Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder** **list** are available on the NICE website.

1. **Company submission** from Galderma UK
2. **Company summary of information for patients (SIP)** from Galderma (UK)
3. **Clarification questions and company responses**
   a. Clarification questions and company responses
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4. **Patient group, professional group and NHS organisation submissions** from:
   a. Eczema Outreach Support
   b. British Association of Dermatologists (BAD)
5. **Expert personal perspectives from:**
   a. Dr Andrew Pink, Consultant Dermatologist – clinical expert, nominated by Galderma UK
   b. Andrew Collinson, Patient Expert, nominated by Eczema Outreach Support
6. **External Assessment Report** prepared by Sheffield Centre for Health and Related Research (ScHARR)
7. **External Assessment Report – factual accuracy check**

Please note that the appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nemolizumab for treating moderate-to-severe atopic dermatitis in people 12 and over [ID6221]

Document B

Company evidence submission

October 2024

File name	Version	Contains confidential information	Date
[ID6221] Nemolizumab Document B 240225 [Redacted]	3.0	Yes	24/02/2025

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Abbreviations

Abbreviation	Definition
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP NRS	average pruritis numerical rating scale
AST	aspartate aminotransferase
BMI	body mass index
BSC	best supportive care
CE	Conformité Européenne
CI	confidence interval
CLA	cutaneous lymphocyte-associated antigen
CMH	Cochran-Mantel-Haenszel
COVID	coronavirus-19 disease
CPRD	Clinical Practice Research Datalink
CSR	clinical study report
DC	dendritic cells
DCS	dual chamber syringe
DLQI	Dermatology Life Quality Index
EAG	External Assessment Group
EASI-75	Eczema Area and Severity Index-75
ECG	electrocardiogram
eCRF	electronic case reporting form
EQ-5D	EuroQol 5-Dimensions
EU	European Union
FDA	US Food and Drug Administration
GI	gastrointestinal
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HCRU	healthcare resource use
HES	hospital episode statistic
HRQoL	health-related quality of life
ICD	International Classification of Diseases 10th Revision
ICF	International Classification of Functioning, Disability and Health
IFSI	International Forum for the Study of Itch
IGA	Investigator's Global Assessment
IL	interleukin
IRR	incidence rate ratio
ITC	indirect treatment comparison
ITT	intent-to-treat
JAK	Janus kinase

LS mean	least squares mean
LTE	long-term extension
MAR	missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MI	multiple imputation
MMRM	mixed effect model for repeated measure
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NK1	neurokinin-1
NK1R	neurokinin-1 receptor
NMA	network meta-analysis
OC	observed cases
OR	odds ratio
PDE-4	phosphodiesterase-4
PGA	Patient Global Assessment
PGAD	Patient Global Assessment of Disease
PGAT	Patient Global Assessment of Treatment
PK	pharmacokinetics
PP NRS	Peak Pruritus Numerical Rating Scale
PPY	per patient year
PT	preferred term
Q2W	Every two weeks
Q4W	every four weeks
QoL	quality of life
RCT	randomised controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SD NDS	Sleep Disturbance Numerical Rating Scale
SE	standard error
SLR	systematic literature review
SOC	standard of care
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment emergent adverse event
Th2	T-helper 2 cell
UK	United Kingdom
ULN	upper limits of normal
US	United States
UV	ultraviolet
VAS	Visual Analogue Scale

WPAI	Work Productivity and Activity Impairment

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

A marketing authorisation application was submitted to the Access Consortium on [redacted] for nemolizumab for the treatment of moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older who are candidates for systemic therapy. An opinion from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) is expected in [redacted].

The submission focuses on part of the technology's marketing authorisation and covers the treatment of adults and adolescents (≥ 12 years) with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated. The proposed position in the treatment pathway for this population is narrower than the marketing authorisation because this is relevant to the anticipated use in NHS clinical practice. It is anticipated that nemolizumab would be used as second-line systemic treatment, in line with the current positioning of the other biologic and Janus kinase (JAK) inhibitor therapies within UK clinical practice.[1-3] The decision problem that this submission addresses is outlined in 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 and over with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.	People aged 12 years and over with moderate-to-severe atopic dermatitis who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.	This second line positioning is in line with the anticipated use of nemolizumab in moderate-to-severe AD in UK clinical practice. This population has been validated by UK clinical experts and is in line with the positioning of dupilumab (TA534),[1] baricitinib (TA681),[2] abrocitinib, tralokinumab and upadacitinib (TA814),[3] and lebrikizumab (TA986) in AD.[4]
Intervention	Nemolizumab	Nemolizumab with BSC	It is anticipated that nemolizumab will be used with BSC (which can include emollients, TCSs, and TCIs), in patients with moderate-to-severe AD.
Comparator(s)	For atopic dermatitis in people who have not previously had a systemic therapy: • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) For atopic dermatitis in people whose condition has not responded to at least 1 other systemic therapy, or these are not suitable: • Abrocitinib • Upadacitinib • Baricitinib • Dupilumab • Tralokinumab • Lebrikizumab	For atopic dermatitis in people 12 years and over whose condition has not responded to at least 1 other systemic therapy, or these are not suitable: • Abrocitinib (adults and adolescents) • Upadacitinib (adults and adolescents) • Baricitinib (adults only) • Dupilumab (adults only) • Tralokinumab (adults only) • Lebrikizumab (adults and adolescents)	Based on the second line positioning of nemolizumab in the treatment pathway, immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) would not be considered a relevant comparator. The comparators listed in the final scope for people with AD whose condition has not responded to at least 1 other systemic therapy, or these are not suitable are appropriate. However, it is important to note that not all the listed comparators are recommended by NICE in both the adult and adolescent AD populations. Dupilumab (TA534),[1] baricitinib (TA681),[2] and tralokinumab (TA814),[3] are recommended in an adult AD population only. Since the publications of TA534 and TA814,[1,3] the marketing authorisations for

			dupilumab and tralokinumab have been extended to include people aged 12 to 17 years, and these treatments are commissioned by NHS England for this population. However, NICE have confirmed via email communication that tralokinumab will likely be considered as a comparator in the adult AD population only. Therefore, based on equivalent recommendation between dupilumab and tralokinumab, these treatments in addition to baricitinib will be considered as comparators for nemolizumab in the adult population only.
Outcomes	The outcome measures to be considered include: • Measures of disease severity • Measures of symptom control including improvement in itch • Disease free period/maintenance of remission • Time to relapse/prevention of relapse • Adverse effects of treatment • Health-related quality of life	The outcome measured to be considered include: • Measures of disease severity and symptom control • Measures of symptom control including improvement in itch • Adverse effects of treatment • Health-related quality of life	Galderma considers most of the outcomes for AD to be appropriate. However, it is important to note the issues that have been previously raised in response to the following endpoints in AD: • Disease free period/maintenance of remission • Time to relapse/prevention of relapse In response to the final scope in TA814,[3] clinical experts informed the External Assessment Group (EAG) that 'disease free period', 'maintenance of remission', 'time to relapse' and 'prevention of relapse' are not terms that are commonly used in AD clinical practice and are not defined for AD. Therefore, the company do not consider these endpoints to be relevant in the context of the clinical benefits of nemolizumab.
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.	As per NICE scope	

	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. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroup will be considered: • People with atopic dermatitis affecting the hands • Skin colour subgroups	If the evidence allows the following subgroup will be considered: • Skin colour subgroups	People with AD affecting the hands are not considered a relevant subgroup in this submission. People with AD affecting the hands are a distinct phenotype of the disease, whereas this submission focuses on a broader AD patient population. Furthermore, subgroup analysis on this population is not feasible based on the lack of data available for this subgroup.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; NICE, National Institute for Health and Care Excellence

B.1.2. Description of the technology being evaluated

Details of the technology being appraised in this submission are summarised in Table 2. The summary of product characteristics and the UK public assessment report are provided in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Nemolizumab (Nemluvio®)
Mechanism of action	Nemolizumab is a humanised monoclonal antibody of the IgG2 subclass that inhibits interleukin-31 (IL-31) signalling by binding selectively to IL-31 receptor alpha chain (IL-31RA). IL-31 is a neuroimmune cytokine that drives pruritus and inflammation, which are important pathophysiological components of AD. IL-31 has an additional barrier dysfunction effect in AD. Multiple cell types express IL-31RA and are activated by IL-31. Those involved in the pathophysiology of AD include immune cells (e.g., mononuclear phagocytes, granulocytes) and structural cells (e.g., neurons, fibroblasts, keratinocytes). Blocking IL-31RA with nemolizumab ameliorates pruritus and inhibits inflammatory responses in AD. Additionally, nemolizumab restores barrier integrity in AD. The mechanism of action of nemolizumab has not been definitively established.
Marketing authorisation/CE mark status	A marketing authorisation application was submitted to the Access Consortium (New Active Substance Work Sharing Initiative [NASWSI]) for nemolizumab for the treatment of atopic dermatitis on [redacted]. An opinion from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The proposed indication for nemolizumab is for the treatment of moderate-to-severe AD in patients aged 12 years and older who are candidates for systemic therapy. Nemolizumab is also indicated for the treatment of PN; however, this is not the focus of the submission.
Method of administration and dosage	Subcutaneous injection (initial loading dose of 60 mg, followed by 30 mg Q4W); after 16 weeks of treatment patients who achieve clinical response switch to 30 mg, Q8W maintenance dose.
Additional tests or investigations	Not applicable
List price	[redacted]/SKU
Patient access scheme (if applicable)	Simple discount

Abbreviations: AD, atopic dermatitis; IgG, immunoglobulin G; IL, interleukin; MHRA, Medicines and Health Product Regulatory Agency; NICE, National Institute for Health and Care Excellence; PASLU, Patient Access Scheme Liaison Unit; Q4W, every 4 weeks; Q8W, every 8 weeks; SKU, stock keeping unit

B.1.3. Health condition and position of the technology in the treatment pathway

Summary

Disease pathophysiology, epidemiology, and burden

- AD is a common, chronic, and flaring inflammatory skin disease which is characterised by persistent, severe itch (pruritis) and painful eczematous lesions.
- IL-31 mediates itch by stimulating neurons and increasing neurite branching in the skin,[5] and therefore plays a central role within AD. In patients with AD, the expression of IL-31 is increased in skin lesions, and serum levels correlate with severity of disease and pruritic symptoms.[6,7]
- There have been two recent analyses of UK CPRD data to ascertain AD prevalence.[8,9] Ameen et al., reported a period prevalence of 1.86% in adults (aged ≥ 18 years) and 4.99% in adolescents patients between 2008–2018.[8] Kleyn et al., reported an overall prevalence of 2.4% per year in adult (aged ≥ 18 years) patients between 2015–2019.[9] Approximately, 7.5–8.3% of patients had moderate-to-severe disease, and of these patients, approximately 60% had received some form of systemic therapy.[9] The variability between estimates may arise due to the different populations considered: Ameen et al. reviewed patients in England,[8] while Kleyn et al. considered patients throughout the UK.[9]
- Itch is the most burdensome symptom associated with AD;[10,11] itch relief is the primary goal for the majority of patients with moderate-to-severe AD.[12,13]
- The itching and discomfort associated with active lesions in moderate-to-severe AD disrupt patient's lives and has wide ranging effects, impacting patient's sleep,[14] mental health,[12,15-19] and quality of life (QoL).[5]
- Across Europe total direct, indirect and out-of-pocket costs for patients with moderate-to-severe AD are estimated to be €10.1 billion, €15.2 billion, and €4.7 billion, respectively.[20]

Clinical pathway and treatment landscape

- A stepwise approach to therapy escalation is described in multiple treatment guidelines,[21-23] and related guidance documents.[1-3,24,25] Patients

initiate on non-pharmacologic options (emollients, moisturisers, educational programmes), escalating when disease is inadequately controlled to topical therapies aimed at reducing inflammation (topical corticosteroids [TCS], topical calcineurin inhibitors [TCI]), followed by first-line systemic treatments (systemic immunosuppressants), and finally second-line systemic treatments (biologics and JAK inhibitors).

- There are limitations with the current treatment options for patients with AD. Systemic immunosuppressants have relatively poor safety profiles and require additional monitoring.[21,26-29] Many patients receiving dupilumab or tralokinumab do not achieve either clinical response (IGA 0/1, 61%[30] and 61%[31] respectively) or itch control (PP NRS improvement ≥ 4, 41%[30] and 55%[31] respectively). In addition, JAK inhibitors are associated with safety concerns and must display warning labels indicating increased risk of major adverse cardiovascular events, malignancy, venous thromboembolism, serious infection, and mortality.[32-34]
- There is an unmet need for new, safe, effective treatment options to increase therapeutic diversity and choice available to patients.[3]

Nemolizumab

- Nemolizumab has a novel mechanism of action and offers an alternative therapeutic option for patients with AD. Nemolizumab blocks the IL-31 receptor α chain and is distinct from the currently licenced biologics that target IL-4/IL-13 signalling (dupilumab, tralokinumab, and lebrikizumab).[35]
- Nemolizumab therapy is not associated with the safety concerns related to JAK inhibitors.
- Patients treated with nemolizumab can benefit from a less intense dosing schedule in comparison to other biologic therapies and JAK inhibitors.[36,37]

B.1.3.1. Disease overview

AD, also known as 'atopic eczema', is a common, chronic, and flaring inflammatory skin disease. AD is a heterogenous disease that is believed to be triggered in people with a genetic susceptibility by exposure to an environmental factor.[38] An estimated

230 million people have AD worldwide.[39] Disease onset commonly occurs in patients below five years of age, but can occur in patients of any age.[40]

AD is characterised by persistent, severe itch (pruritis) and painful eczematous lesions.[38] The distribution of lesions can differ with age. In infants the distribution is widespread with acute lesions characterised by severe erythema, oedema, excoriations, and serous exudate manifesting as oozing and crusting; lesions in infants are characteristically located on the face, cheeks, and the trunk.[38] In childhood, the disease becomes more localised and chronic with paler erythema, xerosis and more ill-defined skin lesions that commonly affect flexor surfaces, and in the most chronic areas the skin is thickened from repetitive scratching.[38] Adolescents and adults can have a diffuse pattern of AD but also localised lesions most typically affecting hands, eyelids, and flexures.[38] The itching and discomfort associated with active lesions in moderate-to-severe AD disrupt patient's lives and can have significant impacts on patient's sleep,[14] mental health,[12,15-19] and QoL.[41]

Diagnosis of AD and assessment of disease severity is based on clinical judgement and patient-reported history and symptoms (objective and subjective measures).[42] Patients who have a minimum affected body surface area of 10%, individual lesions with moderate-to-severe features, highly visible or functionally important areas affected, or significantly impaired QoL, may be diagnosed with moderate-to-severe AD.[43]

B.1.3.1.1. Pathophysiology

A family history of any atopic disease (e.g., eczema, asthma, allergic rhinitis) is a major risk factor for AD,[38] but the strongest association is with a history of parental AD, with risk increasing further when both parents report a history of AD-like symptoms.[44] Association studies have identified over 30 genomic regions that potentially contribute to increased AD risk.[38]

A strong heritability suggests a prominent genetic role in the development of the disease,[39] but genetic predisposition may not be sufficient alone to result in the development of AD. Observed prevalence trends across multiple countries suggest that AD occurs when patients with a genetic predisposition are exposed to one or

more environmental triggers, particularly those related to a Western, industrialised lifestyle.[45] Living in an urban setting, low ultraviolet (UV) light exposure and eating a 'Western diet' have all been identified as risk factors for AD.[46] In addition, patients with AD may experience acute exacerbations of AD, 'flares', that can be triggered by multiple factors, including environmental factors such food allergens, weather and pollen.[40]

Mutations that lead to reduced filaggrin expression are the strongest genetic risk factors for AD.[47] Loss-of-function mutations reduce the amount of natural moisturising factor and immunosuppressing cis-urocanic acid present in the epidermis,[47] with changes observed in both lesional and apparently healthy skin.[38] Exposure to a pathogen or allergen leads to the release of alarmins and an inflammatory cascade, resulting in the itch, inflammation and epidermal barrier disruption that are the hallmarks of AD pathophysiology.[39] A feed-forward loop develops with increasing cutaneous inflammation and worsening epidermal barrier dysfunction, leading to greater disease burden via multiple mechanisms e.g., microbiome alterations, mechanical damage from scratching, and altered lipid profile.[47]

Neuroimmune communication between sensory neurons, keratinocytes and inflammatory mediators contribute to disease progression and presentation,[39] including the release of pruritogens that induce itch, e.g., IL-31.[48,49] Although the physiological function of IL-31 is unclear,[50] it is known to play a central role within AD.[5] In patients with AD, IL-31 expression is increased in skin lesions, and serum levels correlate with disease- and itch-severity.[6,7]

IL-31 binds to its receptor, a heterodimeric complex of IL-31 receptor alpha chain (IL-31RA) and the β-chain of the oncostatin M receptor that are expressed on multiple cell types, including peripheral sensory nerves, basal keratinocytes, fibroblasts and immune cells.[50] Activation of the receptor on sensory nerves leads to the release of neuropeptides and neurogenic inflammation that is experienced as itch.[49-51] IL-31 also stimulates neuronal growth and branching in the skin, ultimately increasing neuronal network density and sensitivity to itch-inducing stimuli.[5] Additionally, IL-31

induces the expression of pro-opiomelanocortin from keratinocytes, a protein that can also drive pruritus.[52]

IL-31 has a proinflammatory effect on IL-31RA-expressing immune cells in skin lesions; basophils stimulated with IL-31 release IL-4 and IL-13,[53] which are themselves essential for the differentiation of naïve T lymphocytes into Th2 cells that induce allergic inflammation,[54,55] while keratinocytes are induced to produce cytokines and chemokines which exacerbate skin inflammation.[56]

IL-31 impacts barrier integrity by impairing epidermal keratinocyte differentiation, decreasing filaggrin gene expression,[57] and inducing keratinocyte cell cycle arrest.[58] The resultant atypical skin development and barrier dysfunction leads to allergen and pathogen penetration, perpetuating an amplification loop.[56]

B.1.3.1.2. Epidemiology

Data from the World Health Organisation (WHO) Global Burden of Diseases initiative reported approximately 230 million people worldwide have AD, with an age-standardised prevalence of 2.7% in all individuals (2017).[39,59] There is limited data available regarding the incidence of AD.[60] The age-standardised prevalence is highest in the paediatric population, with a decline towards adulthood, and then an upward trend in later life.[59] Age-standardised prevalence varies substantially depending on region; for example a prevalence of 4.6% in Western Europe compared with 1.8% in East Asia in all individuals, with a moderate positive correlation between gross domestic product (GDP) and AD prevalence.[59]

There have been two recent analyses of UK CPRD data to ascertain AD prevalence.[8,9] Ameen et al., reported a period prevalence of 1.86% in adults (aged ≥ 18 years) and 4.99% in adolescents patients between 2008–2018.[8] Kleyn et al., reported an overall prevalence of 2.4% per year in adult (aged ≥ 18 years) patients between 2015–2019.[9] The variability between estimates may arise due to the different populations considered: Ameen et al. reviewed patients in England,[8] while Kleyn et al. considered patients throughout the UK.[9] During the 5-year study period, between 7.5% and 8.3% of all patients had moderate-to-severe AD (5,988–9,098 adults), and of these patients, approximately 60% received some form of systemic

therapy.[9] The proportion of patients with moderate-to-severe AD aligns with the NICE TA814 resource impact report.[61]

These findings are broadly paralleled by those of another study which assessed the prevalence of AD among children and adults in England from an alternative primary care database.[62] AD prevalence was found to have a bimodal distribution across the population, peaking in patients below one year of age and ≥ 80 years old, with overall prevalence estimated to be 9.6% in children and 4.3% in adults.

There are statistically significant socio-economic and ethnicity differences in AD prevalence apparent in the UK. AD prevalence is increased in the most deprived quintile of UK patients and in patients living in an urban environment and is more than doubled in Asian and Black patients compared with White patients.[62]

B.1.3.1.3. Clinical presentation

The characteristic symptoms of AD include poorly defined eczematous lesions which are erythematous and blistering at the early stages, but which can be scaling, fissuring and lichenified at the later stages.[39,63] These lesions are associated with persistent, severe itch that leads to scratching, excoriation, bleeding and the formation of haemorrhagic crusts.[39,63]

Itch is reported to be the most burdensome symptom associated with AD,[10] and accordingly itch relief is the primary goal for the majority of patients with moderate-to-severe AD.[12,13] Approximately 42% of adults with moderate-to-severe AD report itching for more than 18 hours per day and 14% describe itching as 'unbearable'.[64] Persistent itching contributes to psychological distress,[8] diminished QoL,[12,17] and impacts patient sleeping habits, with sleep problems noted to interfere with daily function to some degree in 86.4% of patients with uncontrolled moderate-to-severe AD.[14] Chronic itching drives persistent, repetitive scratching, creating a feedback loop: the 'itch-scratch cycle'.[65] As well as the physical pain associated with damage to the skin,[19] scratching creates and exacerbates skin barrier dysfunction, facilitating penetration of pathogens; consequently, patients with moderate-to-severe AD are at high risk of secondary infections, most commonly *Staphylococcus aureus.*[66] Adults with AD are almost three-times as likely to develop an infection than adults without

AD,[67] causing significant morbidity and requiring additional healthcare resource use.[68]

AD is associated with additional comorbidity and mortality burden. Patients with AD have a tendency to develop additional atopic diseases,[69] hypertension, hypercholesterolemia, diabetes, and obesity.[40] Hazards for all-cause and cause-specific mortality are modestly increased across all patients with AD compared with patients without AD, with the largest increases seen in patients with the most severe AD and predominantly due to infections.[70]

B.1.3.1.4. Diagnosis and assessment of severity

Diagnosis of AD and assessment of disease severity is based on clinical judgement and patient-reported history and symptoms.[42] There are no validated biomarker tests for AD.[71] Clinicians may identify moderate-to-severe AD when one or more of the following features are present:[43]

- a minimum affected body surface area of 10%
- individual lesions with moderate-to-severe features
- involvement of highly visible or functionally important areas
- significantly impaired QoL

For adult patients, both objective and subjective measures may be applied; a systematic literature review (SLR) of AD clinical trials identified 62 different severity measure and 28 different QoL measures.[42] The most commonly used physician assessment tools are the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), Physician Global Assessment (PGA, also called Investigator Global Assessment [IGA]), and Body Surface Area (BSA).[71] The most commonly used patient reported outcome assessments are Patient Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI) and Peak Pruritus Numerical Rating Scale (PP NRS).[71] The Harmonizing Outcomes for Eczema (HOME) initiative recommends specific tools to be used in all clinical trials investigating AD: EASI for the assessment of clinical signs, DLQI for patient QoL, and POEM for patient-

reported symptoms.[72] When assessed using EASI, moderate AD is associated with a score of 6.0–22.9 and severe AD scores 23.0–72.[73]

NICE do not provide specific guidance for clinicians treating adolescent or adult patients in the UK. In the paediatric setting, NICE guidance[74] recommends a diagnosis of AD when a child presents with itchy skin plus three or more of the following criteria: visible flexural dermatitis involving skin creases, or visible dermatitis on the cheeks and/or extensor areas in children ≤ 18 months; previous flexural dermatitis or dermatitis on the cheeks and/or extensor areas in children ≤ 18 months; dry skin in the last 12 months; asthma or allergic rhinitis, or a history of atopic disease in a first degree relative of children ≤ 4 years; onset of signs and symptoms under the age of 2 years. Differential diagnoses may be considered for older patients. The guidance gives a holistic description of mild, moderate and severe AD, but does not indicate a preferred tool to be used when assessing AD in the clinic.[74]

B.1.3.1.5. Burden of disease

The burden of AD is significant and multi-faceted, and affects patients, care givers and family members.[75]

Clinical burden

Itch is reported to be the most burdensome symptom associated with AD.[10,11] More than half (56%) of patients with moderate-to-severe AD receiving immunosuppressant therapy assessed their disease as inadequately controlled.[14] Compared with patients with controlled disease, these patients reported greater severity of itching, higher frequency (5.7 vs. 2.7 days per week with some itching and higher proportions with itch duration longer than half a day [22.8% vs. 2.9%]) and greater burden of sleep disruption (more trouble sleeping, longer sleep latency and more frequent disruption). In a longitudinal study of adults with AD, 17% of patients had severe sleep disruption; itch and disease severity were noted as predictors of disruption, while improvements in itch reduced sleep disruption.[76] Sleep disruption in adults with AD has multiple consequences and is associated with impaired overall health, fatigue, daytime sleepiness, missed workdays and doctor visits.[77]

Itch is associated with anxiety, and stress has been shown to exacerbate itch, leading to a vicious cycle that increases disease burden.[78] A UK CPRD/hospital episodes statistics (HES) data study showed that, overall, adults with AD were 14% more likely to be diagnosed with incident depression than adults without AD, with the effect being stronger for patients with more severe AD. Similar results were noted for incident anxiety (17% more likely than non-AD adults); both depression and anxiety are associated with increased morbidity and mortality.[13] A systematic literature review identified higher rates of suicidal ideation and suicidal acts in persons with AD compared with healthy controls; meta-analysis concluded AD increases risk of suicidal ideation (odds ratio 2.62, CI 1.26–3.08; p = 0.003) and suicidal acts (odds ratio 1.53, CI 0.96–2.45; p = 0.08).[79]

Humanistic burden

A significant correlation between itch and reduced QoL is recognised in patients with AD.[41] In an SLR, it was reported that the average health utility value for patients with AD was 0.78 (a 22% reduction in QoL compared with 'perfect health'), and utility decreased with increasing disease severity.[80] The impact of AD on QoL in children and adolescents is greater than for many other chronic conditions (e.g., asthma and epilepsy; only cerebral palsy was measured to present a greater burden),[81] while the impact on QoL in adults is similar to that of diabetes or heart disease.[10] When the impact on patient QoL is converted to disability adjusted life years (DALYs), AD is the leading cause of skin condition-related DALYs worldwide,[59] as a function of its relatively high prevalence and high burden.[82]

Many adults with AD report that their condition limits their lifestyle (51.3%), impacts their activities (43.3%) and causes them to avoid social interactions (39.1%); this is reported across the severity continuum, but is worse in patients with moderate-to-severe disease.[10] In a survey of UK patients, 72–85% of patients with moderate-to-severe AD noted that AD interfered with their ability to do regular daily activities and most (73–80%) patients report that they have tried to hide their AD from someone in their lives.[16] The majority of patients with moderate-to-severe AD report that their disease has negatively affected their school-, work-, social-, family-lives and their sexual intimacy.[16]

Economic burden

Across Europe, direct healthcare costs, such as physician visits, hospital visits and hospitalisations correlate with AD severity; the per patient direct costs associated with severe disease are three-times higher than for moderate disease.[83] The total European annual direct healthcare costs for patients with moderate-to-severe disease have been estimated at €10.1 billion.[20]

In the UK the management of AD is predominantly in primary care.[84] Analysis of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network database (2009–2018) reported the annual rates for primary care consultations and specialist dermatology referral increased over time to 112 consultation and 5 referrals per 100 person-years in 2018, respectively.[84]

In terms of secondary care utilisation, AD accounted for 1,231 hospital admissions in England in 2022–23, of which 440 were emergency admissions, as well as 1,366 finished consultant episodes; based on primary diagnosis.[85] Prior to the introduction of biologic treatments in the UK in 2018, patients with moderate-to-severe AD attended a dermatology clinic 6.6 times per year (mean) and reported 1.6 flares per year (mean).[86] Patients admitted to hospital for infections were associated a mean length of stay of 11 days, while admission for flares incurred a mean length of stay of 3.3 days.[86]

Out-of-pocket costs to patients with AD can be large. Across nine European countries, 95% of adult AD patients report paying out-of-pocket for medications, travel expenses, additional cleaning/washing materials and other costs: an estimated mean cost of £800 per year.[87] Cost increases with severity, with patients with moderate-to-severe AD paying 9% more than patients with mild AD, predominantly for emollients and moisturisers.[87] Total out-of-pocket costs across Europe are estimated at €4.7 billion.[20]

Indirect societal costs associated with AD are substantial, with a considerable proportion due to lost work productivity (absenteeism and presenteeism). In a European study, including the UK, 26% of patients with AD missed 6–10 days of work per year due to AD, while 57% missed 1–5 days. Most missed days were

reported by patients with moderate-or-severe AD, who were receiving systemic treatment, or who reported lower satisfaction with their treatment.[87] Overall work impairment, which considered both absenteeism and presenteeism, increased with disease severity; patients with severe AD recorded 51.6% impairment, approximately double the impairment experienced by moderate patients.[88] Total indirect costs across Europe are estimated at €15.2 billion.[20]

B.1.3.2. Clinical pathway and positioning of nemolizumab

B.1.3.2.1. Treatment guidelines

In the UK, published guidance by NICE includes 'Atopic eczema in under 12s: diagnosis and management' (CG57).[74] However, neither NICE nor the British Association of Dermatologists have published guidelines or quality standards on the diagnosis and management of moderate-to-severe AD in adults or adolescents.

A summary of the NICE clinical knowledge summaries,[24] technology appraisals (TA),[1-3,25] and European[21] and US guidelines,[22,23] that may be clinically relevant to patients in England and Wales are provided in Table 3.

Table 3. Summary of relevant treatment guidelines

Guideline	Recommendation
European guideline (EuroGuiDerm) on atopic eczema[89-91]	
Summary of stepped care plan for adults, and for children and adolescents with atopic eczema	• The stepped care plan for adults with moderate-to-severe AD described baseline therapy as consisting of emollients, the avoidance of allergens and educational programmes. • As disease severity progresses, measures from previous treatment lines are to be to continued and additional therapies selected from those available at the more severe disease level. • Mild disease treatment options are acute TCS, reactive TCI and acute wet wrap therapy. • Moderate disease may be treated with proactive TCS and proactive TCI, phototherapy and psychosomatic counselling. • Severe disease may be treated with conventional immunosuppressants (first-line), monoclonal antibodies (dupilumab and tralokinumab) and JAK inhibitors (second-line treatment). • Treatment lines for children and adolescents are identical except for in the case of severe disease treatment option, based on the relevant licensing agreements per drug.

	Baricitinib is not permitted; dupilumab is indicated for patients ≥ 6 months; abrocitinib, upadacitinib and tralokinumab are indicated for sub-groups of adolescent patients.
Anti-inflammatory treatment	• Proactive therapy with a suitable TCS or TCI is recommended to reduce the risk of relapse and for better disease control.
Systemic treatment	• Systemic therapies are deemed necessary if AD is not adequately controlled with appropriate topical treatment and phototherapy; it may also be used as TCS-sparing option where necessary. • Biologics are considered as a systemic therapy option alongside conventional immunosuppressants in their licensed populations.
American Academy of Dermatology: Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies[92,93]	
Management with topical therapies[93]	• Topical therapies are the mainstay of AD therapy. Topical therapies are often used in combination with other topical, physical or systemic treatments as they address different aspects of AD pathogenesis. • TCS are recommended for patients who fail to respond to good skin care and emollient use alone; medium potency TCS may be used as maintenance therapy to prevent flares/relapse. • TCI are a safe option when there is concern for adverse events secondary to corticosteroid use. • Topical antimicrobials are discussed in the context of treating secondary infections. • Topical therapies such as phosphorodiesterase-4 inhibitors and a topical JAK inhibitor are discussed but are not relevant to the UK setting at time of writing.
Management with phototherapy and systemic agents[92]	• Phototherapy is positioned as a second-line treatment, positioned after the failure of topical therapies to achieve adequate results; however, the recommendation is conditional based on low certainty of evidence. • Systemic immunosuppressants are indicated for patients in whom topical therapies and/or phototherapy do not adequately control disease; however, due to lower certainty evidence relative to newer medications, risk of adverse events, need for monitoring and absence of FDA approval, the guideline 'do not consider these medications to be first-line treatments'. • Systemic corticosteroids are conditionally recommended against, with use exclusively for acute, severe exacerbations and as a short term 'bridging therapy'. • Biologics (dupilumab, tralokinumab) and the JAK inhibitors (upadacitinib, abrocitinib, baricitinib) are all given strong recommendations for use in adults with moderate-to-severe AD.

NICE CKS stepped treatment approach[24]	
Moderate eczema	• A stepped approach is recommended, with treatment stepped up or down according to condition severity. • Treatment of a flare may require a temporary escalation of treatment intensity. • TCI, phototherapy and ciclosporin are noted as being less suitable for the treatment of flares. • Bandaging and oral corticosteroids are unsuitable for use as maintenance treatment. • Moderate AD should be treated with emollients, moderate potency TCS, TCI and bandages; these latter two options are typically prescribed by a specialist. • Specific guidance for each class of topical therapy and for oral corticosteroids is given, however no discussion of biologics or JAK inhibitors is presented.
Severe eczema	• A stepped approach is recommended, with treatment stepped up or down according to condition severity. • Treatment of a flare may require a temporary escalation of treatment intensity. • TCI, phototherapy and ciclosporin are noted as being less suitable for the treatment of flares. • Bandaging and oral corticosteroids are unsuitable for use as maintenance treatment. • Severe AD should be treated with emollients, potent TCS, TCI and bandages (typically prescribed by a specialist) and phototherapy and oral corticosteroids in secondary care. • Specific guidance for each class of topical therapy and for oral corticosteroids is given, however no discussion of biologics or JAK inhibitors is presented.

