindicated to CsA. For week 8, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N; %)]).

For time points beyond week 16, after which responders were re-randomised to tralokinumab Q2W, tralokinumab Q4W or placebo, please complete separate clinical effectiveness table(s) reporting outcomes for the ECZTRA 7-like population, for the three treatment groups at week 24 and later time points and for both the composite estimand and the no censoring for receipt of rescue medication.

LEO response:

We have provided data at all the timepoints requested in the table below. We would like to reaffirm that week 8 and week 24 were not endpoints in ECZTRA 1, or in the tralokinumab STA submission. It is proposed that patients' response to tralokinumab

is assessed at week 16, in line with its license and the guidance for comparator treatments dupilumab and baricitinib.

Due to time constraints, the requested datapoints at week 8 were not generated for the proportion of people achieving EASI 50 + ΔDLQI ≥4 or EASI 75 for the requested estimand (i.e. no censoring for receipt of rescue medication). Instead, we refer the EAG to Figure 1B and Figure S3 in the Wollenberg 2021 publication of the ECZTRA 1 trial for the proportion of people achieving EASI 75 and EASI 50 by visit, respectively, including week 8 using the composite estimand. We also refer the EAG to Figure 2.13 of the ECZTRA 1 CSR for the proportion of people discontinuing treatment by visit, including week 8.

Data for the EASI 50 + ΔDLQI ≥4 endpoint have been updated and are now slightly different from the data that were submitted as part of the STA. In the data previously submitted, the post-hoc analysis only included patients if they had a DLQI strictly greater than 4 at baseline. This has been subsequently amended to include patients who had a DLQI equal to 4 at baseline, increasing the sample of eligible patients. This brings the outcome in line with the analysis of the secondary endpoint ΔDLQI ≥4 which included only patients with baseline DLQI≥4.

Data for the EASI 50 + ΔDLQI ≥4 response definition are not available at week 24, as DLQI was not recorded at this timepoint within the trial. The same is true for EQ-5D. We have therefore provided data at the week 28 timepoint for these outcomes instead. All other outcomes are presented at week 24 as requested.

Due to time constraints, only outcomes assuming no censoring for receipt of rescue medication are presented at weeks 24 and 52 (trial endpoint). Efficacy data were requested for the ECZTRA 7-like subgroup, including for the maintenance phase. Whilst we have provided these data, we caution against using them in any formal analysis because they are underpowered. Further, we are not aware of any evidence or argumentation to suggest that the probability of maintaining a response within the ECZTRA 7-like subgroup differs from the all-patient population. For these reasons, we have provided the all-patient data alongside the ECZTRA 7-like data in maintenance and recommend using the former.

Due to time constraints, we have not been able to present discontinuation or receipt of rescue medication by week 24, conditional on response. Neither is recorded as a time to event outcome, making it challenging and time consuming to report at interim timepoints. Proportion discontinuing treatment has been reported for Week 16 and the end of the study and proportion of requiring use of rescue therapy during treatment has been reported at Week 16 only.

Since ECZTRA 1 is a monotherapy trial, the data for days free from TCS has been entered as not applicable.

Clinical effectiveness at week 16 – ECZTRA-7 like

	Composite estimand		No censoring for receipt of rescue medication	
	Tralokinumab Q2W [redacted]	**Placebo** [redacted]	**Tralokinumab Q2W** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	[redacted]	[redacted]	[redacted]	[redacted]
TCS (%)	[redacted]	[redacted]	[redacted]	[redacted]
Other topical (%)	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid (%)	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressant (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 24 - E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]	**Tralokinumab Q2W** [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 **(WEEK 28) (%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD) **(WEEK 28)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	NR	NR	NR	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 52 - E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]	**Tralokinumab Q2W** [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Baseline characteristics – ECZTRA-7 like

Characteristic	Tralokinumab Q2W	Placebo
Mean age, years (SD)		
Gender, n (%)		
Male		
Median duration of AD, years (IQR)		
Race		
White, n (%)		
Black or African American, n (%)		
Asian, n (%)		
Median EASI score (IQR)		
Baseline IGA score of 4		
Median DLQI score (IQR)		
Median SCORAD score (IQR)		
Median peak pruritus NRS score (IQR)		
Median % BSA affected (IQR)		
Mean baseline EQ-5D-3L score (SD) [N]		
Prior treatment		
OCS, n (%)		
Immunosuppressant, n (%)		
CsA (%)		
Methotrexate (%)		
Mycophenolate (%)		
Other immunosuppressant (%)		
TCS, n (%)		
TCI, n (%)		

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

e) ECZTRA 2[4]

e1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab monotherapy after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);

- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N; %)]).

For time points beyond week 16, after which responders were re-randomised to tralokinumab Q2W, tralokinumab Q4W or placebo, please complete separate clinical effectiveness table(s) reporting outcomes for the ECZTRA 7-like population, for the three treatment groups at week 24 and later time points and for both the composite estimand and the no censoring for receipt of rescue medication.

LEO Response:

We have provided data at all the timepoints requested in the table below. We would like to reaffirm that week 8 and week 24 were not endpoints in ECZTRA 2, or in the tralokinumab STA submission. It is proposed that patients' response to tralokinumab is assessed at week 16, in line with its license and the guidance for comparator treatments dupilumab and baricitinib.

Due to time constraints, the requested datapoints at week 8 were not generated for the proportion of people achieving EASI 50 + ΔDLQI ≥4 or EASI 75 for the requested estimand (i.e. no censoring for receipt of rescue medication). Instead, we refer the EAG to Figure 1B and Figure S3 in the Wollenberg 2021 publication of the ECZTRA 2 trial for the proportion of people achieving EASI 75 and EASI 50 by visit, respectively, including week 8 using the composite estimand. We also refer the EAG to Figure 2.15 of the ECZTRA 2 CSR for the proportion of people discontinuing treatment by visit, including week 8.

Data for the EASI 50 + ΔDLQI ≥4 endpoint have been updated and are now slightly different from the data that were submitted as part of the STA. In the data previously submitted, the post-hoc analysis only included patients if they had a DLQI strictly greater than 4 at baseline. This has been subsequently amended to include patients who had a DLQI equal to 4 at baseline, increasing the sample of eligible patients. This brings the outcome in line with the analysis of the secondary endpoint ΔDLQI ≥4 which included only patients with baseline DLQI≥4.

Data for the EASI 50 + ΔDLQI ≥4 change response definition are not available at week 24, as DLQI was not recorded at this timepoint within the trial. The same is true for EQ-5D. We have therefore provided data at the week 28 timepoint for these outcomes instead. All other outcomes are presented at week 24 as requested.

Due to time constraints, only outcomes assuming no censoring for receipt of rescue medication are presented at weeks 24 and 52 (trial endpoint) as these were the stated preference of the EAG.

Efficacy data were requested for the ECZTRA 7-like subgroup, including for the maintenance phase. Whilst we have provided these data, we caution against using them in any formal analysis because they are underpowered. Further, we are not aware of any evidence or argumentation to suggest that the probability of maintaining a response within the ECZTRA 7-like subgroup differs from the all-patient population.

Due to time constraints, we have not been able to present discontinuation or receipt of rescue medication by week 24, conditional on response. Neither is recorded as a time to event outcome, making it challenging and time consuming to report at interim timepoints. Proportion discontinuing treatment has been reported for Week 16 and the end of the study and proportion of requiring use of rescue therapy during treatment has been reported at Week 16 only.

Since ECZTRA 2 is a monotherapy trial, the data for days free from TCS has been entered as not applicable.

Clinical effectiveness at week 16 – ECZTRA-7 like

	Composite estimand		**No censoring for receipt of rescue medication**	
	Tralokinumab Q2W [redacted]	**Placebo** [redacted]	**Tralokinumab Q2W** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	[redacted]	[redacted]	[redacted]	[redacted]
TCS (%)	[redacted]	[redacted]	[redacted]	[redacted]
Other topical (%)	[redacted]	[redacted]	[redacted]	[redacted]
Systemic steroid (%)	[redacted]	[redacted]	[redacted]	[redacted]
Immunosuppressant (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 24 - E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W [redacted]	**Tralokinumab Q4W** [redacted]	**Tralokinumab Q2W** [redacted]	**Tralokinumab Q4W** [redacted]	**Tralokinumab Q2W** [redacted]	**Tralokinumab Q4W** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 **(WEEK 28) (%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD) **(WEEK 28)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	NR	NR	NR	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Clinical effectiveness at week 52 - E7-like and All-patient – No censoring for receipt of rescue medication

	E7-like (among EASI 75 responders at week 16)			All-patient (among EASI 75 responders at week 16)		
	Tralokinumab Q2W [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]	**Tralokinumab Q2W** [redacted]	**Tralokinumab Q4W** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI) (%)	NR	NR	NR	NR	NR	NR
Number of days free from TCS during treatment (SD)	NA	NA	NA	NA	NA	NA

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NA, not applicable; NR, not reported; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Baseline characteristics - E7-like

Characteristic	Tralokinumab Q2W	Placebo
Mean age, years (SD)		
Gender, n (%)		
Male		
Median duration of AD, years (IQR)		
Race		
White, n (%)		
Black or African American, n (%)		
Asian, n (%)		
Median EASI score (IQR)		
Baseline IGA score of 4		
Median DLQI score (IQR)		
Median SCORAD score (IQR)		
Median peak pruritus NRS score (IQR)		
Median % BSA affected (IQR)		
Mean baseline EQ-5D-3L score (SD) [N]		
Prior treatment		
OCS, n (%)		
Immunosuppressant, n (%)		
CsA (%)		
Methotrexate (%)		
Mycophenolate (%)		
Other immunosuppressant (%)		
TCS, n (%)		
TCI, n (%)		

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

f) ECZTRA 5[5]

f1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab monotherapy after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N;);
- Proportion of people achieving EASI 75 (n/N;);
- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N;)]).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N;);
- Proportion of people achieving EASI 75 (n/N;).

LEO response:

The number of ECZTRA 7-like patients in the ECZTRA 5 study was [redacted], just [redacted] of all randomised patients. The study was designed to assess whether treatment with tralokinumab can affect the body's immune response to vaccines.

Given limited time, we have presented only the baseline characteristics of all patients for reference. Further details regarding the study design, efficacy and safety outcomes are provided in the clinical study report uploaded as part of our response.

Baseline characteristics

	All patients	
Characteristic	**Tralokinumab Q2W (N=107)**	**Placebo (N=108)**
Mean age, years (SD)	[redacted]	[redacted]
Gender, n (%)		
Male	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]
Race		
White, n (%)	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]

Asian, n (%)	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]
Baseline IGA score of 4	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]
Mean BSA affected (SD)	[redacted]	[redacted]
Mean baseline EQ-5D score (SD)	[redacted]	[redacted]
Prior treatment		
OCS, n (%)	[redacted]	[redacted]
Immunosuppressant, n (%) Mycophenolate Cyclosporine Methotrexate Azathioprine Other	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

g) Phase IIb dose ranging study

g1) Adults

Subgroup of adults (aged ≥18 years) who received tralokinumab monotherapy after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N;);
- Proportion of people achieving EASI 75 (n/N;);
- Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study [(n/N;)]).

For time points beyond week 16, for the outcomes below, please report separately the number of people maintaining their response achieved at week 16 versus new responders:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N;);
- Proportion of people achieving EASI 75 (n/N;).

LEO response:

The Phase IIb dose ranging study was not powered to include analyses of an ECZTRA-7-like subgroup and efficacy was only assessed up to week 12. The remaining 10-week off-treatment follow-up period was purely to assess safety. Given limited time, we have been unable to generate the requested data. We refer the EAG to Wollenberg 2018 which presents data for this study.

Section B: Clarification on cost-effectiveness data

[Add subheadings as needed]

B1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

[Add subheadings as needed]

C1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section D. References

1. ClinicalTrials.gov. Tralokinumab in combination with topical corticosteroids in subjects with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine A (ECZTRA 7), 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03761537?term=tralokinumab&draw=2&rank=5. Date accessed: 2 Jun 2021.
2. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *British journal of dermatology* 2021; **184**: 450-63.
3. ClinicalTrials.gov. Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis (ECZTRA 8), 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04587453?term=tralokinumab&draw=2&rank=9. Date accessed: 2 Jun 2021.
4. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *British journal of dermatology* 2021; **184**: 437-49.
5. ClinicalTrials.gov. Vaccine Responses in Tralokinumab-Treated Atopic Dermatitis - ECZTRA 5 (ECZema TRAlokinumab Trial No. 5) (ECZTRA 5), 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03562377?term=tralokinumab&cond=Atopic+Dermatitis&draw=2&rank=7. Date accessed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

August, 2021

File name	Version	Contains confidential information	Date
[ID3960] CompanyResponses MTAAtopicdermatitisEAGCQs	**1**	**Yes**	**07/09/2021**

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to severe-atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A; second-line systemic treatment).

Based on the company submission (CS) for tralokinumab, the Evidence Assessment Group (EAG) has assumed that the company is positioning tralokinumab as a treatment option at second line in the management of AD for adults. The EAG's systematic literature review has identified the key studies evaluating tralokinumab in the treatment of moderate-to-severe AD, some of which present results for a population in which tralokinumab, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment.

The EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England.

Section B: Clarification on cost-effectiveness data

Before the suspension of STA ID3734 (tralokinumab for treating moderate to severe atopic dermatitis), Leo Pharma supplied the ERG with a response to clarification questions. The EAG assumes the data provided in the company's clarification response is still valid and will use the data provided in its analysis, unless otherwise advised by the company.