Abbreviations: AD, atopic dermatitis; CKS, clinical knowledge summaries; FDA, Food and Drug Administration; JAK, janus kinase; NICE, National Institute for Health and Care Excellence; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

B.1.3.2.2. Current treatment of AD

The goals of AD therapy are to reduce itch,[38] improve barrier function,[94] and establish lasting disease control that allows patients to enjoy a higher QoL and higher function in their work-, school- and social-lives.[38] With respect to these goals, a stepwise approach to therapy is taken in multiple treatment guidelines (Table 3 and Figure 1). Patients initiate on non-pharmacologic options (emollients, moisturisers, educational programmes), and then escalate to topical therapies aimed at reducing inflammation (TCSs, TCIs) and then systemic treatments (systemic immuno-suppressants as first-line therapy, followed by biologics or JAK inhibitors as second-line) (Figure 1).

In the European guidelines, systemic corticosteroids are recommended for use as rescue therapy where other systemic treatments are unable to establish disease control. Monitoring is not required for short-term use, but may be used with higher doses or longer term treatment.[21]

Phototherapy is generally positioned after topical therapies and alongside systemic treatments in many guidelines. However, the specific positioning in UK AD treatment pathways is unclear; NICE have previously accepted that phototherapy is not universally available and is used variably across the UK.[61]

B.1.3.2.3. Best supportive care

In the UK, 'best supportive care' (BSC) represents the foundational therapy options upon which systemic treatment lines are added, based on response to therapy or disease flaring. Initially, emollients and moisturisers are used to protect and restore the skin barrier, relieve dryness and reduce itch.[22] They continue to be used at all disease severity stages; liberal, frequent application is recommended.

TCSs are introduced when emollients are insufficient to achieve adequate disease control. They may be used as an acute response or proactively to prevent flares and retain disease control,[21,24] and are used once or twice daily.[25] Long-term TCS use can result in skin atrophy, and this is more likely where the skin is already thin e.g. the face and flexures.[25] Clinicians may choose to use a maintenance regimen for long-term, proactive use, either step-down treatment or intermittent therapy.[25]

TCIs are typically introduced after TCSs for UK patients who do not adequately respond, or may be introduced following emollients where TCS use is contraindicated.[24] TCIs may be used on any part of the body except the mucous membranes; they have a lower risk of skin thinning compared with TCSs, and so may be preferred in some circumstances.[24]

B.1.3.2.4. Systemic immunosuppressants

Of the first-line systemic immunosuppressants commonly used in the UK, only one (ciclosporin) is licensed for use in adult AD patients. Other systemic immunosuppressants commonly prescribed include methotrexate, azathioprine, and mycophenolate mofetil, which are all used off-label.[95] Despite being used off-label,

methotrexate is the preferred systemic immunosuppressant in UK practice.[61] All of the previously mentioned immunosuppressants have relatively poor safety profiles and are associated with a monitoring burden due to the requirement for frequent (~3 monthly) blood tests even when well tolerated.[21,26-29]

B.1.3.2.5. Biologics

There are currently three biologic therapies licensed for use in the treatment of moderate-to-severe AD in the UK.

Dupilumab, a monoclonal antibody (mAb) that blocks IL-13 and IL-4 signalling,[38] was the first biologic approved in 2018 for adult patients with moderate-to-severe AD whose disease did not respond adequately to at least one other systemic therapy or for whom other therapies are contraindicated (second-line treatment).[1] Dupilumab is administered by subcutaneous injection with an initial dose of 600 mg followed by 300 mg every two weeks (Q2W).[96]

Tralokinumab, a mAb that targets IL-13, was approved in 2022 for the same indication (second-line treatment).[3] Tralokinumab is administered by subcutaneous injection with an initial dose of 600 mg followed by 300 mg Q2W.[97] At clinician discretion, dosing every four weeks (Q4W) may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment; however, clinicians have indicated that this typically does not occur in practice. Subsequent to the NICE recommendations for dupilumab and tralokinumab in adult patients; NHS England will commission treatments for patients aged less than 18 years where specific commissioning conditions within a NICE technology assessment (TA) or NHS England policy are met.[98,99]

Lebrikizumab, another mAb that targets IL-13, has recently been approved by NICE for treating moderate-to-severe AD in patients 12 years and over.[4] Lebrikizumab is administered by subcutaneous injection with two dose of 500 mg followed by 250 mg Q2W.[100] Once a clinical response is achieved, the recommended maintenance dose of lebrikizumab is 250 mg Q4W.[100]

Consideration should be given to discontinuing treatment in patients who have shown no clinical response after 16 weeks of treatment with either of the three

approved mAbs. Some patients with initial partial response to lebrikizumab may further improve with continued treatment every other week up to week 24.[96,97,100]

B.1.3.2.6. JAK inhibitors

There are three JAK inhibitors (abrocitinib, baricitinib and upadacitinib) approved for use in adult patients with moderate-to-severe AD in the UK who have not responded to at least one systemic immunosuppressant or for who these are not suitable (second-line treatment); abrocitinib and upadacitinib are also recommended as options for adolescents aged ≥ 12 years.[2,3]

All JAK inhibitors are administered orally. The recommended dose of baricitinib is 4 mg daily.[101] Abrocitinib is initiated at either 100 mg or 200 mg daily; the lowest effective dose should be used for maintenance.[102] Upadacitinib is used at 15 mg or 30 mg daily, with the lowest dose able to achieve disease response being recommended.[103] The recommended dose for upadacitinib in adolescents weighing at least 40 kg is 15 mg.[103] For all JAK inhibitors discussed above, NICE recommends treatment should be stopped if response is inadequate after 16 weeks.[2,3]

JAK inhibitors have been associated with safety concerns at a drug-class level, and all must display additional warning labels indicating increased risk of major adverse cardiovascular events, malignancy, venous thromboembolism, serious infection, and mortality.[32-34] UK government guidance advises against prescribing these medicines unless there are no suitable alternatives in adults aged ≥ 65 years, patients with current or past long-time smoking, and other risk factors for cardiovascular disease or malignancy.[33] Given that AD prevalence has a bimodal distribution, increasing as adults age,[62] JAK inhibitors are not a suitable treatment option for a large number of AD patients.

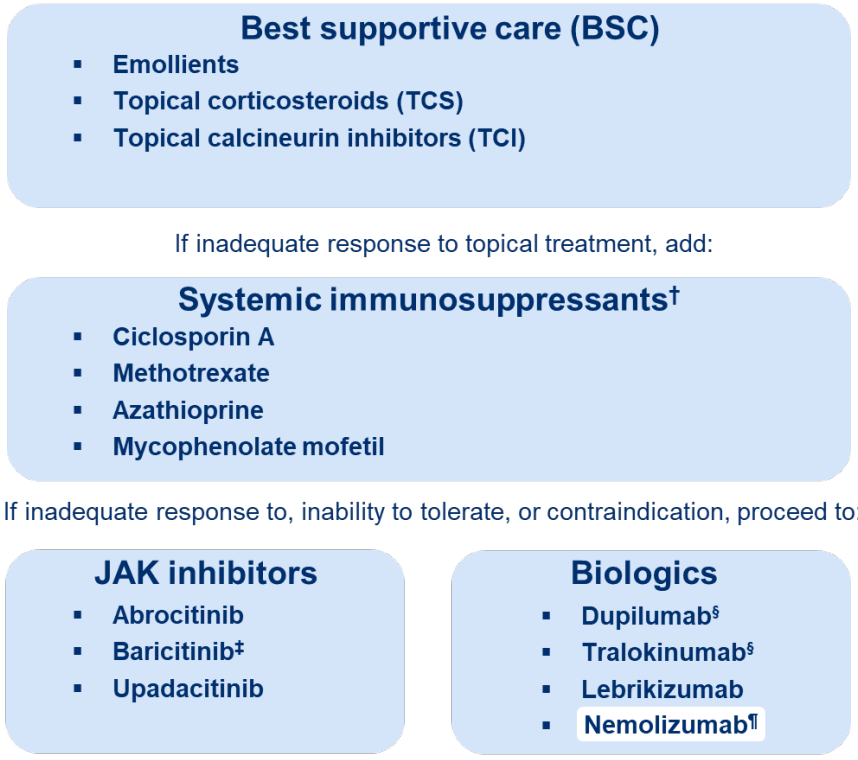

Figure 1. Atopic dermatitis treatment pathway in adolescents and adults

Note: Based on the EuroGuiDerm Guideline for Atopic Eczema and review of NICE committee papers.[1-3,24,89-91] Phototherapy is not shown as it is not universally available and is used variably across the UK.[61]

†First line systemic therapies are conventional immunosuppressants; all use in AD is off-license except ciclosporin in persons over 16 years.

‡ Baricitinib is only approved for treating moderate-to-severe atopic dermatitis in adults.[2]

§ Subsequent to the NICE recommendations for dupilumab and tralokinumab in adult patients; NHS England will commission treatments for patients aged less than 18 years where specific commissioning conditions within a NICE technology assessment (TA) or NHS England policy are met.[98,99]

¶ Aspirational positioning of nemolizumab in the treatment pathway.

Abbreviations: BSC, best supportive care; JAK, Janus Kinase; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor

B.1.3.2.7. Unmet need

AD is a complex disease characterised by heterogeneity in clinical presentation,[38] with patients responding differently to currently available treatments.[104] AD is difficult to clinically manage, especially for patients with moderate-to-severe disease, with a requirement for additional therapeutic options.[63,105-108]

Despite the approval of therapies such as dupilumab, tralokinumab, lebrikizumab and the JAK inhibitors for moderate-to-severe AD, there is an unmet need for additional effective, well-tolerated, and targeted treatment options that address the burdensome symptoms such as itch.[10,11] Current treatment options for moderate-to-severe AD do not rapidly relieve itch experienced by all patients. In the LIBERTY AD CHRONOS trial only 39% of patients achieved a clinical response (IGA score 0/1) and 59% achieved control of itch (PP-NRS improvement ≥ 4) with dupilumab.[30]

Similarly in the ECZTRA 3 trial only 39% of patients achieved a clinical response (IGA score 0/1) and 45% achieved control of itch (PP-NRS improvement ≥ 4) with tralokinumab.[31]

Nemolizumab has a novel mechanism of action and offers an alternative therapeutic option for patients with AD (Figure 2 and further details refer to Section B.1.3.1.1). Nemolizumab blocks the IL-31RA, and is distinct from the currently licenced biologics that target IL-4/IL-13 signalling (dupilumab, tralokinumab, lebrikizumab).[35] IL-31 has emerged as a key neuroimmune cytokine in AD.[5,49] The neuroimmune response triggered by IL-31 leads to itch but also to sustained inflammation and dysfunction of the skin barrier.[7,49,53,56,109-112] In patients with AD the expression of IL-31 is increased in skin lesions, and serum levels correlate with severity of disease and pruritic symptoms.[6,7]

The current therapies, both biologics and JAK inhibitors, are associated with adverse events (AEs). The biologics targeting IL-4/IL-13 immune signalling (dupilumab, tralokinumab, lebrikizumab) are characterised by ocular surface disease and conjunctivitis AEs, limiting their usage in patients with a prior history of ocular complications. A pooled analysis of the dupilumab clinical trials reported a higher incidence of conjunctivitis compared to placebo (8.6% vs. 2.1%),[113] with a similar finding reported for tralokinumab (7.5% vs. 3.2%).[114] Furthermore, the real-world incidence of conjunctivitis (26–62%) and ocular surface disease (45%) appears higher than that reported in the clinical trials for dupilumab.[115,116]

JAK inhibitors are associated with safety concerns and must display additional warning labels indicating increased risk serious heart-related events, lymphoma and lung cancer, blood clots and death (for further details refer to section B.1.3.2.6).[117] Furthermore, JAK inhibitors require continuous blood monitoring, which may restrict their usage in certain patients.[118] Nemolizumab represents an alternative treatment option, with a reduced risk of conjunctivitis and ocular surface disease complications associated with other biologic therapies, and without the safety concerns of the JAK inhibitors.

Nemolizumab benefits from a less intense dosing schedule compared with dupilumab, tralokinumab, and lebrikizumab. Nemolizumab is administered Q4W, less

frequently than the comparator biologics, decreasing to every eight weeks (Q8W) following response, and would be expected to decrease healthcare resource use and environmental impact.[36,37] Compared to the once daily oral JAK inhibitors, nemolizumab as a long-lasting subcutaneous injection, offers a decreased pill burden and convenient regimen, that would be anticipated to result in fewer missed doses and improved adherence.

Patients with moderate-to-severe AD who do not respond to existing biologics or JAK inhibitors, or who are unable to receive them, have no further safe and effective treatment options. A NICE Committee has previously noted that increased therapeutic diversity and a choice of effective treatments is important to patients with AD.[3]

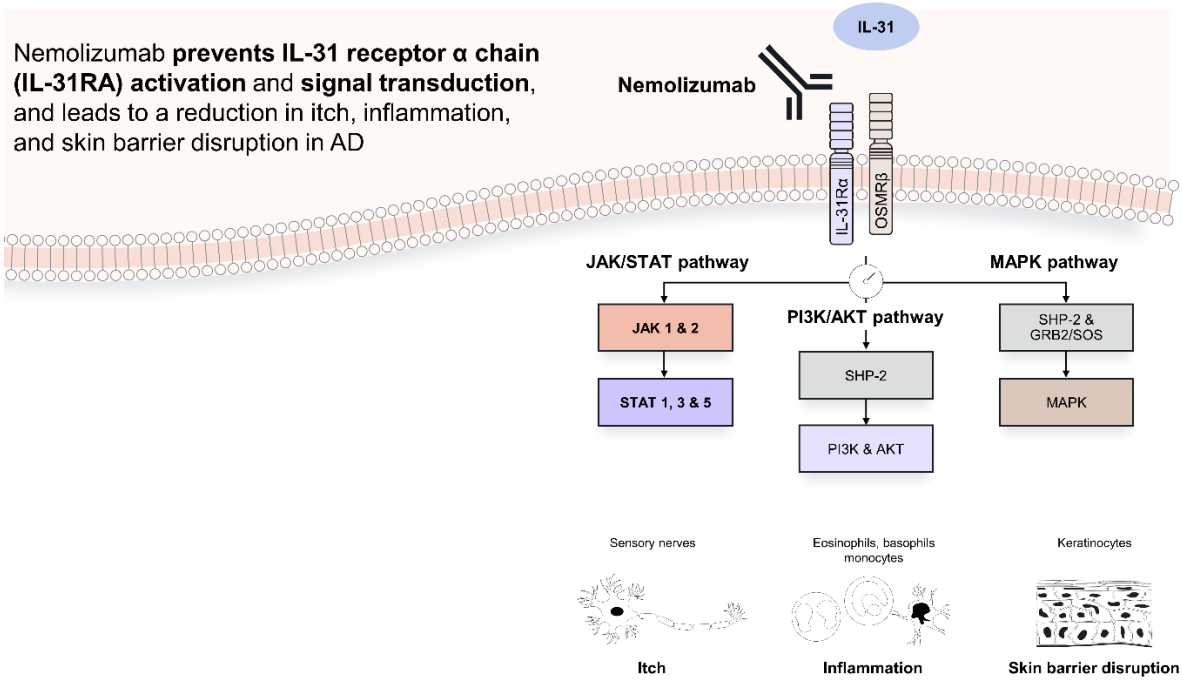

Figure 2. Nemolizumab mechanism of action

Abbreviations: IL-31, interleukin-31; JAK, janus kinase inhibitor; STAT, signal transducer and activator of transcription; SHP-2, SH2 domain-containing protein tyrosine phosphatase-2; PI3K, phosphoinositide 3-kinases; AKT, protein kinase B; GRB2/SOS, growth factor receptor bound protein 2/son of sevenless homolog 1; MAPK, mitogen-activated protein kinase

B.1.3.2.8. Positioning of nemolizumab

Nemolizumab is a first-in-class, humanised mAb that binds IL-31RA with high specificity and affinity, blocking the neuroimmune activity of the cytokine IL-31.[119] By blocking the IL-31 signalling pathway, nemolizumab interrupts the cellular pathways that cause itch, inflammation, and skin barrier disruption in AD (Figure 2).[56,111]

The proposed positioning for nemolizumab in the current treatment pathway is for adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated (second-line treatment); alongside dupilumab, tralokinumab, lebrikizumab, and the JAK inhibitors (Figure 1). It is anticipated that nemolizumab will be used with BSC, which can include emollients, TCSs, and TCIs. Any use of TCSs or TCIs should aim to be tapered and subsequently discontinued when the disease has sufficiently improved. This positioning is considered appropriate by UK clinical experts.[120] The recommendation of nemolizumab would broaden the therapeutic choice available to these patients, given nemolizumab's novel mechanism of action versus the existing options.

B.1.4. Equality considerations

The principles that guide the development of NICE guidance and standards include a commitment by NICE to reducing health inequalities and supporting strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged.[121] The use of nemolizumab is not anticipated to raise or worsen any specific equality issues or result in a recommendation that has a negative differential impact on individuals protected by equality legislation, or those with disabilities, compared with the wider population.

There are statistically significant socio-economic and ethnicity differences in AD prevalence apparent in the UK. AD prevalence is increased in the most deprived quintile of UK patients and in those living in an urban environment and is more than doubled in Asian and Black patients compared with White patients.[62]

There are documented challenges in assessing AD in patients with skin of colour[122,123] which can lead to an underestimation of disease severity.[122] Certain patient populations may therefore be more likely than others to receive sub-optimal treatment. Although specific guidance relating to adult populations with AD are lacking, the impact of skin tone on clinical assessment and outcomes is addressed by NICE in quality standard QS44: 'healthcare practitioners should be aware of the potential difficulties of assessing eczema severity in children with darker skin tones.[74]

In addition, the British Association of Dermatologists (BAD) Skin Diversity Sub-committee provide resources for UK healthcare professionals to improve their knowledge and awareness of how patient skin tone can affect clinical practice.[124] Increased clinical awareness and changes to practice may seek to address the impact of skin of colour on risk of under-treatment; which may contribute to an increase in the number of patients in the UK who may be eligible to receive a biologic or JAK inhibitor.

B.2. Clinical effectiveness

Summary of clinical evidence

Trial overview

- Relevant evidence for the clinical effectiveness of nemolizumab in patients with moderate-to-severe AD is derived from two pivotal phase 3 clinical trials (ARCADIA 1: NCT03985943, ARCADIA 2: NCT03989349),[36,37] a phase 3b clinical trial (ARCADIA-CYCLO: 2021-002166-40),[125] and an ongoing long-term extension (LTE) study (NCT03989206).[126]
- ARCADIA 1 & 2 assessed the efficacy and safety of nemolizumab (with BSC) compared with placebo (with BSC) in adult and adolescent participants with moderate-to-severe AD not adequately controlled with topical treatments.[127,128]
- ARCADIA-CYCLO assessed the efficacy of nemolizumab (with BSC) compared with placebo (with BSC) in adult participants with moderate-to-severe AD who were not adequately controlled with or were not advised to use oral ciclosporin for medical reasons.[129]
- The LTE is an ongoing study to investigate the long-term safety of nemolizumab (with BSC) in adult and adolescent participants with moderate-to-severe AD.[130]
- The ARCADIA 1 & 2 co-primary endpoints were proportion of patients with IGA success (IGA of 0 [clear] or 1 [almost clear] and ≥ 2-grade reduction from baseline) and proportion of patients with Eczema Area and Severity Index-75 (EASI-75) (75% improvement in EASI from baseline) at Week 16.
- The ARCADIA-CYCLO co-primary endpoints were proportion of patients with EASI-75 and proportion of patients with improvement of PP NRS ≥ 4-grade from baseline at Week 16.

Efficacy results

- A statistically significantly greater proportion of participants with IGA success was observed with nemolizumab Q4W compared with placebo at Week 16 (ARCADIA 1, 35.6% vs. 24.6%, strata-adjusted p = 0.0003; ARCADIA 2, 37.7% vs. 26.0%, strata-adjusted p = 0.0006). This response

was continued in the pooled maintenance period up to Week 48 (nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 60.4% vs. 49.7%, strata-adjusted p = 0.0465).

- A statistically significant greater proportion of participants with EASI-75 was observed with nemolizumab Q4W compared with placebo at Week 16 (ARCADIA 1, 43.5% vs.29.0%, strata-adjusted p < 0.0001; ARCADIA 2, 42.1% vs. 30.2%, strata-adjusted p = 0.0006). This response was continued in the pooled maintenance period up to Week 48 (nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 75.7% vs. 63.9%, strata-adjusted [redacted]).
- A statistically significant greater proportion of participants with EASI-75 was observed with nemolizumab Q4W compared with placebo at Week 16 in ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted])
- A statistically significantly greater proportion of participants with an improvement of ≥ 4 from baseline in weekly average PP NRS was observed with nemolizumab Q4W compared with placebo at Week 16 in ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted]).

Safety results

- Nemolizumab demonstrated a favourable safety profile ARCADIA 1 & 2, and ARCADIA-CYCLO. There was no evidence of any safety concerns and no evidence of imbalance between treatment arm for asthma or infections. Incidence of conjunctivitis was low and comparable between trial arms.
- In the ongoing LTE study, no new safety concerns were identified with nemolizumab treatment in the interim data cut (Week 56).

Conclusion

- Nemolizumab is a targeted systemic therapy that has demonstrated significant efficacy across all trials compared with placebo and was well-tolerated with a similar safety profile to placebo over 48 weeks in ARCADIA 1 & 2, and a further 56 weeks in the LTE study. Nemolizumab will help address the unmet need in patients with moderate-to-severe AD for increased therapeutic diversity.

B.2.1. Identification and selection of relevant studies

An SLR was undertaken in line with NICE requirements to identify the clinical-effectiveness (efficacy and safety) associated with nemolizumab and its comparator treatments for patients with moderate-to-severe AD. Database searches were initially conducted from on 05 October 2023, and updated on 07 May 2024. In total 32 trials from 231 separate publications were identified for inclusion in this review. Full details of the review, including the PRISMA diagram and a description of all relevant studies informing the model, are given in appendix D.

B.2.2. List of relevant clinical effectiveness evidence

Relevant evidence for the clinical effectiveness of nemolizumab is derived from two pivotal phase 3 clinical trials (ARCADIA 1: NCT03985943, ARCADIA 2: NCT03989349),[36,37] a phase 3b clinical trial (ARCADIA-CYCLO: 2021-002166-40),[125] and an ongoing LTE study (NCT03989206),[126] summarised in Table 4. ARCADIA 1 & 2 assessed the efficacy and safety of nemolizumab (with BSC) compared with placebo (with BSC) in adult and adolescent participants with moderate-to-severe AD not adequately controlled with topical treatments.[127,128] ARCADIA-CYCLO assessed the efficacy of nemolizumab (with BSC) compared with placebo (with BSC) in adult participants with moderate-to-severe AD who were not adequately controlled with or were not advised to use oral ciclosporin for medical reasons.[129] The LTE is an ongoing study to investigate the long-term safety of nemolizumab (with BSC) in adult and adolescent participants with moderate-to-severe AD.[130] The LTE study includes participants from prior nemolizumab studies, including ARCADIA 1 & 2, and ARCADIA-CYCLO (Figure 3). Concomitant BSC treatments included emollients, moisturisers, TCSs and TCIs (refer to Table 5 for permitted concomitant medications).

Table 4. Clinical effectiveness evidence: ARCADIA 1 & 2, ARCADIA-CYCLO, and LTE study

Study	ARCADIA 1 (NCT03985943)	ARCADIA 2 (NCT03989349)	ARCADIA-CYCLO (2021-002166-40)	LTE study (NCT03989206)
Duration	56 weeks		24 weeks	208 weeks
Population	Adults and adolescents (≥ 12 years) with moderate-to-severe AD		Adults (≥ 18 years) with	Adults and adolescents (≥

			moderate-to-severe AD and inadequate response to, or medically inadvisable to take ciclosporin	12 years) with moderate-to-severe AD
Intervention(s)	Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC [see Table 5 for permitted concomitant medications])		Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC [see Table 5 for permitted concomitant medications])	Nemolizumab (30 mg) by subcutaneous injection (with BSC [see Table 5 for permitted concomitant medications])
Comparator(s)	Placebo (with BSC [see Table 5 for permitted concomitant medications])		Placebo (with BSC [see Table 5 for permitted concomitant medications])	NA
Indicate if study supports application for marketing authorisation	Yes	Yes	Yes	Yes
Indicate if study used in the economic model	Yes	Yes	Yes	Yes
Rationale for use/non-use in the model	Relevant patient population (adult and adolescent patients with moderate-to-severe AD) and outcomes, as described below were reported in the trials, as aligned with the decision problem.			
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16 • Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16		• Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16 • Proportion of participants with improvement of PP NRS ≥ 4 at Week 16	• Incidence and severity AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs
Other outcomes used in the economic	• Proportion of participants with an improvement of PP NRS ≥ 4 • Proportion of participants with PP NRS < 2		• Proportion of participants with PP NRS < 2	• Proportion of participants with an IGA score = 0–1

model/specified in the scope	• Proportion of participants with an improvement of SCORAD from baseline • Proportion of participants with an improvement of SD NRS ≥ 4 • Change in the DLQI/cDLQI total score from baseline • Change in POEM total score from baseline • Change in EQ-5D subscale scores from baseline • Incidence and severity AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs	• Proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) • Proportion of participants with an improvement of SCORAD from baseline • Change in the DLQI total score from baseline • Change in POEM total score from baseline • Change in EQ-5D subscale scores from baseline • Incidence and severity of AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs	• Proportion of participants reporting low disease activity (IGA score ≤ 2) • Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline)

Abbreviations: AD, atopic dermatitis; AE, adverse events; BSC, best supportive care; cDLQI, children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index, EASI, Eczema Area and Severity Index, EQ-5D, EuroQol 5-Dimensions; IGA, Investigator's Global Assessment; LTE, long-term extension; PP NRS, Peak Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; SCORAD, SCORing Atopic Dermatitis; TCI, topical calcineurin inhibitor ; TCS, topical corticosteroids

Source: Galderma data on file ARCADIA 1 & 2, ARCADIA-CYCLO, and LTE clinical study protocols[131-134]

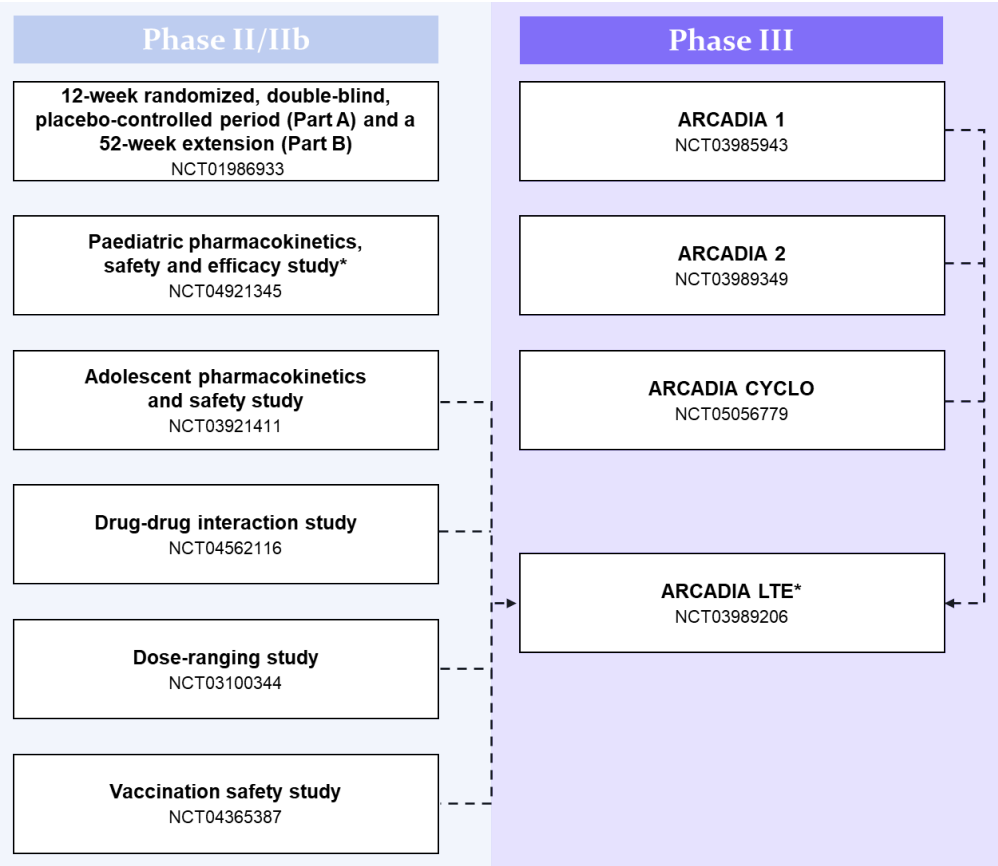

Figure 3. Schematic representation of the participants transitioning into the LTE study from prior nemolizumab clinical trials

*Trial ongoing
--- Participant flow into the LTE study
Abbreviations: AD, atopic dermatitis; LTE, long-term extension

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. ARCADIA 1 & 2

ARCADIA 1 & 2 were phase 3 randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational clinical trials.[131,132] ARCADIA 1 was conducted in 202 centres across 14 countries in Europe (including the UK), North America, and Asia Pacific, and ARCADIA 2 in 163 centres across 11 countries in Europe, North America, and Asia Pacific (Singapore only). The primary objective of both trials was to assess the efficacy and safety of nemolizumab (with BSC) after a 16-week treatment period in adult and adolescent participants with moderate-to-severe AD not adequately controlled with topical treatments. The secondary objective of both

trials was to evaluate the efficacy and safety of maintenance treatment with nemolizumab (with BSC) for up to an additional 32 weeks.

The study design for ARCADIA 1 & 2 is illustrated in Figure 4 and summarised in Table 5.[131,132,135,136] Randomisation was performed by interactive response technology (IRT). Participants were randomised (2:1) to receive nemolizumab (30 mg) or placebo via subcutaneous injection every 4 weeks (Q4W) in the initial treatment period. Randomisation was stratified by disease severity (IGA = 3, IGA = 4 and itch severity [PP NRS ≥ 7, PP NRS < 7]). Participants who were randomised to nemolizumab in the initial treatment period and achieved clinical response (EASI-75 or IGA 0/1) at Week 16 were re-randomised (1:1:1) to receive either nemolizumab Q4W, nemolizumab Q8W, or placebo Q4W in the maintenance period. This enabled the comparison of the two dosing schedules. The baseline characteristics of ARCADIA 1 & 2 participants are described in section B.2.6.

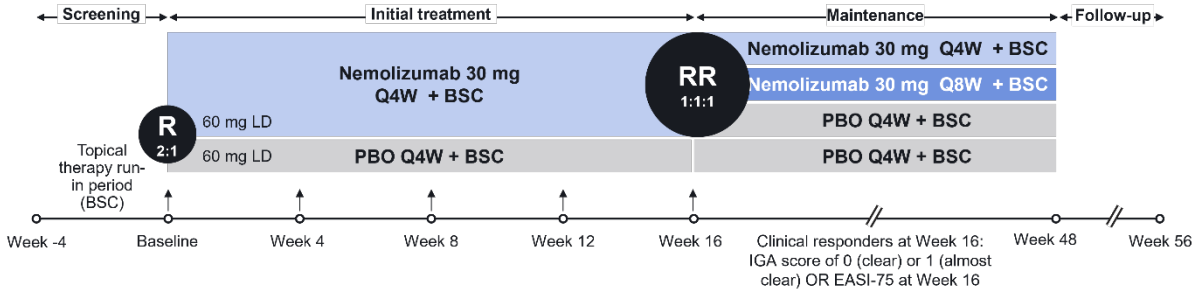

Figure 4. Study design: ARCADIA 1 & 2
Abbreviations: BSC, best supportive care; LD, loading dose; PBO, placebo; R, randomisation; RR, re-randomisation Q4W, every 4 weeks; Q8W, every 8 weeks; W, week
Note: Re-randomisation of treatment-arm participants was restricted to participants who had shown clinical response at Week 16.
Source: Galderma data on file ARCADIA 1 & 2 CSRs[127,128]

B.2.3.2. ARCADIA-CYCLO

ARCADIA-CYCLO was a phase 3b randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational clinical trial conducted in 58 centres across six countries in Europe.[133] The primary objective was to assess the efficacy of nemolizumab (with BSC) in adult participants with moderate-to-severe AD who were not adequately controlled with/not advised to use oral ciclosporin for medical reasons. The secondary objective was to assess the safety of nemolizumab (with BSC) in the same population.