Clinical effectiveness data

B1. Please provide the treatment-emergent adverse events occurring in greater than 5% of patients in the tralokinumab trials

a) Please provide rates for each trial (ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7), treatment arm (tralokinumab Q2W, tralokinumab Q4W, placebo, tralokinumab Q2W + TCS, tralokinumab Q4W + TCS and placebo +TCS) and treatment period (initial and maintenance) separately

b) Please provide rates which pool the tralokinumab arms in the monotherapy trials (ECZTRA 1 and ECZTRA 2)

    i. Please provide separate analyses for the ECZTRA 7-like population.

c) Please provide rates which pool the tralokinumab arms in the combination trials (ECZTRA 7 and ECZTRA 3)

    i. Please provide separate analyses for the ECZTRA 7-like population.

d) Please clarify the time frame each adverse event rate represents and convert these to annual probabilities.

LEO response:

Given the short timeframe for response, the volume of data requested in parts a, b and c of this question and the request for calculations to be undertaken in order to respond to part d, we have presented all the requested data in a separate Excel file. In each worksheet, we present the treatment-emergent adverse events which occurred in >5% of patients in any arm of the trial. We present not only the proportion of patients experiencing the event, but the number of events occurring and the rate per 100 patient-years of exposure (rate / 100 PYE). As requested in part d of the question, we have provided the time frame represented and converted these to annual probabilities. We note, however, that the recurring nature of some events is best accounted for in terms of the rate. We therefore call attention to the approach to adverse events that we used in our submitted network meta-analysis and cost-effectiveness model, which compared treatments in terms of the rate of notable adverse events, rather than the proportion experiencing them at least once.

The data requested in question B1a are provided in the cited worksheets below. Data from ECZTRA 7 are presented for the entire 26-week treatment period. Data from ECZTRA 1, ECZTRA 2 and ECZTRA 3 are separated by initial and maintenance periods.

- B1a.ECZTRA1_initial_period
- B1a.ECZTRA1_maintenance_period
- B1a.ECZTRA2_initial_period
- B1a.ECZTRA2_maintenance_period
- B1a.ECZTRA3_initial_period
- B1a.ECZTRA3_maintenance_period
- B1a.ECZTRA7_initial_period

The data requested in question B1b are provided in the following worksheets, also separated by initial and maintenance phases, and with ECZTRA 7-like subgroup data:

- B1b.E1&E2_initial_period
- B1b.E1&E2_maintenance_period
- B1bi.E1&E2_initial_E7-like
- B1bi.E1&E2_maintenance_E7-like

The data requested in question B1c are provided in the below worksheets. Data through week 16 from ECZTRA 3 is combined with data through week 26 from ECZTRA 7 and presented for all patients as well as the ECZTRA 7-like subgroup. Because of the difference in timepoint, we did not convert the event probabilities to annual probabilities, though the rates per 100 patient-years of exposure is informative. We have also provided the ECZTRA 7-like subgroup breakdown for ECZTRA 3 during the initial and maintenance periods.

- B1c.E3&E7_initial
- B1ci.E3&E7_initial_CIC-IR
- B1ci.E3_initial_CIC-IR
- B1ci.E3_maintenance_E7-like

Additionally, in terms of the adverse event profile of comparators in this multiple technology appraisal, we would like to draw your attention to the Sep 1st, US FDA announcement that it requires revisions to the boxed warnings for JAK inhibitors tofacitinib, baricitinib and upadacitinib to include information about the risks of serious heart-related events, malignancy, blood clots and death.

The announcement follows the FDA's review of the final results of Pfizer's post-marketing study, ORAL Surveillance (1133), of tofacitinib in rheumatoid arthritis, which showed a higher rate of serious heart-related events at both doses compared to tumour necrosis factor blockers (TNF blockers).

There is evidence of dose-dependent increased risk of Major Adverse Cardiovascular Events (MACE) and all-cause mortality, and of non-dose-dependent increased risk for malignancy excluding nonmelanoma skin cancer (NSMC), at both tofacitinib doses when compared to treatment with TNF blockers. For MACE, the estimated hazard ratio and 95% CI associated with the combined tofacitinib regimens relative to TNF blockers were 1.33 (0.91, 1.94).

For malignancies excluding NMSC, the estimated hazard ratio and 95% CI associated with the combined Xeljanz regimens relative to TNF blockers were 1.48 (1.04, 2.09). The data showed evidence of a dose-dependent increased risk for MACE, all-cause mortality, and thrombosis at both doses of tofacitinib when compared to treatment with TNF blockers.

Additionally, the data showed evidence of a non-dose-dependent increased risk for malignancy excluding NMSC at both doses of tofacitinib when compared to TNF blockers.

While baricitinib and upadacitinib have not been studied in similar large safety clinical trials, the FDA considers this finding a JAK inhibitor class risk that would be shared by other JAK inhibitors.

The FDA has limited JAK inhibitor use to patients non-responsive or intolerant to anti-TNFs, within the currently FDA approved indications.

Finally, in Europe, this topic was also addressed by way of a Direct Healthcare Professional Communication for tofacitinib in agreement with EMA in March this year, followed by an update to the product information for tofacitinib in June. Following this update, tofacitinib should only be used in patients over 65 years of age, in patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors if no suitable treatment alternatives are available.

We bring this to the EAG's attention as it may have implications for what AEs are included in the economic model as well as how they are factored in given a lifetime horizon.

B2. On page 130 of the CS it states, "The annual rate of discontinuation from tralokinumab due to adverse events or lack of efficacy in ECZTEND was 2.6% among patients who achieved EASI 50 & ΔDLQI ≥ 4 in their parent study. The rate was similar when using other definitions of response, so the same discontinuation rate was used across all response definitions." Please fill out the below table by exploring:

a) the annual probability of discontinuation using the EASI 75 definition of response;

b) all reasons for discontinuation (e.g. adding patient or physician preference);

c) the ECZTRA-7 like population in ECZTEND;

d) For each annual probability please provide the mean, 95% confidence interval and n/N (n/N as per the rate taken from the trial).

LEO response:

Please note that we have used a more precise method to estimate annual discontinuation within ECZTEND. This leads to an annual discontinuation rate of 2.3% due to adverse events or lack of efficacy, instead of the 2.6% previously reported, for patients who achieved an EASI 50 and ΔDLQI≥4.

Table 1. Annual probability of discontinuation from tralokinumab

Population	Discontinuation due to adverse events or lack of efficacy		All reasons for discontinuation	
	EASI 50 + DLQI 4	EASI 75	EASI 50 + DLQI 4	EASI 75

Full population in ECZTEND (%) [95% CI]	[redacted] (2.3%)	[redacted]	[redacted]	[redacted]
ECZTRA-7 like population in ECZTEND	[redacted]	[redacted]	[redacted]	[redacted]

Health related quality of life data

For all utility analyses requested below, please provide the data and utility calculations in a separate excel file.

B3. The EAG would like the company to perform the following monotherapy analyses of EQ-5D-5L data (mapped to EQ-5D-3L):

a) **For all patients from EZCTRA 1 & 2 (all-observed data set), please run the MMRM regression excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. Please use regression inputs for the EZCTRA 7-like population of EZCTRA 1 & 2 (all-observed data set).**

   i. **Please run the same analysis, where only statistically significant covariates are included in the regression.**

b) **For the ECZTRA 7-like subgroup from EZCTRA 1 & 2 (all-observed data set), please run the MMRM regression excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. Please use regression inputs for the EZCTRA 7-like population of EZCTRA 1 & 2 (all-observed data set).**

   i. **Please run the same analysis, where only statistically significant covariates are included in the regression.**

c) **Please fill out the below table for each regression requested in B3 a & b. Please provide mean utility values and standard errors. To obtain utility values that are non-treatment specific, please explore models without a treatment covariate.**

LEO response:

Due to the time constraint and volume of additional analysis requested, we have performed a subset of the analyses, focusing on those that were likely to be most relevant. For parts a and b, we ran only the analysis requested in subsection i, focusing on the statistically significant covariates of the MMRM regression after excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. MMRM regressions were run for the initial period and maintenance periods separately. Please note that the maintenance period regressions are based on less data than the initial period due to the fact that only initial phase tralokinumab responders could be included. Limiting the regression to the ECZTRA 7-like population (part b) further reduced the amount of data included. The maintenance period regression analyses are therefore associated with a high degree of uncertainty.

To estimate initial period health state utility values, we used the ECZTRA 7-like population of ECZTRA 1 & 2. Baseline values (age, proportion male, baseline EASI and EQ-5D scores) were based on the mean across all ECZTRA 7-like patients. Mean change from baseline in EASI score was generated for each treatment and broken down by response status at the end of the initial period using the treatment policy estimand, which is consistent with the all-observed data set.

For the maintenance period we used inputs from the all randomised patient population because the ECZTRA 7-like population was too small to inform several parameters, particularly among those losing response between week 16 and 52. In order to generate an internally consistent set of health state utility values for the EAG, we used common baseline EASI and EQ-5D scores across the arms, set equal to those generated from the initial phase analyses for all EASI 75 responders at week 16, regardless of treatment received.

Based on the design of the ECZTRA 1 & 2 trials, only patients who achieved an EASI 75 at week 16 on tralokinumab Q2W were eligible for inclusion and re-randomisation in the maintenance period. For this reason, we could not generate utility values for the EASI 50 + ΔDLQI≥4 response definition after week 16. Therefore, only utility values for patients sustaining or losing EASI 75 response at week 52 are presented.

Complete results of the regression analyses, including variance-covariance matrices, as well as baseline and mean change inputs are provided in a separate Excel file (Question_B3&B4). These were synthesised to produce the mean health state utility values presented in the following tables. We have not presented standard errors for these values as their uncertainty is a product of the underlying uncertainty in the regression outputs and independent variable inputs.

Table 2 presents the utility values generated in response to question B3ai and

Table 3 presents the results for question B3bi. Table 4 and Table 5 present the same analyses, but exclude the treatment covariate from the regression (B3c).

Table 2: B3ai EZCTRA 1 & 2 (all-observed data set) MMRM utility regression in the All-patient population, with EZCTRA 7-like inputs from EZCTRA 1 & 2 (all-observed data set).

Adults	Monotherapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 3: B3bi EZCTRA 1 & 2 (all-observed data set) MMRM utility regression in the ECZTRA-7-like subgroup, with EZCTRA 7-like inputs from EZCTRA 1 & 2 (all-observed data set).

Adults	Monotherapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 4: B3c.ai EZCTRA 1 & 2 (all-observed data set) MMRM utility regression in the All-patient population, with EZCTRA 7-like inputs from EZCTRA 1 & 2 (all-observed data set), no treatment effect.

Adults	Monotherapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]

Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 5: B3c.bi EZCTRA 1 & 2 (all-observed data set) MMRM utility regression in the ECZTRA-7-like subgroup, with EZCTRA 7-like inputs from EZCTRA 1 & 2 (all-observed data set), no treatment effect.

Adults	Monotherapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

B4. The EAG would like the company to perform the following combination therapy analyses of EQ-5D-5L data (mapped to EQ-5D-3L):

a) For all patients from EZCTRA 3 & 7 (all-observed data set), please run the MMRM regression excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. Please use regression inputs for the ECZTRA 7 and EZCTRA 7-like population of EZCTRA 3 (all-observed data set).

i. **Please run the same analysis, where only statistically significant covariates are included in the regression.**

b) **For the ECZTRA 7 and EZCTRA 7-like population of EZCTRA 3 (all-observed data set), please run the MMRM regression excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. Please use regression inputs for the ECZTRA 7 and EZCTRA 7-like population of EZCTRA 3 (all-observed data set).**

   i. **Please run the same analysis, where only statistically significant covariates are included in the regression.**

c) **For all patients from ECZTRA 7 (all-observed data set), please run the MMRM regression excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. Please use regression inputs for the ECZTRA 7 and EZCTRA 7-like population of EZCTRA 3 (all-observed data set).**

   i. **Please run the same analysis, where only statistically significant covariates are included in the regression.**

d) **Please fill out the below table for each regression requested in B4 a, b & c. Please provide mean utility values and standard errors. To obtain utility values that are non-treatment specific, please explore models without a treatment covariate.**

LEO response:

Due to the time constraint and volume of additional analysis requested, we have performed a subset of the analyses, focusing on those that were likely to be most relevant. For parts a, b and c we ran only the analysis requested in subsection i, focusing on the statistically significant covariates of the MMRM regression after excluding the worst pruritus score and the interaction term for EASI score and worst pruritus. MMRM regressions were run for the initial period and maintenance periods separately, where appropriate. Please note that the maintenance period regressions are based on less data than the initial period due to the fact that only initial phase tralokinumab responders could be included. Limiting the regression to the ECZTRA 7-like population (part b) further reduced the amount of data included. The maintenance period regression analyses are therefore associated with a high degree of uncertainty.

To estimate initial period health state utility values, we used the ECZTRA 7 and ECZTRA 7-like population of ECZTRA 3. Baseline values (age, proportion male, baseline EASI and EQ-5D scores) were based on the mean across all ECZTRA 7-like patients. Mean change in EASI score from baseline was generated for each treatment and broken down by response status at the end of the initial period using the treatment policy estimand, which is consistent with the all-observed data set.

For the maintenance period we used inputs from the all randomised patient population because the ECZTRA 7-like population was too small to inform several parameters, particularly among those losing response between week 16 and 32. In order to generate an internally consistent set of health state utility values for the EAG, we used common baseline EASI and EQ-5D scores across the arms, set equal to those generated from the initial phase analyses for all EASI 75 responders at week 16, regardless of treatment received.

Based on the design of the ECZTRA 3 trial, only patients who achieved an EASI 75 at week 16 on tralokinumab Q2W were eligible for inclusion and re-randomisation in the maintenance period. For this reason, we could not generate utility values for the EASI 50 + ΔDLQI≥4 response definition after week 16. Therefore, only utility values for patients sustaining or losing EASI 75 response at week 32 are presented. As no maintenance phase patients were re-randomised to placebo, only values for tralokinumab Q2W and Q4W are presented.