The study design for ARCADIA-CYCLO is illustrated in Figure 5 and summarised in Table 5.[133,137] Randomisation was performed by IRT. Participants were randomised (1:1) to receive nemolizumab (30 mg) or placebo Q4W via subcutaneous injection in the treatment period. Randomisation was stratified by disease severity (IGA = 3, IGA = 4) and prior exposure to ciclosporin. The baseline characteristics of ARCADIA-CYCLO participants are described in section B.2.6.1.2.

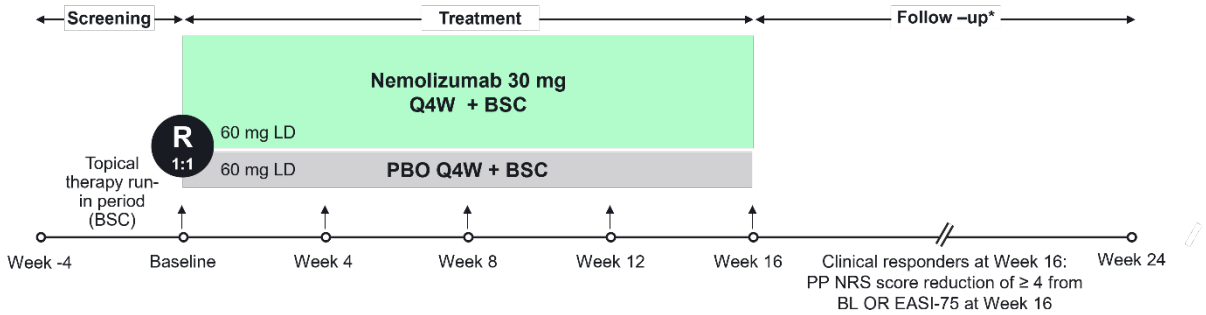

Figure 5. Study design: ARCADIA-CYCLO
Abbreviations: BL, baseline; BSC, best supportive care; LD, loading dose; Q4W, every 4 weeks; W, week
*Applicable for participants who did not participate in the LTE study only.
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

B.2.3.3. LTE study

The LTE is a phase 3, prospective, open-label, multicentre, multinational, long-term extension study, currently being conducted in 343 centres across 22 countries in Europe (including the UK), North America, and Asia Pacific. The primary objective is to assess the long-term safety of nemolizumab (with BSC) in adult and adolescent participants with moderate-to-severe AD. The study's secondary objective is to assess the long-term efficacy of nemolizumab (with BSC) in the same population. The study design for LTE study is illustrated in Figure 6 and summarised in Table 5. The LTE study includes participants from prior nemolizumab AD phase 2b dose-ranging (NCT03100344), phase 2 adolescent pharmacokinetics/safety (NCT03921411), phase 2 vaccination safety (NCT04365387), phase 2 drug-drug interaction (DDI) (NCT04562116), phase 3b (ARCADIA-CYCLO, 2021-002166-40), and the phase 3 pivotal ARCADIA 1 & 2 clinical trials and adolescents from selected sites in Australia, Austria, Canada and the US who had not previously participated in a nemolizumab study (Figure 3). Baseline characteristics for the LTE participants are described in section B.2.6.1.3. Participants received nemolizumab (30 mg) Q4W via subcutaneous injection in the treatment period (200 weeks).

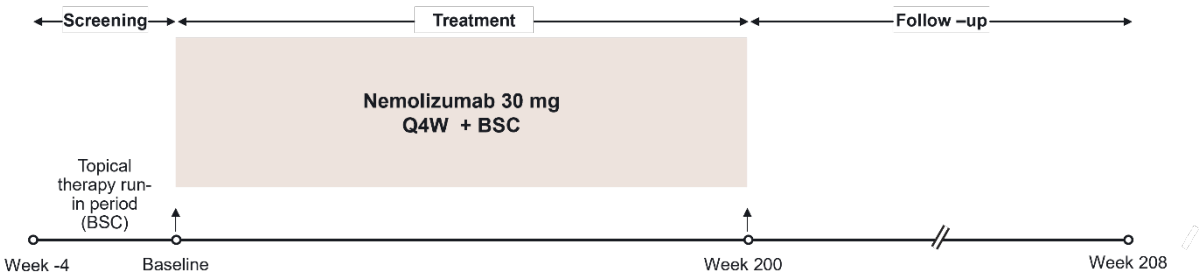

Figure 6. Study design: LTE study

Abbreviations: BSC, best supportive care; Q4W, every 4 weeks
Galderma data on file ARCADIA LTE study[130]

Table 5. Summary of trial methodology: ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study

	ARCADIA 1 (NCT03985943)	ARCADIA 2 (NCT03989349)	ARCADIA-CYCLO (2021-002166-40)	LTE study (NCT03989206)
Indication	Adult and adolescent (≥ 12 years) participants with moderate-to-severe AD. Eligible participants must have a documented history of inadequate response to topical AD medication(s)		Adult participants with moderate-to-severe AD who are not adequately controlled with or are not advised to use oral ciclosporin for medical reasons	Adult and adolescent (≥ 12 years) participants with moderate-to-severe AD.
Locations	202 clinical centres across 14 countries in Europe (including the UK), North America, and Asia Pacific	163 clinical centres across 11 countries in Europe (excluding the UK), North America, and Asia Pacific	163 clinical centres across 11 countries in Europe (excluding the UK), North America, and Asia Pacific (Singapore only)	343 clinical centres across 22 countries in Europe (including the UK), North America, and Asia Pacific
Trial design	Phase 3 randomised, double-blind, placebo-controlled, multicentre (ARCADIA 1 includes the UK), parallel-group study comparing nemolizumab (30 mg) (with BSC) versus placebo (with BSC) Initial treatment period 16 weeks (Q4W) followed by maintenance period 32 weeks (Q4W/Q8W)		Phase 3b randomised, double-blind, placebo-controlled, multicentre (excluding the UK), parallel-group study comparing nemolizumab (30 mg) (with BSC) versus placebo (with BSC) Treatment period 16 weeks (Q4W)	Phase 3, prospective, multicentre (including the UK), open-label, long-term extension (LTE) study of nemolizumab (30 mg) (with BSC) Treatment period 200 weeks (Q4W)
Duration	56 weeks		24 weeks	208 weeks
Eligibility criteria for participants	• Male or female participants aged ≥ 12 years at the screening visit • Chronic AD for at least 2 years • EASI score ≥ 16, IGA score ≥ 3, BSA ≥ 10%, PP NRS score of at least 4 • Inadequate response to TCS treatments (with or without TCI) • Female participants of childbearing potential must agree either to be strictly abstinent throughout the study and for 12 weeks after the last study drug injection, or to use an adequate and approved		• Participants aged ≥ 18 years at the screening visit • Chronic AD for at least 2 years • EASI score ≥ 20, IGA score ≥ 3, BSA ≥ 10%, PP NRS score of at least 4 • Inadequate response to, or medically inadvisable to take ciclosporin • Inadequate response to TCS treatments (with or without TCI)	Participants who may benefit from study participation in the opinion of the investigator and had participated in a prior nemolizumab study for AD: • phase 2b dose-ranging (NCT03100344) • phase 2 adolescent pharmacokinetics/safety (NCT03921411)

	method of contraception throughout the study and for 12 weeks after the last study drug injection			• phase 2 vaccination safety (NCT04365387) • phase 2 drug-drug interaction (DDI) (NCT04562116) • phase 3b (ARCADIA-CYCLO, 2021-002166-40) • phase 3 pivotal ARCADIA 1 (NCT03985943) and ARCADIA 2 (NCT03989349) • Adolescents from selected sites in Australia, Austria, Canada and the US who had not previously participated in a nemolizumab study
Expected enrolment (actual)	750 (941)	750 (788)	270 (276)	1700 (1740)
Interventions	Initial treatment period 16 weeks: • Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC), Q4W • Placebo (with BSC), Q4W Maintenance period 32 weeks: • Nemolizumab 30 mg by subcutaneous injection (with BSC), Q4W and Q8W • Placebo (with BSC), Q4W		Treatment period 16 weeks: • Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC), Q4W • Placebo (with BSC), Q4W	Treatment period 200 weeks: • Nemolizumab (30 mg) (with BSC), Q4W
Permitted concomitant medication	• Basic skin care (cleansing and bathing) • Moisturisers • Bleach baths • Topical therapies (TCSs/TCIs) • Topical anaesthetics • Antihistamines without a sedative effect			
Prohibited concomitant medication	• Coal tar products • Topical PDE-4 inhibitor • Non-authorised medium- or low-potency TCS • Higher-potency TCS • Topical medications, including authorised TCSs/TCIs, with occlusive dressings (e.g., wet wraps)			

	• Systemic corticosteroids (corticosteroid inhalers are permitted) • Phototherapy • Tanning bed use • Immunosuppressive or immunomodulatory drugs • Biologics • Dupilumab • Live attenuated vaccine • Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants, SSRIs, or SNRIs (except if these treatments were taken at a stable dose for at least 3 months before screening)‡ • Gabapentinoids • Cannabinoids • Alternative medicine for AD (e.g., traditional Chinese medicine) • Non-live vaccine† • Investigational topical or systemic medication†		
Permitted rescue therapies	• Higher potency of TCSs • Oral corticosteroids • Biologics (including their biosimilars) • Systemic nonsteroidal immunosuppressants/immunomodulators • Phototherapy		
Primary outcomes	• Proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16 • Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16	• Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16 • Proportion of participants with improvement of PP NRS ≥ 4 at Week 16	• Incidence and severity AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs
Pre-planned subgroups	Subgroup analyses of the co-primary efficacy endpoints: • Region (Europe, North America, Asia-Pacific) • Age group (12–17, 18–65 and > 65) • Sex (male, female) • Race (White, Black, or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other [including multiple]) • Baseline IGA score (moderate [3], severe [4]) • Baseline PP NRS (≥7, <7) – random stratification factor	NA	NA

	• Previous use of any systemic therapy for AD (yes, no) • Previous use of any biologic therapy for AD (yes, no) • Previous use of any immunosuppressive or immunomodulatory drugs for AD (yes, no) • Previous use of dupilumab for AD (yes, no) • Previous use of ciclosporin for AD (yes, no) • Country		

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; DLQI, dermatology life quality index; EASI, eczema area and severity index; LTE, long-term extension; NICE, National Institute for Health and Care Excellence; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids
† Specified in the protocol for ARCADIA-CYCLO only
‡ Not specified in the LTE study
Source: Galderma data on file ARCADIA 1 & 2, ARCADIA-CYCLO, and LTE CSRs, clinical study protocols and statistical analysis plans[127-138]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Summaries of the statistical analyses for ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study are provided in Table 6, Table 7, and Table 8, respectively, as informed by the corresponding statistical analysis plans.[135-138]

Table 6. ARCADIA 1 & 2 statistical analysis and study groups

	ARCADIA 1	ARCADIA 2
Analysis populations	The **Intent-to-Treat (ITT) population** consisted of all randomised patients. All primary and secondary efficacy endpoints were analysed based on the ITT population. All analyses of the ITT population were analysed under the treatment group 'as randomised. Maintenance period - ITT population included only participants who were re-randomised after the Initial treatment period. The **Per-Protocol (PP) population** consisted of participants in the ITT population who received at least one dose of study drug and had no major protocol deviations that would have a significant effect on the efficacy of the study treatment. Only primary and selected secondary efficacy endpoints were analysed using the PP population under the treatment group as randomised. The **maintenance period population** consisted of all participants from the ITT population who were re-randomised to or continued placebo after the initial treatment period. The **safety population** consisted of all participants in ITT population who receive at least one dose of study drug. All safety data was summarised based on the safety population under the treatment group as randomised.	
Statistical analysis of primary endpoints	The co-primary endpoints were analysed using a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomised stratification variables (IGA severity [3 = moderate, 4 = severe] and PP NRS [≥7, <7] for full population; IGA severity only for baseline PP NRS ≥7 population) at 2.5% significance level (2-sided). In addition, an unadjusted CMH test was performed. For each co-primary endpoint, the estimate of treatment unadjusted difference with the corresponding two-sided 95% CI and strata-adjusted difference with the corresponding 2-sided 97.5% CI, and p-values were presented.	
Statistical analysis of secondary endpoints	Continuous endpoints (change from baseline to each visit) were analysed using an analysis of covariance (ANCOVA) including treatment group and randomization stratification variables as factors and appropriate baseline values as a covariate, if applicable. Missing values were imputed using multiple imputation (MI) under missing at random (MAR) assumption approach. The least squares mean, estimated standard error, and 95% confidence interval (CI) for each endpoint were presented for each treatment group and analysis visit. The estimated treatment difference for each endpoint at each analysis visit were summarized by presenting the difference in least squares means between treatment groups, the two-sided 95% CI, and associated p-value. In addition, change from baseline to each analysis visit in EASI, PP-NRS, and SCORAD and percent change from baseline in PP-NRS and SD-NRS were analysed using a mixed models for repeated measures (MMRM) approach, including terms of treatment group, stratification variables, appropriate baseline values, visit, and interactions between baseline score with visit and treatment group with visit.	

	Kenward-Roger approximation was used to estimate denominator degrees of freedom. An unstructured covariance was used to model the within-patient errors in the analysis. A linear contrast was used, within the MMRM framework, to estimate difference between nemolizumab and placebo. The least squares mean, estimated standard error, and 95% CI for each endpoint were presented for each treatment group and scheduled analysis visit. The estimated treatment difference for each endpoint at each visit were summarized by presenting the difference in least squares means between treatment groups, the two sided 95% CI, and associated p-value. The itch-free days were summarized descriptively using the observed data (no observed data after participants have received rescue therapy were excluded, no imputation was performed for missing data). Binary endpoints were analysed using a CMH test adjusted for the randomized stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥7, <7] for full population; IGA severity only for Baseline PP NRS >=7 population). Any participants with missing data at respective weeks were regarded as a non-responder.
Statistical analysis of safety endpoints	Safety assessments were conducted for all participants at the screening visit and at every subsequent visit. Safety was assessed on the basis of AEs, unexpected adverse reactions, clinical laboratory data, vital signs, physical examination, respiratory examination and assessments, and ECGs. AEs were coded using MedDRA Version 25.0. TEAEs were summarised using the number and percentage of participants reporting each SOC and PT for each study period, sorted alphabetically by SOC and by descending frequency of PT within SOC for the nemolizumab group. Participants who experienced multiple events within the same SOC were counted once in the SOC summary. Participants who experienced multiple occurrences of events with the same PT were counted once in the PT summary. When summarising by causality or maximum severity, if a subject experienced more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug was used in summary tables. TEAE related to study drug/study procedure were those that were identified as having a reasonable possibility. If relationship or severity was missing, the event was considered as an AE related to study drug/study procedure or a severe AE. In addition, the exposure-adjusted incidence rate (i.e., number of participants per 100 patient-years) was summarised for all TEAEs (all causalities) and study drug-related TEAEs during the treatment period. Exposure-adjusted incidence rates of TEAEs was defined as the number of participants exposed to treatment and experiencing a certain event divided by the total time of all participants who were at risk for the event.
Sample size and power calculation	With a 2:1 randomisation, 180 participants in nemolizumab and 90 participants in placebo were required to detect differences in both co-primary endpoints to achieve 90% power. • IGA Success: To detect a difference of 18%, assuming IGA response for nemolizumab 30% and placebo 12% at Week 16. • EASI-75 Response: To detect a difference of 30%, assuming EASI-75 response for nemolizumab 49% and placebo 19% at Week 16.

	To ensure sufficient exposure with nemolizumab and to ensure sufficient size of the safety database, sample size was increased to 750 participants in total with randomisation ratio 2:1, providing > 99% power to detect the treatment difference for both co-primary endpoints at 2.5% significance level.
Handling of missing data and participant withdrawals	The primary methods to impute missing values were as follows: • Continuous endpoints: for continuous secondary endpoints during the initial treatment period, the MI MAR assumption approach and the MMRM approach were used to handle the missing data for the selected secondary endpoints. • Quality of life endpoints: may have been imputed using last observation carried forward (LOCF), where applicable. • Binary endpoints: all missing values were treated as non-responders for the binary endpoints for primary, key secondary, and secondary endpoints during the initial treatment period. To assess the robustness of non-responder analysis for primary and key secondary endpoints, a tipping point analysis was performed. The MI MAR assumption, LOCF, and observed cases (OC) were used as sensitivity analyses to impute the missing values for the primary and key secondary endpoints. • If a subject received any rescue therapy, data on or after receipt of rescue therapy were considered treatment failures. • AEs and concomitant medications/procedures: missing assessment times had imputed times for the purposes of assessing treatment emergence for AEs or classifying medications/procedures into prior/concomitant. However, the assessment date and time without imputation were presented in the listings. • If an AE had the start date completely missing and the stop date on/after the first dose date of study drug, the AE was considered a TEAE. If a medication/procedure had the stop date completely missing, this medication/procedure was considered as ongoing and concomitant. If the start date of a medication/procedure was completely missing and impossible to identify differently by stop date, this medication was considered as concomitant.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; IGA, investigator's global assessment; ITT, intent-to-treat; MMRM, mixed models for repeated measures; MI MAR, multiple imputation under missing at random; OC, observed cases ;PP, per protocol; PP NRS, Peak Pruritus Numerical Rating Scale; SD NRS, Sleep Disturbance Numerical Rating Scale; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA 1 & 2 statistical analysis plans[135,136]

Table 7. ARCADIA-CYCLO statistical analysis and study groups

	ARCADIA-CYCLO
Analysis populations	The **Intent-to-Treat (ITT) population** consisted of all randomised patients. All primary and secondary efficacy endpoints were analysed based on the ITT population. All analyses of the ITT population were analysed under the treatment group 'as randomised. The **Per-Protocol (PP) population** consisted of participants in the ITT population who received at least one dose of study drug and had no major protocol deviations that would have a significant effect on the efficacy of the study treatment. Only primary and selected secondary efficacy endpoints were analysed using the PP population under the treatment group as randomised. The **safety population** consisted of all participants in ITT population who receive at least one dose of study drug. All safety data was summarised based on the safety population under the treatment group as randomised.
Statistical analysis of primary endpoints	The primary efficacy endpoints were analysed on the ITT set, using a CMH) test adjusted for the randomised stratification variables (baseline IGA severity and prior ciclosporin exposure). The estimate of stratified treatment difference and the corresponding two-sided 95% CI using CMH stratum-weight estimator, and p-values from the CMH test were presented. A hierarchical testing procedure was followed, where proportion of participants with EASI-75 was tested first and proportion of participants with an improvement of PP NRS ≥ 4 was tested second.
Statistical analysis of secondary endpoints	Continuous endpoints were analysed at each visit using an ANCOVA, also descriptive statistics will be displayed and change from baseline by visit. For this summary, if any rescue medications were received, and data collected post-rescue receipt, then the data was summarized as observed (i.e. not set to missing). These endpoints were analysed using the MMRM which includes treatment group, stratification factors (baseline IGA severity, prior ciclosporin exposure), visit, interaction term between treatment and visit, and appropriate baseline value (baseline values for the corresponding parameter tested) as independent variables (if applicable). An unstructured variance-covariance matrix will be assumed; if convergence becomes an issue, other structures will be considered based on the data. Least-squares means, standard errors, 95% confidence intervals for change or percent change from baseline in each score will be presented for each treatment group at each study visit. Additionally, the LS mean treatment difference will be displayed for each score, with corresponding 95% confidence intervals and p-values at each study visit. For this summary, if any rescue medications were received, and data collected post-rescue receipt, then the data was summarized as observed (i.e. not set to missing). For PP NRS and SD NRS endpoints, visit and interaction term between treatment and visit were replaced by week and interaction term between treatment and week. Binary endpoints were be analysed at each visit using a CHM test adjusting for the randomization stratification factors of baseline IGA severity and prior ciclosporin exposure. Participants receiving rescue therapies and with all their data collected post-rescue receipt will be regarded as non-response. P-values from CHM test, and common risk difference and 95% CI

	between nemolizumab and Placebo from CHM stratum-weight estimation will be displayed for each visit according to the schedule of assessments.
Statistical analysis of safety endpoints	All safety analyses were conducted on the Safety Set. Safety assessments were conducted for all participants at the screening visit and at every subsequent visit. A TEAE was defined as any AE with an onset date on or after the date of the first injection (Baseline/Day 1) through the last study visit (follow-up visit), whether it was considered causally related to the study drug.
Sample size and power calculation	With a 1:1 randomisation, 115 participants in nemolizumab and 115 participants in placebo were required to detect differences in both co-primary endpoints to achieve 90% power at a 5% significance level. • EASI-75 response: To detect a difference of 20%, assuming EASI-75 response for nemolizumab 42% and placebo 122% at Week 16 • PP NRS Success: To detect a difference of 40%, assuming IGA response for nemolizumab 60% and placebo 20% at Week 16
Handling of missing data and participant withdrawals	Multiple imputation method for missing data (or where rescue medication was received): for participants who had insufficient EASI or PP NRS data (including baseline data), missing EASI scores and PP NRS scale values were imputed separately, and responses at Week 16 were determined based on the imputed values. For participants who discontinued early from study drug or who took rescue medication, Week 16 responses were the same as in the primary analysis; missing data before receipt of rescue medication were changed from non-responder to responder, and data for all visits after rescue therapy were treated as treatment failure (imputed to non-response).

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; IGA, investigator's global assessment; ITT, intent-to-treat; MMRM, mixed models for repeated measures; PP, per protocol; PP NRS, Peak Pruritus Numerical Rating Scale; SD NRS, Sleep Disturbance Numerical Rating Scale; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA-CYCLO statistical analysis plan[137]

Table 8. LTE study statistical analysis and study groups

	LTE study
Analysis populations	The **safety population** consisted of all participants who received at least one dose of study drug. The statistical analyses were performed on this population. The **pharmacokinetics (PK) population** consisted of all participants in the safety set who had at least one post-baseline evaluable drug concentration value and did not include any biologically implausible value. This population was used for the PK analysis.
Statistical analysis of primary endpoints (safety endpoints)	All safety data were summarised by study period (treatment period and follow-up period) based on the safety population. All TEAEs were coded using MedDRA Version 25.0. Treatment-emergent AEs were defined as those AEs occurring on or after the first administration of study treatment until the end of the study. All TEAEs were summarised using the number and percentage of participants reporting each SOC and PT and sorted alphabetically by SOC and descending frequency of PT within SOC. Participants who experienced multiple events within the same SOC were counted once in the SOC summary. Participants who experienced multiple occurrences of events with the same PT were counted once in the PT summary. When summarizing by causality or maximum severity, if a subject experienced more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug was used in summary tables. TEAEs related to study drug/study procedure were those that were identified as having a reasonable possibility of relationship to study drug/study procedure. If relationship or severity were missing, the event was considered as an AE related to study drug/study procedure or severe AE.
Statistical analysis of secondary endpoints	Unless otherwise stated, continuous variables were summarized using the descriptive statistics. Categorical variables were summarized using frequency and percentages of participants for each category.
Sample size and power calculation	No formal sample size calculations were performed for this LTE study. A sample size of approximately 1700 participants, including adult and adolescent (12-17 years of age) participants, was projected to support long-term safety and efficacy evaluation of nemolizumab. It was planned to enrol a total of approximately 200 adolescents from lead-in studies or direct enrolment to achieve 120 participants treated for 1 year.
Handling of missing data and participant withdrawals	Observed data were used to summarize all efficacy and safety endpoints. For AEs and concomitant medications/procedures, any missing assessment times had imputed times for the purposes of assessing treatment emergence for AEs or classifying medications into prior/concomitant. If an AE had the start date completely missing and the stop date on/after the first dose date of study drug, the AE was considered as treatment-emergent (a TEAE). If a medication had the stop date completely missing, the medication was considered as ongoing and concomitant. If the start date of a medication was completely missing and impossible to identify differently by the stop date, this medication was considered as concomitant.

Abbreviations: AE, adverse event; LTE, long-term extension; PK, pharmacokinetics; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
Source: Galderma data on file LTE study statistical analysis plan[138]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study. The quality assessments for trials are summarised in Table 9 and with the full assessment provided in Appendix D.

Table 9. Quality assessment results: ARCADIA 1 & 2 and ARCADIA-CYCLO

Trial	ARCADIA 1	ARCADIA 2	ARCADIA-CYCLO	LTE study
Was randomisation carried out appropriately?	Yes – a 2:1 (initial treatment period) and 1:1:1 (maintenance period) randomisation was selected to minimise the number of patients exposed to placebo for an extended period. Randomisation through interactive response technology (IRT) guarded against selection bias. Randomisation in the initial treatment period was stratified by disease severity (IGA = 3, IGA = 4) and pruritus severity (PP NRS ≥ 7, PP NRS < 7).		Yes – a 2:1 randomisation was selected to minimise the number of patients exposed to placebo for an extended period. Randomisation through interactive response technology (IRT) guarded against selection bias. Randomisation was stratified by disease severity (IGA = 3, IGA = 4) and prior ciclosporin exposure.	NA – no re-randomisation occurred for the LTE study
Was the concealment of treatment allocation adequate?	Yes – to avoid bias and to ensure the integrity of the blind, personnel directly involved with the conduct of the study from the sponsor, blinded statistical team at the CRO, or other investigational study centres do not have access to any information that may lead to unblinding.			Yes – while the LTE study uses an open-label design, due to the fact that the LTE study was ongoing while phase 3 and phase 3b studies were still blinded, a blinded loading dose was required for applicable patients in order to maintain the blind of the previous study
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes – see section B.2.6.1.1	Yes – see section B.2.6.1.1	Yes – see section B.2.6.1.2	NA – This LTE study is conducted as a single-arm trial
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes – to avoid bias and to ensure the integrity of the blind, personnel directly involved with the conduct of the study from the sponsor, blinded statistical team at the CRO, or other investigational study centres do not have access to any information that may lead to unblinding.			Yes – while the LTE study uses an open-label design, due to the fact that the LTE study was ongoing while phase 3 and phase 3b studies were still blinded, a blinded loading dose was

				required for applicable patients in order to maintain the blind of the previous study
Were there any unexpected imbalances in dropouts between groups?	No – see section B.2.6.1.1	No – see section B.2.6.1.1	No – see section B.2.6.1.2	No – see section B.2.6.1.3
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – all outcomes that were recorded in the trials have been reported in the CSRs, with those outcomes related to the scope included in this submission.			
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 – MI method for missing data (or where rescue medication was received), assuming all missing data were MAR. The ITT population was the primary population for all efficacy analyses. In all analyses of the ITT population, patients were included in the treatment group to which they were randomised.			No – See section B.2.4

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[139]
Abbreviations: CRO: contract research organization; CSR: clinical study report; IGA: Investigator's Global Assessment; IRT: interactive response technology (IRT); ITT: intent-to-treat; LTE, long-term extension, MAR: missing at random; MI, multiple imputation; NA, not applicable; PP NRS: Peak Pruritus Numerical Rating Scale
Source: Galderma data on file ARCADIA 1 & 2, ARCADIA-CYCLO, and LTE study CSRs, clinical study protocols and statistical analysis plans[127-138]

B.2.6. Clinical effectiveness results of the relevant studies

B.2.6.1. Patient dispositions and baseline characteristics

B.2.6.1.1. ARCADIA 1 & 2

Patient disposition for ARCADIA 1 & 2 including the number randomised, treated, completed, and discontinued treatment are in Table 10.[127,128]

Table 10. Patient disposition: ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period		Initial treatment period	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	620	321	522	265
Randomised, n (%)	620 (100)	321 (100)	522 (100)	265 (100)
Re-randomised, n (%)	NA	NA	NA	NA
Treated, n (%)	616 (99.4)	321 (100)	519 (99.4)	263 (99.2)
Completed treatment, n (%)	560 (90.3)	296 (92.2)	470 (90.0)	241 (90.9)
Discontinued treatment, n (%)	56 (9.0)	25 (7.8)	49 (9.4)	22 (8.3)
Primary reason for discontinuation of treatment, n (%)				
Pregnancy	2 (0.3)	0	0	0
Lack of efficacy	5 (0.8)	2 (0.6)	3 (0.6)	0
AE	9 (1.5)	9 (2.8)	17 (3.3)	4 (1.5)
Participants request	25 (4.0)	11 (3.4)	24 (4.6)	15 (5.7)
COVID-19	0	0	0	0
Lost to follow-up	10 (1.6)	0	1 (0.2)	1 (0.4)
Protocol deviation	4 (0.6)	3 (0.9)	3 (0.6)	2 (0.8)
Physician/principle investigator decision	1 (0.2)	0	1 (0.2)	0
Other	0	0	0	0
Completed/exited the study after initial treatment period/maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from the study during initial treatment period/maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Primary reason for discontinuation from the study, n (%)				
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Proceeded to LTE study after initial treatment period/maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed follow-up after initial treatment period/ maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

†Participants in placebo group are not part of ITT population. Placebo group in maintenance period is for all placebo-treated participants who were randomised.
Abbreviations: AE, adverse event; ITT, intention to treat; LTE, long term extension; n, number; NA, not applicable, Q4W, every 4 weeks; Q8W, every 8 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Demographics and baseline characteristics of patients enrolled in the ARCADIA 1 & 2 trials are summarised in Table 11.[140] Demographics were generally similar between treatment groups prior to the first study drug injection (or prior to randomisation for participants randomised but not treated) in the initial treatment period. In ARCADIA 1, the mean age was 33.5 years in the nemolizumab treatment group and 33.3 years in the placebo treatment group. In each treatment group, most participants were male (≥ 52%), and White (≥ 73%). The percentage of adolescent participants (aged 12–17 years) was similar in the nemolizumab and placebo treatment groups (14% and 15%, respectively). Most participants were enrolled in Europe and North America (84%).

In ARCADIA 2, the mean age was 34.9 years in the nemolizumab treatment group and 35.2 years in the placebo treatment group. In each treatment group, most participants were female (≥ 51%) and White (≥ 86%). The percentage of adolescent participants (aged 12 to 17 years) was similar in the nemolizumab and placebo treatment groups (17% and 16%, respectively). Most participants were enrolled in Europe and North America (98%).

Table 11. Demographics and baseline characteristics: ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period		Initial treatment period	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	620	321	522	265
Age, mean (SD)	33.5 (15.9)	33.3 (15.6)	34.9 (17.7)	35.2 (17.0)
Sex, n (%)				
Male	323 (52)	177 (55)	252 (48)	129 (49)
Female	297 (48)	144 (45)	270 (52)	136 (51)
Region, n (%)				
Asia pacific	98 (16)	52 (16)	10 (2.0)	4 (2.0)
Europe	316 (51)	164 (51)	381 (73)	197 (74)
North America	206 (33)	105 (33)	131 (25)	64 (24)
Ethnicity, n (%)				
Hispanic or Latino	64 (10)	32 (10)	44 (8)	19 (7)
Not Hispanic nor Latino	552 (89)	288 (90)	464 (89)	244 (92)
Not reported	2 (<1)	1 (<1)	12 (2)	2 (<1)
Unknown	2 (<1)	0	2 (<1)	0
Race, n (%)				
White	451 (73)	244 (76)	458 (88)	227 (86)
Black or African America	36 (6)	18 (6)	25 (5)	20 (8)
Asian	117 (19)	51 (16)	35 (7)	18 (7)
American Indian or Alaska native	2 (<1)	3 (<1)	1 (<1)	0
Hawaiian or other Pacific Islander	1 (<1)	0	1 (<1)	0
Other	3 (<1)	1 (<1)	2 (<1)	0
Multiple	10 (2)	4 (1)	0	0

Weight (kg) at baseline, mean (SD)	75.1 (18.6)	76.9 (18.9)	74.6 (17.5)	73.4 (19.6)
BMI (kg/m^2), mean (SD)	26.0 (5.7)	26.5 (5.8)	25.9 (5.2)	25.6 (6.3)
IGA category, n (%)				
Moderate (3)	438 (71)	236 (74)	352 (67)	185 (70)
Severe (4)	182 (29)	85 (26)	170 (33)	80 (30)
EASI score				
Mean (SD)	27.77 (10.6)	27.06 (9.4)	27.43 (10.8)	27.58 (10.9)
Weekly average PP NRS, n	618	320	521	264
Mean (SD)	7.2 (1.4)	7.2 (1.4)	7.0 (1.5)	7.2 (1.5)
Weekly average SD NRS, n	610	320	517	263
Mean (SD)	5.938 (2.1399)	5.742 (2.2615)	5.754 (2.3033)	5.723 (2.3573)
BSA (%) of AD involvement				
Mean (SD)	44.85 (19.892)	43.81 (18.652)	44.61 (19.420)	44.95 (19.278)
SCORAD	619	321	NR	NR
Mean (SD)	64.1 (11.6)	63.3 (11.3)	64.9 (12.0)	64.9 (13.3)
DLQI total score at baseline, n	540	279	440	228
Mean (SD)	15.4 (6.6)	15.5 (6.8)	14.5 (6.9)	14.2 (7.0)
cDLQI total score at baseline, mean (SD)	71	37	75	30
Mean (SD)	12.7 (6.7)	12.5 (5.8)	12.2 (6.0)	12.4 (5.4)

Abbreviations: AD, atopic dermatitis; AP NRS, Average Pruritus Numeric Rating Scale; BSA, body surface area; BMI, body mass index; cDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent-to-treat; N, number of participants in the treatment group; n, number of participants with available data; PP NRS, Peak Pruritus Numeric Rating Scale; Q1, first quartile; Q3, third quartile; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SD NRS, Sleep Disturbance Numeric Rating Scale
Source: Silverberg et al.,[140]

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B.2.6.1.2. ARCADIA-CYCLO

Patient disposition for ARCADIA-CYCLO including the number randomised, treated, completed, and discontinued treatment are in Table 12.[129]

Table 12. Patient disposition: ARCADIA-CYCLO

	Nemolizumab 30 mg Q4W	Placebo Q4W	Total
All screened participants, n (%)†			
Screen failure participants			
Randomised			
Received any treatment dose			
Primary reason for early treatment termination, n (%)			
Subject's request			
AE			
Lost to follow-up			
Protocol deviation			
Physician/principal investigator decision			
Other			
Completed the study‡			
Early terminated‡			
Primary reason for early study termination, n (%)			
Subject's request			
AE			
Lost to follow-up			
Protocol deviation			
Continued to long-term extension, n (%)§			
Yes			
No			
Not applicable			

Abbreviations: AE: adverse event
†Percentages were based on the number of participants screened.
‡Percentages were based on the number of randomised participants
§Percentages for participants who continued to the long-term extension were based on Safety Set.
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Demographics and baseline characteristics of patients enrolled in the ARCADIA-CYCLO trial are summarised in Table 13.[129] Demographics were generally similar between treatment groups. In each treatment group, most participants were male

([redacted]) and White ([redacted]). The mean age was [redacted] years in the nemolizumab treatment group and [redacted] years in the placebo treatment group.

Table 13. Demographics and baseline characteristics: ARCADIA-CYCLO

Characteristic	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]
Age (years)		
Mean (SD)	[redacted]	[redacted]
Sex, n (%)		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race, n (%)		
Asian	[redacted]	[redacted]
White	[redacted]	[redacted]
Other	[redacted]	[redacted]
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Weight (kg) at baseline		
Mean (SD)	[redacted]	[redacted]
Body mass index (kg/m²)		
Mean (SD)	[redacted]	[redacted]
EASI score, n (%)		
Mean (SD)	[redacted]	[redacted]
IGA category, n (%)		
Moderate (3)	[redacted]	[redacted]
Severe (4)	[redacted]	[redacted]
Body surface area (%)		
Mean (SD)	[redacted]	[redacted]
SCORing Atopic Dermatitis		
Mean (SD)	[redacted]	[redacted]
PP NRS		
Mean (SD)	[redacted]	[redacted]
SD NRS		
Mean (SD)	[redacted]	[redacted]
DLQI total score	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Patient-oriented eczema measure	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
EuroQoL 5-Dimension - mobility, n (%)		
No problems in walking about	[redacted]	[redacted]
Some problems in walking about	[redacted]	[redacted]

Confined to bed	[redacted]	[redacted]
EuroQoL 5-Dimension - self-care, n (%)		
No problems with self-care	[redacted]	[redacted]
Some problems washing or dressing	[redacted]	[redacted]
Unable to wash or dress myself	[redacted]	[redacted]
EuroQoL 5-Dimension – usual activities, n (%)		
No problems with performing usual activities	[redacted]	[redacted]
Some problems with performing usual activities	[redacted]	[redacted]
Unable to perform usual activities	[redacted]	[redacted]
EuroQoL 5-Dimension – pain/discomfort, n (%)		
No pain or discomfort	[redacted]	[redacted]
Moderate pain or discomfort	[redacted]	[redacted]
Extreme pain or discomfort	[redacted]	[redacted]
EuroQoL 5-Dimension – anxiety/depression, n (%)		
Not anxious or depressed	[redacted]	[redacted]
Moderately anxious or depressed	[redacted]	[redacted]
Extremely anxious or depressed	[redacted]	[redacted]
EuroQoL 5-Dimension – visual analogue scale	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

Abbreviations: DLQI, dermatology life quality index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; N, number of participants in the treatment group; n, number of participants with available data; PP NRS, Peak Pruritus Numerical Rating Scale; Q1, first quartile; Q3, third quartile; SD NRS, Sleep Disturbance Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SD NRS, Sleep Disturbance Numeric Rating Scale
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

B.2.6.1.3. LTE study

Patient disposition for the LTE study including the number randomised, treated, completed, and discontinued treatment are in Table 14.[130] Baseline characteristics of patients enrolled in the LTE study are summarised in Table 15.[130] In the LTE, the mean age was 33.7 years, 50.9% were male, and 78.7% White. Most participants were enrolled in Europe and North America (91.6%).

Table 14. Patient disposition: LTE study (interim data cut Week 56)

	Treatment period (safety population)					
	Nemolizumab 30 mg Q4W	By treatment before LTE				
		Previously treated with nemolizumab			Nemolizumab naive	Blinded lead-in study
		All	Continuous nemolizumab	Re-treatment		
Total, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated, n (%)	1740[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation of treatment, n (%)						
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician/principle investigator decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed the study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from the study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Primary reason for discontinuation from the study, n (%)						
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LTE, long term extension; n, number of participants with available data; Q4W, every 4 weeks
Source: Galderma data on file LTE study interim CSR[130]

Table 15. Baseline characteristics: LTE study (interim data cut Week 56)

	Treatment period (safety population)					
	Nemolizumab 30 mg Q4W	**By treatment before LTE**				
		Previously treated with nemolizumab			**Nemolizumab naive**	**Blinded lead-in study**
		All	**Continuous nemolizumab**	**Re-treatment**		
Total, n	N=1740	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%)						
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia pacific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic nor Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple: White, Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple: White, Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple: White, Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg) at baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA category, n (%)						
Clear (0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Almost clear (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate (3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Not reported						
EASI score						
Mean (SD)						
BSA (%) of AD involvement, mean (SD)						
Mean (SD)						
SCORAD						
Mean (SD)						
DLQI total score at baseline						
Mean (SD)						
cDLQI total score at baseline, mean (SD)						
Mean (SD)						

Abbreviations: AD, atopic dermatitis; AP NRS, Average Pruritus Numeric Rating Scale; BSA, body surface area; BMI, body mass index; cDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent-to-treat; N, number of participants in the treatment group; n, number of participants with available data; PP NRS, Peak Pruritus Numeric Rating Scale; Q1, first quartile; Q3, third quartile; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; SD NRS, Sleep Disturbance Numeric Rating Scale
Source: Galderma data on file LTE study interim CSR[130]

B.2.6.2. Efficacy of nemolizumab with best supportive care in adolescents and adults with moderate-to-severe atopic dermatitis: ARCADIA 1 & 2

B.2.6.2.1. Co-primary endpoints – initial treatment period

Disease severity: proportion of participants with IGA success

Nemolizumab (with BSC) demonstrated statistically significant and clinically meaningful skin response compared to placebo (with BSC) as measured by IGA success. A greater proportion of participants with IGA success (IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) was observed with nemolizumab compared with placebo at Week 16 (ARCADIA 1, 35.6% vs. 24.6%, strata-adjusted p = 0.0003; ARCADIA 2, 37.7% vs. 26.0%, strata-adjusted p = 0.0006) as shown in Table 16 and Figure 7.[127,128]

Table 16. Proportion of participants with IGA success at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	620	321	522	265
IGA success, n (%)	221 (35.6)	79 (24.6)	197 (37.7)	69 (26.0)
Strata-adjusted proportion difference, %	11.5	-	12.2	-
Strata-adjusted 97.5% CI	4.7, 18.3	-	4.6, 19.8	-
Strata-adjusted p-value	0.0003	-	0.0006	-

Abbreviations: CI, confidence intervals; IGA, Investigator's Global Assessment; ITT, intention-to-treat; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

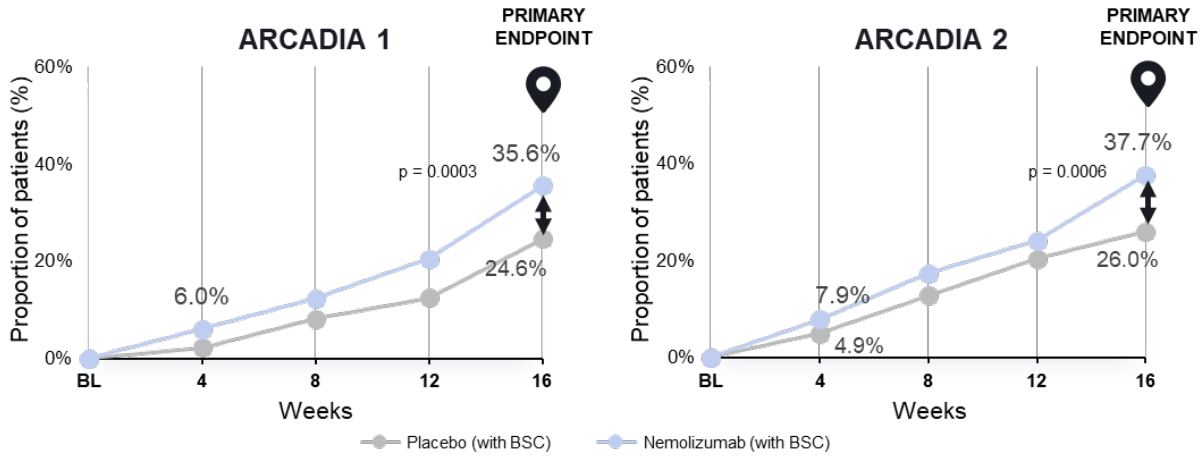

Figure 7. Proportion of participants with IGA success from baseline through to Week 16 – ARCADIA 1 & 2

Abbreviations: BL, baseline; BSC, best supportive care; IGA, Investigator's Global Assessment
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Disease severity: proportion of participants with EASI-75

Nemolizumab (with BSC) demonstrated statistically significant and clinically meaningful skin response compared to placebo (with BSC) as measured by EASI-75. A greater proportion of participants with EASI-75 (a ≥ 75% improvement from baseline) was observed with nemolizumab compared with placebo at Week 16 (ARCADIA 1, 43.5% vs.29.0%, strata-adjusted p < 0.0001; ARCADIA 2, 42.1% vs. 30.2%, strata-adjusted p = 0.0006) as shown in Table 17 and Figure 8.[127,128]

Table 17. Proportion of participants with EASI-75 at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	620	321	522	265
EASI-75 improvement, n (%)	270 (43.5)	93 (29.0)	220 (42.1)	80 (30.2)
Strata-adjusted proportion difference, %	14.9	-	12.5	-
Strata-adjusted 97.5% CI	7.8, 22.0	-	4.6, 20.3	-
Strata-adjusted p-value	< 0.0001	-	0.0006	-

Abbreviations: CI, confidence intervals; EASI, eczema area and severity index; ITT, intention-to-treat; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

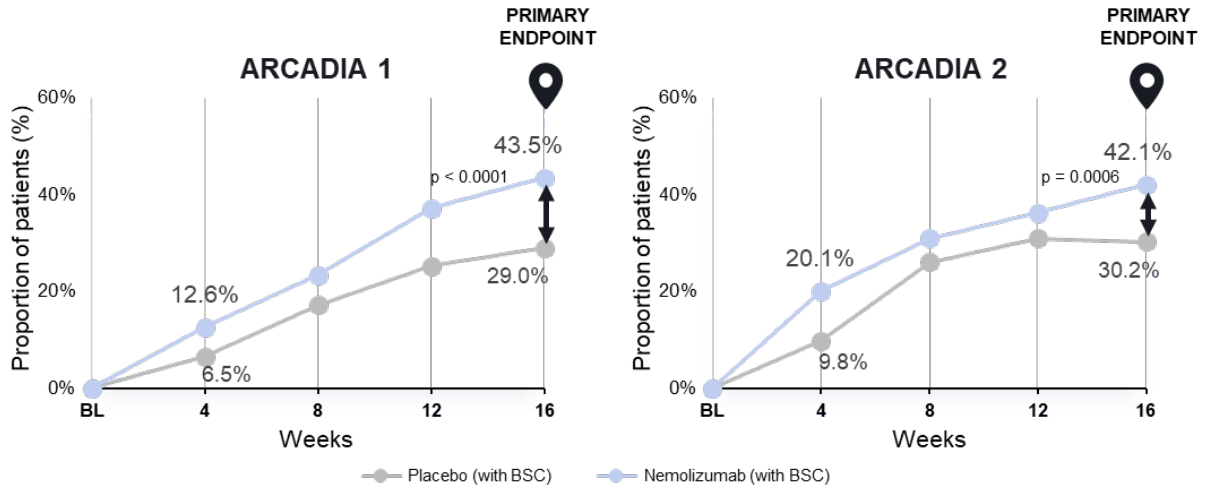

Figure 8. Proportion of participants with EASI-75 through to Week 16 – ARCADIA 1 & 2

Abbreviations: BL, baseline; BSC, best supportive care; EASI, eczema area and severity index
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

B.2.6.2.2. Secondary endpoints – initial treatment period

Itch: proportion of participants with PP NRS improvement of ≥ 4 from baseline and a PP NRS < 2

Nemolizumab (with BSC) demonstrated statistically significant and clinically meaningful itch relief compared to placebo (with BSC) as measured by PP NRS. A greater proportion of participants with an improvement of ≥ 4 from baseline in weekly average PP NRS was observed with nemolizumab compared with placebo (plus BSC) at Week 16 in ARCADIA 1 (42.7% vs. 17.8%, strata-adjusted p < 0.0001) and ARCADIA 2 (41.0% vs. 18.1%, strata-adjusted p < 0.0001) (Table 18). [127,128] A greater proportion of participants with a weekly average PP NRS < 2 was observed with nemolizumab compared with placebo at Week 16 in ARCADIA 1 (30.6% vs. 11.2%, strata-adjusted p < 0.0001) and ARCADIA 2 (28.4% vs. 11.3%, strata-adjusted p < 0.0001).[127,128]

Table 18. Proportion of participants with PP NRS improvement of ≥ 4 from baseline at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W

Total, n	620	321	522	265
Improvement of ≥ 4 from baseline in PP NRS, n (%)	265 (42.7)	57 (17.8)	214 (41.0)	48 (18.1)
Strata-adjusted proportion difference, (%)	24.9	-	23.2	-
Strata-adjusted 97.5% CI	18.4, 31.5	-	16.1, 30.3	-
Strata-adjusted p-value	< 0.0001	-	< 0.0001	-
PP NRS <2, n (%)	190 (30.6)	36 (11.2)	148 (28.4)	30 (11.3)
Strata-adjusted proportion difference, (%)	19.5	-	17.1	-
Strata-adjusted 97.5% CI	13.7, 25.2	-	10.9, 23.3	-
Strata-adjusted p-value	< 0.0001	-	< 0.0001	-

Abbreviations: CI, confidence intervals; ITT, intention-to-treat; PP NRS, peak pruritus numerical rating scale; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Sleep disturbance: proportion of participants with SD NRS improvement of ≥ 4 from baseline

Nemolizumab (with BSC) demonstrated decreased sleep disturbance compared to placebo (with BSC) as measured by SD NRS. A clinically and statistically significantly greater proportion of participants with an improvement of ≥ 4 from baseline in weekly average SD NRS was observed with nemolizumab compared with placebo at Week 16 in ARCADIA 1 (37.9% vs. 19.9%, strata-adjusted p < 0.0001) and ARCADIA 2 (33.5% vs. 16.2%, strata-adjusted p < 0.0001) (Table 19).[127,128]

Table 19. Proportion of participants with SD NRS success at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	620	321	522	265
Improvement of ≥4 from baseline in SD NRS, n (%)	235 (37.9)	64 (19.9)	175 (33.5)	43 (16.2)
Strata-adjusted proportion difference, (%)	17.9	-	17.5	-
Strata-adjusted 97.5% CI	11.3, 24.5	-	10.8, 24.3	-
Strata-adjusted p-value	<0.0001	-	<0.0001	-

Abbreviations: CI, confidence intervals; ITT, intention-to-treat; Q4W, every 4 weeks; SD NRS, sleep disturbance numerical rating scale
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Disease severity: change in SCORAD from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the SCORAD compared with baseline at Week 16 in ARCADIA 1 (LS mean difference -9.17; 95% CI -12.35, -5.99; [redacted]) and ARCADIA 2 (LS mean difference -8.10; 95% CI -11.39, -4.82; [redacted]) (Table 20).[127,128]

Table 20. Change in SCORAD from baseline at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	619	321	522	265
% change from baseline in SCORAD, LS mean (%)	-26.52 (1.081)	-17.35 (1.409)	-28.32 (1.061)	-20.21 (1.451)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	-9.17 (-12.35, -5.99)	-	-8.10 (-11.39, -4.82)	-
p- value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, intention-to-treat; LS, least squares; Q4W, every 4 weeks; SCORAD, SCORing atopic dermatitis
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Quality of life: change in DLQI total score from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the mean DLQI total score compared with baseline at Week 16 in ARCADIA 1 (LS mean difference -2.50; 95% CI -3.63, -1.37; [redacted]), and ARCADIA 2 (LS mean difference -2.44; 95% CI -3.58, -1.30; [redacted]) (Table 21).[127,128]

Table 21. Change in DLQI score from baseline at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	540	279	440	228
Change in DLQI from baseline, LS mean (SE)	-7.76 (0.371)	-5.26 (0.497)	-6.96 (0.361)	-4.52 (0.489)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95%) CI	-2.50 (-3.63, -1.37)	-	-2.44 (-3.58, -1.30)	-
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; DLQI, Dermatology Life Quality Index; ITT, intention-to-treat; LS, least square; Q4W, every 4 weeks; SE, standard error
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Patient-reported outcomes: change in POEM total score from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the POEM total score compared with baseline at Week 16 in ARCADIA 1 (LS mean difference -4.04; 95% CI -5.09, -2.99; [redacted]) and ARCADIA 2 (LS mean difference -3.93; 95% CI -5.07, -2.78; [redacted]) (Table 22).[127,128]

Table 22. Change in POEM score from baseline at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	612	316	515	259
% change from baseline in POEM, LS mean (%)	-9.04 (0.350)	-5.00 (0.465)	-8.87 (0.365)	-4.95 (0.504)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI)	-4.04 (-5.09, -2.99)	-	-3.93 (-5.07, -2.78)	-
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, intention-to-treat; LS, least squares; POEM, patient-oriented eczema measure; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

Quality of life: change in EQ-5D subscale scores from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in increasing the EQ-5D VAS score compared with baseline at Week 16 in ARCADIA 1 (LS mean difference 2.56; 95% CI 0.16, 4.95; [redacted]), however it did not reach statistical significance in ARCADIA 2 (LS mean difference 2.39; 95% CI -0.30, 5.09; [redacted]) (Table 23).[127,128]

Table 23. Change in EQ-5D score from baseline at Week 16 – ARCADIA 1 & 2

	ARCADIA 1		ARCADIA 2	
	Initial treatment period (Week 16)		Initial treatment period (Week 16)	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	611	316	515	256
Change in EQ-5D VAS from baseline, LS mean (SE)	13.51 (0.804)	10.95 (1.061)	12.97 (0.852)	10.57 (1.182)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95%) CI	2.56 (0.16, 4.95)	-	2.39 (-0.30, 5.09)	-
p-value	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; EQ-5D, EuroQoL 5-Dimension; ITT, intention-to-treat; LS, least squares Q4W, every 4 weeks; SE, standard error
Source: Galderma data on file ARCADIA 1 & 2 CSR[127,128]

B.2.6.2.3. Efficacy endpoints – pooled maintenance period

Disease severity: proportion of participants with IGA success and EASI-75

A pooled analysis of the maintenance periods of ARCADIA 1 & 2 was performed for efficacy and select safety endpoints.[141] Nemolizumab (with BSC) demonstrated continued efficacy in skin response in the pooled maintenance period of ARCADIA 1 & 2. The proportion of participants with IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from initial baseline) was higher in the nemolizumab Q4W to Q4W and nemolizumab Q4W to Q8W groups compared with nemolizumab Q4W to placebo at most timepoints (nemolizumab Q4W to Q4W compared to nemolizumab Q4W to placebo at Week 48, 61.5% vs. 49.7%, strata-adjusted [redacted]; nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 60.4% vs. 49.7%, strata-adjusted [redacted]) (Table 24 and Figure 9).

The proportion of participants with EASI-75 (a ≥ 75% improvement from initial baseline) was higher in the nemolizumab Q4W to Q4W and nemolizumab Q4W to Q8W compared with nemolizumab Q4W to placebo at all timepoints (nemolizumab Q4W to Q4W compared to nemolizumab Q4W to placebo at Week 48, 76.3% vs. 63.9%, strata-adjusted [redacted]; nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 75.7% vs. 63.9%, strata-adjusted [redacted]) (Table 25 and Figure 9).

Table 24. Proportion of participants with IGA success at Week 48 – ARCADIA 1 & 2

	Pooled maintenance period (Week 48)		
	ITT population		
	Nemolizumab 30 mg Q4W to Q4W	**Nemolizumab 30 mg Q4W to Q8W**	**Nemolizumab 30 mg Q4W to placebo**
Total, n	169	169	169
IGA success, n (%)	104 (61.5)	102 (60.4)	84 (49.7)
Strata-adjusted proportion difference, %	[redacted]	[redacted]	[redacted]
Strata-adjusted 95% CI	[redacted]	[redacted]	[redacted]
Strata-adjusted p-value	0.0290	0.0465	-

Abbreviations: CI, confidence intervals; IGA, Investigator's Global Assessment; ITT, intention-to-treat; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 pooled analysis[141]

Table 25. Proportion of participants with EASI-75 at Week 48 – ARCADIA 1 & 2

	Pooled maintenance period (Week 48)		
	ITT population		
	Nemolizumab 30 mg Q4W to Q4W	**Nemolizumab 30 mg Q4W to Q8W**	**Nemolizumab 30 mg Q4W to placebo**
Total, n	169	169	169
EASI-75, n (%)	129 (76.3)	128 (75.7)	108 (63.9)
Strata-adjusted proportion difference, %	[redacted]	[redacted]	[redacted]
Strata-adjusted 95% CI	[redacted]	[redacted]	[redacted]
Strata-adjusted p-value	0.0129	0.0179	-

Abbreviations: CI, confidence intervals; EASI, eczema area and severity index; ITT, intention-to-treat; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA 1 & 2 pooled analysis[141]

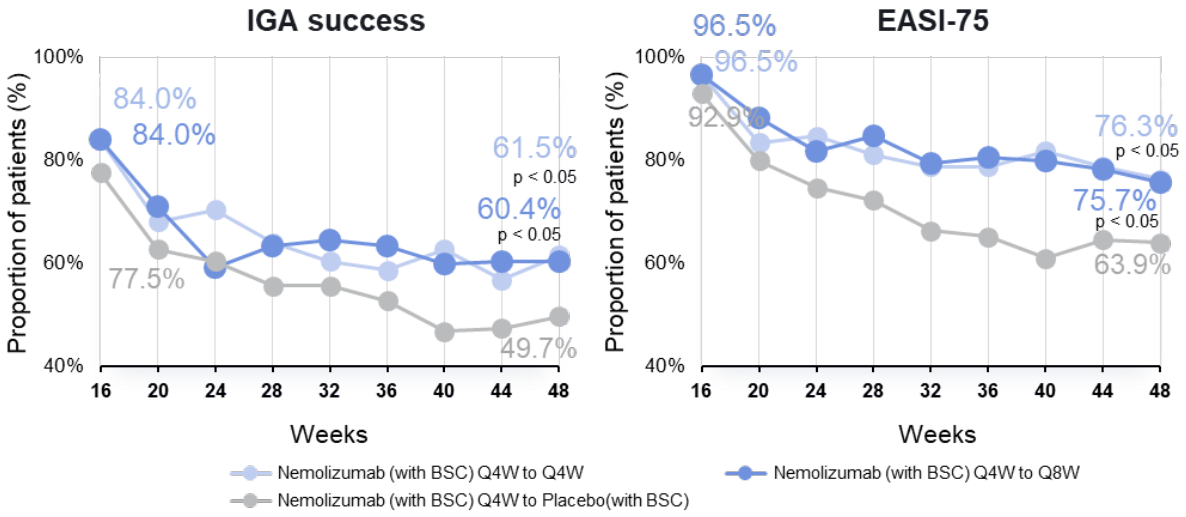

Figure 9. Proportion of participants with IGA success and EASI-75 from maintenance baseline through Week 48 – ARCADIA 1 & 2

Abbreviations: BSC, best supportive care; EASI, eczema area and severity index; IGA, Investigator's Global Assessment; Q4/8W, every 4/8 weeks
Source: Galderma data on file ARCADIA 1 & 2 pooled analysis[141]

B.2.6.3. Efficacy of nemolizumab with best supportive care in adults who were not adequately controlled with/not advised to use oral ciclosporin for medical reasons: ARCADIA-CYCLO

B.2.6.3.1. Co-primary endpoints

Disease severity: proportion of participants with EASI-75

Nemolizumab (with BSC) demonstrated statistically significant and clinically meaningful skin response compared to placebo (with BSC) as measured by EASI-

75. A greater proportion of participants with EASI-75 (a ≥ 75% improvement from baseline) was observed with nemolizumab compared with placebo at Week 16 in ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted]) as shown in Table 26 and Figure 10.[129]

Table 26. Proportion of participants with EASI-75 at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]
EASI-75 improvement, n (%)	[redacted]	[redacted]
Strata-adjusted proportion difference, %	[redacted]	[redacted]
Strata-adjusted 95% CI	[redacted]	[redacted]
Strata-adjusted p-value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; EASI, eczema area and severity index; ITT, ITT, intention-to-treat; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

[redacted]

Figure 10. Proportion of participants with EASI-75 from baseline through to Week 16 – ARCADIA-CYCLO

Abbreviations: BL, baseline; BSC, best supportive care; EASI, eczema area and severity index
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Itch: proportion of participants with PP NRS improvement of ≥ 4 from baseline and a PP NRS < 2

Nemolizumab (with BSC) demonstrated statistically significant and clinically meaningful itch relief compared to placebo (with BSC) as measured by PP NRS. A clinically and statistically significantly greater proportion of participants with an improvement of ≥ 4 from baseline in weekly average PP NRS was observed with nemolizumab compared with placebo at Week 16 in ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted]) as shown in Table 27 and

Figure 11.[129] Although not a primary endpoint a clinically and statistically significantly greater proportion of participants with a weekly average PP NRS < 2 was observed with nemolizumab compared with placebo at Week 16 in the full populations of

ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted]) as shown in Table 27 and Figure 11.[129]

Table 27. Proportion of participants with PP NRS success at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]
Improvement of ≥4 from baseline in PP NRS, n (%)	[redacted]	[redacted]
Strata-adjusted proportion difference, (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	[redacted]
PP NRS <2, n (%)	[redacted]	[redacted]
Strata-adjusted difference in proportions, (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, ITT, intention-to-treat; PP NRS, peak pruritus numerical rating scale; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

[redacted]

Figure 11. Proportion of participants with PP NRS improvement of ≥ 4 from baseline and a PP NRS < 2 – ARCADIA-CYCLO

Abbreviations: BL, baseline; BSC, best supportive care; PP NRS, peak pruritus numerical rating scale
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

B.2.6.3.1. Secondary endpoints

Sleep disturbance: proportion of participants with SD NRS improvement of ≥ 4 from baseline

A clinically and statistically significantly greater proportion of participants with an improvement of ≥ 4 from baseline in weekly average SD NRS was observed with nemolizumab (with BSC) compared with placebo (with BSC) at Week 16 in the full population of ARCADIA-CYCLO ([redacted] vs. [redacted], strata-adjusted [redacted]) (Table 28).[129]

Table 28. Proportion of participants with SD NRS improvement of ≥ 4 from baseline at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W

Total participants, n	[redacted]	[redacted]
Improvement of ≥4 from baseline in SD NRS, n (%)	[redacted]	[redacted]
Strata-adjusted proportion difference, (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p-value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, ITT, intention-to-treat; Q4W, every 4 weeks; SD NRS, sleep disturbance numerical rating scale
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Disease severity: change in SCORAD and from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the SCORAD compared with baseline at Week 16 in the full population of ARCADIA-CYCLO (LS mean percent difference [redacted]; 95% CI [redacted]; [redacted] (Table 29).[129]

Table 29. Change in SCORAD from baseline at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	**Placebo Q4W**
Total participants, n	[redacted]	[redacted]
% change from baseline in SCORAD, LS mean (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]
p- value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, ITT, intention-to-treat; LS, least squares; Q4W, every 4 weeks; SCORAD, SCORing atopic dermatitis
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Quality of life: change in DLQI total score from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the mean DLQI total score compared with baseline at Week 16 in the full population of ARCADIA-CYCLO (LS mean difference [redacted]; 95% CI [redacted]; [redacted]) (Table 30).[129]

Table 30. Change in DLQI score from baseline at Week 16 – ARCADIA-CYCLO

	Initial treatment period (Week 16)
	ITT population

	Nemolizumab 30 mg Q4W	Placebo Q4W
Total participants, n	[redacted]	[redacted]
Change in DLQI from baseline, LS mean (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]
p- value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; DLQI, Dermatology Life Quality Index; ITT, ITT, intention-to-treat; LS, least square; Q4W, every 4 weeks; SE, standard error
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Patient-reported measures: change in POEM total score from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in reducing the POEM total score compared with baseline at Week 16 in the full population of ARCADIA-CYCLO (LS mean difference [redacted]; 95% CI [redacted]; [redacted]) (Table 31).[129]

Table 31. Change in POEM score from baseline at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W
Total participants, n	[redacted]	[redacted]
% change from baseline in POEM, LS mean (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]
p- value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; ITT, ITT, intention-to-treat; LS, least squares; POEM, patient-oriented eczema measure; Q4W, every 4 weeks
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

Quality of life: change in EQ-5D VAS from baseline

Nemolizumab (with BSC) was more effective than placebo (with BSC) in increasing the EQ-5D VAS score compared with baseline at Week 16 in the full population of ARCADIA-CYCLO (LS mean difference [redacted]; 95% CI [redacted]; [redacted] (Table 32).[129]

Table 32. Change in EQ-5D score from baseline at Week 16 – ARCADIA-CYCLO

	Treatment period (Week 16)	
	ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]
Change in EQ-5D VAS from baseline, LS mean (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
LS mean difference (95% CI)	[redacted]	[redacted]
p- value	[redacted]	[redacted]

Abbreviations: CI, confidence intervals; EQ-5D, EuroQoL 5-Dimension; ITT, ITT, intention-to-treat; LS, least squares Q4W, every 4 weeks; SE, standard error
Source: Galderma data on file ARCADIA-CYCLO CSR[129]

B.2.7. Subgroup analysis

ARCADIA 1 & 2 included pre-planned subgroup analysis of the co-primary endpoints to estimate the treatment difference, corresponding two-sided 95% CI and strata-adjusted p-values for between-group comparisons.[142] Due to the limited population in each subgroup, a pooled analysis of ARCADIA 1 & 2 was conducted when considering subgroups. This increased the number of participants considered, making the analysis more robust and the conclusions of the analysis more meaningful. The pre-planned subgroups relevant to the submission include:

- Race (White, Black, or African American, Asian)
- Previous use of any systemic therapy for AD (yes, no)
- Previous use of any immunosuppressive or immunomodulatory drugs for AD (yes, no); previous use of dupilumab for AD (yes, no)
- Previous use of ciclosporin for AD (yes, no)

The proportion of participants in the full population with EASI-75 (a ≥ 75% improvement from baseline) at Week 16 by subgroup in ARCADIA 1 & 2 is shown in Figure 12. The results show that nemolizumab (with BSC) resulted in a statistically significant number of participants with EASI-75 regardless of previous use of any systemic therapy, immunosuppressive or immunomodulatory drug, and ciclosporin (i.e., analysis for first- and second-line patients separately). Due to the small number of participants with available data in the Black or African-American, Asian, and other subgroups for race, these results are difficult to interpret any meaningful conclusions.

Similar results were seen in the subgroups analyses considering the proportion of participants with IGA success (IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) at Week 16 in ARCADIA 1 & 2 (Figure 13).