Results of the regression analyses, including variance covariance matrices, as well as baseline and mean change inputs are provided in the Excel file (Question_B3&B4). These were synthesised to produce the mean health state utility values presented in the following tables. We have not presented standard errors for these values as their uncertainty is a product of the underlying uncertainty in the regression outputs and independent variable inputs.

Table 6, Table 7 and Table 8 present the utility values generated in response to questions B4ai, B4bi and B4ci, respectively. Table 9, Table 10 and Table 11 present the same analyses but exclude the treatment covariate from the regressions (B4d).

Table 6: B4ai EZCTRA 3 & 7 (all-observed data set) MMRM utility regression in the All-patient population, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set).

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-32 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 7: B4bi EZCTRA 3 & 7 (all-observed data set) MMRM utility regression in the ECZTRA-7-like subgroup, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set).

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-32 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 8: B4ci EZCTRA 7 (all-observed data set) MMRM utility regression in the All-patient population, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set).

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: B4d.ai EZCTRA 3 & 7 (all-observed data set) MMRM utility regression in the All-patient population, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set), no treatment effect.

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]

Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 10: B4d.bi EZCTRA 3 & 7 (all-observed data set) MMRM utility regression in the ECZTRA-7-like subgroup, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set), no treatment effect.

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-32 (second line population)				
Baseline (week 16, EASI 75 responders)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

*For the estimation of other maintenance period utility values, the baseline values at week 16 were assumed to be common across arms and set to the all EASI 75 responder utility expected at week 16 from the initial period.

Table 11: B4d.ci EZCTRA 7 (all-observed data set) MMRM utility regression in the ECZTRA-7-like subgroup, with EZCTRA 7-like inputs from EZCTRA 3 & 7 (all-observed data set), no treatment effect.

Adults	Combination therapy			
	Tralokinumab Q2W	Tralokinumab Q4W	Placebo	All patients
	Estimate			
Week 0-16 (second line population)				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16-52 (second line population)				
Baseline (week 16)	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 50 + DLQI 4)	[redacted]	[redacted]	[redacted]	[redacted]
Responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]
Non responder (EASI 75)	[redacted]	[redacted]	[redacted]	[redacted]

Section C: Textual clarification and additional points

C1. The EAG is unclear how TCS was offered to patients in the ECZTEND trial. Figure 40 of the CS Appendix is titled, "Design of the ECZTEND Trial for Tralokinumab in Combination with TCS in Moderate-to-Severe AD" while page 115 of the CS states, "treated with tralokinumab (±TCS) for 2 years" and page 282 of the Appendix states, "Concomitant use of mid-potency TCS (Europe class ≤ 3 and US class ≥ 4) is allowed in this trial". Please clarify if tralokinumab should be considered as a monotherapy treatment or combination treatment in this trial. If the trial contains a mix of patients who did and did not receive TCS in combination with tralokinumab, please provide these proportions and any other information you think would be useful to describe the use of TCS.

LEO response:

TCS use was optional in the ECZTEND trial. Further information is available in Section 4.1.4.1 of the clinical study report, quoted below.

'Subjects can use TCS (US class ≥4 or Europe class ≤3) or Topical calcineurin inhibitors (TCI) at the investigator's discretion. If TCS are used, the subject should be monitored for signs of local or systemic TCS toxicity, and the safety and appropriateness of continued or repeated courses of TCS therapy should be evaluated by site staff.'

Some 57% percent of the ECZTEND patients reported using TCS at some point during ECZTEND. These data were collected according to method outlined in Section 9.6 of the clinical study report, quoted below.

'At all site visits and telephone visits, subjects should be asked whether they have used TCS or TCI (see below) during the past week – to make it possible to assess

whether the individual efficacy response is achieved with or without topical therapy and to get an impression of topical medication use.'

C2. On page 135 of the CS it states, "it was assumed that patients treated with SC formulations would receive training regarding how to self-administer the drug...Training will be provided free of charge for tralokinumab, so is not included for this comparator." Please clarify how the company expects to implement this is in practice and if this proposal still holds for the purposes of the MTA.

LEO response:

Tralokinumab is administered as a subcutaneous injection and LEO Pharma have contracted two Pharma funded homecare companies to provide a Nurse Training / Administration Programme (NTV) that will be available throughout the UK in the form of Nurse Visits or Virtual Nurse Training Visits. The referring clinical team as well as the patient's approval must be provided for a patient to access the Virtual Nurse Training Visits. Nurse Visits will last approximately 60 minutes and will include device use, device disposal, rotation of stock, rotation of injection site, injection site observation, storage and competency sign off. Nurses will provide a minimum of 1 and a maximum of 3 visits within the first six months on service and the actual number of visits will be driven by the patient / competency assessment. Nurses will also record all clinical activities within the patient's record and a copy of the Clinical Evaluation Form will be sent to the clinical team via secure NHS.net within two business days. This proposal reflects the expected zero cost to the NHS in providing homecare support by LEO Pharma.

C3. Please provide the latest CSR for ECZTEND.

LEO response:

A copy of the CSR for ECZTEND has been provided alongside this document. ECZTEND (LP0162-1337) is an ongoing trial and the CSR for ECZTEND is based on an interim data-cut from April 30.2020.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

September, 2021

File name	Version	Contains confidential information	Date
		Yes/no	

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

Additional questions

B5. For Question B2, it is stated a more precise definition has been used to estimate annual discontinuation. Please describe this further.

a) **In addition, please list what is included in the reasons for "all cause discontinuation".**

b) **Please provide the relevant page numbers in the ECZTEND CSR for the data used to inform the discontinuation data in Table 1.**

LEO response:

The original estimate of 2.6% annual discontinuation, as a result of adverse events or loss of efficacy in ECZTEND, reported in the NICE submission was based on an extrapolation from week 48 to week 52. The decision to extrapolate was based on a misunderstanding of the data available at different time points. The updated figure of 2.3% reflects the annual discontinuation, as observed at week 52, without extrapolation.

a) All-cause discontinuation can be broken down into the following reasons:
   - Adverse events
   - Lost to follow up
   - Withdrawal by subject
   - Lack of efficacy
   - Other reasons

b) The discontinuation figures presented in Table 1 of the response to clarification question B2 was informed by post-hoc analysis that is not included in the ECZTEND CSR. Discontinuation data for the whole of the ECZTEND trial is discussed in section 7.1 of the CSR (pages 39-42).

B6. For the responses to Question B3c, please explain why the utilities are different for tralokinumab Q2W, Q4W and placebo. The EAG expected that by removing the treatment effect, utility values would no longer be treatment specific. As such, should the "all patient" values for the response B3 ai and bi be considered as the non-treatment specific utility values?

LEO response:

Each regression includes a covariate for total EASI score. The health state utility values presented for responders and non-responders at the end of the initial phase

and maintenance phases are calculated using total EASI scores at endpoint, which vary according to response (Y/N) and treatment (tralokinumab/placebo).

All hypothetical patients in the model start with a common total EASI score based on baseline values from the ECZTRA studies. The total EASI score at endpoint is derived by applying the mean change from baseline in EASI score to the baseline score. The mean change in EASI depends on the treatment received, responder status and definition of response. For example, a non-responder to tralokinumab has a larger mean change in EASI score than a non-responder to placebo. Similarly, a non-responder based on EASI 75 has a larger mean change in EASI score than a non-responder based on EASI 50 + ΔDLQI ≥4.

The health state utility values presented in Table 4 and Table 5 of our response to clarification question B3c are still treatment specific because, although there is no treatment covariate included in the regression, the total EASI score at endpoint is different for tralokinumab and placebo. The “All patients” values in these tables are the best reflection of response-specific but treatment non-specific health state utilities. They are based on a regression without a treatment covariate and the total EASI score input is broken down by response status regardless of treatment.

The “All patients” values presented in Table 2 and Table 3 in response to clarification questions B3a and B3b are based on regressions that include a treatment covariate; therefore, although the total EASI score input is broken down by response status regardless of treatment, the proportion of tralokinumab-treated and placebo-treated patients within each response category is included.

The same approach was used in the estimation of utility values presented in response to clarification question B4.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

August, 2021

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic Dermatitis EAG CQs response _HE questions_[Redacted]	1	Yes	2 September 2021

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
Document B			
4	☒ Commercial in confidence ☐ Academic in confidence ☐ Depersonalised data	Unpublished wording from the draft SmPC	Until MA is granted
6-7, 10, 12,14,16,19-23	☐ Commercial in confidence ☒ Academic in confidence ☐ Depersonalised data	Unpublished data from abrocitinib clinical trial programme	Publication plan to be decided

Note: In our clinical response we stated that we would share top-line data from JADE DARE in our CE response, however we do not yet have access to this. We plan to share data to incorporate into an NMA from JADE DARE by 17 September 2021.

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A [CsA]; second-line systemic treatment).

Based on the company submission (CS) for abrocitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning abrocitinib as a treatment option at second line in the management of AD for adolescents and adults. The

EAG's systematic literature review has identified the key studies evaluating abrocitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which abrocitinib, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment. In line with the protocol for the MTA, for adults, the population of interest is that referred to as the "restricted population" in the CS. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment.

For the purposes of the MTA, the EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. The EAG notes that the company specifies that the use of rescue medication was prohibited in all studies evaluating abrocitinib, and therefore the EAG has assumed that there is no censoring of patients for receipt of rescue medication from the analyses. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating abrocitinib and, therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA.

Clinical effectiveness data

B1. On page 17 of the CS it states, "*The SmPC advises that discontinuation of abrocitinib should be considered if no evidence of therapeutic benefit is shown after 24 weeks of treatment*" Please clarify why a stopping rule after 24 weeks of abrocitinib treatment is not included in the model.

The latest version of the SmPC states that discontinuation of abrocitinib should be considered if no evidence of therapeutic benefit is shown after 12 weeks of treatment.

In the model, a stopping rule of 16 weeks has been applied based on feedback from clinicians that it would be appropriate to assess response to treatment

for abrocitinib at 16 weeks, as per current clinical practice for dupilumab and baricitinib treatment.

A similar scenario was considered by the NICE committee in the appraisal of baricitinib. The SmPC for baricitinib[1] states that "consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit after 8 weeks of treatment," however in the final guidance[2] NICE suggest that response should be assessed from 8 weeks but a stopping rule applied at 16 weeks.

NICE also comment in the final guidance that if a stopping rule at 8 weeks for baricitinib was modelled then this would be expected to improve cost-effectiveness. Similarly, abrocitinib would be more cost-effective if a stopping rule at 12 weeks was applied, with a 16 week stopping rule for comparator treatments.

As illustrated in Section B.2.6 of the abrocitinib submission, response rates at 12 and 16 weeks are similar across relevant endpoints (e.g., EASI response and DLQI≥4) in JADE COMPARE. However, a small number of patients do achieve response between 12 and 16 weeks. As stated in the draft SmPC, some patients with initial partial response may subsequently improve with continued treatment beyond 12 weeks.

No assessment can be made for JADE TEEN, MONO-1 or MONO-2 studies given treatment was until 12 weeks only.

B2. Please provide the 95% confidence interval and number of responders at Week 44/48/52 by the number of responders at Week 12/16 (n/N) informing each conditional response probability in Table 138 of Appendix O.

The requested conditional response probabilities (based on EASI 50 & DLQI ≥4 response) have been provided in Table 1. Conditional response data was used within sensitivity analysis in the abrocitinib submission given the precedence from the baricitinib NICE appraisal for modelling using conditional discontinuation data in the base case.

[1] Olumiant, INN-baricitinib (europa.eu)
[2] Baricitinib for treating moderate to severe atopic dermatitis (nice.org.uk)

As described in Appendix O, only 44-week response data for patients coming from JADE COMPARE and 48-week data for patients coming from JADE MONO-1 & -2 and JADE TEEN is available from the EXTEND trial, and therefore this has been used to calculate conditional response probabilities for abrocitinib patients who were responders at 12 or 16 weeks depending on the parent trial.

Data for conditional response is based on the full trial population as sample sizes in the generalisable/restricted populations were deemed too small to reliably inform the analysis.

Amongst JADE TEEN patients that subsequently entered JADE EXTEND, only 13 of 105 had reached 48 weeks at the time of the latest data cut and it was not feasible to reliably assess conditional response given the very small sample size. Instead, the probabilities from JADE COMPARE have been assumed to hold for adolescents on combination therapy.

Similarly, the sample size amongst adolescents from JADE MONO1/2 that subsequently entered JADE EXTEND and reached 48 weeks is small (n=33 across abrocitinib 100mg and 200mg doses). Therefore, we have assumed that probabilities from MONO-1/2 for adults hold also for adolescents.

Table 1: Conditional probability of EASI 50 & DLQI ≥4 response at 52-weeks conditional on EASI 50 & DLQI ≥4 response at 12/16 weeks

	Adults combination therapy	Adults monotherapy	Adolescents combination therapy	Adolescents monotherapy
Abrocitinib 200 mg n/N,% (CI)	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 100 mg n/N,% (CI)	[redacted]	[redacted]	[redacted]	[redacted]

Response data for EXTEND is for 44-weeks for patients coming from JADE COMPARE and 48-weeks for patients coming from JADE MONO-1 & -2 and JADE TEEN. Conditional response probabilities are for responders at 12 or 16 weeks depending on the parent trial.
Full trial population data is used as sample sizes in the generalisable/restricted populations were deemed too small to reliably inform the analysis. Probabilities from JADE COMPARE have been assumed to hold for adolescents on combination therapy given the immature data for JADE TEEN patients entering EXTEND. Probabilities from MONO-1/2 for adults are assumed to hold for adolescents, given the small sample size for adolescents.