Figure 12. Forest plot of proportion of patients with an EASI-75 success at Week 16 – initial treatment period (ITT population)

Abbreviations: CI, confidence intervals; EASI, eczema area and severity index; ITT, intent-to-treat; NE, not estimated; N, number of participants in the population; n, number of participants

Note: Percentages (%) are based on number of participants in each treatment group. Baseline value is the last valid value prior to first injection of study treatment of initial period. If a subject received any rescue therapy, the data after receipt of rescue therapy is considered treatment failure. Participants with missing result at a visit is considered non-responders for that visit. Strata adjusted p-values are from Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization stratification variables (IGA severity [3 = moderate, 4 = severe] and PP NRS ≥ 7, < 7] for full population

Source: Galderma data on file Nemolizumab Integrated ARCADIA 1 & 2 Summary of Efficacy[142]

Figure 13. Forest plot of proportion of patients with an IGA success at Week 16 – initial treatment period (ITT population)

Abbreviations: CI, confidence intervals; IGA, Investigator's Global Assessment; ITT, intent-to-treat; NE, not estimated; N, number of participants in the population; n, number of participants with available data; PP NRS, Peak Pruritus Numeric Rating Scale

Note: Percentages (%) are based on number of participants in each treatment group. Baseline value is the last valid value prior to first injection of study treatment of initial period. If a subject received any rescue therapy, the data after receipt of rescue therapy is considered treatment failure. Participants with missing result at a visit is considered non-responders for that visit. Strata adjusted p-values are from Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization stratification variables (IGA severity [3 = moderate, 4 = severe] and PP NRS ≥ 7, < 7] for full population

Source: Galderma data on file Nemolizumab Integrated ARCADIA 1 & 2 Summary of Efficacy[142]

B.2.8. Meta-analysis

A meta-analysis was not conducted for this submission. Indirect Treatment Comparison (ITC) was performed; see Section B.2.9 for details.

B.2.9. Indirect and mixed treatment comparisons

Key points

- In the adult second-line population, equal efficacy at week 16 based on EASI-75 is assumed between nemolizumab 30 mg Q4W and baricitinib (4 mg QD), tralokinumab (300 mg Q2W), upadacitinib (15 mg QD), abrocitinib (200 mg QD), dupilumab (300 mg Q2W) and lebrikizumab (250 mg Q2W), as differences in treatment effect were non-statistically significant. Nemolizumab 30 mg Q4W is statistically significantly more likely to achieve EASI-75 than placebo, but statistically significantly less likely than upadacitinib 30 mg QD.
- In the adolescent first-line population, equal efficacy at week 16 based on EASI-75 is assumed between nemolizumab 30 mg Q4W and lebrikizumab (250 mg Q2W), upadacitinib (15 mg QD) and abrocitinib (200 mg QD and 100 mg QD) and placebo, as differences in treatment effect were non-statistically significant. No data was available for comparators in second-line adolescent patients, limiting the analysis to first-line adolescents.

The key methodological considerations and results of the indirect treatment comparison (ITC) and supporting network meta-analyses (NMA) are shown below. Full methodological details are given in Appendix M to this submission. Note, the ITC was conducted from a global perspective and included populations and comparators outside of those considered in the decision problem. Only information relevant to the current submission and scope are included below.

B.2.9.1. Network meta-analysis

There are no randomised controlled trials (RCT) that provide a head-to-head comparison of nemolizumab with other active treatments for moderate-to-severe AD. Network meta-analyses (NMAs) can be used to estimate the relative efficacy of

treatments that have not been directly compared in head-to-head trials. The NMAs described below were based on evidence identified in a SLR of published evidence from RCT regarding the clinical efficacy and safety of nemolizumab, dupilumab, tralokinumab, lebrikizumab and JAK inhibitors at Week 16 for moderate-to-severe AD. Full details of the methods employed to identify and select relevant clinical evidence are given in Appendix D.

A total of 158 records reporting on 26 unique clinical trials (19 phase 3 trials, five phase 2 trials, and one phase 4 study; all were double-blind, parallel group studies) met the eligibility criteria and were included in the SLR. The remaining study was a crossover trial in which blinding of treatment assignment appeared to have been broken. None of the identified evidence directly compared nemolizumab to an active comparator.

The evidence collected was reviewed in a feasibility assessment (FA) to evaluate their suitability for inclusion in an NMA. Although 26 clinical trials were identified by SLR, additional inclusion criteria were applied to reflect the setting of interest (UK) and the scope of the current submission, of which 19 are relevant to the current submission (Table 33).

Table 33. Summary of the trials used to carry out ITC

Reference of trial	Phase	Intervention	Comparator
ARCADIA 1[127]	3	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
ARCADIA 2[128]	3	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
ARCADIA-CYCLO[129]	3b	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
AD Up[143]	3	Upadacitinib + TCS/TCI	Placebo + TCS/TCI
ADhere[144]	3	Lebrikizumab + TCS/TCI	Placebo + TCS/TCI
ADhere-J[145]	3	Lebrikizumab + TCS/TCI	Placebo + TCS/TCI
ADvantage[146]	3	Lebrikizumab + TCS	Placebo + TCS
BREEZE AD-4[147]	3	Baricitinib + TCS	Placebo + TCS
BREEZE AD-7[148]	3	Baricitinib + TCS	Placebo + TCS
DUPISTAD[149]	4	Dupilumab + TCS	Placebo + TCS

Reference of trial	Phase	Intervention	Comparator
ARCADIA 1[127]	3	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
ECZTRA 3[31]	3	Tralokinumab + TCS	Placebo + TCS
ECZTRA 7[150]	3	Tralokinumab + TCS	Placebo + TCS
ECZTRA 8[151]	3	Tralokinumab + TCS/TCI	Placebo + TCS/TCI
JADE COMPARE[152]	3	Dupilumab + TCS/TCI Abrocitinib + TCS/TCI	Placebo + TCS/TCI
JADE DARE[153]	3	Abrocitinib + TCS/TCI	Dupilumab + TCS/TCI
JADE TEEN[154]	3	Abrocitinib + TCS/TCI	Placebo + TCS/TCI
LIBERTY AD CAFÉ[155]	3	Dupilumab + TCS/TCI	Placebo + TCS/TCI
LIBERTY AD CHRONOS[30]	3	Dupilumab + TCS/TCI	Placebo + TCS/TCI
Rising UP[156]	3	Upadacitinib + TCS/TCI	Placebo + TCS/TCI

Abbreviations: RCT, randomised controlled trial; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

The FA considered both representation of the evidence network for comparison of nemolizumab to key comparators, and the heterogeneity of trial designs. The trials included in the FA were considered broadly similar in terms of study design, patient characteristics, treatment regimens and outcome measures. For some comparators, there were no purely adult second-line population data available; therefore despite heterogeneity, a mixed first-line/second-line adult network was used to allow comparison to all relevant comparator treatments. Data for an adolescent population who had previously failed ciclosporin were not available for any comparators, hence the analysis was restricted to a first-line, ciclosporin-naïve adolescent population.

An NMA was then undertaken to evaluate the comparative efficacy of nemolizumab versus comparator systemic therapies for the treatment of moderate-to-severe AD in:

- Adults (≥ 18 years), second-line (ciclosporin-experienced)
- Adolescents (12–17 years), first-line (ciclosporin-naïve)

Outcomes of interest were EASI-50, EASI-75, EASI-90, PP-NRS, IGA, DLQI, TEAEs, DAEs, and a composite of EASI-50 and DLQI, all at Week 16 (the timepoint of the primary endpoints in ARCADIA 1 & 2).

Full details of the methods employed to assess study heterogeneity, derive evidence networks, the use of fixed effects and random effects models and the assessment of fit are given in the full ITC report, Appendix M.

B.2.9.1.1. Results

Based on the SLR, 26 RCT underwent FA for inclusion in the NMA, for the EASI-75 and composite EASI-50 + DQLI endpoints. One trial was excluded as it did not include a comparator used in the settings of interest, and three trials were excluded as they did not report relevant outcomes. Nineteen trials were included in NMAs relevant to the current decision problem. Generally, heterogeneity across the studies and networks was deemed to be either low or 'some heterogeneity but assumed comparable.' In instances where it was higher, data was excluded, and where appropriate the impact explored in sensitivity analysis.

Based on the results of the SLR and FA, for EASI 75 overall connected networks (included in Appendix M) were formed allowing the comparison of nemolizumab with the comparator treatments abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab, and upadacitinib via placebo in second-line adults, and with abrocitinib, lebrikizumab and upadacitinib via placebo in first-line adolescents. Networks for each relevant outcome per population are presented in the respective results sections below and in Appendix M.

For the composite EASI-50 + DQLI endpoint, overall connected networks were formed allowing the comparison of nemolizumab with just baricitinib, dupilumab and lebrikizumab via placebo in adults second-line, and no comparator data was available for adolescents. Therefore, based on the limited network for the composite EASI-50 + DLQI, EASI-75 was considered the most appropriate endpoint for the submission.

Key results from the NMA used in economic modelling supporting this submission are given below. Full results of NMA are given in Appendix M.

B.2.9.1.2. Second-line Adults

For EASI-75 responders at Week 16 in an adult second-line population, a network of eleven phase 3 trials allowed comparison of nemolizumab with abrocitinib, baricitinib,

dupilumab, lebrikizumab, tralokinumab, and upadacitinib.[127-129,143,144,146-148,150,153,155]

No data was available for abrocitinib 100 mg QD in this population.

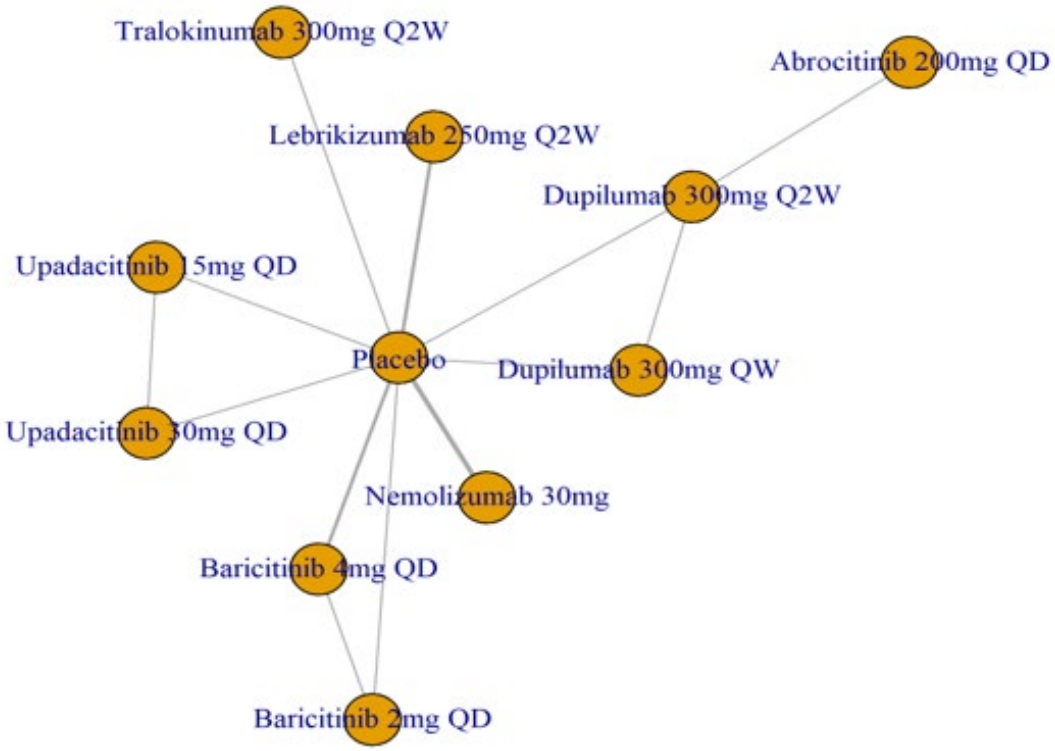

Figure 14. Network geometry for EASI-75 at Week 16 in adult second-line population

Abbreviations: QD, once daily; Q2W, once every 2 weeks

With respect to the likelihood of achieving EASI-75, nemolizumab 30 mg was associated with:

- statistically significantly higher odds than placebo: OR [95% CrI]: [redacted]
- statistically significantly lower odds than upadacitinib (30 mg QD): OR [95% CrI]: [redacted]
- non-statistically different differences compared with baricitinib (4 mg QD), tralokinumab (300 mg Q2W), upadacitinib (15 mg QD), abrocitinib (200 mg QD), dupilumab (300 mg Q2W), lebrikizumab (250 mg Q2W)

Point estimate results for the second-line adult population results are shown in Table 34.

Table 34. Point estimates of relative effects of comparators versus nemolizumab for EASI-75 responders at Week 16 in adult second-line population for random effects model with informative priors

Treatment	OR (95% CrI)	Favours nemolizumab or comparator	Statistically significant
Abrocitinib 200 mg QD	[redacted]	Comparator	Not statistically significant
Baricitinib 4 mg QD	[redacted]	Comparator	Not statistically significant
Dupilumab 300 mg Q2W	[redacted]	Comparator	Not statistically significant
Lebrikizumab 250 mg Q2W	[redacted]	Comparator	Not statistically significant
Tralokinumab 300 mg Q2W	[redacted]	Nemolizumab	Not statistically significant
Upadacitinib 15 mg QD	[redacted]	Comparator	Not statistically significant
Upadacitinib 30 mg QD	[redacted]	Comparator	Statistically significant
Placebo	[redacted]	Nemolizumab	Statistically significant

Abbreviations: CrI, credible interval; OR, odds ratio, QD, once daily; Q2W, every 2 weeks

Where non statistically significant differences were observed, an OR of 1 was allocated to each comparator in the economic analyses. Alternative scenarios are explored where specific point estimates are applied for each comparator, even where non-statistically significant differences were observed in ITC (Section B.3.10.3).

B.2.9.1.3. Adolescents

Data for an adolescent population who had previously failed ciclosporin were not available for any comparators, hence restricting analysis to a first-line, ciclosporin-naïve adolescent population. For EASI-75 responders at Week 16 in an adolescent first-line population, a network of six phase 3 trials allowed comparison of nemolizumab with abrocitinib, lebrikizumab, and upadacitinib.[127-129,143,144,154,156] Results for upadacitinib 30mg are not presented as the recommended dose for upadacitinib in adolescents weighing at least 40 kg is 15 mg.[103]

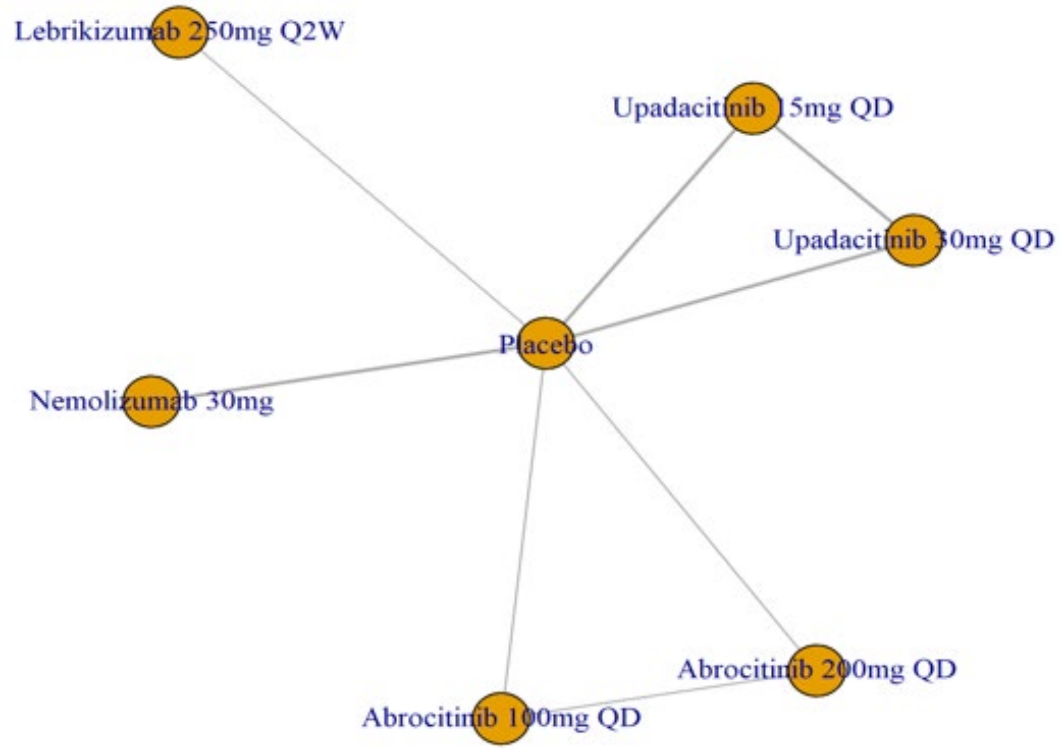

Figure 15. Network geometry for EASI-75 at Week 16 for adolescent first-line population

Abbreviations: QD, once daily; Q2W, once every 2 weeks

With respect to the likelihood of achieving EASI-75, nemolizumab 30 mg was associated with:

- non-statistically different differences compared with placebo, lebrikizumab (250 mg Q2W), upadacitinib (15 mg QD) and abrocitinib (200 mg QD and 100 mg QD).

Point estimate results for the second-line adult population results are shown in Table 35.

Table 35. Point estimates of relative effects of comparators versus nemolizumab for EASI-75 responders at Week 16 in adolescent 1L population for random effects model with informative priors

Treatment	OR (95% CrI)	Favours nemolizumab or comparator	Statistically significant
Abrocitinib 100 mg QD	[redacted]	Comparator	Not statistically significant
Abrocitinib 200 mg QD	[redacted]	Comparator	Not statistically significant
Lebrikizumab 250 mg Q2W	[redacted]	Comparator	Not statistically significant
Upadacitinib 15 mg QD	[redacted]	Comparator	Not statistically significant
Placebo	[redacted]	Nemolizumab	Not statistically significant

Abbreviations: CrI, credible interval; OR, odds ratio, QD, once daily; Q2W, every 2 weeks

Where non statistically significant differences were observed, an OR of 1 was allocated to each comparator in the economic model. Alternative scenarios are explored where specific point estimates are applied for each comparator, even where non-statistically significant differences were observed in ITC (Section B.3.10.3).

B.2.9.1.4. Conclusions

Where no statistically significant differences between treatments were found based on EASI-75 at week 16, a value of 1 was allocated as an odds ratio, assuming equal efficacy. This occurred in the adult second-line population, where equal efficacy was assumed between nemolizumab (30 mg Q4W) and baricitinib (4 mg QD), tralokinumab (300 mg Q2W), upadacitinib (15 mg QD), abrocitinib (200 mg QD), dupilumab (300 mg Q2W) and lebrikizumab (250 mg Q2W), and in the adolescent first-line population, where equal efficacy was assumed between nemolizumab (30 mg Q4W) and lebrikizumab (250 mg Q2W), upadacitinib (15 mg QD) and abrocitinib (200 mg QD and 100 mg QD) and placebo. Statistically significant results were found favouring upadacitinib (30 mg QD) for achieving EASI-75 compared with nemolizumab in the adult second-line populations. Statistically significant results favouring nemolizumab were found for odds of achieving EASI-75 compared with placebo in the adult second-line populations.

B.2.9.1.5. Uncertainties in the indirect and mixed treatment comparisons

Sensitivity analyses were primarily focused on exploring the inclusion/exclusion of certain trials/trial programmes e.g., the inclusion of studies of interest that were excluded in the base-case; the exclusion of studies that were included but which were recommended as focus of sensitivity analyses; the exploration of the impact of informed vs. uninformed priors. A summary of sensitivity analyses conducted to explore uncertainties is given as Table 36. Results of sensitivity analyses are included in Appendix M.

Table 36. Sensitivity analyses performed as part of ITC

Sensitivity analysis	Rationale
Second-line treatment based only on ARCADIA-CYCLO data	ARCADIA-CYCLO enrolled only second-line patients. ARCADIA 1 & 2 enrolled first-line and second-line patients, necessitating data manipulation for comparison; exclusive use of ARCADIA-CYCLO data explores uncertainties in how ARCADIA 1 & 2 data was handled.
Placebo adjustment	NMA placebo regression adjustment models at least two trials comparing the same comparator with placebo to enable the assessment of incidence rates in the placebo arm and to adjust for this, then assess the impact on NMA estimates.
Impact of missing data	Patients who discontinued treatment or started rescue therapy in ARCADIA 1 & 2 were set to 'missing' in the primary analysis and their data imputed using multiple imputation. The impact of this was tested using the observed case approach, in which no data were imputed for these patients; data post-rescue were analysed as observed by ignoring the use of rescue medication.
Impact of NMA model choice	Previous NMAs in AD modelled EASI-50, EASI-75 and EASI-90 altogether in an NMA ordinal model.[157] Sensitivity analysis exploring the type of model tests the robustness of estimates.

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; ITC, indirect treatment comparison; NMA, network meta-analysis

B.2.10. Adverse reactions

Key points

- Nemolizumab (with BSC) was generally well tolerated and had a safety profile comparable to that of placebo in the ARCADIA 1 & 2 clinical trials, including with respect to incidence of conjunctivitis.
- In ARCADIA-CYCLO, the overall safety profile of nemolizumab (with BSC) was favourable and consistent with that observed in ARCADIA 1 & 2. This supports nemolizumab's safe use in participants with moderate-to-severe AD who were not adequately controlled with or who were not advised to use oral ciclosporin for medical reasons.
- Across the phase 3 trials, the majority of TEAEs were of mild or moderate severity; no patients died at any point in these trials.
- TEAEs were similar between arms in the initial periods of ARCADIA 1 & 2.
- In ARCADIA-CYCLO, the incidence of TEAEs and study drug-related TEAEs was similar between arms, with no particular clustering pattern suggestive of a new safety finding observed.
- In a pooled analysis of ARCADIA 1 & 2 maintenance periods, TEAEs observed were similar regardless of the regimen being followed (nemolizumab 30 mg Q4W, nemolizumab 30 mg Q8W, or placebo).
- In the interim data cut (Week 56) of the LTE study, [redacted] of participants treated with nemolizumab (with BSC) experienced at least one TEAE, the majority of which were mild or moderate in severity. Study drug-related TEAEs were experienced by [redacted] of participants, and treatment emergent SAEs were experienced by [redacted] of participants. The most common TEAEs experienced were similar to those seen in ARCADIA 1 & 2.

B.2.10.1. ARCADIA 1 & 2

B.2.10.1.1. Initial treatment period – baseline through to Week 16

In ARCADIA 1 & 2 nemolizumab (with BSC) was shown to be well tolerated with a comparable safety profile to that of placebo (with BSC). The majority of TEAEs in either treatment group were mild or moderate in severity, with no concerning AEs

being observed, and those that were recorded were both tolerable and easily managed.[127,128]

In ARCADIA 1, a total of 306 (49.7%) nemolizumab and 146 (45.5%) placebo participants experienced at least one TEAE during the initial treatment period (Table 37). Study drug-related TEAEs were experienced by 123 (20.0%) nemolizumab and 42 (13.1%) placebo participants. Study drug-related TEAEs were predominantly mild in both treatment arms (nemolizumab: [redacted]; placebo: [redacted]). In ARCADIA 2, a total of 215 (41.4%) nemolizumab and 117 (44.5%) placebo participants experienced at least one TEAE during the initial treatment period (Table 37). Study drug-related TEAEs were experienced by 67 (12.9%) nemolizumab and 29 (11.0%) placebo participants. Study drug related TEAEs were predominantly mild or moderate in both treatment arms (nemolizumab: mild [redacted] and moderate [redacted]; placebo: mild [redacted] and moderate [redacted]).

Serious adverse events (SAEs) were experienced by 6 (1.0%) nemolizumab and 4 (1.2%) placebo participants in ARCADIA 1, with none considered study drug-related (Table 37). SAEs were experienced by 13 (2.5%) nemolizumab and 3 (1.1%) placebo participants in ARCADIA 2 (Table 37). SAEs considered study drug-related were experienced by 5 (1.0%) participants in the nemolizumab arm (Table 37).

In ARCADIA 1, TEAEs leading to study drug withdrawal were experienced by 11 (1.8%) nemolizumab and 13 (4.0%) placebo participants, and 9 (1.5%) nemolizumab and 3 (0.9%) placebo participants experienced a TEAE leading to study discontinuation. Treatment-emergent adverse events of special interest (AESI) were experienced by 56 (9.1%) nemolizumab participants and 20 (6.2%) placebo participants. No TEAEs leading to death were recorded during the initial treatment period. In ARCADIA 2, TEAEs leading to study drug withdrawal were experienced by 18 (3.5%) nemolizumab and 3 (1.1%) placebo participants, and 15 (2.9%) nemolizumab and 3 (1.1%) placebo participants experienced a TEAE leading to study discontinuation (Table 37). Treatment-emergent AESI were experienced by 47 (9.1%) nemolizumab participants and 21 (8.0%) placebo participants (Table 37). No TEAEs leading to death were recorded during the initial treatment period.

A summary of TEAEs experienced by ≥ 1.0% of trial participants in ARCADIA 1 & 2 is provided in Table 38. The most common TEAEs (reported by ≥ 5.0% of participants in either group) were dermatitis atopic (12.2% nemolizumab, 10.6% placebo) and asthma (5.4% nemolizumab, 4.0% placebo) in ARCADIA 1, dermatitis atopic (7.1% nemolizumab, 5.7% placebo) in ARCADIA 2. In ARCADIA 1 & 2, the incidence of conjunctivitis in the initial treatment period was low and comparable across both treatment groups (ARCADIA 1: nemolizumab: [redacted]; placebo: [redacted]; ARCADIA 2: nemolizumab: [redacted]; placebo: [redacted]).

Table 37. Summary of TEAEs in the initial treatment period

Participants with at least 1:	ARCADIA 1		ARCADIA 2	
	Safety population		Safety population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total participants, n	616	321	519	263
TEAE, n (%)	306 (49.7)	146 (45.5)	215 (41.4)	117 (44.5)
TEAE by maximum severity				
Mild, n (%)	168 (27.3)	89 (27.7)	113 (21.8)	66 (25.1)
Moderate, n (%)	120 (19.5)	49 (15.3)	81 (15.6)	44 (16.7)
Severe, n (%)	18 (2.9)	8 (2.5)	21 (4.0)	7 (2.7)
Study drug-related TEAE†, n (%)	123 (20.0)	42 (13.1)	67 (12.9)	29 (11.0)
Study drug-related TEAE by maximum severity†‡				
Mild, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Severe, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to protocol procedure (including topical background therapy), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAE, n (%)	6 (1.0)	4 (1.2)	13 (2.5)	3 (1.1)
SAE related to study drug, n (%)	0	0	5 (1.0)	0
Severe TEAE, n (%)	18 (2.9)	8 (2.5)	21 (4.0)	7 (2.7)
TEAE leading to study drug interruption, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to study drug withdrawal, n (%)	11 (1.8)	13 (4.0)	18 (3.5)	3 (1.1)
TEAE leading to study discontinuation, n (%)	9 (1.5)	3 (0.9)	15 (2.9)	3 (1.1)
Treatment-emergent AESIs by categories, n (%)	56 (9.1)	20 (6.2)	47 (9.1)	21 (8.0)
Injection-related reactions, n (%)	1 (0.2)	0	0	0
Newly diagnosed asthma or worsening of asthma, n (%)	32 (5.2)	11 (3.4)	15 (2.9)	8 (3.0)

Infections, n (%)	20 (3.2)	10 (3.1)	20 (3.9)	12 (4.6)
Peripheral oedema: limbs, bilateral; facial oedema, n (%)	7 (1.1)	1 (0.3)	12 (2.3)	1 (0.4)
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN), n (%)	0	0	0	0
TEAE leading to death, n (%)	0	0	0	0
TEAE related to study drug leading to death, n (%)	0	0	0	0

† Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).
‡ If participants experienced multiple events, the participants were counted once at the event with maximum severity
Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0. Where between trial differences result in no data being available, this is shown as 'not reported' (NR)
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of participants in the treatment group; n, number of participants with available data; NR, not recorded Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal
Source: Galderma data on file ARCADIA 1 & 2 CSRs[127,128]

Table 38. TEAEs experienced by ≥ 1.0% of participants in the initial treatment period by system organ class and preferred term

	ARCADIA 1		**ARCADIA 2**	
	Safety population		**Safety population**	
	Nemolizumab 30 mg Q4W	**Placebo Q4W**	**Nemolizumab 30 mg Q4W**	**Placebo Q4W**
Total, n	[redacted]	[redacted]	[redacted]	[redacted]
Participants with at least 1 TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Vaccination site pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Infections and Infestations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Covid-19, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Folliculitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Herpes simplex, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Peak expiratory flow rate decreased, n (%)	[redacted]		[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Back pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Athralgia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Headache, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cough, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis allergic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pruritis , n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia areata, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
Abbreviations: N, number of participants in the treatment group; n, number of participants who experienced the events; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA 1 & 2 CSRs[127,128]

B.2.10.1.2. Pooled maintenance period – through to Week 48

The percentage of participants who experienced at least one TEAE was similar across the treatment groups (range: [redacted] to [redacted]) (Table 39). Study drug-related TEAEs were experienced by [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]) participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W and nemolizumab Q4W to

placebo groups, respectively. Treatment emergent SAEs were experienced by [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]) participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W and nemolizumab Q4W to placebo groups, respectively (Table 39). SAEs considered study drug-related were experienced by [redacted] ([redacted]) participant in both nemolizumab Q4W to Q4W and nemolizumab Q4W to placebo groups (Table 39). Treatment-emergent AEs leading to study drug withdrawal were experienced by [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]) participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W and nemolizumab Q4W to placebo groups, respectively (Table 39). Adverse events of special interest were experienced by [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]) participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W, and nemolizumab Q4W to placebo groups, respectively. Treatment-emergent AEs leading to study discontinuation were experienced by [redacted] ([redacted]), [redacted] ([redacted]), and [redacted] ([redacted]) participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W,and nemolizumab Q4W to placebo groups, respectively (Table 39). No subject died during the Maintenance Period.

A summary of TEAEs experienced by ≥ 2.0% of trial participants is provided in Table 40. The most common TEAEs (reported by ≥ 5.0% of participants in any group) across treatment groups were COVID-19 (range: [redacted] to [redacted]), dermatitis atopic (range: [redacted] to [redacted]), nasopharyngitis (range: [redacted] to [redacted]), and upper respiratory tract infection (range: [redacted] to [redacted]). Conjunctivitis was not common across treatment groups (range: [redacted] to [redacted]).