The requested data for conditional response probabilities based on EASI-75 has been provided in the supplementary table below. Similar assumptions to those for

EASI 50 + DLQI≥4 have been made given the limitations for adolescent combination and adolescent monotherapy data.

Supplementary table: Conditional probability of EASI 75 response at 52-weeks conditional on EASI 75 response at 12/16 weeks

	Adults combination therapy	Adults monotherapy	Adolescents combination therapy	Adolescents monotherapy
Abrocitinib 200 mg n/N,% (CI)	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 100 mg n/N,% (CI)	[redacted]	[redacted]	[redacted]	[redacted]

Response data for EXTEND is for 44-weeks for patients coming from JADE COMPARE and 48-weeks for patients coming from JADE MONO-1 & -2 and JADE TEEN. Conditional response probabilities are for responders at 12 or 16 weeks depending on the parent trial.
Full trial population data is used as sample sizes in the generalisable/restricted populations were deemed too small to reliably inform the analysis. Probabilities from JADE COMPARE have been assumed to hold for adolescents on combination therapy given the immature data for JADE TEEN patients entering EXTEND. Probabilities from MONO-1/2 for adults are assumed to hold for adolescents, given the small sample size for adolescents.

B3. Please clarify if the use of rescue medication was prohibited in EXTEND. If the use of rescue medication was not prohibited in EXTEND:

a) Please provide the proportion of people in the full trial population requiring use of rescue medication during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI). Please provide results using adult combination therapy data and adult monotherapy data separately.

b) Please clarify if the conditional response probabilities in Table 138 of Appendix O reflect the ITT population or a population, where patients are prohibited from receiving rescue medication (and provide results in the alternative population, if available)

c) Please clarify if the conditional discontinuation probabilities in Table 64 of the CS reflect the ITT population or a population where patients are prohibited from receiving rescue medication (and provide results in the alternative population, if available).

In discussion within our clarification meeting, the AG confirmed that the rationale for exploring this topic was to understand if data on the use of rescue medications could be used as a proxy for rates of flares considering data from JADE EXTEND (i.e., a

similar methodology to that employed for dupilumab and baricitinib trials where rescue medications were permitted).

In JADE EXTEND only medicated and non-medicated topical treatments for AD were permitted, per the treating physician's usual practice; systemic treatments for AD however were prohibited throughout the study. Therefore, it would not be appropriate to inform flare rates.

In JADE REGIMEN, flare was defined according to the protocol - a loss of response associated with a decrease of at least 50% of the EASI response achieved during the initial 12 week open-label treatment and an IGA score ≥ 2. As described in Section B.3.3.3 data on the use of rescue medications from REGIMEN has been used to estimate the annual rate of flares for modelling.

Health related quality of life data

For all utility analyses requested below, please provide the data and utility calculations in a separate Excel file.

B5. Please provide the following requested data for patients on abrocitinib 200mg, abrocitinib 100mg, dupilumab (JADE COMPARE only) and placebo:

a) JADE MONO-1 & MONO-2 (adults) – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 2, 4, 8, 12 and 16. Please provide results for both the full and restricted populations separately.

Available timepoints

Week 16 data is not available for JADE MONO-1/2 as the treatment duration is 12 weeks. EQ-5D data was collected at weeks 0,2,4,8 and 12.

Available populations

Data has been provided for the restricted population (i.e., patients who previously failed or were intolerant to ciclosporin) as requested. For our initial submission data for this population was generated to align more closely with available comparator evidence for dupilumab and baricitinib, and to explore more of a like-for-like comparison within the NMA. However, for the utility analysis we would continue to strongly advocate for the generalisable population to be used. This population is

larger and has greater relevance to clinical practice given that in addition to ciclosporin, other immunosuppressants, e.g. methotrexate, azathioprine and mycophenolate mofetil are routinely used unlicensed for treatment of atopic dermatitis, as demonstrated in a recent study using the UK The Health Improvement Network (THIN) database[3].

[3]Eckert, L., Amand, C., Gadkari, A., Rout, R., Hudson, R., & Ardern-Jones, M.. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). Journal of Dermatological Treatment 2020; 31(8), 815-820.

Table 2: EQ-5D utility values by week: JADE MONO-1 & MONO-2, adults

Week		FULL POPULATION				GENERALISABLE POPULATION				RESTRICTED POPULATION			
		Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total
0	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
2	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
4	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
8	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
12	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											

b) JADE MONO-1 & MONO-2 (adolescents) – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 2, 4, 8, 12 and 16. Please provide results for both the full and restricted populations separately.

Available timepoints

Week 16 data is not available for JADE MONO-1/2 as the treatment duration is 12 weeks. EQ-5D data was collected at weeks 0,2,4,8 and 12.

Available populations

The adolescent monotherapy data from MONO1/2 has been provided for the generalisable as well as restricted populations as per the rationale provided above (Section 5a).

Table 3 EQ-5D utility values by week: JADE MONO-1 & MONO-2, adolescents

Week		FULL POPULATION				GENERALISABLE POPULATION				RESTRICTED POPULATION			
		Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total
0	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
2	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
4	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
8	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
12	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											

c) JADE COMPARE – Number of patients in the completing the EQ-5D-5L questionnaire and mean ED-5D utility (EQ-5D-5L mapped to EQ-5D-3L) for weeks 0, 12, 16, 20 and 24. Please provide results for both the full and restricted populations separately.

Available timepoints:

The treatment duration in JADE COMPARE was 20 weeks with a primary efficacy assessment at Week 12, and key secondary efficacy assessments at Week 2 and Week 16.

EQ-5D data was only collected at weeks 0,12,16 and 20, although the sample size at week 20 is too small to present the data.

Available populations

JADE COMPARE data has been provided for the generalisable as well as restricted populations as per the rationale provided above (Section 5a).

Table 4 EQ-5D utility values by week: JADE COMPARE, adults

Week		FULL POPULATION					GENERALISABLE POPULATION					RESTRICTED POPULATION				
		Placebo	Abro 100mg	Abro 200mg	Dupi	Total	Placebo	Abro 100mg	Abro 200mg	Dupi	Total	Placebo	Abro 100mg	Abro 200mg	Dupi	Total
0	Mean	[redacted]														
	SD	[redacted]														
	N	[redacted]														
12	Mean	[redacted]														
	SD	[redacted]														
	N	[redacted]														
16	Mean	[redacted]														
	SD	[redacted]														
	N	[redacted]														

d) JADE TEEN – Number of patients completing the EQ-5D-5L questionnaire and mean ED-5D-5Y for weeks 0, 2, 4, 8, 12 and 16. Please provide results for both the full and restricted populations separately.

Available timepoints

Week 16 data is not available for JADE TEEN as the treatment duration is 12 weeks.

Available populations

JADE COMPARE data has been provided for the generalisable as well as restricted populations as per the rationale provided above (Section 5a).

Table 5: EQ-5D utility values by week: JADE TEEN, full population

Week		FULL POPULATION				GENERALISABLE POPULATION				RESTRICTED POPULATION			
		Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total	Placebo	Abro 100mg	Abro 200mg	Total
0	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
2	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
4	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
8	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											
12	Mean	[redacted]											
	SD	[redacted]											
	N	[redacted]											

B6. On page 176 of the CS it states, "*The models were fit for the full trial population, to make best use of all available data although predicted values for use in the model have been generated using the characteristics of the generalisable population*."

a) Please explore an analysis where the models are fit to the full trial population and predicted values for the models are generated using the characteristics of the restricted population (patients who previously failed or were intolerant to ciclosporin).

b) Please use the results from these models to fill in Table 1 below. Please provide mean values and standard errors. To obtain utility values that are not treatment specific, please explore models without a treatment covariate.

c) For each model, please provide the coefficient, standard error and p value for each covariate.

As above we would continue to strongly advocate for the generalisable population utility data to be used although we have presented predicted values for the generalisable as well as restricted populations in the tables below (in both cases the models were fit using the full population).

Utility values are presented in Table 6, Table 7, Table 8 and Table 9 with the results of the regression models defining response as EASI 50 + DLQI ≥4 and EASI 75 presented separately. The estimations for monotherapy patients have been taken from JADE MONO-1 & MONO-2. Values for the adult and adolescent combination populations have been taken from JADE COMPARE and JADE TEEN respectively. Data has not been presented for EASI 75 in the monotherapy populations, as this is not an option in the model

The values have been calculated using a common set of baseline characteristics as per the economic model as detailed in Section B.3.4 in our submission. They are therefore not associated with any standard errors. The baseline EQ-5D scores used to calculate these values are the total baseline values presented in Section B5. The baseline age is as per Table 55 of the company submission.

Table 10 and Table 11 present the utility values from models that do not include any treatment covariates.

Coefficients for the regression models have been provided within a supplementary excel.

Table 6: Modelled utility values for the generalisable population using EASI 50 + DLQI 4 as the measure of response

	Monotherapy				Combination therapy				
	Abrocitinib 100 mg	**Abrocitinib 200 mg**	**BSC**	**All patients**	**Dupilumab**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**BSC**	**All patients**
Adults									
Baseline	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 50 + DLQI≥4)	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 50 + DLQI≥4)*	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Adolescents									
Baseline	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 50 + DLQI≥4)	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 50 + DLQI≥4)*	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A

*Please provide treatment-specific values for abrocitinib, not the mean values of abrocitinib and BSC

Table 7: Modelled utility values for the restricted population using EASI 50 + DLQI 4 as the measure of response

	Monotherapy				Combination therapy				
	Abrocitinib 100 mg	**Abrocitinib 200 mg**	**BSC**	**All patients**	**Dupilumab**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**BSC**	**All patients**
Adults									
Baseline	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 50 + DLQI≥4)	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 50 + DLQI≥4)*	[redacted]	[redacted]	[redacted]	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Adolescents									
Baseline	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 50 + DLQI≥4)	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 50 + DLQI≥4)*	[redacted]	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A

*Please provide treatment-specific values for abrocitinib, not the mean values of abrocitinib and BSC

Table 8: Modelled utility values for the generalisable population using EASI 75 as the measure of response

	Monotherapy				Combination therapy				
	Abrocitinib 100 mg	**Abrocitinib 200 mg**	**BSC**	**All patients**	**Dupilumab**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**BSC**	**All patients**
Adults									
Baseline	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 75)	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 75)	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Adolescents									
Baseline	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 75)	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 75)	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A

Table 9: Modelled utility values for the restricted population using EASI 75 as the measure of response

	Monotherapy				Combination therapy				
	Abrocitinib 100 mg	**Abrocitinib 200 mg**	**BSC**	**All patients**	**Dupilumab**	**Abrocitinib 100 mg**	**Abrocitinib 200 mg**	**BSC**	**All patients**
Adults									
Baseline	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 75)	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 75)	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	N/A
Adolescents									
Baseline	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Week 12/16	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Responder (EASI 75)	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A
Non responder (EASI 75)	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	N/A

*Please provide treatment-specific values for abrocitinib, not the mean values of abrocitinib and BSC

Table 10: Modelled utility values for models for the generalisable population without treatment coefficients

	Adults monotherapy, EASI 50 + DLQI 4	Adolescents monotherapy, EASI 50 + DLQI 4	Adults combination therapy EASI 50 + DLQI 4	Adolescents combination therapy EASI 50 + DLQI 4	Adults combination therapy EASI 75	Adolescents combination therapy EASI 75
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Modelled utility values for models for the generalisable population without treatment coefficients

	Adults monotherapy, EASI 50 + DLQI 4	Adolescents monotherapy, EASI 50 + DLQI 4	Adults combination therapy EASI 50 + DLQI 4	Adolescents combination therapy EASI 50 + DLQI 4	Adults combination therapy EASI 75	Adolescents combination therapy EASI 75
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

August, 2021

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic Dermatitis EAG CQ response Abrocitinib 31 August 2021_[Redacted]	v1	Yes	31 August 2021

Notes for ERGs and NICE [TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
Document B			
6-8, 13-15, 17-19, 21-23, 25-27, 2-36	☐ Commercial in confidence ☒ Academic in confidence ☐ Depersonalised data	Unpublished data from abrocitinib clinical trial programme	Publication plan to be decided

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A [CsA]; second-line systemic treatment).

Based on the company submission (CS) for abrocitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning abrocitinib as a treatment option at second line in the management of AD for adolescents and adults. The EAG's systematic literature review has identified the key studies evaluating abrocitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which abrocitinib, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment. In line with the protocol for the MTA, for adults, the population of interest is that referred to as the "restricted population" in the CS. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment.

For the purposes of the MTA, the EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. The EAG notes that the company specifies that the use of rescue medication was prohibited in all studies evaluating abrocitinib, and therefore the EAG has assumed that there is no censoring of patients for receipt of rescue medication from the analyses. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating abrocitinib and, therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA.

Where possible, the EAG has sourced relevant data from the CS, specifying the time point for reporting of results. Please confirm that the extracted data are correct. If data are available for additional time points of clinical assessment, please complete separate clinical effectiveness tables for the time points for the outcomes requested.

Data on clinical effectiveness

A1. Please complete the tables below for individual studies to provide data on the outcomes specified in the protocol for population of interest, together with

baseline characteristics of the patients from which data on clinical effectiveness are derived.

a) JADE COMPARE[1]

a1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 16 data is provided in the tables below.

Week 24 data is not available for JADE COMPARE. The treatment duration in JADE COMPARE was 20 weeks with a primary efficacy assessment at Week 12, and key secondary efficacy assessments at Week 2 and Week 16.

Available populations

Data has been provided for the restricted population (i.e., patients who previously failed or were intolerant to ciclosporin) as requested. For our initial submission data for this population was generated to align more closely with available comparator evidence for dupilumab and baricitinib, and to explore more of a like-for-like comparison within the NMA. However, it should be noted that our restricted population is not fully aligned with that of dupilumab and baricitinib because contraindication to ciclosporin was not captured in the JADE trials.