Table 39. Summary of TEAEs in maintenance period

Participants with at least 1:	Safety population		
	Nemolizumab 30 mg Q4W to Q4W	Nemolizumab 30 mg Q4W to Q8W	Nemolizumab 30 mg Q4W to placebo
Total, n	[redacted]	[redacted]	[redacted]
TEAE, n (%)	[redacted]	[redacted]	[redacted]
Study drug-related TEAE†, n (%)	[redacted]	[redacted]	[redacted]
TEAE related to protocol procedure (including topical background therapy), n (%)	[redacted]	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]	[redacted]
SAE related to study drug, n (%)	[redacted]	[redacted]	[redacted]
Severe TEAE, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to temporary discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]

TEAE leading to permanent discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to permanent discontinuation from study discontinuation, n (%)	[redacted]	[redacted]	[redacted]
Treatment-emergent AESIs by categories, n (%)	[redacted]	[redacted]	[redacted]
Injection-related reactions, n (%)	[redacted]	[redacted]	[redacted]
Newly diagnosed asthma or worsening of asthma, n (%)	[redacted]	[redacted]	[redacted]
Infections, n (%)	[redacted]	[redacted]	[redacted]
Peripheral oedema: limbs, bilateral; facial oedema, n (%)	[redacted]	[redacted]	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN), n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to death, n (%)	[redacted]	[redacted]	[redacted]
TEAE related to study drug leading to death, n (%)	[redacted]	[redacted]	[redacted]

† Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).
Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of participants in the treatment group; n, number of participants who experienced the events; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal
Source: Galderma data on file ARCADIA 1 & 2 pooled analysis[141]

Table 40. TEAEs experienced by ≥ 1.0% of participants in the maintenance period by system organ class and preferred term

	Safety population		
	Nemolizumab 30 mg Q4W to Q4W	**Nemolizumab 30 mg Q4W to Q8W**	**Nemolizumab 30 mg Q4W to placebo**
Total, n	[redacted]	[redacted]	[redacted]
Participants with at least 1 TEAE, n (%)	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorder, n (%)	[redacted]	[redacted]	[redacted]
Neutropenia, n (%)	[redacted]	[redacted]	[redacted]
Eye Disorders, n (%)	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic, n (%)	[redacted]	[redacted]	[redacted]
Dry eye, n (%)	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders, n (%)	[redacted]	[redacted]	[redacted]
Abdominal pain upper, n (%)	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]
Nausea, n (%)	[redacted]	[redacted]	[redacted]
Angular cheilitis, n (%)	[redacted]	[redacted]	[redacted]
Duodenal ulcer, n (%)	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease, n (%)	[redacted]	[redacted]	[redacted]
Vomiting, n (%)	[redacted]	[redacted]	[redacted]

Dyspepsia, n (%)	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions, n (%)	[redacted]	[redacted]	[redacted]
Pyrexia, n (%)	[redacted]	[redacted]	[redacted]
Vaccination site pain, n (%)	[redacted]	[redacted]	[redacted]
Infections and Infestations, n (%)	[redacted]	[redacted]	[redacted]
Nasopharyngitis, n (%)	[redacted]	[redacted]	[redacted]
COVID-19, n (%)	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]
Gastroenteritis, n (%)	[redacted]	[redacted]	[redacted]
Herpes dermatitis, n (%)	[redacted]	[redacted]	[redacted]
Oral herpes, n (%)	[redacted]	[redacted]	[redacted]
Pharyngitis, n (%)	[redacted]	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]	[redacted]
Asymptomatic COVID-19, n (%)	[redacted]	[redacted]	[redacted]
Influenza, n (%)	[redacted]	[redacted]	[redacted]
Tonsilitis, n (%)	[redacted]	[redacted]	[redacted]
Tooth abscess, n (%)	[redacted]	[redacted]	[redacted]
Folliculitis, n (%)	[redacted]	[redacted]	[redacted]
Gastrointestinal infection, n (%)	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]
Cellulitis, n (%)	[redacted]	[redacted]	[redacted]
Rhinitis, n (%)	[redacted]	[redacted]	[redacted]
Sinusitis, n (%)	[redacted]	[redacted]	[redacted]
Sinusitis bacterial, n (%)	[redacted]	[redacted]	[redacted]
Injury, Poisoning and Procedural Complications, n (%)	[redacted]	[redacted]	[redacted]
Ligament sprain, n (%)	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]	[redacted]	[redacted]
Peak expiratory flow rate decreased, n (%)	[redacted]	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Disorders, n (%)	[redacted]	[redacted]	[redacted]
Neck pain, n (%)	[redacted]	[redacted]	[redacted]
Arthralgia, n (%)	[redacted]	[redacted]	[redacted]
Arthritis, n (%)	[redacted]	[redacted]	[redacted]
Nervous System Disorders, n (%)	[redacted]	[redacted]	[redacted]
Headache, n (%)	[redacted]	[redacted]	[redacted]
Psychiatric Disorders, n (%)	[redacted]	[redacted]	[redacted]
Depression, n (%)	[redacted]	[redacted]	[redacted]
Reproductive System and Breast Disorders, n (%)	[redacted]	[redacted]	[redacted]
Pelvic pain, n (%)	[redacted]	[redacted]	[redacted]

Respiratory, Thoracic and Mediastinal Disorders, n (%)	[redacted]	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]	[redacted]
Dyspnoea, n (%)	[redacted]	[redacted]	[redacted]
Cough, n (%)	[redacted]	[redacted]	[redacted]
Oropharyngeal pain, n (%)	[redacted]	[redacted]	[redacted]
Wheezing, n (%)	[redacted]	[redacted]	[redacted]
Rhinitis allergic, n (%)	[redacted]	[redacted]	[redacted]
Rhinorrhoea, n (%)	[redacted]	[redacted]	[redacted]
Skin and Subcutaneous Tissue Disorders, n (%)	[redacted]	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]	[redacted]
Urticaria, n (%)	[redacted]	[redacted]	[redacted]
Acne, n (%)	[redacted]	[redacted]	[redacted]
Pruritus, n (%)	[redacted]	[redacted]	[redacted]
Vascular Disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
Abbreviations: N, number of participants in the treatment group; n, number of participants who experienced the events; PT, Preferred Term; Q4W, every 4 weeks; SOC, System Organ Class; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA 1 & 2 pooled analysis[141]

B.2.10.2. ARCADIA-CYCLO

The safety profile observed in ARCADIA-CYCLO aligns with ARCADIA 1 & 2. In ARCADIA-CYCLO nemolizumab (with BSC) was shown to be well tolerated with a comparable safety profile to that of placebo (with BSC). The majority of TEAEs in either treatment group were considered mild or moderate in severity, with no concerning AEs being observed, and those that were recorded were both tolerable and easily managed.[129]

A total of [redacted] ([redacted]) nemolizumab participants and [redacted] ([redacted]) placebo participants experienced at least one TEAE during the treatment period (Table 41). Study drug-related TEAEs were experienced by [redacted] ([redacted]) nemolizumab participants and 15 ([redacted]) placebo participants.

SAEs were experienced by [redacted] ([redacted]) nemolizumab participants and [redacted] ([redacted]) placebo participants (Table 41). SAEs considered study drug-related were experienced by [redacted] ([redacted]) participant in each nemolizumab and placebo arms (Table 41).

TEAEs leading to study drug withdrawal were experienced by [redacted] ([redacted]) nemolizumab and placebo participants each (Table 41); [redacted] ([redacted]) nemolizumab participants and [redacted] ([redacted]) placebo participants experienced a TEAE leading to study discontinuation.

Adverse events of special interest (AESI) were experienced by [redacted] ([redacted]) nemolizumab participants and [redacted] ([redacted]) placebo participants (Table 41). No TEAEs leading to death were recorded during the initial treatment period.

A summary of TEAEs experienced by ≥ 2.0% of trial participants is provided in Table 42. The most common TEAEs (reported by ≥ 5.0% of participants in either group) were nasopharyngitis ([redacted] nemolizumab, [redacted] placebo), dermatitis atopic ([redacted] nemolizumab, [redacted] placebo), and COVID-19 ([redacted] nemolizumab, [redacted] placebo).

Table 41. Summary of TEAEs in the treatment period

Participants with at least 1:	Safety set	
	Nemolizumab 30mg Q4W	Placebo 30mg Q4W
Total participants, n	[redacted]	[redacted]
TEAE, n (%)	[redacted]	[redacted]
TEAE by maximum severity†		
Mild, n (%)	[redacted]	[redacted]
Moderate, n (%)	[redacted]	[redacted]
Severe, n (%)	[redacted]	[redacted]
Study drug-related TEAE‡, n (%)	[redacted]	[redacted]
TEAE related to protocol procedure, n (%)	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]
SAE related to study drug, n (%)	[redacted]	[redacted]
TEAE leading to study drug withdrawal, n (%)	[redacted]	[redacted]
TEAE leading to study discontinuation, n (%)	[redacted]	[redacted]
AESI, n (%)	[redacted]	[redacted]
TEAE leading to death, n (%)	[redacted]	[redacted]
TEAE related to study drug leading to death, n (%)	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
† If the severity of an AE was missing, the AE was reported as 'Severe'.
‡ Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).
Abbreviations: AE, adverse event; AESI, adverse event of special interest; N, number of participants in the population; n, number of participants who experienced the event; SAE, serious adverse event; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA-CYCLO CSR[133]

Table 42. TEAEs experienced by ≥ 2.0% of participants in either group by system organ class and preferred term

	Safety set	
	Nemolizumab 30mg Q4W	Placebo 30mg Q4W
Total participants, n	[redacted]	[redacted]
Participants with at least 1 TEAE, n (%)	[redacted]	[redacted]
Infections and infestations, n (%)	[redacted]	[redacted]
Bronchitis, n (%)	[redacted]	[redacted]
COVID-19, n (%)	[redacted]	[redacted]
Nasopharyngitis, n (%)	[redacted]	[redacted]
Rhinitis, n (%)	[redacted]	[redacted]
Tonsillitis, n (%)	[redacted]	[redacted]
Upper respiratory tract infection, n (%)	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]	[redacted]
Peak expiratory flow rate decreased, n (%)	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]
Back pain, n (%)	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
Abbreviations: N, number of participants in the treatment group; n, number of participants who experienced the events; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event
Source: Galderma data on file ARCADIA-CYCLO CSR[133]

B.2.10.3. LTE study

A total of [redacted] ([redacted]) participants treated with nemolizumab (with BSC) experienced at least one TEAE during the treatment period (Table 43). The majority of TEAEs were considered mild or moderate in severity. Study drug-related TEAEs were experienced by [redacted] ([redacted]) participants. Treatment-emergent SAEs were experienced by [redacted] ([redacted]) participants. Serious AEs experienced by more than one participant were dermatitis atopic ([redacted] [redacted] participants) and myocardial infarction, cholecystitis acute, COVID-19, COVID-19 pneumonia, cellulitis, syncope, and urinary retention ([redacted] [redacted] participants each). Treatment-emergent AEs leading to study drug withdrawal were experienced by [redacted] ([redacted]) participants; [redacted] ([redacted]) participants experienced a TEAE

leading to study discontinuation. Adverse events of special interest (by Investigator) were experienced by [redacted] ([redacted]) participants. No subject died during the Treatment Period.

The most common (≥ 5.0%) TEAEs in the treatment period were COVID-19 ([redacted]), dermatitis atopic ([redacted]), nasopharyngitis ([redacted]), and upper respiratory tract infection ([redacted]) Table 44).

Table 43. Summary of TEAEs in the treatment period (interim data cut Week 56)

Participants with at least 1:	Safety population
	Nemolizumab 30 mg Q4W
Total participants, n	1740
TEAE	[redacted]
TEAE by maximum severity†	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
Study drug-related TEAE	[redacted]
Study drug-related TEAE by maximum severity†	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
TEAE related to protocol procedure	[redacted]
SAE	[redacted]
SAE related to study drug	[redacted]
Severe TEAE	[redacted]
TEAE leading to study drug interruption	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to study discontinuation	[redacted]
AESIs by categories (by Investigator)	[redacted]
Injection-related reactions	[redacted]
Newly diagnosed asthma or worsening of asthma	[redacted]
Infections	[redacted]
Peripheral edema: limbs, bilateral; facial edema	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN)	[redacted]
AESIs by categories (MedDRA search)	[redacted]

Injection-related reactions	[redacted]
Newly diagnosed asthma or worsening of asthma	[redacted]
Infections	[redacted]
Peripheral edema: limbs, bilateral; facial edema	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN)	[redacted]
TEAE leading to death	[redacted]
TEAE related to study drug leading to death	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
† If participants experienced multiple events, the participants were counted once at the event with maximum severity
Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in the population; n=number of participants who experienced the events; NA, not applicable Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal
Source: Galderma data on file LTE study interim CSR[130]

Table 44. TEAEs experienced by ≥ 1.0% of participants in the treatment period (interim data cut Week 56) by system organ class and preferred term

	Safety population
	Nemolizumab 30 mg Q4W
Total, n	1740
Participants with at least 1 TEAE, n (%)	[redacted]
Eye disorders, n (%)	[redacted]
Conjunctivitis allergic, n (%)	[redacted]
Gastrointestinal disorders, n (%)	[redacted]
Diarrhoea, n (%)	[redacted]
General disorders and administrative site conditions, n (%)	[redacted]
Pyrexia, n (%)	[redacted]
Fatigue, n (%)	[redacted]
Infections and infestations, n (%)	[redacted]
COVID-19, n (%)	[redacted]
Nasopharyngitis, n (%)	[redacted]
Upper respiratory tract infection, n (%)	[redacted]
Urinary tract infection, n (%)	[redacted]
Asymptomatic COVID-19, n (%)	[redacted]
Impetigo, n (%)	[redacted]
Oral herpes, n (%)	[redacted]
Pharyngitis, n (%)	[redacted]
Rhinitis, n (%)	[redacted]
Sinusitis, n (%)	[redacted]
Bronchitis, n (%)	[redacted]
Respiratory tract infection, n (%)	[redacted]
Investigations, n (%)	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]

Peak expiratory flow rate decreased, n (%)	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]
Back pain, n (%)	[redacted]
Arthralgia, n (%)	[redacted]
Nervous system disorders, n (%)	[redacted]
Headache, n (%)	[redacted]
Respiratory, thoracic and mediastinal disorders, n (%)	[redacted]
Asthma, n (%)	[redacted]
Cough, n (%)	[redacted]
Dyspnoea, n (%)	[redacted]
Oropharyngeal pain, n (%)	[redacted]
Rhinorrhoea, n (%)	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]
Dermatitis atopic, n (%)	[redacted]
Urticaria, n (%)	[redacted]
Acne, n (%)	[redacted]
Alopecia, n (%)	[redacted]
Vascular disorders, n (%)	[redacted]
Hypertension, n (%)	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
Abbreviations: N, number of participants in the population; n, number of participants who experienced the events; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event
Source: Galderma data on file LTE study interim CSR[130]

B.2.11. Ongoing studies

B.2.11.1. LTE study

The LTE study is ongoing at the time of submission. The expected duration for each subject's participation may be up to 212 weeks, or until 26 August 2026, whichever comes first.[130]

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings from the clinical evidence

AD is a complex disease characterised by heterogeneity in clinical presentation,[38] with patients responding differently to currently available treatments.[104] AD is difficult to clinically manage, especially for patients with moderate-to-severe disease, with a critical need for additional therapeutics that are effective, safe, and address the burdensome symptoms such as itch.

In ARCADIA 1 & 2 nemolizumab (with BSC) treatment resulted in a clinically meaningful and statistically significant improvement in the co-primary endpoints for disease severity and itch in patients with moderate-to-severe AD. A greater proportion of participants treated with nemolizumab achieved IGA success and EASI-75, and an improvement in PP NRS compared with placebo at Week 16.[127,128]

Nemolizumab also demonstrated clinically meaningful and statistically significant differences in key secondary endpoints, including those addressing burdensome symptoms (refer to section B.1.3.1.5) including itch (PP NRS and SCORAD), sleep disturbance (SD NRS), and quality of life (DLQI, EQ-5D).[127,128] Furthermore, in a pooled analysis of the maintenance periods, nemolizumab at two dosing schedules (Q4W/Q8W) demonstrated continued improvement in disease severity with a greater proportion of participants with IGA success and EASI-75 compared with placebo up to Week 48.[141]

In ARCADIA-CYCLO, nemolizumab (with BSC) treatment resulted in clinically and statistically significant improvement in the co-primary endpoints for disease severity and itch comparable to ARCADIA 1 & 2, with a greater proportion of participants with EASI-75 and improvement in PP NRS at Week 16.[129] These results support the use of nemolizumab in a population with moderate-to-severe AD who were not adequately controlled with or who were not advised to use oral ciclosporin for medical reasons.

There were no new safety concerns identified during either the ARCADIA 1 & 2, ARCADIA-CYCLO or the LTE study to date; with the frequency of TEAEs being similar between treatment arms in all studies.[127-130]

B.2.12.2. Strengths and limitation of the clinical evidence base

Strengths

Evidence used to support the efficacy and safety of nemolizumab in patients with moderate-to-severe AD is provided by an extensive clinical development programme, including the phase 3 ARCADIA 1 & 2, ARCADIA-CYCLO, and the ongoing LTE study.[127-129,133] These studies are all well-designed, high quality RCTs, with appropriate sample sizes (exceeded planned enrolment), power, statistical

analysis, multiple endpoints, and length of follow-up (up to 200 weeks on treatment for participants in the LTE study), which allows for the rigorous evaluation of efficacy and safety data.

All trial participants were diagnosed with moderate or severe AD, in line with the decision problem. Furthermore, in all the RCT nemolizumab was used alongside BSC which is in line with the anticipated use of nemolizumab in UK clinical practice.[120] Furthermore, these studies include evidence for nemolizumab in patients (≥ 12 years old) with moderate-to-severe AD who are candidates for systemic therapy who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated, which aligns with the decision population. The trial participants were stratified by baseline disease severity with no upper limit, making the trials representative of the full patient population seen in clinical practice. The trial populations were predominantly European (including 16 participants in the UK) and north American which make the results generalisable to a UK population.

The clinically relevant endpoints utilised in ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study matched those stated in the decision problem and have been utilised in previous NICE submissions in moderate-to-severe AD.[1-4]

The nemolizumab clinical development programme has extensive follow-up data, with ARCADIA 1 & 2 maintenance periods spanning 48 weeks and demonstrating the long-term efficacy and safety of nemolizumab treatment in patients with moderate-to-severe AD. The length of follow-up in the trials completed to date is comparable to the trials of the comparator treatments; at the completion of the LTE study, no comparator treatment appraised by NICE for AD to date will have as long a follow-up period (up to 208 weeks).

Limitations

The studies have some limitations; however, they must be considered alongside the many strengths of the trials included in this clinical programme. The ARCADIA 1 & 2, and ARCADIA-CYCLO studies compared nemolizumab with placebo. Therefore,

there is no direct evidence versus comparator therapies included in the decision problem, such as biologics and JAK inhibitors, necessitating an ITC (section B.2.9).

The ARCADIA 1 & 2 trials included both first-line (who had not previously received at least one systemic immunosuppressive therapy) and second-line patients combined, which does not fully align with the second-line population in the decision problem. However, these trials were sufficiently powered to enable sub-population analysis for first- and second-line patients separately (section B.2.7). Additionally, the results of ARCADIA 1 & 2 are supported by those of the ARCADIA-CYCLO study, which included a purely second-line population who were not adequately controlled with or not advised to use oral ciclosporin for medical reasons. The results of ARCADIA-CYCLO are comparable with and support the results from the larger ARCADIA 1 & 2 trials.

The ARCADIA-CYCLO study included adult patients only, which does not fully align with the adult and adolescent population in the decision problem. However, the ARCADIA-CYCLO study is supported by ARCADIA 1 & 2, and the LTE study, which included both adults and adolescent patients as a combined population. These studies were sufficiently powered to allow sub-population analysis for adult and adolescent patients separately. Furthermore, NICE have previously concluded that submissions encompassing adult and adolescent patients with moderate-to-severe AD are appropriate.[3]

ARCADIA 2 and ARCADIA-CYCLO did not include study locations in the UK. The results of these trials can however be considered generalisable to a UK population, as most participants enrolled were European or North American. Furthermore, the results in these trials are comparable to those of ARCADIA 1, which included 16 participants in the UK.

Previous NICE submissions in moderate-to-severe AD have utilised a composite endpoint of EASI-50 and DLQI in the economic model.[1] Opinion on the most appropriate endpoint varies. In the NMA, we present improvements for patients through the measurement of EASI-75, although the ARCADIA trial programme also shows improvement across multiple other secondary endpoints. In alignment with NICE and EAG opinion at the lebrikizumab appraisal, we consider EASI-75 the most

patient-relevant measure in the contemporary setting, and that it is likely comparable to the EASI-50 and DLQI composite endpoint.[4] Furthermore, EASI-75 allows comparison versus a number of comparators included in the decision problem compared to the composite EASI-50 and DLQI endpoint.

Although not a limitation it is worth noting the LTE study has been deliberately performed at a Q4W dosing schedule, and not the market authorisation maintenance dosing schedule of Q8W, to adopt a conservative approach to the safety evaluation.

B.3. Cost effectiveness

Model overview

- An economic model was developed to determine the cost-effectiveness of nemolizumab (with BSC) versus all relevant comparators (with BSC) in adults and adolescent (≥ 12 years) patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one other systemic immunosuppressive treatment, or for whom these are not suitable.
- Separate economic analyses were conducted for the adult (> 18) and adolescent populations (≥ 12 years and < 18 years). In the adult population nemolizumab was compared against dupilumab, abrocitinib, upadacitinib, baricitinib, tralokinumab and lebrikizumab. In the adolescent population nemolizumab was compared against abrocitinib, upadacitinib and lebrikizumab. Subsequent treatment following treatment failure in both populations includes BSC, biologics and JAK inhibitors.
- A hybrid model structure was developed which includes a 52-week decision tree followed by a subsequent long-term three-state Markov model to facilitate the inclusion of the short- and long-term treatment effects of nemolizumab.
    - This model structure is aligned with the models developed in TA814[3] and TA986[4] and has been validated by UK health economic and clinical experts.
    - In the 52-week decision tree, response was determined at Week 16 using the EASI-75 endpoint, based on data from the ARCADIA 1 & 2, and ARCADIA-CYCLO (for the adult population only) clinical trials. Responders at Week 16 continued treatment until Week 52, while non-responders switched to subsequent therapy.
    - At Week 52, the patients exited the short-term decision tree and progressed into a long-term Markov model, which included three health states: ‘Maintained response,’ ‘No response,’ and ‘Dead’.

- The model considers patient's QoL with utility values by response status based on EQ-5D data from ARCADIA 1 & 2, ARCADIA-CYCLO (for adult population only), and the LTE study and utility decrements for adverse events and flares. The model also considers patient costs, including treatment costs, disease management and monitoring costs and costs associated with adverse events and flares.

Cost-effectiveness analysis results

- Nemolizumab (with BSC) was dominant versus all comparators (with BSC) in both the adult and adolescent populations.
- Long-term projections indicated that nemolizumab was associated with greater QALYs compared to all comparators in both the adult and adolescent populations.
- Nemolizumab was associated with lower costs versus all comparators in both the adult and adolescent populations.
- Extensive sensitivity and scenario analyses demonstrated that the cost-effectiveness estimates were robust to changes in model parameters and assumptions.

Conclusions

- Despite the number of treatments available to patients with AD, there is an unmet need for increased therapeutic diversity. Nemolizumab is a novel, safe, and effective treatment, that represents a cost-effective use of NHS resources versus all relevant comparators in both the adult and adolescent populations.

B.3.1. Published cost-effectiveness studies

An SLR, supplemented by an additional updated SLR were conducted to identify all relevant cost-effectiveness studies in moderate-to-severe AD. The objective of the review was to identify an optimal modelling framework for treatments of moderate-to-severe AD in the UK. The review was primarily focused on cost-effectiveness models which have been previously designed and developed for submissions of previously recommended treatments in the UK. Database searches were initially conducted on 25 September 2023 and subsequently updated on 08 May 2024. In total, 24 economic evaluations were identified for inclusion in this review (Table 45). Full details of the review are given in Appendix G.

Table 45. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chalmers et al.[158]	2022	Budget impact analysis exploring the impact of varying the proportion of patients on tralokinumab Q4W over 52 weeks on the budget impact of from a UK NHS perspective over a 5-year period	Adults with moderate-to-severe AD treated with tralokinumab or dupilumab (mean: NR)	NR	Results by proportion of patients switching to Q4W dosing: - 0%: average net budget saving of £9,821,579 - 10%: average net budget saving of £10,926,151 - 25%: average net budget saving of £12,583,009) - 50%: average net budget saving of £15,344,440	NR
Fenske et al.[159]	2021	Budget impact analysis over a 5-year period with a payer perspective to estimate the budget impact of adding baricitinib to a commercial managed-care formulary for treatment of moderate-to-severe AD from a US payer perspective	Patients with moderate-to-severe AD with inadequate response to topical treatments	NR	Net budget impact over 5 years: - Moderate AD population: -$4,393,706 - Severe AD population: -$372,200 - Moderate-to-severe AD population: -$4,719,710	NR
Heinz et al.[160]	2022	Cost-utility analysis using a Markov cohort model for upadacitinib versus dupilumab in patients with moderate-to-severe AD from a UK NHS and PSS perspective	Adults, 18 years or older, with moderate-to-severe AD who have exhausted all previous lines of therapies due to loss of response	Dupilumab: 14.124; Upadacitinib: 14.147	Dupilumab vs. Upadacitinib 30 mg: - Intervention and adverse event costs: £18,147.46 vs. £23,460.54	ICER Upadacitinib vs. Dupilumab: £219,733.88 per QALY

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					- Other healthcare costs: £96,433.64 vs. £96,224.34 - Total costs: £114,581.10 vs. £119,684.88	
Johansson et al.[161]	2023	Cost-utility analysis with a Italian healthcare payer perspective using a Markov cohort model to assess the cost-effectiveness of baricitinib, as compared to dupilumab, both in combination with TCS therapy, in patients with moderate-to-severe AD who failed, have contraindications, or cannot tolerate ciclosporin	Adults, 18 years or more, with moderate-to-severe AD for at least 12 months, inadequate response to existing topical medication within the last 6 months, eligible for systemic therapy, and experienced failure to ciclosporin, or were intolerant to, or had a contraindication to ciclosporin	Total QALYs - Dupilumab: 18.172 - Baricitinib: 18.133 - Incremental: 0.038 [reference: Baricitinib]	Total cost Dupilumab: €135,780 Baricitinib: €129,586 Incremental: €6,194	ICER: €160,905 per QALY [Baricitinib as reference]
Kanevsky et al.[162]	2023	Budget impact analysis from an Argentinian third-party payer perspective over a 5-year period, estimated using a hypothetical cohort of 1,000,000 participants	Moderate-to-severe AD patients.	NR	Net budget impact (USD): Social security perspective 1 year = -$335,710 5 year = -$3,681,014 Private Sector 1 year = -$347,417 5 year = -$3,810,134	NR
ICER[163]	2017	Budget impact analysis with a US payer perspective to estimate the	Adults aged 18 years and older with	NR	Average Annual Per Patient Budget Impact -	NR

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		potential total budgetary impact of dupilumab for the treatment of adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable	moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable		using wholesale acquisition ($37,000 per year): Dupilumab vs. Usual care Difference: $22,348 Average Annual Per Patient Budget Impact - using Discounted wholesale acquisition cost, ($31,000 per year): Dupilumab vs. Usual care Difference: $18,357	
Zimmerman et al.[164]	2018	Cost-utility analysis with a US healthcare payer perspective using a Markov model to identify the cost-effectiveness of Dupilumab compared to usual care in adults with moderate-to-severe AD	Adults with moderate-to-severe AD	QALYs, Dupilumab vs. Usual care - Incremental: 1.91	NR	Cost per additional QALY, Dupilumab vs. Usual care - Incremental using List/Net Price: $124,541/$101,830 per QALY
NICE[2]	2021	Cost-utility analysis from payer perspective using a Markov model	Adults with moderate-to-severe AD in treatment with baricitinib or dupilumab	NR	NR	Baricitinib vs. best supportive care (Company's deterministic base case): - quality-of-life waning scenario 1: £27,037/QALY - quality-of-life waning scenario 2: £28,396/QALY Baricitinib vs. best supportive care (ERG base case): - quality-of-life waning scenario 1 (with no quality-of-life waning on

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						best supportive care): £70,825/QALY - quality-of-life waning scenario 2 (with quality-of-life waning on best supportive care): £26,987/QALY
NICE[1]	2018	Cost-utility analysis, payer perspective using a Markov state-transition model	Adults with moderate-to-severe AD who could not have ciclosporin, or whose condition had not responded to ciclosporin.	NR	NR	Dupilumab plus topical corticosteroids vs. best supportive care alone (range across base case and sensitivity analysis): £27,410/QALY to £28,495/QALY
CADTH[165]	2022	Reimbursement recommendation for abrocitinib	Adolescents and adults with AD	NR	NR	Abrocitinib 100 mg + SOC = $156,735 per QALY Abrocitinib 200 mg + SOC = $231,013 per QALY compared to abrocitinib 100 mg + SOC
PBAC[166]	2021	Cost comparison analysis with an Australian health care payer perspective	Adult patients who have severe AD (PGA=4 and EASI ≥ 20), uncontrolled despite TCS therapy.	NR	Total costs for Dupilumab: $28,477.05	NR
PBAC[167]	2021	Cost-minimisation analysis	Patients aged 12 years or older with severe AD, affecting the whole body or the face and hands, who are	NR	NR	NR

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			inadequately controlled on topical therapies as per the criteria for the listing of dupilumab			
		Cost-utility analysis, perspective	Adults with severe AD, defined as IGA = 4 and EASI ≥ 20 at baseline in line with the PBS eligibility criteria.	Incremental QALYs, Upadacitinib vs. Dupilumab: 0.2394	NR	Upadacitinib vs. dupilumab: $55,000 to < $75,000 /QALY
ICER[163]	2017	Budget impact analysis with a US payer perspective to estimate the potential total budgetary impact of dupilumab for the treatment of adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable	Adults aged 18 years and older with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable	-	Average Annual Per Patient Budget Impact - using wholesale acquisition cost , ($37,000 per year): Dupilumab vs. Usual care Difference: $22,348 Average Annual Per Patient Budget Impact - using Discounted wholesale acquisition cost ($31,000 per year): Dupilumab vs. Usual care Difference: $18,357	-
Tanaka et al.[168]	2024	Cost-effectiveness analysis with a Japanese societal perspective using a Markov-Decision Tree hybrid to assess the cost-effectiveness of abrocitinib with SoC versus SoC alone in adults	Adults age> 18 years with moderate-to-severe AD and previous exposure to immunosuppressants	Deterministic results (base case), Abrocitinib vs. SOC:	Deterministic results (base case), Abrocitinib vs. SOC: Incremental cost: ¥2,270,386	Deterministic results, abrocitinib vs. SoC: ¥3,034,514 per QALY

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		with moderate-to-severe AD in Japan using a societal perspective as the base case	who were eligible for systemic therapy	Total LY: 46.05 vs. 46.05 Total QALY: 18.86 vs. 18.11 Incremental QALY: 0.75	Total costs: ¥16,004,964 vs. ¥11,528,187	
Romero Jimenez et al.[169]	2024	Cost-effectiveness analysis from a Spanish NHS perspective using a Decision Tree – Markov model hybrid to assess the cost effectiveness of abrocitinib (200 mg) compared with dupilumab (300 mg), tralokinumab (300 mg), baricitinib (2 and 4 mg), and upadacitinib (15 and 30 mg) for the treatment of patients with severe AD who showed an inadequate response or inability to tolerate topical treatments or required systemic treatment to control the disease.	Adults with severe AD inadequately controlled with topical therapy or for whom topical therapies were medically inadvisable or required systemic treatment to control the disease.	Incremental QALYs, abrocitinib vs: Dupilumab: 0.49 Tralokinumab: 0.60 Baricitinib 2mg: 0.64 Baricitinib 4mg: 0.43 Upadacitinib 15mg: 0.45 Upadacitinib 30mg: 0.08	Incremental cost, abrocitinib vs: Dupilumab: - €22,097 Tralokinumab: - €24,140 Baricitinib 2mg: - €14,825 Baricitinib 4mg: - €7,116 Upadacitinib 15mg: - €12,805 Upadacitinib 30mg: - €45,189	ICER (abrocitinib vs) Dupilumab: dominant Tralokinumab: dominant Baricitinib 2mg: dominant Baricitinib 4mg: dominant Upadacitinib 15mg: dominant Upadacitinib 30mg: dominant
Edwards et al.[170]	2024	Cost-effectiveness analysis from an NHS England perspective using a Decision Tree – Markov model hybrid 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 or second-line dupilumab and baricitinib).	Those with moderate-to-severe AD, irrespective of previous treatment and of age	NR	NR	ICER (vs. ciclosporin + TCS), EASI 75, adult 1st line <u>Deterministic results:</u> Abrocitinib 100mg + TCS: £91,156 Abrocitinib 200mg + TCS: £79,392 Upadacitinib 15mg + TCS: £79,969 Upadacitinib 30mg + TCS: £146,465

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						ICER (vs. dupilumab), monotherapy, EASI 50 + DLQI ≥ 4, adult 2nd line <u>Deterministic results:</u> Abrocitinib 100mg: dominant Abrocitinib 200mg: dominant Upadacitinib 15mg: dominant Upadacitinib 30mg: £66,324 Tralokinumab: £406,187 ICER (vs. dupilumab), combination therapy, EASI 50 + DLQI ≥ 4, adult, 2nd line <u>Deterministic results:</u> Abrocitinib 100 mg: £169,480 Abrocitinib 200 mg: dominant Upadacitinib 15 mg: £181,649 Upadacitinib 30 mg: £130,198 Tralokinumab: £220,333

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						ICER (vs. dupilumab), EASI 75, adolescent monotherapy Deterministic results: Abrocitinib 100mg: dominant Abrocitinib 200mg: dominant Upadacitinib 15mg: dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI. Eczema Area Severity index; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LY, life years; NHS, National Health Service; NR, not reported; PBS, Pharmaceutical Benefits Scheme; PGA, Patient Global Assessment; PSS, personal social services; QALY, quality adjusted life years; SoC, standard of care; TCS, topical corticosteroids; UK, United Kingdom; US, United States; USD, United States Dollar

B.3.2. Economic analysis

B.3.2.1. Choice of modelling approach

The cost-effectiveness SLR identified 24 economic models in moderate-to-severe AD. Of the models identified, the cost-effectiveness model developed for the NICE Multiple Technology Appraisal (MTA) TA814 (abrocitinib, tralokinumab, or upadacitinib) provided the most comprehensive cost-effectiveness analysis of biologic and JAK inhibitor treatments for adult and adolescent patients with moderate-to-severe AD in the UK. The TA814 cost-effectiveness model was developed by the External Assessment Group (EAG) and was considered appropriate for decision making by the NICE Committee.