We used data from the generalisable population (i.e., patients who have been previously treated with at least one systemic treatment for AD) as the primary analysis for interpretation within the NMA with the restricted population used as a secondary analysis. The generalisable population is larger and has greater relevance to clinical practice given that in addition to ciclosporin, other

immunosuppressants, e.g. methotrexate, azathioprine and mycophenolate mofetil are routinely used unlicensed for treatment of atopic dermatitis, as demonstrated in a recent study using the UK The Health Improvement Network (THIN) database[1]. Further, the outcomes between the generalisable and restricted populations are similar within JADE studies.

We would continue to strongly advocate for the generalisable population to be used as the primary analysis within the NMA with the restricted population for sensitivity analysis because this would be the most clinically relevant population.

[1]Eckert, L., Amand, C., Gadkari, A., Rout, R., Hudson, R., & Ardern-Jones, M.. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). Journal of Dermatological Treatment 2020; 31(8), 815-820.

Clinical effectiveness at week 16, generalisable and restricted populations, JADE COMPARE

	Generalisable				Restricted			
	Abrocitinib 200 mg OD plus TCS [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]	**Abrocitinib 200 mg OD plus TCS** [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L index score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F							
Proportion of patients who discontinue treatment at week 16 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted							
Number of days free from TCS during treatment, LSM, N*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	Discussed not required at clarification meeting because the study completed at week 20, following that eligible patients entered EXTEND which was not placebo-controlled
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid. *Subjects who had used topical corticosteroids during treatment period were included in the analysis.	

Clinical effectiveness at week 8, generalisable and restricted populations, JADE COMPARE

	Generalisable				Restricted			
	Abrocitinib 200 mg OD plus TCS [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]	**Abrocitinib 200 mg OD plus TCS** [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	Cannot be reported as DLQI was not measured at week 8 in JADE COMPARE							
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index								

Baseline characteristics, generalisable and restricted populations, JADE COMPARE

Characteristic	Generalisable				Restricted			
	Abrocitinib 200 mg OD plus TCS [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]	**Abrocitinib 200 mg OD plus TCS** [redacted]	**Abrocitinib 100 mg OD plus TCS** [redacted]	**Dupilumab 300 mg Q2W plus TCS** [redacted]	**Placebo plus TCS** [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gender, n (%)	[redacted]							
Male	[redacted]							
Mean duration of AD, years (SD)	[redacted]							
Race	[redacted]							
White, n (%)	[redacted]							
Black or African American, n (%)	[redacted]							
Asian, n (%)	[redacted]							
Other, n (%)	[redacted]							
Mean EASI score (SD)	[redacted]							
Baseline IGA score of 4, n (%)	[redacted]							
Mean DLQI score (SD)	[redacted]							
Mean SCORAD score (SD)	[redacted]							
Mean peak pruritus NRS score (SD)	[redacted]							
Mean % BSA affected (SD)	[redacted]							
Mean baseline EQ-5D Score (SD)	[redacted]							
Prior treatment	[redacted]							
Oral/injectable corticosteroids, n (%)	[redacted]							
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]							
Biologics (excluding dupilumab*)	[redacted]							
TCS, n (%)	[redacted]							
TCI, n (%)	[redacted]							

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Patients with prior use of dupilumab were excluded from the JADE COMPARE trial

b) RCT comparing abrocitinib versus dupilumab, both in combination with topical corticosteroids as background therapy (ClinicalTrials.gov identifier: NCT04345367)

Note: As discussed at clarification meeting that JADE DARE data (NCT04345367) is not yet available – an initial press release from 30 August 2021 is here. We will aim to share top-line data from the full trial population within the response to the cost effectiveness clarification questions, if available.

b1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Clinical effectiveness at week 16

	Abrocitinib 200 mg OD plus TCS (N=)	Dupilumab 300 mg Q2W plus TCS (N=)
Proportion of people achieving EASI 50 + ΔDLQI ≥4		
Proportion of people achieving EASI 75		
Change in EQ-5D score from baseline		
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation)		
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency,	N/A	N/A

TCS very high potency, systemic steroids, TCI)		
Number of days free from TCS during treatment		
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved		
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; N/A, not applicable; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.		

Baseline characteristics

Characteristic	**Abrocitinib 200 mg OD plus TCS (N=)**	**Dupilumab 300 mg Q2W plus TCS (N=)**
Mean age, years		
Gender, n (%)		
Male		
Mean duration of AD, years (SD)		
Race		
White, n (%)		
Black or African American, n (%)		
Asian, n (%)		
Mean EASI score (SD)		
Baseline IGA score of 4		
Mean DLQI score (SD)		
Mean SCORAD score (SD)		
Mean peak pruritus NRS score (SD)		
Mean % BSA affected (SD)		
Mean baseline EQ-5D Score (SD)		
Prior treatment		
OCS, n (%)		
Immunosuppressant, n (%)		

TCS, n (%)		
TCI, n (%)		
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.		

c) JADE TEEN[2]

c1) Adolescents

Trial population was adolescents (aged ≥12 years to <18 years) who received abrocitinib plus background TCS. For weeks 8 and 16, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 24 data is not available for JADE TEEN. The treatment duration in JADE TEEN was 12 weeks.

Available populations

Data has been provided for the full population in JADE TEEN as requested. Data for the generalisable population (i.e., patients who have been previously treated with at least one systemic treatment for AD) is presented within Section B.2.7.2 in the main submission.

Clinical effectiveness at week 12, full population, JADE TEEN

	Abrocitinib 200 mg OD plus TCS (N=94)	Abrocitinib 100 mg OD plus TCS (N=95)	Placebo plus TCS (N=96)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	67/93 (72.0)	61/89 (68.5)	39/94 (41.5)
Change in EQ-5D score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F		
Proportion of patients who discontinue treatment (additional request from clarification meeting), n/N (%)	3/94 (3.2)	3/95 (3.2)	6/96 (6.3)
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted		
Number of days free from TCS during treatment, LSM, N*	[redacted]	[redacted]	[redacted]
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	Discussed not required at clarification meeting because the study completed at week 12, following that eligible patients entered EXTEND which was not placebo-controlled		

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

Clinical effectiveness at week 8, full population, JADE TEEN

	Abrocitinib 200 mg OD plus TCS (N=94)	Abrocitinib 100 mg OD plus TCS (N=95)	Placebo plus TCS (N=96)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	63/92 (68.5)	55/91 (60.4)	31/93 (33.3)

Baseline characteristics, full population, JADE TEEN

Characteristic	Abrocitinib 200 mg OD plus TCS (N=94)	Abrocitinib 100 mg OD plus TCS (N=95)	Placebo plus TCS (N=96)
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Gender, n (%)	-	-	-
Male	56 (59.6)	45 (47.4)	44 (45.8)
Mean duration of AD, years (SD)	9.7 (5.3)	9.8 (5.4)	10.5 (4.8)
Race	-	-	-
White, n (%)	52 (55.3)	52 (54.7)	56 (58.3)
Black or African American, n (%)	5 (5.3)	9 (9.5)	3 (3.1)
Asian, n (%)	31 (33.0)	31 (32.6)	32 (33.3)
Other, n (%)	5 (5.3)	3 (3.2)	2 (2.1)
Mean EASI score (SD)	29.5 (12.2)	31.0 (12.8)	29.2 (12.7)
Baseline IGA score of 4, n (%)	33 (35.1)	38 (40.0)	39 (40.6)
Mean CDLQI score (SD)	13.6 (7.0)	14.3 (6.1)	14.0 (6.7)
Mean SCORAD score (SD)	66.2 (13.3)	67.6 (13.5)	68.5 (13.4)
Mean peak pruritus NRS score (SD)	6.8 (2.0)	7.0 (1.8)	7.2 (1.7)
Mean % BSA affected (SD)	48.7 (21.7)	51.2 (21.7)	45.8 (22.4)
Prior treatment	-	-	-
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]
Other non-biologics systemic (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]

Biologic (i.e. dupilumab or other)	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

d) JADE MONO-1[3]

d1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 16 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 16 and week 24 data is not available for JADE MONO-1 as the treatment duration was 12 weeks.

Available populations

The adult analysis data has been provided for the restricted and generalisable populations in JADE MONO-1, as per the rationale provided for JADE COMPARE.

Clinical effectiveness at week 12, generalisable and restricted populations, adults, JADE MONO-1

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L index score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F					
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted					
Number of days free from TCS during treatment, LSM, N	N/A, medicated topical treatments were not permitted					
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	Discussed not required at clarification meeting because the study completed at week 12, following that eligible patients entered EXTEND which was not placebo-controlled					
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.						

Clinical effectiveness at week 8, generalisable and restricted populations, adults, JADE MONO-1

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index						

Baseline characteristics, generalisable and restricted populations, adults, JADE MONO-1

	Generalisable			Restricted		
Characteristic	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment						
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

d2) Adolescents

Subgroup of adolescents (aged ≥12 years to <18 years) who received abrocitinib. For weeks 8, 16 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 16 and week 24 data is not available for JADE MONO-1 as the treatment duration was 12 weeks.

Available populations

Data has been provided for the full adolescent population in JADE MONO-1 as requested. Data for the generalisable population (i.e., patients who have been previously treated with at least one systemic treatment for AD) is presented within Section B.2.7.2 in the main submission.

Clinical effectiveness at week 12, full population, adolescents, JADE MONO-1

	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F		
Proportion of patients who discontinue treatment (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted		
Number of days free from TCS during treatment, LSM	N/A, medicated topical treatments were not permitted		
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	Discussed not required at clarification meeting because the study completed at week 12, following that eligible patients entered EXTEND which was not placebo-controlled		
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.			

Clinical effectiveness at week 8, full population, adolescents, JADE MONO-1

	Abrocitinib 200 mg OD	Abrocitinib 100 mg OD	Placebo
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]

Baseline characteristics, full population, adolescents, JADE MONO-1

Characteristic	Abrocitinib 200 mg OD	Abrocitinib 100 mg OD	Placebo
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4	[redacted]	[redacted]	[redacted]
Mean CDLQI score (SD)	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D score (SD)	[redacted]	[redacted]	[redacted]
Prior treatment			
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]
Other non-biologics systemic (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]

Biologic (i.e. dupilumab or other)	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.			

e) JADE MONO-2[4]

e1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 16 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 16 and week 24 data is not available for JADE MONO-2 as the treatment duration was 12 weeks.

Available populations

The adult analysis data has been provided for the restricted and generalisable populations in JADE MONO-2, as per the rationale provided for JADE COMPARE.

Clinical effectiveness at week 12, generalisable and restricted populations, adults, JADE MONO-2

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L index score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F					
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted					
Number of days free from TCS during treatment, LSM, N*	N/A, medicated topical treatments were not permitted					
Proportion of people maintaining for a set period of time the level of	Discussed not required at clarification meeting because the study completed at week 12, following that eligible patients entered EXTEND which was not placebo-controlled					

response (as defined in the study) initially achieved	

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

Clinical effectiveness at week 8, generalisable and restricted populations, adults, JADE MONO-2

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

Baseline characteristics, generalisable and restricted populations, adults, JADE MONO-2

Characteristic	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]			
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment				[redacted]	[redacted]	[redacted]
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

e2) Adolescents

Subgroup adolescents (aged ≥12 years to <18 years) who received abrocitinib. For weeks 8, 16 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional response; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 16 and week 24 data is not available for JADE MONO-2 as the treatment duration was 12 weeks.

Available populations

Data has been provided for the full adolescent population in JADE MONO-2 as requested. Data for the generalisable population (i.e., patients who have been previously treated with at least one systemic treatment for AD) is presented within Section B.2.7.2 in the main submission.

Clinical effectiveness at week 12, full population, adolescents, JADE MONO-2

	Abrocitinib 200 mg OD [redacted]	Abrocitinib 100 mg OD [redacted]	Placebo [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]
Change in EQ-5D score from baseline (LSM CFB, N)	[redacted]	[redacted]	[redacted]
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	Discussed at clarification meeting and agreed to refer to the full trial population data. See data from JADE EXTEND in Section F		
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted		
Number of days free from TCS during treatment, LSM, N*	N/A, medicated topical treatments were not permitted		
Proportion of people maintaining for a set period of time the level of response (as defined in the study) initially achieved	Discussed not required at clarification meeting because the study completed at week 12, following that eligible patients entered EXTEND which was not placebo-controlled		

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Subjects who had used topical corticosteroids during treatment period were included in the analysis.

Clinical effectiveness at week 8, full population, adolescents, JADE MONO-2

	Abrocitinib 200 mg OD	Abrocitinib 100 mg OD	Placebo
	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]

Baseline characteristics, full population, adolescents, JADE MONO-2

Characteristic	Abrocitinib 200 mg OD	Abrocitinib 100 mg OD	Placebo
	[redacted]	[redacted]	[redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]
Mean CDLQI score (SD)	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (Q1-Q3)	[redacted]	[redacted]	[redacted]
Mean % BSA affected (Q1-Q3)	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D score (Q1-Q3)	[redacted]	[redacted]	[redacted]

Prior treatment	[redacted]	[redacted]	[redacted]
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]
Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.			

f) JADE EXTEND

Data presented below is discontinuation at week 52 from those who achieved response (measured as EASI 50 + (C)DLQI≥4) at week 12/16. In this abrocitinib submission this is referred to as conditional discontinuation data.

Conditional discontinuation data for abrocitinib from EXTEND for patients responding to treatment at Week 12 for MONO-1/2 and Week 16 for COMPARE. adult combination therapy data was assumed to apply for the adolescent combination analyses as the number of adolescent patients completing Week 52 in the EXTEND trial who were previously in TEEN was low. For the other parent studies, the large majority of patients had reached Week 48 in EXTEND ([redacted] for abrocitinib 200mg and [redacted] for abrocitinib 100mg for patients from COMPARE).

To align with previous submissions in AD, discontinuation data in the JADE trials were restricted to discontinuation by either lack of efficacy, adverse event or withdrawal by patient. Death was excluded as a reason for discontinuation, as this is already accounted for in the model.

Discontinuation rates are for the full trial population for abrocitinib as those for the generalisable population are unreliable given that the sample size for the subgroup of patients who have been exposed to a previous systemic therapy, achieved a response at Week 12/16 and entered EXTEND, is relatively small (n=[redacted] for abrocitinib 100 mg/200 mg from COMPARE). The patient population for the restricted population would be even smaller.

Further, data from EXTEND is for patients who remained on the same dose of abrocitinib. For patients who entered EXTEND from MONO-1/2, only those who remained on monotherapy were considered.

Conditional discontinuation data, full trial population

	Abrocitinib 200 mg OD	**Abrocitinib 100 mg OD**
Adult combination therapy JADE COMPARE → EXTEND	[redacted]	[redacted]
Adolescent combination therapy JADE TEEN → EXTEND	As per adult combination analysis	
Adult monotherapy JADE MONO 1/2 adults → EXTEND	[redacted]	[redacted]
Adolescent monotherapy	[redacted]	[redacted]

JADE MONO1/2 adolescents→ EXTEND		

g) Phase II study reported by Gooderham et al.[5]

g1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8, 16 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Available timepoints

Week 8 and week 12 data is provided in the tables below.

Week 16 and week 24 data is not available for the Phase II study as the treatment duration was 12 weeks.

Available populations

For the adult analysis data has been provided for the restricted and generalisable populations in the Phase II study, as per the rationale provided for JADE COMPARE.

Clinical effectiveness at week 12, generalisable and restricted populations, Phase II study

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in EQ-5D-5L index score from baseline (LSM CFB, N)	N/A, EQ-5D was not assessed in the trial					
Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (discontinuation at week 52 conditional on response at week 16)	N/A, the study completed at week 12					
Proportion of patients who discontinued treatment at week 12 (additional request from clarification meeting), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available, e.g., TCS high potency, TCS very high potency, systemic steroids, TCI)	N/A, rescue treatments were not permitted					
Number of days free from TCS during treatment, LSM, N*	N/A, monotherapy trial					
Proportion of people maintaining for a set period of time the level of	Discussed not required at clarification meeting because the study completed at week 12.					

response (as defined in the study) initially achieved	
Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL-5D; LSM, least squares mean; N/A, not applicable; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid. *Subjects who had used topical corticosteroids during treatment period were included in the analysis.	

Clinical effectiveness at week 8, generalisable and restricted populations, Phase II study

	Generalisable			Restricted		
	Abrocitinib 200 mg OD [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index						

Baseline characteristics, generalisable and restricted populations, Phase II study

	Generalisable			Restricted		
Characteristic	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]	**Abrocitinib 200 mg OD** [redacted]	**Abrocitinib 100 mg OD** [redacted]	**Placebo** [redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	N/A, EQ-5D was not assessed in the trial					
Prior treatment	-	-	-	-	-	-
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (i.e., dupilumab and other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

[Add subheadings as needed]

B1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

B3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

[Add subheadings as needed]

C1. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C2. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

C3. [ERG: please enter your clarification question here]

[Company: please enter your answer to this question here]

Section D. References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Clarification questions

September, 2021

File name	Version	Contains confidential information	Date
ID3960 MTA Atopic Dermatitis EAG CQ response Abrocitinib JADE DARE 17 Sept_[Redacted]	v1	Yes	17 Sept

Section A: Clarification on effectiveness data

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
Document B			
6-9	☐ Commercial in confidence x☒ Academic in confidence ☐ Depersonalised data	Unpublished data from abrocitinib JADE DARE clinical trial	Publication plan to be decided

The populations of interest to the Multiple Technology Appraisal (MTA) evaluating the clinical and cost effectiveness of abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (AD) are:

- those having inadequate response to topical treatments and who have not yet received, but are eligible for, systemic therapy (first-line systemic treatment);

and

- those who have an inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (for the purposes of the MTA, first-line systemic treatment is limited to cyclosporin A [CsA]; second-line systemic treatment).

Based on the company submission (CS) for abrocitinib, the Evidence Assessment Group (EAG) has assumed that the company is positioning abrocitinib as a treatment option at second line in the management of AD for adolescents and adults. The EAG's systematic literature review has identified the key studies evaluating abrocitinib in the treatment of moderate-to-severe AD, most of which present results for a population in which abrocitinib, either in combination with topical corticosteroids or as a monotherapy, was given as both a first- and a second-line systemic treatment. In line with the protocol for the MTA, for adults, the population of interest is that referred to as the "restricted population" in the CS. For adolescents, because CsA is not licensed for use in people aged <16 years, the EAG requests data for all adolescents evaluated, irrespective of prior treatment.

For the purposes of the MTA, the EAG has defined the intention-to-treat population to include those who receive rescue medication during treatment because, based on advice from clinical experts, use of rescue medication more closely reflects what occurs in clinical practice in England. The EAG notes that the company specifies that the use of rescue medication was prohibited in all studies evaluating abrocitinib, and therefore the EAG has assumed that there is no censoring of patients for receipt of rescue medication from the analyses. Additionally, the EAG recognises that contraindication to CsA was not captured in trials evaluating abrocitinib and,

therefore, the population evaluated is limited to those who did not achieve an adequate response to CsA.

Where possible, the EAG has sourced relevant data from the CS, specifying the time point for reporting of results. Please confirm that the extracted data are correct. If data are available for additional time points of clinical assessment, please complete separate clinical effectiveness tables for the time points for the outcomes requested.

Data on clinical effectiveness

A1. Please complete the tables below for individual studies to provide data on the outcomes specified in the protocol for population of interest, together with baseline characteristics of the patients from which data on clinical effectiveness are derived.

b) RCT comparing abrocitinib versus dupilumab, both in combination with topical corticosteroids as background therapy (ClinicalTrials.gov identifier: NCT04345367)

Top-line JADE DARE data (NCT04345367) has become available since the initial clinical (31 August 2021) and cost-effectiveness (3 September 2021) clarification responses.

Available timepoints

Week 8, 16 and week 26 data has been provided.

Responses at Week 24 were not collected during the trial.

Available populations

Data has been provided for the generalisable population (i.e., patients who have been previously treated with at least one systemic treatment for AD [excluding patients who only received oral corticosteroids previously]) and restricted population (i.e., patients who previously failed or were intolerant to ciclosporin) as per the data for other trials in our clinical clarification response.

We used data from the generalisable population as the primary analysis for interpretation within the NMA in our submission with the restricted population used as a secondary analysis. The generalisable population is larger and has greater relevance to clinical practice given that in addition to ciclosporin, other

immunosuppressants, e.g. methotrexate, azathioprine and mycophenolate mofetil are routinely used unlicensed for treatment of atopic dermatitis, as demonstrated in a recent study using the UK The Health Improvement Network (THIN) database[1]. Further, the outcomes between the generalisable and restricted populations are similar within JADE studies.

We would continue to strongly advocate for the generalisable population to be used as the primary analysis within the NMA with the restricted population for sensitivity analysis because this would be the most clinically relevant population.

Data for the full trial population is also provided for completeness.

Available endpoints

Data has been provided for EASI 50 + DLQI≥4 and EASI-75 to support the NMA. Data for other endpoints has not yet been analysed by the Pfizer statistical teams.

Notes on analysis:

The analysis for the response data was based non-responder imputation, i.e. if a subject withdrew from the study, then this subject was counted as non-responder after withdrawal.

[1]Eckert, L., Amand, C., Gadkari, A., Rout, R., Hudson, R., & Ardern-Jones, M.. Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN). Journal of Dermatological Treatment 2020; 31(8), 815-820.

b1) Adults

Subgroup of adults (aged ≥18 years) who received abrocitinib plus background TCS after inadequate response to, inability to tolerate, or contraindicated to CsA. For weeks 8 and 24, and later time points if available, please provide data on:

- Proportion of people achieving EASI 50 + ΔDLQI ≥4 (n/N; %);
- Proportion of people achieving EASI 75 (n/N; %);
- Proportion of people who discontinue treatment for any reason after a response at a set time point as defined in the study (conditional discontinuation; n/N; %).

Clinical effectiveness at week 16, generalisable and restricted populations, JADE DARE

	Full		Generalisable		Restricted	
	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.

Clinical effectiveness at week 8, generalisable and restricted populations, JADE DARE

	Full		Generalisable		Restricted	
	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]					
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.

Clinical effectiveness at week 26, generalisable and restricted populations, JADE DARE

			Generalisable		Restricted	
	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of people achieving EASI 75, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; TCS, topical corticosteroid.

Baseline characteristics

Baseline characteristics, generalisable and restricted populations, JADE DARE

Characteristic	Full		Generalisable		Restricted	
	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])	Abrocitinib 200 mg OD plus TCS ([redacted])	Dupilumab 300 mg Q2W plus TCS ([redacted])
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of AD, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Black or African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other or not reported, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean EASI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA score of 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean DLQI score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean SCORAD score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean peak pruritus NRS score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean % BSA affected (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean baseline EQ-5D Score (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment			[redacted]	[redacted]	[redacted]	[redacted]
Oral/injectable corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other non-biologic systemics (i.e., ciclosporin or other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics (excluding dupilumab*)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Topical JAK inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; SCORAD, SCORing Atopic Dermatitis

Section D. References

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Eczema Outreach Support (EOS)

Your position in the organisation: [redacted]

Brief description of the organisation: EOS is a national support charity offering a range of direct and personalised support services to families of children with eczema in the UK. The organisation's membership counts over 2,600 families. It is funded by a range of trusts and foundations, donations

Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?

Yes. EOS has received unrestricted grants towards its charitable activities.

If so, please state the name of manufacturer, amount, and purpose of funding.

- Leo Pharma - £5,000: online support activities for children
- Abbvie - £10,000: charitable activities
- Pfizer - £30,000: charitable activities

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

The daily struggles of children with eczema and their families in the UK

Families dealing with moderate to severe childhood eczema face daily battles and emotional struggles due to the relentless and painful nature of the condition. Because

eczema is a complex disease shaped by genetic, immunologic and environmental factors, its management is unique to each individual and based on a long process of trial and error.

There is no cure for eczema, but education and support can transform the experiences of families struggling to cope.

Our members spend hours daily treating their child's skin with ointments, steroids, topical antibiotics, bandages; they may even require immuno-suppressants, 3-weekly UV treatments or recurrent hospital admissions. On top of this, they deal with sleepless nights alongside the stress of dealing with constant scratching and unpredictable flares.

Eczema is also associated with other atopic diseases such as hay-fever, food allergies and asthma.

Alongside treatments, a crucial way to manage eczema flares is to find and then try to avoid triggers such as certain foods, irritants or environmental allergens; sadly this restricts further our children's access to activities such as swimming, messy play, sports (sweating), school trips etc. Because eczema has a substantial and long-term negative effect on people's ability to carry out normal daily tasks, it is recognised as a disability under the Equality Act 2010 and many of our young members receive the disability living allowance (DLA) for it.

"*Eczema is far more than dry skin or a bit of an itch. Eczema can demand an all consuming lifestyle and coping techniques which need to be embraced by not only the sufferer but their family as well. Only when people fully understand the far reaching impact of this relentlessly itchy, intolerable skin condition, can we hope for better treatment and acceptance.*" **Mother of a child with eczema.**

The evidenced impact of eczema in the literature

As a result of the impact of eczema on life, the condition can have a devastating effect on not only a person's physical but also psychological wellbeing: 20% of children with eczema are bullied at school (NES, 2008) and One in two has low self-esteem (APEL Quality of Life, 2010). Psychologically, this can affect an individual well into adult life: indeed children with severe eczema have increased risks of developing psychiatric illnesses later in life.

A 2012 British Skin Foundation survey found that 47% of respondents with skin disease had been victims of verbal abuse and a further one in six people having self-harmed as a result of their condition. One in three mothers admit to feelings of helplessness, frustration and anger. Sleep deprivation can also lead to high anxiety levels and elevated risks of depression (Manchester University, 2006).

Our latest survey

Between December 2020 and February 2021, we surveyed 3,945 children and young people with eczema and parents/carers of children with eczema across the UK to find out about the true impact eczema has on their lives.

Itch and flare-ups

• 51.70% of young people and parents/carers of children aged 0-17 with eczema reported that itching was an issue 'most days'
• 69.49% of young people with the severest form of eczema (self-reported) said itching is an issue 'most days'
• 47.20% of young people and parents/carers reported that they themselves/their child had at least 26 flare-ups in the past 6 months
"It stops me doing every-day activities like holding a pen." (15-year-old with eczema)

Mental health
• 52.25% of parents/carers reported that when their child's eczema was at its worst, it made their mood low
• 39.12% of parents/carers reported that their eczema made their child feel less confident.