The one-year decision tree model used in TA814 captures the treatment induction phase and patients' initial response in the first year of treatment, as initial response assessment periods are well defined in UK clinical practice. The subsequent Markov model captures long-term treatment benefits and monitoring from year 2 onwards and is considered to capture all relevant health states and clinically plausible transitions between health states for patients with AD. Further, the model structure reflects the most important treatment outcomes for most patients with AD; treatment response with respect to extent and severity of AD, QoL, and adverse events. As a result, the TA814 model framework, which was also adopted by the recent lebrikizumab submission (TA986),[4] was used in this appraisal to inform conceptualisation of a *de novo* cost-effectiveness model for nemolizumab in the treatment of moderate-to-severe AD.[3]

In line with the NICE reference case, all analyses have been conducted from the payer perspective, i.e., the NHS and personal social services (PSS). Key assumptions were validated by UK clinical experts specialising in AD.

B.3.2.2. Patient population

The economic analysis considers the use of nemolizumab in adults (≥ 18 years) and adolescents (≥ 12 years and < 18 years) with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one other

systemic immunosuppressive treatment, or for whom these are not suitable. The following populations were therefore considered separately in the economic analysis:

- Adults (≥ 18 years) with moderate-to-severe AD after failure of at least one systemic immunosuppressive treatment or for whom these are not suitable (second-line systemic therapy)

- Adolescents (≥ 12 years and < 18 years) with moderate-to-severe AD after failure of at least one systemic immunosuppressive treatment or for whom these are not suitable (second-line systemic therapy)

The baseline characteristics for the adult and adolescent populations incorporated into the economic analysis were sourced from data for the adult systemic-exposed and the adolescent systemic-eligible populations in TA814 (Table 46), which were based on a pooled analysis of patients enrolled in the Measure UP 1, Measure UP 2, and AD UP clinical trials.[3,171,172]

Table 46. Baseline characteristics in adult and adolescent population

Parameter	Adults	Adolescents	Source
Age, years	34.61	15.54	TA814[3]
Proportion of cohort male, %	67.4%	50.00%	
Weight, kg	75.92	63.06	

Abbreviations: TA, technology appraisal

B.3.2.3. Model structure

B.3.2.3.1. Model overview

A hybrid model with a one-year decision tree and subsequent three-state Markov model was developed to assess the value of nemolizumab (with BSC) versus all relevant comparators (with BSC). This model structure is in line with the cost-effectiveness model developed by the EAG and presented in TA814[3] and TA986[4] and has been validated with clinical and health economics experts to assure its alignment with clinical practice and methodological appropriateness.[173]

The model performs cost-effectiveness analyses by projecting patients' health state occupancy over the time horizon along with transient events (flares and treatment-

emergent adverse events [TEAEs]), and valuing health states and events to derive cost and health outcomes. The model reports costs, life years (LYs), and quality-adjusted life years (QALYs), along with differences in cost, LY, and QALY outcomes between intervention and comparators and the incremental cost-effectiveness ratio (ICER) per LY gained and QALY gained.

B.3.2.3.2. Modelling approach

To model both the short-term and long-term treatment effect of nemolizumab, and the impact of AD on patients with moderate-to-severe disease, a hybrid model including a decision tree and Markov framework was used. Costs and clinical outcomes are simulated and recorded over a lifetime. The model was developed and implemented in Microsoft Excel® as an interactive tool using a combination of worksheets and Visual Basic for Applications (VBA) functionalities.

B.3.2.3.2.1. Decision tree

The decision tree component of the model (summarised in Figure 16) evaluates patients over the first year of treatment. All patients who enter the model initiate treatment and continue for 16 weeks (treatment induction phase). At Week 16, the response to treatment, defined as achieving EASI-75 is evaluated. Responders at Week 16 in the intervention and comparator arms of the model persist with treatment until Week 52. Non-responders at Week 16 discontinue treatment and switch to subsequent therapy, entering the long-term Markov model at Week 52 in the ‘No response’ health state.

At Week 52, responders may discontinue treatment and subsequently enter the long-term Markov model in the ‘No response’ health state. Discontinuation at Week 52 is determined by conditional discontinuation data, denoting the proportion of patients discontinuing treatment at Week 52 among those who achieved response at Week 16. Responders at Week 16 who do not discontinue at Week 52 enter the long-term Markov model in the ‘Maintained response’ health state and continue treatment.

B.3.2.3.2.2. ***Markov model***

After the first year of treatment, patients exit the short-term decision tree and progress into a long-term Markov model consisting of three health states: ‘Maintained response’, ‘No response’, and ‘Dead’ (Figure 16).

Patients who respond at Week 16 and maintain a response at Week 52 enter the Markov model through the ‘Maintained response’ health state, where they remain until the loss of response via either treatment effect waning or discontinuation of treatment for any reason (all-cause discontinuation). In the event of loss of response, patients transition to the ‘No response’ health state where they discontinue treatment and receive subsequent therapy. Over time, patients might experience a diminishing response to active treatment, and therefore treatment effect waning was included within the ‘Responders’ health state of the model. As lack of efficacy is one of the reasons for treatment discontinuation, there was a risk of overlap between the proportion of patients losing response to treatment and the long-term discontinuation of treatment for all causes. Although there was a lack of data on the size of this overlap, treatment effect waning was not expected to be observed at Week 52, the time point at which the long-term discontinuation data was obtained. The overlap was therefore expected to be minimal. The assumptions used in the economic model for long-term discontinuation and treatment waning are aligned with the approach used in TA814[3] and have subsequently been validated with UK clinical experts via a modified Delphi process and interviews.[120,173]

Patients who do not respond to treatment at Week 16 or who have discontinued treatment at Week 52 enter the Markov model through the ‘No response’ health state and remain there until death (they transition to ‘Dead’ health state). At any point in the model, patients have the potential to transition to the ‘Dead’ health state, which is an absorbing health state from which no transitions are possible. A summary of the combined model structure is illustrated in Figure 16.

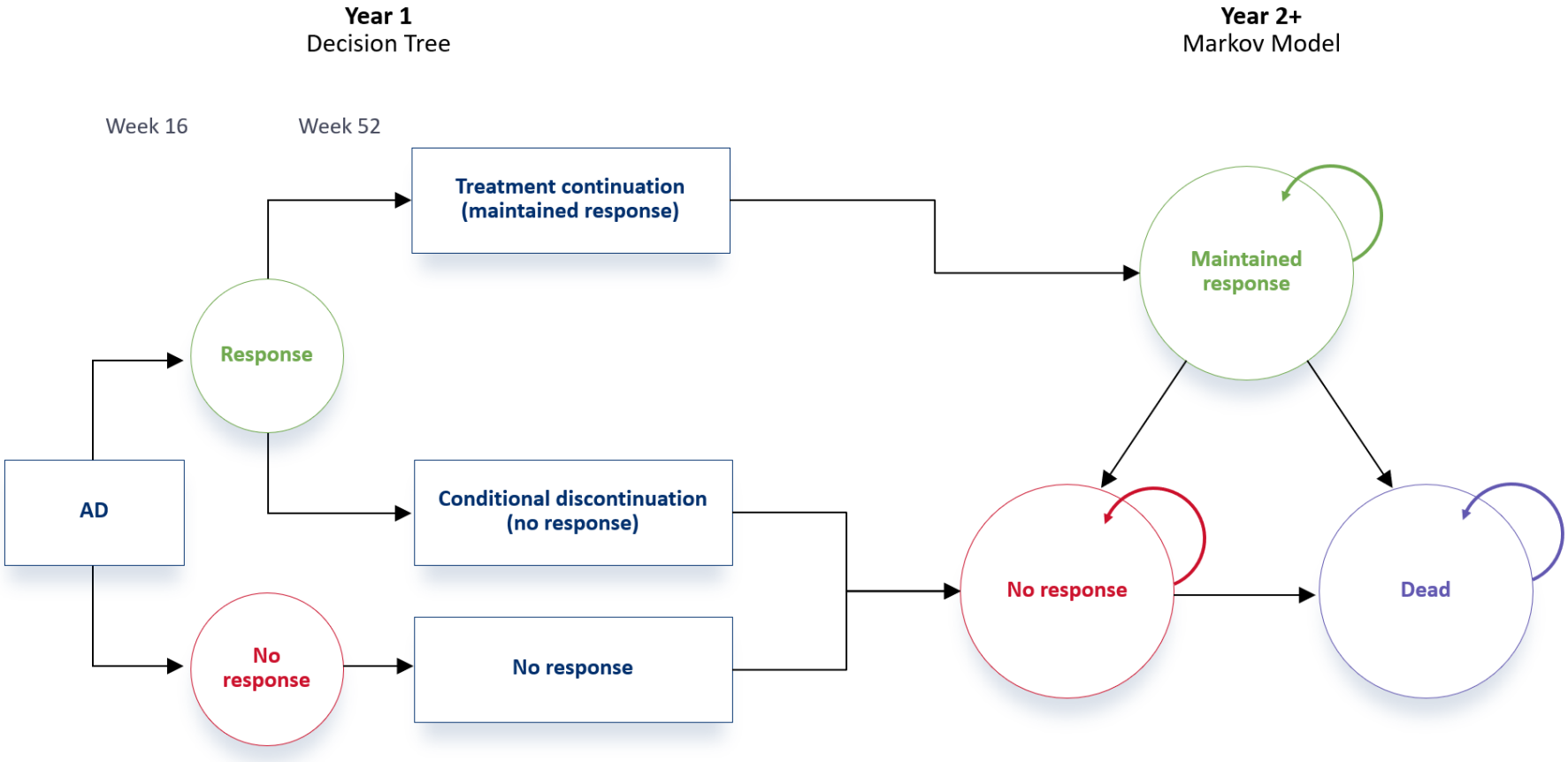

Figure 16. Overview of combined model structure
Abbreviations: AD, atopic dermatitis

B.3.2.4. Features of the economic analysis

Table 47 summarises the features of this economic analysis and compares these with the published NICE MTA for abrocitinib, tralokinumab or upadacitinib (TA814)[3] and the technology appraisals for dupilumab (TA534)[1] and lebrikizumab (TA986).[4]

Table 47. Features of the economic analysis

	Previous appraisals			Current appraisal	
Factor	**NICE TA814[3]**	**NICE TA534[1]**	**NICE TA986[4]**	**Chosen values**	**Justification**
Population	Adults with moderate-to-severe AD who are eligible for systemic treatment (ciclosporin) on inadequate response to topical treatments. Adults who achieve inadequate response to, cannot tolerate, or are contraindicated to ciclosporin monotherapy and combination therapy. Adolescents, irrespective of prior therapy	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	People 12 years and over with moderate-to-severe AD who are candidates for systemic therapy	Adolescents (≥ 12 years and < 18 years) and adults (≥ 18 years) with moderate-to-severe AD who have not responded to at least one other systemic immunosuppressive treatment or for whom these are not suitable	This population was chosen to align with the anticipated use nemolizumab in UK clinical practice and is supported by the ARCADIA clinical trials[127-130]
Intervention	Abrocitinib, tralokinumab and upadacitinib	Dupilumab	Lebrikizumab	Nemolizumab with BSC	In line with UK clinical practice and treatment guidelines, active treatment is administered with BSC, which can consist of emollients, TCSs and TCIs. This is consistent with the ARCADIA clinical trials[127-130]

Comparators	Dupilumab (with/without TCS), ciclosporin+TCS, Baricitnib+TCS	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	People for whom systemic therapy is suitable and have not previously received a systemic therapy: • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) People whose condition has not responded to at least one other systemic therapy, or these are not suitable: • Abrocitinib • Tralokinumab • Upadacitinib • Dupilumab • Baricitinib	Adult population: Dupilumab + BSC Abrocitinib, + BSC Upadacitinib + BSC Baricitinib + BSC Tralokinumab + BSC Lebrikizumab + BSC Adolescent population: Abrocitinib, + BSC Upadacitinib + BSC Lebrikizumab + BSC	The comparators chosen are in line with current UK clinical practice and NICE recommendations[1-3]
Perspective	The NHS and PSS Perspective	The NHS and PSS Perspective	The NHS and PSS Perspective	The NHS and PSS Perspective	Consistent with NICE modelling guideline[174]
Model structure	A hybrid decision tree Markov state-transition model with patients on/off treatment, depending on treatment response status	A hybrid decision tree Markov state-transition model with patients on/off treatment, depending on treatment response status	A hybrid decision tree Markov state-transition model with patients on/off treatment, depending on treatment response status	A hybrid decision tree Markov state-transition model with health states depending on treatment response status	Consistent with the approved moderate-to-severe AD modelling method by NICE; reflects the different nature of the treatment effect in short- and long-term[175]
Cycle length	One year	One year	One year	One year	Consistent with the moderate-to-severe AD modelling method approved by NICE, appropriate time interval to capture long-term

					treatment effect of moderate-to-severe AD systemic treatments[174]
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Consistent with NICE modelling guideline[174]
Outcomes	Total and incremental costs with subcategories (treatment and other) Total and incremental QALYs Total and incremental LYs ICER	Total and incremental costs with subcategories (treatment and other) Total and incremental QALYs Total and incremental LYs ICER	Total and incremental costs with subcategories (treatment and other) Total and incremental QALYs Total and incremental LYs ICER Net monetary benefit	Total and incremental costs with subcategories (treatment and other) Total and incremental QALYs Total and incremental LYs ICER	Consistent with NICE modelling guideline[174]
Discounting	3.5% per annum; applied to costs and benefits (QALYs)	3.5% per annum; applied to costs and benefits (QALYs)	3.5% per annum; applied to costs and benefits (QALYs)	3.5% per annum; applied to costs and benefits (QALYs)	Consistent with NICE modelling guideline[174]
WTP threshold	The cost-effectiveness threshold used in the base case will be £20,000 - £30,000 per QALY gained	The cost-effectiveness threshold used in the base case will be £20,000 - £30,000 per QALY gained	The committee concluded that an acceptable ICER would be below £20,000 per QALY gained	The cost-effectiveness threshold used in the base case will be £20,000 - £30,000 per QALY gained	Consistent with NICE modelling guideline[174]
Societal perspective	Not included in base-case	Not included in base-case	Not included in base-case	Not included in base-case	Consistent with NICE modelling guideline[174]

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-year; MTA, multiple technology appraisal; NICE, National Institute of Health and Care Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life-years; TA, technology appraisal; TCS, topical corticosteroids; WTP, willingness-to-pay.

B.3.2.4.1. Treatment sequencing

In previous NICE technology appraisals in AD, Committees have concluded that in clinical practice treatments would likely be used in sequence, where patients can transition to subsequent biologic/JAK inhibitors rather than reverting to BSC alone. As such, the NICE Committees concluded that treatment sequencing should be considered in cost-effectiveness analyses. However, previous appraisals in AD have not incorporated treatment sequencing into their economic analyses, citing a lack of data on the number of patients that would transition to alternative therapies and a paucity of efficacy data specific to their use in the subsequent treatment line.

To more accurately reflect contemporary UK treatment practices and to incorporate previous committee and UK clinical expert feedback through a modified Delphi process,[120] the base-case analyses assume that for patients who do not respond to second-line systemic therapy, a proportion will switch to receive subsequent biologic or JAK inhibitor therapies, and be subject to the costs and clinical benefits of these treatments.

Patients enter the economic model to receive second-line systemic therapy for AD and can receive either nemolizumab or a comparator treatment. Following loss of treatment response (i.e., non-responders), patients in all treatment arms can receive subsequent therapy, reflecting biologics and JAK inhibitors available as second-line systemic therapies for patients with AD in the UK. The expected proportion of patients receiving each subsequent treatment in UK clinical practice was derived from a panel of clinical experts through a modified Delphi process.[120]

B.3.2.4.2. Response measures

In previous AD technology appraisals (TA534,[1] TA681,[2] and MTA814),[3] the composite endpoint of EASI-50 + DLQI has been used for final decision making. Previous criticisms of EASI-50 + DLQI by NICE committees include that it does not correlate well with QoL improvements based on available trial data, it is unclear if it is relevant in UK clinical practice, and it may not capture the additional benefits of EASI-75.[2]

Taking the limitations of the composite endpoint into consideration, the recent NICE technology appraisal of lebrikizumab in AD (TA986)[4] incorporated EASI-75 into the base-case economic analysis.[4] The composite outcome of EASI-50 + DLQI was not collected in the primary lebrikizumab trials and indirectly derived response rates using EASI-75 results from a NMA were incorporated into the base-case economic analysis. The submitting company noted that it had taken this approach because the composite endpoint results were not publicly available for all comparator treatments and that EASI-75 was considered to have the closest relative response to the composite endpoint. The EAG questioned the similarity of EASI-75 and the composite endpoint but acknowledged that the approach to apply EASI-75 as the primary response outcome in the economic analysis may be appropriate in the absence of further data. Clinical experts consulted during the appraisal also indicated that EASI-75 response is harder to achieve than the composite endpoint, noting that a reduction in DLQI would closely match a decrease in EASI score, so the relative effect is likely to be the same. Overall, the NICE Committee concluded that in the absence of results for the composite endpoint, it was satisfied that using EASI-75 to indirectly inform treatment response was appropriate for decision making.

In line with the NICE Committees' preferences in TA986,[4] EASI-75 is applied as the measure of response in the base-case economic analyses. This assumption is considered appropriate given that the composite endpoint EASI-50 + DLQI results are still not publicly available for the majority of the comparators included in the decision problem and indirect comparison would not be feasible. Furthermore, the use of EASI-75 in the base-case economic analyses has been further validated with UK clinical experts.[173]

Alternative clinical endpoints explored as scenarios in the model include the PP NRS and IGA, which are endpoints in ARCADIA 1 & 2, and ARCADIA-CYCLO.

B.3.2.5. Intervention technology and comparators

B.3.2.5.1. Intervention

The intervention in the economic analysis is nemolizumab administered Q4W during the induction phase (first 16 weeks) followed by Q8W in maintenance phase for

patients who respond to treatment at Week 16. Nemolizumab is administered via subcutaneous injection.[176,177]

Nemolizumab in both the adult and adolescent populations is administered with BSC, which includes emollients, TCSs, and TCIs.[127-130] The proportion of patients receiving BSC treatments is dependent on response to treatment; BSC use was assumed to be equal for the nemolizumab and comparator arms and the adult and adolescent populations. The proportion of BSC treatments included in the model were sourced from UK clinical experts at a Delphi panel to reflect the proportion of each therapy used in contemporary UK clinical practice (Table 48).[120] For ease, nemolizumab with BSC will be referred to as nemolizumab throughout the remainder of the document.

Table 48. BSC treatments received in the economic model base-case

Medication	Responders	Non-responders
TCIs	87.5%	77.5%
TCSs	81.3%	76.3%
Emollients	91.3%	83.8%
Biologics*	0.0%	47.2%
JAK inhibitors*	0.0%	46.3%

*Non-responders may switch to subsequent biologic and JAK inhibitors in combination with BSC to reflect treatment sequencing in UK clinical practice – see Section B.1.3.2

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

B.3.2.5.2. Comparator

For the adult population, the comparator arms for the economic analysis included the treatments currently available in the UK to treat moderate-to-severe AD in adults (≥ 18 years) after failure of at least one systemic immunosuppressive treatment or for whom these are not suitable:[1-3] dupilumab; abrocitinib; upadacitinib; baricitinib; tralokinumab; and lebrikizumab.

For the adolescent population, the comparator arms for the economic analysis included the treatments currently available to treat moderate-to-severe AD in adolescents (≥ 12 years and <18 years) in the UK after failure of at least one systemic immunosuppressive treatment or for whom these are not suitable:[1-3] abrocitinib; upadacitinib; and lebrikizumab.

All comparator treatments in both the adult and adolescent population are administered with BSC, including emollients, TCSs, and TCIs. The proportion of patients receiving BSC are presented in Table 48 and are dependent on response to treatment; BSC use was assumed to be equal for the nemolizumab and comparator arms and the adult and adolescent populations. For ease, the comparator treatments with BSC will be referred to as the treatment name only throughout the document.

B.3.2.5.3. Subsequent treatment

As outlined in section B.3.2.4.1, non-responders in the nemolizumab and comparator treatment arms of the base-case analyses can switch to receive subsequent biologics and JAK inhibitor treatment rather than reverting to BSC alone. The proportion of non-responders switching to each subsequent treatment are presented in Table 48. The subsequent treatments were assumed to be treatment independent and equal for the adult and adolescent populations. The proportion of each biologic and JAK inhibitor received as a subsequent treatment in the economic analyses has been validated with UK clinical experts at a modified Delphi panel to reflect likely UK clinical practice and is presented in Table 49.[120]

Table 49. Distribution of patients across biologics and JAK inhibitors used as subsequent treatments

Medication	Distribution
Biologics	
Dupilumab	59.2%
Tralokinumab	40.8%
Lebrikizumab	0.0%
JAK inhibitors	
Upadacitinib 15 mg	0.0%
Upadacitinib 30 mg	37.5%
Abrocitinib 100 mg	0.0%
Abrocitinib 200 mg	36.1%
Baricitinib	26.4%

Abbreviations: JAK, Janus Kinase

B.3.3. Clinical parameters and variables

The clinical evidence for treatment effect at Week 16 for the nemolizumab arm were taken from the ARCADIA 1 & 2, and ARCADIA-CYCLO trials for the adults population, and from the ARCADIA 1 & 2 trials for adolescent population.[127-129] For both the adult and adolescent populations, discontinuation rates at Week 52 to inform discontinuation from treatment in the long-term (at and beyond Week 52) were obtained from ARCADIA 1 & 2 trials for the nemolizumab arm,[127,128] and from TA986 for the comparator arms.[4]

In addition to the parameters above, ARCADIA 1 & 2 trial data,[127,128] data identified from the published literature,[148,155,172,178-180] and previous submissions (TA534, TA814, and TA986),[1,3,4] were used to obtain additional clinical data required in the model:

- Treatment effect waning
- Probability of flares
- Probability of TEAEs

B.3.3.1. Response rate at Week 16

The primary treatment outcome evaluated in the model was treatment response at Week 16, defined as achieving EASI-75 (Table 50). As described in Section B.3.2.4.2, measurement of response with EASI-75 in the base-case analyses allows comparison to the widest range of UK relevant comparators, is aligned with Committee's preferences for decision making in the recent appraisal of lebrikizumab (TA986),[4] and has been validated by UK clinical experts to be reflective of patient relevant outcomes for the UK population with AD.[173] The definition of treatment response at Week 16 was explored in scenario analyses using PP NRS and IGA as alternative measures.

Probability of response at Week 16 for nemolizumab was calculated based on patient-level data from ARCADIA 1 & 2, and ARCADIA-CYCLO clinical trials for the adult population, and the ARCADIA 1 & 2 clinical trials for the adolescent population.[127-129] There are no head-to-head RCT data to compare the effectiveness of nemolizumab versus the relevant comparators for the treatment of moderate-to-severe AD, thus relative treatment effects are informed by an ITC, described in section B.2.9.

To calculate the response rate for each treatment, the efficacy dataset from clinical trial was filtered to investigate only those who were randomised to receive nemolizumab. Response was determined by evaluating the change in EASI score at Week 16 from the index date for each patient. If patients received rescue therapies prior to Week 16, they were automatically classified as non-responders. From the final total patient population in each arm, the rate was calculated as the proportion of patients who responded at Week 16:

$$Response\ rate = \frac{Number\ of\ responders}{Number\ of\ randomised\ patients}$$

Table 50. EASI-75 response rate at Week 16 for nemolizumab in adult and adolescent populations

Treatment	EASI-75	
	Adults	Adolescents
Nemolizumab	[redacted]	[redacted]
Source	ARCADIA 1,[127] ARCADIA 2[128] and ARCADIA-CYCLO[129]	ARCADIA 1[127] and ARCADIA 2[128]

Abbreviations: EASI, Eczema Area and Severity Index; NA, not applicable

B.3.3.2. Implementation of ITC outputs

Response rates for comparators were estimated based on response rate for nemolizumab and odds ratio (OR) between each comparator and nemolizumab determined within the ITC, as outlined in B.2.9, Table 51, and the ITC report (Appendix M). Response probabilities for each comparator were calculated based on the response probability for nemolizumab and the relative measure of efficacy, OR, using the formula presented below:

$$p_2 = \frac{p_1 * OR}{1 - p_1 + p_1 * OR}$$

Mean ORs with standard error (SE) and confidence intervals were obtained from the ITC analysis using a random effects/priors model as recommended by NICE.[1] For non-statistically significant differences, an OR of 1 is allocated to reflect the relative comparability between treatments from the ITC. This assumption was considered appropriate by UK clinical experts[173] and has been explored in scenario analysis, where point estimates were used for the OR at week 16. Indirect comparison versus abrocitinib 100 mg in the adult population was not feasible based on the lack of clinical data available to support this comparison. Therefore, it was not considered appropriate for abrocitinib 100 mg to be included in the economic analysis in the adult population based on the significant uncertainty that would be associated with the cost-effectiveness estimates.

Table 51. Odds ratio for response rate (EASI-75) at Week 16 between nemolizumab and comparators in adult and adolescent populations

Treatment	Mean OR (SE; 95% CI)	
	Adults	Adolescents
Upadacitinib 15 mg	1.0000 (0.10000)	1.0000 (0.10000)
Upadacitinib 30 mg	[redacted]	N/A
Abrocitinib 100 mg	N/A	1.0000 (0.10000)
Abrocitinib 200 mg	1.0000 (0.10000)	1.0000 (0.10000)
Baricitinib	1.0000 (0.10000)	N/A
Dupilumab	1.0000 (0.10000)	N/A
Tralokinumab	1.0000 (0.10000)	N/A
Lebrikizumab	1.0000 (0.10000)	1.0000 (0.10000)

Abbreviations: BSC, best supportive care; CI, confidence interval; EASI, Eczema Area and Severity Index; N/A, not applicable; OR, odds ratio

B.3.3.3. Conditional discontinuation at Week 52

Conditional discontinuation refers to the all-cause stopping rate for people who responded to treatment at Week 16 but who withdrew from treatment at Week 52. This considers that loss of response is not the only reason for treatment discontinuation in Week 16 responders, as patients may not be able to tolerate longer-term treatment due to adverse events or for other reasons.

Conditional discontinuation at Week 52 for nemolizumab was calculated based on patient-level data from ARCADIA 1 & 2 trials for both the adult and adolescent populations.[127,128] This captured patients who responded (based on EASI-75 or composite EASI-50 + DLQI) at Week 16 and withdrew from treatment at Week 48 (Table 52). As there were no conditional discontinuations observed in the adolescent population on nemolizumab treatment, the same value as in adults was assumed.

Conditional discontinuation for the comparator treatments were based on the Committee's preferred assumptions in TA986,[4] which were based on estimates suggested by clinical experts. In line with the Committee's preferred assumptions class-specific conditional discontinuation rates for the biologic and JAK inhibitor comparators were used. The same conditional discontinuation rates were assumed for the adult and adolescent population (Table 52).

Table 52. Conditional discontinuation rate at Week 52 in adult and adolescent populations

Treatment	Adults	Adolescents*	Source / assumption
Nemolizumab	[redacted]	[redacted]	ARCADIA 1[127] and ARCADIA 2[128]
Upadacitinib 15 mg	10.0%	10.0%	NICE TA986[4]
Upadacitinib 30 mg	10.0%	N/A	
Lebrikizumab	3.9%	3.9%	
Dupilumab	3.9%	N/A	
Tralokinumab	3.9%	N/A	
Baricitinib	10.0%	N/A	
Abrocitinib 100 mg	N/A	10.0%	
Abrocitinib 200 mg	10.0%	10.0%	

* The same discontinuation values for the adult and adolescent population were assumed
Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal

B.3.3.4. Long-term discontinuation

No long-term (year 2 onwards) treatment discontinuation data are available for the intervention or any of the comparators considered in the economic analyses. Therefore, in both the adult and adolescent populations, long-term discontinuation rates were assumed to be equal to the conditional discontinuation rates at Week 52 applied for both nemolizumab and comparators arms.

The approach taken to assume equal long-term discontinuation and conditional discontinuation rates for each treatment is aligned to the assumptions made in TA814[3] and TA986.[4] The assumption of long-term discontinuation being equal to that observed between Week 16 and 52 was critiqued by clinical experts during TA814 based on a lack of face validity.[3] However, given the lack of data to inform alternative assumptions, the approach was considered suitable for decision making.

For the comparator treatments, in line with the Committee's preferred assumption in TA986[4] class-specific long-term discontinuation rates were applied. However, a lower long-term discontinuation rate was applied for nemolizumab compared to the comparator treatments. This assumption was considered appropriate based on the lower discontinuation rate for nemolizumab in the ARCADIA 1 & 2 clinical trials compared to the discontinuation rates available for the comparators.[127,128]

Furthermore, the discontinuation rate for nemolizumab was validated by UK clinical experts.[173]

B.3.3.5. Treatment effect waning

Due to the lack of long-term efficacy data on systemic therapies in moderate-to-severe AD, and in line with the modelling approach used in TA814[3] and TA986,[4] it was assumed that treatment effect may wane over time. It was assumed that in years two, three, four, and five onwards, 2%, 5%, 7%, and 8% of patients, respectively, lose response to and discontinue active treatment. Equal discontinuation rates due to efficacy waning were applied to the nemolizumab and comparator arms for both the adult and adolescent populations. The treatment effect waning values were validated with UK clinical experts[173] and different treatment effect waning assumptions were explored in scenario analyses.

B.3.3.6. Mortality

Moderate-to-severe AD is not expected to have any significant impact on mortality; thus, the mortality rates within the moderate-to-severe AD population are equivalent to those of the general population. Age- and gender-adjusted all-cause mortality applied in the model is estimated based on national life tables (for England and Wales) from the Office for National Statistics.[181] This assumption was validated with UK clinical experts.[173]

B.3.3.7. Flares

As outlined in Section B.1.3.1.1, patients with moderate-to-severe AD may encounter sudden worsening of symptoms, referred to as flares. The occurrence of flares can vary based on the treatment administered, although the treatments for managing flares remain similar. Flare rates were treatment specific, and were used to estimate the costs associated with treating a flare and potential disutility due to their occurrence.[1,31,148,171,172,178,180,182,183] Rates of flares for each treatment were applied in each cycle and based on Week 16 data obtained from the ARCADIA 1 & 2 trials,[127,128] published literature and previous NICE technology appraisals (Table 53). The values were recalculated to obtain annual rates for use in the economic analyses.

Table 53. Treatment specific flare rates at Week 16 in adult and adolescent populations

Treatment	Adults	Adolescents	Source / assumption
Nemolizumab	[redacted]	[redacted]	ARCADIA 1,[127] ARCADIA 2,[128], Kabashima (2022)[178]
Upadacitinib 15 mg	5.30%	10.23%	Reich (2021)[172], Pooled Measure UP 1&2[171]
Upadacitinib 30 mg	5.40%	N/A	Reich (2021)[172]
Lebrikizumab	0.00%	0.00%	NICE TA986 (ADhere week 0–16 data)[4]
Dupilumab	0.10%	N/A	NICE TA534 (adjusted for 16 weeks)[1], Simpson (2020)[184]
Tralokinumab	2.80%	N/A	Silverberg (2021)[31]
Baricitinib	5.41%	N/A	Reich (2020)[148]
Abrocitinib 100 mg	N/A	0.33%	Bieber (2021) (adjusted for 16 weeks)[180]
Abrocitinib 200 mg	0.12%	0.12%	

Abbreviations: BSC, best supportive care; TA, technology appraisal; NA, not available; NICE, National Institute for Health and Care Excellence

B.3.3.8. Treatment-emergent adverse events

Safety profiles were assessed based on the clinical trial data for each treatment.[127,128] Serious adverse events that occurred in at least 5% of patients in any treatment arm were included in the economic analyses.

Rates of TEAEs at Week 16 were sourced from the ARCADIA 1 & 2 trials for the nemolizumab arm.[127,128] Adverse event rates for all comparators were sourced from their associated clinical trials. The rates of TEAEs for the adult and adolescent populations are presented in Table 54 and Table 55, respectively. The values were converted to annual rates for use in the cost-effectiveness analyses.