"My daughter feels that people will always see her skin before her. Old teachers have called her moody and one even vocalised 'it's only itching?!' Which she has heard, internalised and I haven't been able to unlock yet for her so am really hoping the counsellor can help when they are involved - the GP has actively supported this referral." (Parent/carer of children with eczema over 5-years of age)

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

- Treating flares
- Keeping skin under control (extend time between flares)
- Reduce intensity of itch
- Improve sleep
- Better quality of life and improved mental health
- To cure the eczema
- Fewer skin infections – less antibiotics
- Less visible difference
- Improve school attendance/ improved experience of school

The above issues are different for each family depending on how the eczema impacts the individual family. As such, it is challenging to rate them in order of importance as eczema impacts families differently at different times.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Currently available NHS care

- Impact of COVID on access to healthcare professionals for parents/carers has been voiced.
- Members mention that they are still finding it a challenge to get a face to face appointment GP/dermatology
- Sending photos of the skin from phones instead of face-to-face appointments doesn't feel as a suitable alternative to actually seeing the skin in person

- A growing number of our members have mentioned seeking the advice from dermatologists in private practice due to waiting times to see NHS dermatology teams
- At the moment, many patients' treatment plans are not updated and additional treatments are given after a phone consultation. Often in these cases, members are not always told how these new treatments fit with their current treatment plan
- Healthcare professionals don't have capacity to do follow-ups with patients resulting in patients using treatments that don't work or the same treatment for long periods
- Families have reported that there can be an inconsistent approach to treating eczema amongst different healthcare professionals treating the same patient.

Specific treatments

- Some members describe how their GPs prescribe treatments such topical steroids often without giving specific guidance. This can result in families feeling unprepared of what to do if the skin worsens. Tapering of treatments is sometimes missed and written treatment plans often not provided
- Parents who are advised by dermatology teams that calcineurin inhibitors or a systemic immunosuppressant is the next treatment to consider, can often feel that they aren't given enough information to help them to make that decision. Some feel frightened of the potential side effects
- Phototherapy doesn't seem to be widely accessible across the UK
- Ichthammol paste bandages seem to be prescribed in some areas of the UK and not in others. Patients tell us that there might be areas where this treatment isn't available. Members tell us that they don't always get clear guidance on how to use it
- Antihistamines can be prescribed but many families do not know what they have been prescribed to treat. For example, some believe they are to manage the itch. Some use them in the longer term and are unaware of the NICE guidance to only use them in the short term. Patients can continue to use them regularly despite being unsure about their effectiveness.

Preferred treatments

- Many families would prefer not to use steroid treatments
- Many are seeking a cure for eczema and the treatment that would provide this
- Phototherapy seems a more acceptable option for many families as it feels less risky than immunosuppressants, for example.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability

- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

All treatments:

- New treatment options can increase the psychological wellbeing of an entire family unit that is affected by eczema. At the point in a child's eczema journey when they would receive these treatments, their parent/carer can have often felt hopeless, that they are at the end of the road and that 'nothing is working for their child'. The option to try something different brings motivation and a higher rate of treatment compliance as the family feel more positive that something will work
- The potential improvement in the patient's quality of life through these new treatment options would have a significantly positive impact on the mental health of both the carer and patient
- An improvement in sleep and school attendance/engagement with education or the workplace
- Easing the itch and reducing the risk of skin infections
- Reducing the impact of visible difference on the patient, particularly important for teenagers
- Improved relationships e.g. parent/child, intimate relationships etc.

Abrocitinib and Upadacitinib

- Administered orally negating the need for injections for those that are uncomfortable with injected treatments; thereby increasing treatment compliance and reducing anxiety.

Tralokinumab:

- Administered via injection so more practical and appealing for those who struggle to take medication orally; thereby increasing treatment compliance.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

- Phototherapy can very successful for many patients but is very time intensive in terms of travelling three times a week to a potentially distant location. Also, remission is temporary. Cost of transport can also be an issue. These new treatments could provide a reduced requirement to visit the hospital in comparison to phototherapy.
- If you do not need to use the treatments in conjunction with topical steroids, this could have an advantage for those who are concerned about using steroids

(particularly those concerned about topical steroid withdrawal) and could improve treatment compliance
- Would be helpful if use with topical treatments that can sting or cause discomfort can be avoided (e.g. steroids/calcineurin inhibitors) as these increase the anxiety of the parent and child and reduce treatment compliance.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

All treatments:
- For some, the idea of trying a new drug offers huge hope, but others see it as a bigger risk
- If other treatments are still required alongside (e.g. topical treatments), it is adding to the workload of a carer and can feel overwhelming and some might wonder if it is worth the extra workload.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

- Many read the leaflets provided for their treatments and have concerns about the side effects lists, e.g. atrophy for steroids, cancer for calcineurin inhibitors, kidney/liver function for some systemic immunosuppressant treatments
- Phototherapy not being available in their area
- The psychological support often required to support the patient with eczema's wellbeing isn't widely available. Parents hear from other families that they have access to psychodermatology and impact it can have on their child's eczema.
- Some of our members will say that they aren't aware of new, available treatments for eczema

- There are concerns about the postcode lottery which means that some people do not have access to the treatments that others have easy access to
- Brexit is a concern for some that this will affect the supply of the drugs they are currently prescribed. We have heard reports of pharmacies being unable to fill prescriptions
- Families are sometimes advised that they need to go to a hospital pharmacy to get their prescribed treatments.

Please list any concerns patients or carers have about the treatment(s) being appraised.

All treatments:

- Patients have concerns when treatments are new on the market as the long-term side effects might be unknown
- Concerns that their child might not be able to access this treatment due to age restrictions
- Wil these treatments mean that my child will be immunocompromised?
- COVID – will my child be more at risk as a result of Covid by using these treatments? Can they still attend school/social events and what will be the resulting impact on their wellbeing if they cannot?
- Will we still need to use topical treatments in conjunction with these treatments to control the eczema?

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

All treatments:

- If the treatments require regular blood tests, some patients and their cares find this anxiety provoking but others are reassured by them
- Some think it's too risky to try a new treatment but others think the impact of eczema on their child's quality of life is so debilitating that it's worth the risk.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

All treatments:

- Patients where other systemic treatments have not worked would benefit from having another treatment to try
- Patients whose quality of life and mental health has been impacted by the severity of their eczema would benefit hugely.

Upadacitinib and Abrocitini:

- Patients who struggle with treatments being administered via injection would benefit from the fact these two treatments are given orally.

Tralokinumab:

- In reverse to the above, patients who struggle to take medication orally would benefit from this treatment being given via injection.

Are there any groups of patients who might benefit less from the

treatment(s) than others? If so, please describe them and explain why.

Tralokinumab:

- Patients uncomfortable with needles or associated phobias may find it too stressful a treatment to undertake.

Upadacitinib and Abrocitini:

- Some patients struggle with taking medicine in tablet form.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐ Yes ☒ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular

protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

- The treatments might not be available equally across different health authorities, resulting in a postcode lottery
- Awareness of treatments can be lower amongst certain patients due to lack of understanding as to where to find information on treatments, language barriers or access to the internet to research treatment options
- The treatments could be inaccessible to patients with skin of colour unless the guidance is inclusive of all skin tones e.g. avoid the term "redness" when describing the symptoms of eczema.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

All treatments;

- Some families can be uncomfortable with blood tests and children and young people can require support with this aspect of treatment
- Some patients with additional sensory needs can struggle with many eczema treatments, including the ones being appraised. Our evidence is based on conversations with families who tell us that:
    - Topical treatments are difficult due to sensory overload with touch
    - Swallowing can be challenging (orally administered treatments)
    - The light and space confinement can be challenging during phototherapy
    - Eczema garments are not tolerated
    - Hospital visits can be stressful (applicable to any treatments that require regular hospital visits)
- Patients with ASD may struggle with any changes to their treatments including the introduction of new treatments and may need extra support for treatment compliance.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The families we work with will perceive these treatments as innovative as they bring new hope and fresh options which in itself feels innovative. The psychological impact of new treatments being available should not be underestimated, especially for families who believe they are at the "end of the road" with current options.

Are there any other issues that you would like the Appraisal Committee to consider?

- It is important to our patient group that treatments are widely available across all areas of England
- Any guidance and information about any of these drugs should be fully inclusive of all skin types
- In some areas there are Psychodermatology services that help with the psycho-social impact of the condition also with treatment compliance. The benefits of this on patients and their families are high.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- The positive psychological impact on families of the availability of these new treatments should not be underestimated
- Wide availability of these treatments should be considered, where possible, to reduce the risk of postcode lotteries & ensure more patients can benefit
- Limiting the requirement to access treatments in hospitals would increase the inclusivity of these treatments, particularly for single parent households/those without access to cars/lower income families
- The guidance/literature that accompanies the treatments must take into account people's different skin colours to ensure the treatments are inclusive & accessible to all.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

X **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Abrocitinib for treating moderate to severe atopic dermatitis in people aged 12 and over [ID3768]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	National Eczema Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	National Eczema Society is the UK charity for people of all ages living with eczema and those who care for them. We support people with information and advice about eczema and its management and treatment, which we deliver through our website, social media platforms, publications and nurse-supported Helpline. We are the campaigning voice for people with eczema and raise awareness of the needs of people with eczema with healthcare professionals, teachers and the government. We are funded by membership fees, donations from the public and organisations, and our corporate partners (pharmaceutical and emollient companies that sell products or services for people with eczema). We have approximately 2,600 members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	National Eczema Society has not received any funding from Pfizer, manufacturer of the technology, in the last twelve months. Eli Lilly (manufacturer of a comparator product) has been a Corporate Member of National Eczema Society since May 2019, and the corporate membership agreement complies with the ABPI code of practice. The annual Corporate Membership fee paid by the company is £10,000 plus VAT. The Corporate Membership Scheme allows company partners to demonstrate public support for the important work of the Society. The funding helps pay for the charity's core operating costs with the purpose of helping the Society achieve its overall objective of supporting people living with eczema.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	National Eczema Society operates a nurse-supported Helpline service, responding to telephone and email enquiries from people affected by eczema who are seeking advice either on their own behalf or for a loved one. The calls and emails we receive give us a valuable insight into the experiences of people living with eczema and the many challenges they face. In 2020 we responded to over 1,500 Helpline enquiries. We also gain insights from the conversations and comments shared by people with eczema on our busy social media platforms. We carried out a survey with over 1,000 patients and carers in the UK in 2020, which revealed further insights into the lived experience of eczema and how it affects physical health, mental health, quality of life and people's life chances.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Atopic eczema is a chronic dry skin condition. Its major symptom is itchiness, which can be intense, relentless and unbearable. Constant scratching causes the skin to split and bleed, and leaves it open to infection. Even when the eczema is mild to moderate (as opposed to severe), when it is not well-controlled it can have a significant impact on quality of life. In the UK, one in five children and one in ten adults has eczema. Constant itchiness is one of the most challenging aspects of eczema; it can result in reduced social interaction and inability to work and study. In addition to the pain and discomfort brought about by scratching, itchiness often makes sleeping extremely difficult. Lack of sleep can compromise people's

	ability to concentrate at work and school/university and carry out everyday tasks effectively. It also damages personal relationships – as can itchiness alone. Eczema can have a significant negative impact on the whole family. People who are constantly itchy and/or have eczema on visible areas of their body can feel extremely self-conscious about their condition and appearance, and reluctant to leave their home. Eczema self-care is very time-consuming for patients. In addition to applying emollients at least twice a day, and every few hours when the skin is very dry, people who scratch a lot overnight may have to wash their bedding every day to remove blood and skin flakes. People who have a mental health condition (e.g. anxiety or depression) as a result of their eczema, or in addition to it, often find it difficult to manage both conditions effectively. Even people who haven't been diagnosed with a mental health condition can find daily eczema management onerous and dispiriting. At school, adolescents may feel embarrassed at having to leave their class to apply creams several times a day. Caring for a child or adult with eczema can be time-consuming and exhausting, both physically and emotionally. Carers may need to apply topical treatments to the person in their care multiple times a day, try to distract them when they are itchy, provide emotional support and take them to regular GP or hospital appointments. Carers' ability to sleep is compromised when the person in their care is unable to sleep because of itchiness. Carers often need to get up several times during the night to apply emollient and comfort the person for whom they are caring. Lack of sleep for carers, as for people with eczema, can lead to their experiencing a diminished ability to concentrate at work and other activities, and carry out tasks effectively. Recent reports and surveys have highlighted the significant psychosocial impacts of eczema on children and adolescents, including low self-confidence and self-esteem, and related problems like making and maintaining friendships. Attendance and performance at school, feeling self-conscious and being bullied are other commonly cited impacts of childhood eczema. In the National Eczema Society patient survey referred to earlier, conducted in 2020, a third of parents who responded said they regularly cancelled family activities or trips because of their child's eczema, while 1 in 5 parents felt it had damaged their relationship with their other children.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Many patients and carers consider the current treatments available for eczema on the NHS to be limited in number and effectiveness. In the patient survey referred to earlier, 42% of adult respondents and 30% of parent respondents said they did not have confidence in the abilities of healthcare professionals to treat their own or their child's eczema. These findings, mirrored in other patient surveys, reflect the limited effective treatment options currently available to treat inflammation in eczema. Many patients are reluctant to use topical steroids on a routine basis to control their symptoms because of concerns about adverse effects, notably 'topical steroid addiction/withdrawal' and skin thinning. Access to topical calcineurin inhibitors is limited, being prescribed for areas of delicate skin only. Current second-line treatments for eczema include phototherapy, oral steroids, immunosuppressant drugs (azathioprine, ciclosporin, methotrexate and mycophenelate mofetil) and a biologic drug (dupilumab). Baricitinib, a JAK1 and JAK2 inhibitor, was approved by NICE in March 2021 to treat moderate to severe atopic eczema in adults. Second-line treatments can be effective for many people with eczema. However, a large proportion of people with eczema and their families have serious concerns about the potential for significant long-term harm through severe adverse side effects associated with immunosuppressant drugs. These concerns have been further highlighted with the Covid-19 pandemic. Dupilumab has fewer potential side effects than immunosuppressant drugs, but is only available to people who have tried and failed on at least one immunosuppressant drug and those who would not be eligible to take them. In addition, it is not effective for everyone who tries it, or suitable for people with certain co-morbidities. Baricitinib, available under the same circumstances as dupilumab, also has fewer potential side effects than immunosuppressant drugs, but is only available to adults. It is also unlikely to be effective for everyone who tries it.
8. Is there an unmet need for patients with this condition?	People with moderate to severe eczema are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, or starting phototherapy (which is not universally

	available) or immunosuppressant drugs of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. The biologic drug dupilumab has fewer potential side effects than immunosuppressant drugs, but it is only available to people under limited circumstances (see above), and does not work effectively for everyone. JAK inhibitors such as abrocitinib and baricitinib, which have a different mechanism of action to biologics, are likely to work more effectively for some people than biologics. Abrocitinib is a JAK1-selective inhibitor and baricitinib an inhibitor of JAK1 and JAK2; different people may respond better to one type than another. Even if abrocitinib is only made available under the same circumstances as dupilumab and baricitinib, it will constitute an additional treatment option for people with moderate to severe eczema, increasing the likelihood that they will find a treatment that works effectively for them. This is very important and necessary given the heterogeneous nature of eczema. Abrocitinib appears to be associated with a different set of adverse reactions than dupilumab. As side effect profile often determines which drug is used for an individual, a drug with a different side effect profile gives more options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The phase 3 JADE COMPARE trial evaluated the safety and efficacy of both doses of abrocitinib (100mg and 200mg) and background topical therapy against dupilumab and placebo in adult patients with moderate to severe atopic eczema. The advantages of abrocitinib were shown to be as follows in the trial results, published in the New England Journal of Medicine (March 25, 2021): • Both doses of abrocitinib worked very quickly in regard to itch. The 200mg dose was superior to dupilumab in regard to itch response at week 2. Given the debilitating nature of itch for people with moderate to severe eczema, a rapid improvement in this symptom represents a significant advantage. • Both doses resulted in significantly greater reductions in signs and symptoms of moderate to severe eczema than placebo at weeks 12 and 16 (based on Investigator Global Assessment (IGA)

	response and Eczema Area and Severity Index (EASI) improvement). • Abrocitinib was generally well-tolerated by adolescents and adults with moderate to severe eczema. That it is well-tolerated by adolescents was shown in the JADE MONO-1 phase 3 trial and the top-line results from the JADE TEEN trial. • Abrocitinib has the advantage of being taken in pill form, in a single daily dose. Many people with eczema, especially adolescents, prefer oral over injectable drugs.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In the JADE COMPARE trial, the overall incidence of adverse events was higher in the 200mg abrocitinib arm than in the other groups (i.e. the 100mg, dupilumab and placebo arms). The most common adverse effects included nausea and acne. Median platelet counts decreased among patients taking abrocitinib, which would make it less acceptable to people with blood-clotting disorders. Abrocitinib is unlikely to work effectively for everyone eligible to use it. Some patients may start treatment and not receive sufficient benefit to warrant continuing, which would be incredibly demoralising and result in a longer period of poorly controlled symptoms.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with moderate to severe eczema for whom topical treatments are insufficiently effective and who must progress to second-line treatments would benefit from the introduction of a new second-line treatment option. Patients with moderate to severe eczema who are concerned about the potential side effects of immunosuppressant drugs would benefit from the introduction of a new second-line treatment option, particularly a new type of treatment (a JAK inhibitor). Abrocitinib would also benefit people with eczema who are fearful of injections.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The efficacy and safety of abrocitinib for people with different skin colours needs to be taken into account. About two thirds of participants in the JADE COMPARE trial were white.
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • The treatment options for atopic eczema currently available on the NHS are limited and insufficient. The introduction of abrocitinib has the potential to broaden patient choice, and increase the likelihood that patients with moderate to severe eczema would find a treatment that is effective for them. • Trial data results show that abrocitinib can not only improve, but rapidly improve, the symptoms of eczema that most people with the condition report as being the most debilitating. The improvement in itch is particularly rapid for the 200mg dose.	

- Many people with eczema and their families have serious concerns about the potential for significant long-term harm through severe adverse side effects associated with immunosuppressant drugs. Adverse events in the abrocitinib trials were mainly mild and moderate.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

Tralokinumab for treating moderate to severe atopic dermatitis [ID3734]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Eczema Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	National Eczema Society is the UK charity for people of all ages living with eczema and those who care for them. We support people with information and advice about eczema and its management and treatment, which we deliver through our website, social media platforms, publications and nurse-supported Helpline. We are the campaigning voice for people with eczema and raise awareness of the needs of people with eczema with healthcare professionals, teachers and the government. We are funded by membership fees, donations from the public and organisations, and our corporate partners (pharmaceutical and emollient companies that sell products or services for people with eczema). We have approximately 2,600 members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes, the manufacturer LEO Pharma has been a Corporate Member of National Eczema Society since January 2019 and the corporate membership agreement complies with the ABPI code of practice. The annual Corporate Membership fee paid by the company is currently £10,000 plus VAT. The Corporate Membership Scheme allows company partners to demonstrate public support for the important work of the Society. The funding helps pay for the charity's core operating costs with the purpose of helping the Society achieve its overall objective of supporting people living with eczema. National Eczema Society worked in association with LEO Pharma on the Eczema Unmasked survey and report published in 2020. LEO Pharma funded the survey and production of the report. Sanofi (manufacturer of dupilumab) is a Corporate Member of National Eczema Society. The annual Corporate Membership fee paid by the company is currently £20,000 plus VAT. Sanofi also provided project-specific funding in 2020 to National Eczema Society of £6,900 (including VAT), to part-fund an upgrade of the charity's database software that was needed to facilitate flexible working in response to Covid-19.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	National Eczema Society operates a nurse-supported Helpline service, responding to telephone and email enquiries from people affected by eczema who are seeking advice either on their own behalf or for a loved one. The calls and emails we receive give us a valuable insight into the experiences of people living with eczema and the many challenges they face. In 2020 we responded to over 1,500 Helpline enquiries. We also gain insights from the conversations and comments shared by people with eczema on our busy social media platforms. We carried out a survey with over 1,000 patients and carers in the UK in 2020, which revealed further insights into the lived experience of eczema and how it affects physical health, mental health, quality of life and people's life chances.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Atopic eczema is a chronic dry skin condition. Its major symptom is itchiness, which can be intense, relentless and unbearable. Constant scratching causes the skin to split and bleed, and leaves it open to infection. Even when the eczema is mild to moderate (as opposed to severe), when it is not well-controlled it can have a significant impact on quality of life. In the UK, one in five children and one in twelve adults has eczema. Constant itchiness is one of the most challenging aspects of eczema; it can result in reduced social interaction and inability to work and study. In addition to the pain and discomfort brought about by scratching, itchiness often makes sleeping extremely difficult. Lack of sleep can compromise people's

	ability to concentrate at work and when studying, and carry out everyday tasks effectively. It also damages personal relationships – as can itchiness alone. Eczema can have a significant negative impact on the whole family. People who are constantly itchy and/or have eczema on visible areas of their body can feel extremely self-conscious about their condition and appearance, and reluctant to leave their home. Eczema self-care is very time-consuming for patients. In addition to applying topical treatments at least twice a day, and every few hours when the skin is very dry, people who scratch a lot overnight may have to wash their bedding every day to remove blood and skin flakes. People who have a mental health condition (e.g. anxiety or depression) as a result of their eczema, or in addition to it, often find it difficult to manage both conditions effectively. Even people who haven't been diagnosed with a mental health condition can find daily eczema management onerous and dispiriting. Caring for an adult with eczema can be time-consuming and exhausting, both physically and emotionally. Carers may need to apply topical treatments to the person for whom they are caring multiple times a day, try to distract them when they are itchy, provide emotional support and take them to regular GP or hospital appointments. Carers' ability to sleep is compromised when the person in their care is unable to sleep because of itchiness. Carers may need to get up several times during the night to apply emollient and comfort the person for whom they are caring. Lack of sleep for carers, as for people with eczema, can lead to their experiencing a diminished ability to concentrate at work and other activities, and carry out tasks effectively.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Many patients and carers consider the current treatments available for eczema on the NHS to be limited in number and effectiveness. In the patient survey referred to earlier conducted in 2020, 42% of adult respondents and 31% of parent respondents said they did not have confidence in the abilities of healthcare professionals to treat their child's eczema. These findings, mirrored in other patient surveys, reflect the limited effective treatment options currently available to treat inflammation in eczema. Many patients are reluctant to use topical steroids on a routine basis to control their symptoms because of concerns about adverse effects, notably 'topical steroid addiction/withdrawal' and skin thinning. Access to

	topical calcineurin inhibitors is limited, being prescribed for areas of delicate skin only. Current second-line treatments for eczema include phototherapy, oral steroids, immunosuppressant drugs (azathioprine, ciclosporin, methotrexate and mycophenelate mofetil) and a biologic drug (dupilumab). Second-line treatments can be effective for many people with eczema. However, a large proportion of people with eczema and their families have serious concerns about the potential for significant long-term harm through severe adverse side effects associated with immunosuppressant drugs. These concerns have been further highlighted with the Covid-19 pandemic. Dupilumab has fewer potential side effects than immunosuppressant drugs, but is only available to people who have tried and failed on at least one immunosuppressant drug and those who would not be eligible to take them. In addition, it is not effective for everyone who tries it, or suitable for people with certain co-morbidities.
8. Is there an unmet need for patients with this condition?	People with moderate to severe eczema are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, or starting phototherapy (which is not universally available) or immunosuppressant drugs of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. For people who have tried and failed on at least one immunosuppressant drug, or who would not be eligible to take immunosuppressant drugs, dupilumab (at present the only biologic drug approved for atopic eczema) is the only option. Dupilumab, which has fewer potential side effects than immunosuppressant drugs, works by blocking both the IL-13 and IL-4 pathways. IL-13 and IL-4 are the two interleukins thought to contribute to the underlying inflammation in eczema. Tralokinumab works by binding specifically to IL-13, thereby preventing downstream IL-13 signalling. The relative contributions of IL-13 and IL-4 to atopic eczema development is unclear. Since people's eczema responds differently to the targeting of different pathways, tralokinumab is likely to work more effectively for some people than dupilumab. Dupilumab, while highly efficacious for many people, does not work effectively for everyone.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The advantages of tralokinumab are that it significantly improves eczema severity and itch; its beneficial effects appear to start soon after starting treatment and are long-lasting; it has the potential to reduce topical steroid use; and it has a good safety profile. Tralokinumab has undergone three Phase 3 trials (ECZTRA 1, 2 and 3), the results of which have been published in the British Journal of Dermatology. In the three Phase 3 trials, tralokinumab met its primary endpoints at week 16 as assessed by the Investigator Global Assessment score of clear or almost clear skin (IGA 0/1) and at least a 75% improvement in the Eczema Area and Severity Index score (EASI-75). It also demonstrated significant improvements in secondary endpoints at week 16 including extent and severity of skin lesions, itch and health-related quality of life measures. These improvements at week 16 were generally sustained. In ECZTRA 1 and 2, the majority of patients treated with tralokinumab 300 mg every two weeks who achieved a clinical response at week 16, maintained this response at week 52 without any use of rescue medication, including topical steroids. Patients reported meaningful improvements in itch, sleep and quality of life as early as 1-2 weeks after starting tralokinumab, and it was well-tolerated up to 52 weeks of treatment in the ECZTRA 1 and 2 trials. ECZTRA 3 was a combination trial with topical steroids. In this trial, nine out of ten patients who achieved clear or almost clear skin with tralokinumab 300 mg in combination with topical steroids at week 16 maintained this response at week 32 when randomized to dosing every two weeks. Eight out of ten patients randomized to dosing every four weeks at week 16 maintained clear or almost clear skin at week 32, showing that going down to a lower dose – which would mean fewer hospital visits for patients – was not dissimilar to a higher dose in terms of results.

	Patients in the tralokinumab arm of this trial also saw early improvements (within 2-3 weeks) in specific symptoms, such as intensity of itching and in health-related quality of life. In addition, they used significantly less topical steroid compared with those in the placebo arm. Given patients' safety concerns over long-term topical steroid use, being able to reduce topical steroid use would be a major advantage of tralokinumab. The risk of conjunctivitis, which is the most common side effect for dupilumab, may be lower with tralokinumab.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One disadvantage of the technology is that it is unlikely to work effectively for everyone eligible to use it. Some patients may start treatment and not receive sufficient benefit to warrant continuing, which would be incredibly demoralising and result in a longer period of poorly controlled symptoms. Adverse events that were higher for people on tralokinumab compared with placebo included upper respiratory tract infections (mainly common cold), conjunctivitis, headaches, and injection site reactions.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with moderate to severe eczema for whom topical treatments are insufficiently effective and must progress to second-line treatments would benefit from the introduction of another second-line treatment option. Patients with moderate to severe eczema who are concerned about the potential side effects of immunosuppressant drugs would benefit from the introduction of a new second-line treatment option.

	Patients for whom dupilumab has not proven effective would benefit from the introduction of a different biologic drug option.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • The treatment options for eczema currently available on the NHS are limited and insufficient. The introduction of tralokinumab has the potential to broaden patient choice, and would increase the likelihood that patients with moderate to severe eczema would find a treatment that is effective for them. • Since eczema is a heterogeneous condition, and responds differently to the targeting of different pathways in different people, tralokinumab is likely to work more effectively for some people than dupilumab. • Tralokinumab significantly improves eczema severity and itch; its beneficial effects appear to start soon after starting treatment and are long-lasting; and it seems to reduce topical steroid use. It has the potential to make a significant difference to the lives of people with eczema for whom it works effectively. • Many people with eczema and their families have serious concerns about the potential for significant long-term harm through severe adverse side effects associated with immunosuppressant drugs. Adverse events in tralokinumab trials were mainly mild and moderate.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.