Table 54. TEAEs rates at Week 16 in adult population

Treatment	ISR	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Asthma	Source / assumption
Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ARCADIA 1,[127] ARCADIA 2,[128] Kabashima (2022)[178]
Upadacitinib 15 mg	0.00%	0.00%	1.15%	3.83%	7.66%	9.58%	0.00%	Reich (2021)[172]
Upadacitinib 30 mg	0.00%	0.77%	0.77%	8.85%	7.31%	13.85%	0.00%	
Lebrikizumab	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Adhere (TA986)[4]
Dupilumab	5.53%	10.60%	5.53%	2.76%	3.69%	0.00%	0.00%	De Bruin-Weller (2018)[155], Boguniewicz (2021)[179]
Tralokinumab	6.70%	11.10%	0.00%	0.4%	1.50%	0.00%	0.00%	NICE TA814[3]; ECZTRA 3[31]; ECZTRA 1+2 [185]
Baricitinib	0.00%	0.00%	0.00%	3.60%	2.70%	3.60%	0.00%	Reich (2020) [148]
Abrocitinib 200 mg	0.10%	1.30%	4.00%	1.80%	12.00%	6.60%	0.00%	NICE TA814[3]; Bieber (2021) (adjusted for 16 weeks)[180]

Abbreviations: ISR, injection site reaction; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TEAE, treatment-emergent adverse event

Table 55. TEAEs rates at Week 16 in adolescent population

Treatment	ISR	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Asthma	Source / assumption
Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ARCADIA 1,[127] ARCADIA 2,[128], Kabashima (2022)[178]
Upadacitinib 15 mg	0.00%	1.33%	0.00%	0.00%	14.67%	13.33%	0.00%	Pooled Measure UP 1 & 2[171]
Lebrikizumab	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	Assumption
Abrocitinib 100 mg	0.00%	0.00%	0.00%	1.10%	9.50%	3.20%	0.00%	Eichenfield (2021) (week 12 data)[154]
Abrocitinib 200 mg	0.00%	0.00%	0.00%	2.10%	10.60%	5.30%	0.00%	Eichenfield (2021) (week 12 data)[154]

Abbreviations: BSC, best supportive care; ISR, injection site reaction; TEAE, treatment-emergent adverse event

B.3.3.9. Role of clinical experts

Throughout this submission development, UK clinical experts were consulted extensively to ensure that any assumptions made align to UK clinical practice, especially during the development of the economic model. The main consultation process was a modified Delphi panel exercise held in June 2024.[120] This consisted of a survey that included 29 statements regarding current treatments for AD aiming to determine a consensus among clinicians from the UK and Canada. To inform the NICE submission, results were stratified by UK and Canadian experts to ensure that any consensus reached was applicable to the UK. Participants were selected due to their expertise in treating AD within the UK clinical setting.

In addition, two rounds of follow-up interviews were held with one clinical expert and one health economist from the UK[173]. These interviews confirmed the findings of the Delphi panel exercise and how they influenced assumptions made in the economic modelling.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

In line with the NICE reference case, utility values used in the cost-effectiveness analyses are based on health-related quality-of-life (HRQoL) measurements collected using the EQ-5D-3L instrument in the ARCADIA 1 & 2, ARCADIA-CYCLO, and LTE study.[127-130] Utility values at baseline for the whole cohort, at Week 16 for responders and non-responders, and at weeks 48 and 104 for responders, were estimated based on data from these clinical trials. LTE study results are presented for patients who were treated with nemolizumab before entering the LTE study.

Individual patient questionnaires contain responses for the five reported EQ-5D-3L dimensions of HRQoL and the VAS. The EQ-5D-3L instrument has two components. The first is the assessment of five separate health state dimensions by asking the patient to agree with one of three statements about that dimension (Table 56). The second is the single-dimension assessment of general wellbeing on a scale of 0–100 (the VAS). Whilst neither assessment is entirely independent of the preferences of the population being assessed, the VAS is considered unanchored to the

preferences of the general population and so is not intended to generalise, particularly between populations. It is used to support the assessments of the EQ-5D-3L instrument, particularly with respect to perception of changing QoL.

Table 56. EQ-5D-3L dimensions

Dimension	Scoring
Mobility	1 = I have no problems in walking about 2 = I have some problems in walking about 3 = I am confined to bed
Self-care	1 = I have no problems with self-care 2 = I have some problems washing or dressing myself 3 = I am unable to wash or dress myself
Usual activities	1 = I have no problems with performing my usual activities 2 = I have some problems with performing my usual activities 3 = I am unable to perform my usual activities
Pain/discomfort	1 = I have no pain or discomfort 2 = I have moderate pain or discomfort 3 = I have extreme pain or discomfort
Anxiety/depression	1 = I am not anxious or depressed 2 = I am moderately anxious or depressed 3 = I am extremely anxious or depressed

For each complete questionnaire, an index was derived from the five dimensions of the EQ-5D-3L health profile data to provide a single preference score of the self-assessed health states that would be representative of the preference of a patient in the UK population reporting to the same health states. This index was as determined by Dolan,[186] using the time-trade-off (TTO) method. The disutilities derived from the Dolan formula were subtracted from a baseline utility of 1 to give an index in the range of -0.595 to 1, where 1 represents perfect QoL, 0 represents no preference for further survival, and values less than 0 represent a negative preference for further survival.

For questionnaires where any dimension was scored 2 or greater, the disutility values was greater than 0 and was determined by the following formula, with variable names and associated coefficient values in Table 57:

$$disutility = \alpha + \beta_1 M_O + \beta_2 S_C + \beta_3 U_A + \beta_4 P_D + \beta_5 A_D + \beta_6 M_2 + \beta_7 S_2 + \beta_8 U_2 + \beta_9 P_2 + \beta_{10} A_2 + \beta_{11} N_3$$

Table 57. Values of variables for disutility formula

Variable name	Variable	Associated coefficient	Coefficient Value
-	-	α	0.081
M_O	1 if Mobility = 2 2 if Mobility = 3	β_1	0.069
S_c	1 if Self-care = 2 2 if Self-care = 3	β_2	0.104
U_A	1 if Usual Activities = 2 2 if Usual Activities = 3	β_3	0.036
P_D	1 if Pain/Discomfort = 2 2 if Pain/Discomfort = 3	β_4	0.123
A_D	1 if Anxiety/Depression = 2 2 if Anxiety/Depression = 3	β_5	0.071
M_2	1 if Mobility = 3	β_6	0.176
S_2	1 if Self-care = 3	β_7	0.006
U_2	1 if Usual Activities = 3	β_8	0.022
P_2	1 if Pain/Discomfort = 3	β_9	0.140
A_2	1 if Anxiety/Depression = 3	β_{10}	0.094
N_3	1 if any score = 3	β_{11}	0.269

B.3.4.2. Health-related quality-of-life studies

An HRQoL SLR supplemented by an additional updated SLR was conducted to identify published studies on HRQoL for the analysed population. Database searches were initially conducted on 25 September 2023 and subsequently updated on 08 May 2024. In total 16 studies from 18 publications met the eligibility criteria and were included in this review. Full details of the reviews, including PRISMA diagrams and a description of relevant studies informing the model, are provided in Appendix H.

B.3.4.3. Health-related quality-of-life data used in the cost-effectiveness analysis

To capture the impact of treatment with nemolizumab compared with comparator therapies on health-related quality of life, QALYs were evaluated in the model using health-state specific utility values. An additive approach was used to account for utility decrease due to transient events. For each health state in the model, a utility score was assigned which was calculated based on ARCADIA 1 & 2, ARCADIA-

CYCLO, and the LTE study for the adult population and the ARCADIA 1 & 2, and the LTE study for the adolescent population.[127-130]

In both the adult and adolescent populations, utilities were treatment independent and based on response to treatment and time from treatment initiation. The utility values in the base-case analysis for the adult and adolescent populations are presented in Table 58 and Table 59, respectively.

For the first 8 weeks of treatment, patients from both the adult and adolescent populations were assumed to have baseline utility value based on the full cohort to reflect the delay in clinical effects. Based on the results from the LTE study,[130] utility increase over time is observed for responders to treatment. Therefore, different utility values were used for responders for different time periods from treatment initiation. Utilities for responders at Weeks 9-52 (year 1) and 53-104 (year 2) were based on responders at Week 16 and 48, respectively, from the ARCADIA 1 & 2, and ARCADIA-CYCLO (for adult population only).[127-129] Utilities for responders at Weeks 104+ (year 3+) were based on clinical trial data for responders at Week 56 from the LTE study. The assumption for increase utility for responders over time was applied to both the adult and adolescent populations and was validated with UK clinical experts who confirmed that HRQoL increases over time for responders, as although itch relief is observed shortly after treatment is initiated, it takes longer for skin lesions to heal.

For both adults and adolescents who did not respond to treatment, it was assumed that the utility applied following the first 8 weeks of treatment was based on clinical trial data for non-responders at week 16 and was maintained until end of life.

Table 58. Summary of utility values for cost-effectiveness analysis for adult population

State	Utility value‡	SE†	Reference
First 8 weeks of treatment	0.648	0.014	ARCADIA 1,[127] ARCADIA 2[128] and ARCADIA-CYCLO[129]
Maintained response weeks 9-52 (year 1)	0.885	0.010	
Maintained response year 2*	0.928	0.006	
Maintained response year 3+	0.971	0.003	ARCADIA LTE[130]
No response	0.753	0.013	ARCADIA 1,[127] ARCADIA 2[128] and ARCADIA-CYCLO[129]

Abbreviations: LTE, long-term extension; NICE, National Institute for Health and Care Excellence; SE, standard error
† Where values for standard errors (SE) are not available and could not be calculated using standard deviation, a default value of 10% of the mean value has been used.
‡ Utility for responders after treatment switching to systemic therapy is assumed to be the same as for responders to initial therapy.
* For the adult population week 48 EQ-5D observations were unavailable - average of Week 16 and week 104 EQ-5D values were applied as an alternative for this period

Table 59. Summary of utility values for cost-effectiveness analysis for adolescent population

State	Utility value / disutility‡	SE†	Reference
First 8 weeks of treatment	0.842	0.005	ARCADIA 1[127] and ARCADIA 2[128]
Maintained response weeks 9-52 (year 1)	0.921	0.005	
Maintained response year 2	0.935	0.008	
Maintained response year 3+	0.971	0.003	ARCADIA LTE[130]
No response	0.785	0.008	ARCADIA 1[127] and ARCADIA 2[128]

Abbreviations: LTE, long-term extension; SE, standard error
† Where values for standard errors (SE) are not available and could not be calculated using standard deviation, a default value of 10% of the mean value has been used.
‡ Utility for responders after treatment switching to systemic therapy is assumed to be the same as for responders to initial therapy

B.3.4.4. Adverse reactions and other transient events

The rates of flares and TEAEs in the economic analyses are discussed in Section B.3.3.7 and Section B.3.3.8, respectively. In line with the recent lebrikizumab appraisal (TA986),[4] the economic analyses for both the adult and adolescent populations include utility decrements associated with adverse events and flares. This assumption has been explored in scenario analysis.

To calculate QALY loss due to adverse events and flares, disutilities are applied for the time period that equals average event duration. The disutilities and event duration for TEAEs and flares are presented in Table 60 and Table 61, respectively. The disutilities for TEAEs were based on inputs sourced from TA986,[4] reports from the Institute for Clinical and Economic Review (ICER)[163] and published literature;[187] event duration was sourced from UK clinical experts.[173] The disutility and event duration for flares were sourced from TA986.[4]

Table 60. Adverse event disutility and event duration

Adverse event	Disutility‡ (SE)	Event duration (years)	Reference
Injection site reaction	0.004 (0.0004)	0.0055	ICER report[163]
Allergic conjunctivitis	0.03 (0.0030)	0.0192	
Infectious conjunctivitis	0.03 (0.003)	0.0192	
Oral herpes	0.05 (0.005)	0.0192	TA986[4]
Upper respiratory tract infection	0.037 (0.0037)	0.0383	
Acne	0.050 (0.0050)	0.0383	
Asthma	0.021 (0.0021)	0.0383	Sullivan et al, 2006[187]

Abbreviations: ICER, Institute for Clinical and Economic Review; SE, standard error, TA, technology appraisal
† Where values for standard errors (SE) are not available and could not be calculated using standard deviation, a default value of 10% of the mean value has been used.

Table 61. Flares disutility and event duration

	Disutility (SE)	Event duration (years)	Reference
Flare	0.03 (0.003)	0.0192	TA986[4]

Abbreviations: SE, standard error, TA, technology appraisal

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An economic SLR supplemented by an additional updated SLR was conducted to identify direct costs and healthcare resource use related to the management of moderate-to-severe AD. Database searches were initially conducted on 25 September 2023 and subsequently updated on 08 May 2024. In total 45 studies from 53 publications met the eligibility criteria and were included in this review. Full details of the review, including a description of all relevant studies informing the model, are given in Appendix I.

All costs were sourced from national databases and literature and were inflated to the present year. Where necessary and where available, appropriate proxy data was used to fill data gaps and was validated by experts.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Drug acquisition costs

Costs were accounted for from a UK healthcare payer perspective. All costs were reported as 2024 pounds sterling (GBP). Unit costs of each drug were obtained from the NICE British National Formulary (BNF).[188]

Dosing of treatments included in the economic analysis was determined based on the ARCADIA 1 & 2 trials,[127,128] TA814[3], and the anticipated UK license for nemolizumab. The same dosing and pricing for comparators were assumed for adult and adolescent populations.

B.3.5.1.2. Drug administration costs

When calculating drug administration costs, it was assumed that patients receive 30 minutes of training from a healthcare professional on how to self-administer subcutaneous therapies (dupilumab, tralokinumab, lebrikizumab, and nemolizumab). The costs associated with training were based on 30 minutes of patient contact with a hospital-based Band 6 nurse, sourced from the UK Personal Social Services Research Unit (PSSRU) 2023 (each hour spent with a patient requires 2.5 paid hours).[189] This training is implemented in the model as a one-off cost associated with treatment in the first model cycle; after this, patients self-administer therapy and no administration costs are incurred for the remainder of the time horizon.[3] Drugs administered orally (upadacitinib, abrocitnib, and baricitinib) had no administration cost assigned. The same cost of drug administration was assumed for adult and adolescent populations.

B.3.5.1.3. Summary of intervention and comparators' dosing and costs

A summary of dosing, acquisition and administration costs of intervention and comparators is presented in Table 62.

Table 62. Summary of nemolizumab and comparator dosing and costs (annual cost) in adult and adolescent populations

Treatment	Loading phase dosing	Induction phase dosing	Maintenance phase dosing	Drug administration cost (one-off GBP)	Units per pack	Drug acquisition cost (per pack GBP)	Source / assumption
Nemolizumab (with PAS)	60 mg x1	30 mg Q4W	30 mg Q8W	£58.00	1	[redacted]	Galderma
Nemolizumab (without PAS)	60 mg x1	30 mg Q4W	30 mg Q8W	£58.00	1	[redacted]	
Upadacitinib 15 mg	NA	15 mg daily	15 mg daily	£0.00	28	£805.56	NICE TA814[3], BNF[188]
Upadacitinib 30 mg	NA	30 mg daily	30 mg daily	£0.00	28	£1,281.54	
Lebrikizumab	500 mg at week 0 and 2	250 mg Q2W	250 mg Q4W	£58.00	2	£2,271.29	Lilly (2022)[190], BNF[188]
Baricitinib	NA	4 mg daily	4 mg daily	£0.00	28	£805.56	NICE TA814[3], BNF[188]
Dupilumab	600 mg x1	300 mg Q2W	300 mg Q2W	£58.00	2	£1,264.89	
Tralokinumab	600 mg x1	300 mg Q2W	300 mg Q2W	£58.00	4	£1,070.00	
Abrocitinib 100 mg	NA	100 mg daily	100 mg daily	£0.00	28	£893.76	
Abrocitinib 200 mg	NA	200 mg daily	200 mg daily	£0.00	28	£893.76	

Abbreviations: BNF, British National Formulary; GBP, 2024 pounds sterling; NICE, National Institute for Health and Care Excellence; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; TA, technology appraisal

B.3.5.1.4. Best supportive care costs

BSC was administered with active treatment for responders and as a subsequent treatment for non-responders. In the economic analysis the same approach for modelling the BSC costs was used for the adult and adolescent populations. Based on TA814,[3] TA986[4] and the anticipated use of nemolizumab in UK clinical practice, it was assumed that BSC includes a combination of the following therapies:

- TCSs, e.g., mometason 0.1% ointment
- TCIs, e.g., tacrolimus 0.1% ointment
- Emollients

BSC usage was assumed to be different for responders and non-responders. Resource use for the medications included in BSC is presented in the Table 63. Unit costs of treatments used in BSC were sourced from the BNF.[188]

Table 63. BSC resource use and cost for responders and non-responders per week for adult and adolescent populations

Medication	Amount per year		Cost per year (GBP)		Source
	Responders	Non-responders	Responders	Non-responders	
TCI					
Protopic 0.1% ointment (g per week)	0	1.52	£0	£51.99	NICE TA814[3], BNF[188]
TCS					
Mometasone 0.1% ointment (g per week)	29.59	58.46	£324.55	£641.32	NICE TA814[3], BNF[188]
Emollient (packs per week; emollient cost is averaged)					
Aveeno cream (500 ml)	26.09	52.18	£168.80	£337.60	NICE TA814[3], BNF[188]
Cetraben ointment (500 g)	26.09	52.18	£147.93	£295.85	
Dermol cream (500 g)	26.09	52.18	£172.97	£345.94	
Epaderm ointment (1 kg)	13.04	26.09	£169.71	£339.42	
Hydromol ointment (1 kg)	13.04	26.09	£71.75	£143.49	
White soft paraffin 50% / Liquid paraffin 50% ointment (500 g)	26.09	52.18	£119.23	£238.46	
Oilatum cream (1000 ml)	13.04	26.09	£68.88	£137.75	

Abbreviations: BSC, best supportive care; BNF, British National Formulary; GBP, 2024 pounds sterling; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor

B.3.5.2. Health-state unit costs and resource use

B.3.5.2.1. Cost of disease management and monitoring

Health state costs were incurred by patients for each cycle that they reside in a given health state (apart from the death state). Health state costs capturing disease management costs such as medical appointments, accident & emergency (A&E) visits, hospitalisations, and blood tests. It was assumed that health state costs were equal for adult and adolescent populations.

A summary of annual healthcare resource use (HCRU) and costs, stratified by responders and non-responders, is presented in Table 64. The unit cost for each healthcare resource was sourced from NHS reference costs.[191] The resource use presented in Table 64 was sourced from previous NICE technology appraisals for dupilumab and baricitinib (TA534 and TA681, respectively).[1,2] Resource use values were validated by UK clinical experts and updated to ensure that they represent UK clinical practice.

Table 64. HCRU and costs for responders and non-responder, per year, in adult and adolescent populations

Resource use	Resource use		Unit cost (GBP)	Annual cost (GBP)		Source
	Responders	Non-responders		Responders	Non-responders	
Dermatologist outpatient consultation	4.320	6.000	£164.94	£712.56	£989.66	NICE TA534 and TA681[1,2]
Dermatologist nurse visit	0.350	0.460	£29.00	£10.15	£13.34	
GP consultation	6.150	12.810	£49.00	£301.35	£627.69	
A&E visit	0.021	0.082	£262.69	£5.52	£21.54	
Hospitalisation	0.017	0.130	£1,812.40	£30.81	£235.61	
Day case	0.000	0.200	£518.41	£0.00	£103.68	
Full blood count test	4.000	4.000	£3.00	£12.00	£12.00	
Phototherapy	0.000	0.060	£765.00	£0.00	£45.90	
Psychological support	0.000	0.070	£257.46	£0.00	£18.02	
Total	**N/A**			**£1,072.38**	**£2,067.45**	**N/A**

Abbreviations: A&E, accident and emergency; GBP, 2024 pounds sterling; GP, general practitioner; HCRU, healthcare resource use; NA, not applicable

B.3.5.3. Adverse reaction and other transient events unit costs and resource use

The model incorporated the costs associated with flares and TEAE via the application of one-off event-related costs sourced from the published literature for the UK. The costs and resource use inputs were validated by UK clinical experts.[173] The same approach was used for adult and adolescent populations.

A proportion of the modelled cohort incurred TEAE-related costs, conditional on receipt of treatment and modelled incidence of each event in each cycle. Costs per event are presented in Table 65.

Table 65. TEAE costs in adult and adolescent populations

Event	Resource use	Cost per event (GBP)	Source
Injection site reaction	Dermatologist visit – consultation (WF01A-WF01D, WF02A-WF02D)	£166.39	PSSRU 2023[189]
Allergic conjunctivitis	GP consultation	£49.00	
Infectious conjunctivitis	80% GP consultation and 20% opthamologist consultation (WF01B)	£72.15	TA814,[3] PSSRU 2023,[189] NHS reference costs 2023[191]
Oral herpes	GP consultation	£49.00	TA814,[3] PSSRU 2023[189]
Upper respiratory tract infection	GP consultation	£49.00	
Acne	GP consultation, dermatologist visit – consultation; Epiduo and oral lymecycline (one bottle)	£296.95	TA814,[3] PSSRU 2023,[189] NHS reference costs 2023[191]
Asthma	GP consultation (x2), inhaler (one unit)	£99.50	KOL assumption, PSSRU 2023,[189] BNF[188]

Abbreviations: BNF, British National Formulary; GBP, 2024 pounds sterling; GP, General Practitioner; KOL, key opinion leader; PSSRU, Personal and Social Services Research Unit; TA, technology appraisal; TEAE, treatment-emergent adverse event

A proportion of the modelled cohort incurred flare-related costs, conditional on receipt of treatment and modelled incidence of each event in each cycle.

Medications used to manage flares in the UK are presented in Table 66. These values were validated with UK clinical experts to assure that they reflect UK clinical practice.[173]

Table 66. Flare treatment cost in adult and adolescent populations

Medication group	Medication	Packs per flare	Unit cost (GBP)	Distribution	Source
TCS potent	Betamethasone valerate cream	1	£2.62	42%	TA814,[3] BNF[188]
	Cutivate 0.005% ointment	3.33	£4.24		
TCS very potent	Eumovate 0.05% ointment	1	£5.44	23%	
	Dermovate 0.05% cream	1	£7.90		
Systemic steroid	Prednisolone 5 mg	1	£0.75	29%	
TCI	Protopic 0.1% ointment	0.4	£34.16	0%	
Total cost			**£10.32**		

* in adults, based on dupilumab combination therapy; the same distribution was assumed for adolescents.
Abbreviations: BNF, British National Formulary; GBP, 2024 pounds sterling; TA, technology appraisal; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

B.3.5.4. Indirect costs

The impact of including the societal perspective is explored in scenario analyses via the incorporation of indirect costs. In this scenario, the cost of lost productivity is estimated via the human capital approach.[192] Under the human capital approach, costs associated with loss of productivity were estimated as the product of user-defined variables:

- The proportion of the population employed (employment rate)
- Average annual salary
- Number of workdays lost due to the disease, specified by response status

The employment rate was based on data from ONS; the average annual salary for full time employees in the UK was reported as £34,963 (April 2023). Monthly workdays lost for both responders and non-responders were derived from a study which estimated the number of workdays lost due to moderate-to-severe AD in a multinational setting (including the US, France, and Germany).[193] In the study, number of workdays for placebo was used as a proxy for non-responders and the number for biologics Q2W was used for responders. These values were validated with the UK experts (Table 67).

Table 67. Productivity loss inputs for responders and non-responders

Parameter	Responders	Non-responders	Reference
Number of workdays lost per patient per cycle	3.5	9.1	De Bruin et al, 2020[193]
Employment rate (%)	75.10%		ONS 2023[194]
Average annual salary	£34,963		ONS 2023[194]

Abbreviations: ONS, Office for National Statistics.

In addition to productivity loss, sleep duration stratified by response status and work impairment due to sleep disturbance were included in the indirect cost calculations (Table 68). Sleep duration for responders and non-responders was estimated based on the ARCADIA 1 & 2 clinical trials[127,128] and work impairment due to sleep disturbance was obtained from Hafner et al.[195]

Table 68. Sleep duration and work impairment for responders and non-responders

Sleep duration	Responders	Non-responders	Work impairment
< 6 hours	[redacted]	[redacted]	2.36%
6-7 hours	[redacted]	[redacted]	1.47%
> 7 hours	[redacted]	[redacted]	0.00%

The total indirect costs calculated based on productivity loss and work impairment due to sleep disturbance for responders and non-responders are [redacted] and [redacted] respectively (Table 69).

Table 69. Annual indirect costs for responders and non-responders

Patients with moderate-to-severe AD	Annual indirect costs
Annual indirect costs due to workdays lost	
Responders	£353.46
Non-responders	£919.00
Annual indirect costs due to sleep duration reduction	
Responders	[redacted]
Non-responders	[redacted]

Total annual indirect costs	
Responders	[redacted]
Non-responders	[redacted]

Abbreviations: AD, atopic dermatitis

B.3.6. Severity modifier

Nemolizumab does not meet the criteria for a severity weighting. As expected for treatments for AD and in line with the conclusions from previous AD appraisals assessing QALY shortfall, absolute QALY shortfall is < 12 and proportional QALY shortfall is < 0.85, thus achieving a QALY weighting of 1.0.

B.3.7. Managed access proposal

The company is not intending to submit a managed access proposal at this time. It is considered unlikely that additional data collection through the managed access scheme would provide evidence to address the key uncertainties within the submission.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A summary of the base-case analysis inputs is provided in Appendix N.

B.3.8.2. Assumptions

During the development of an economic model, assumptions are required where there is a lack of available evidence. Key model assumptions are listed in Table 70.

Table 70. Key model assumptions and limitations

Aspect	Assumption	Current approach/rationale
Treatment sequencing	Treatment sequencing included in the base-case	It was assumed in the model that after failure of active treatment, patients move to the 'No response' health state where they may receive another active treatment (biologic or JAK inhibitor) with BSC. This treatment sequencing is applied to reflect how non-responders would be treated in UK clinical practice, and to address NICE/EAG concerns from previous appraisals in AD regarding the simplified assumption of switching to BSC alone.

		This assumption has been validated by UK clinical experts.[120]
Discontinuation at Week 52	Treatment class-specific conditional discontinuation rates at Week 52 for the comparator treatment	The condition discontinuation rates at week 52 for the comparators were aligned with the Committee's preferred assumption in TA986.[4]
Treatment effect waning	Treatment effect waning leads to treatment discontinuation and transition to the 'No response' health state	The inclusion of treatment effect waning in the economic analysis is aligned with NICE preference, outlined in TA814,[3] and was validated by UK clinical experts.[173] Furthermore, this assumption was explored in scenario analysis.
Response rate at Week 16	Response to treatment at Week 16 was defined by EASI-75	EASI-75 was considered the most appropriate measurement of response, and in line with the approach used in the recent lebrikizumab technology appraisal (TA986).[4] The use of EASI-75 in the base-case allows for indirect comparison with the widest group of UK relevant comparators. UK clinical experts confirmed that this outcome measure is appropriate for decision making and reflects relevant patient outcomes in the UK.[173] Furthermore, this assumption has been explored in scenario analysis.
Response rate at Week 16	Comparators with a non-statistically significant difference in EASI-75 at week 16 were assumed to have an OR of 1	For non-statistically significant differences an OR of 1 is allocated to reflect the relative comparability between treatments from the ITC. This assumption was validated by UK clinical experts [173] and explored in scenario analysis.
Utility	Utilities were determined by response status and are independent of treatment	This assumption was aligned with the preferred approach in TA814.[3] It was assumed that utilities were independent of treatment and were based on response to treatment, the time from treatment initiation and if the patient was an adult or adolescent.
Responder utility	Utility value for responders was assumed to increase over time. Different responder utility values were used for weeks up to 104 and beyond	This assumption was considered appropriate based on the LTE study,[130] which showed an increase in utility values for nemolizumab over time. This assumption was validated with UK clinical experts who confirmed that itch relief is observed shortly after treatment initiation; however, it takes more time for all skin lesions to be cleared.[173] This assumption was applied to the nemolizumab and comparator arms.
Monitoring costs	Monitoring costs were assumed uniform for both the adult and adolescent population	It was assumed that adolescents generally follow the same treatment pathway as adults in moderate-to-severe AD.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; EAG, External Assessment Group; EASI, Eczema Area and Severity Index; LTE, long term extension; NICE, National Institute for Health and Care Excellence; TA, technology appraisal

B.3.9. Base-case results

B.3.9.1. Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness results for nemolizumab are presented in Table 71 and Table 72. The cost-effectiveness analysis results for nemolizumab are presented with the PAS price applied.

In both the adult and adolescent population, nemolizumab was associated with improved QALYs versus all comparators with the incremental discounted QALYs ranging from [redacted] to [redacted] in the adult population and from [redacted] to [redacted] in the adolescent population. In both the adult and adolescent populations there were no incremental differences in total LYs for nemolizumab versus the comparators.

In both the adult and adolescent populations, nemolizumab with PAS was associated with reduced costs versus all of the comparator treatments, with incremental discounted costs ranging from [redacted] to [redacted] in the adult population and from [redacted] to [redacted] in the adolescent population.

Nemolizumab was dominant versus all comparators in both the adult and adolescent population. Therefore, based on a willingness-to-pay (WTP) threshold of £30,000 per QALY gained nemolizumab can be considered a cost-effective use of NHS resources in both adults and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.

Table 71. Base-case results (adult population) with PAS

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	44.859	[redacted]	[redacted]	N/A	[redacted]	N/A
Dupilumab	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 30 mg	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Baricitinib	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Tralokinumab	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	44.859	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 72. Base-case results (adolescent population) with PAS

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	56.509	[redacted]	[redacted]	N/A	[redacted]	N/A
Abrocitinib 100 mg	[redacted]	56.509	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	56.509	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	56.509	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	56.509	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life yea

B.3.10. Sensitivity analyses

B.3.10.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of input parameters. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution:

- costs, age, and AEs and flare duration: gamma
- ORs, normal; response rate, safety, and utilities parameters: beta

These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters. Reproducibility of results was achieved via the inclusion of a random number seed.

Several inputs are derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 10% of the mean value for the purposes of the PSA.

Results of PSA for the adult and adolescent populations are summarised in Table 73 and Table 74, respectively. Scatterplots for the base-case analyses (with PAS) for the adult and adolescent populations, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 17 to Figure 23 for the adult population and Figure 25 to Figure 28 for the adolescent population. Cost-effectiveness acceptability curves (CEACs) appraising nemolizumab versus all comparators are depicted in Figure 24 and Figure 29 for adults and adolescents, respectively.

Based on PSA, the probability that nemolizumab is cost-effective at a WTP threshold of £30,000 per QALY gained is [redacted] versus all comparators in both the adult and the adolescent population.

Table 73. PSA results (adults) with PAS

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	45.186	[redacted]	[redacted]	N/A	[redacted]	N/A
Dupilumab	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 30 mg	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Baricitinib	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Tralokinumab	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	45.186	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: ICER: incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 17. ICER scatterplot (nemolizumab versus dupilumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 18. ICER scatterplot (nemolizumab versus abrocitinib 200 mg in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 19. ICER scatterplot (nemolizumab versus upadacitinib 15 mg in adult population, in adults) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 20. ICER scatterplot (nemolizumab versus upadacitinib 30 mg in adult population, in adults) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 21. ICER scatterplot (nemolizumab versus baricitinib in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 22. ICER scatterplot (nemolizumab versus tralokinumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 23. ICER scatterplot (nemolizumab versus lebrikizumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 24. Cost-effectiveness acceptability curve (nemolizumab versus all comparators in adult population) with PAS

Abbreviations: WTP, willingness to pay

Table 74. PSA results (adolescents) with PAS

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	56.598	[redacted]	[redacted]	N/A	[redacted]	N/A
Abrocitinib 100 mg	[redacted]	56.598	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	56.598	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	56.598	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	56.598	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years

[redacted]

Figure 25. ICER scatterplot (nemolizumab versus abrocitinib 100 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

[redacted]

Figure 26. ICER scatterplot (nemolizumab versus abrocitinib 200 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

[redacted]

Figure 27. ICER scatterplot (nemolizumab versus upadacitinib 15 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

[redacted]

Figure 28. ICER scatterplot (nemolizumab versus lebrikizumab in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

[redacted]

Figure 29. Cost-effectiveness acceptability curve (nemolizumab versus all comparators in adolescent population) with PAS

Abbreviations: WTP, willingness to pay

B.3.10.2. Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs and ICER. Each parameter is allocated a 'high' value and a 'low' value; for all parameters apart from discount rates, the high value and low value is +/- 20% of the mean value. By adjusting each parameter one at a time, the DSA assesses the impact of uncertainty around individual input parameters on the model outcomes. Results are presented in tornado plots, which clearly present the parameters that have the greatest effect on the relevant model outcomes. The ten most influential parameters are presented.

Results of the DSA (with PAS) in the adult and adolescent populations are presented (Figure 30 through Figure 40) and demonstrate the impact of specific parameters on ICER estimates. Overall, the cost-effectiveness results for the adult and adolescent populations were mostly robust to parameter uncertainty. A variety of parameters were observed to impact model results, with the most sensitive parameter to uncertainty being the utility value for the 'Maintained response health' state for the adult population. While this was also one of the most influential parameters in the adolescent population, in most cases the input most sensitive to changes was observed as being QALY discounting.

Figure 30. Tornado plot (nemolizumab versus dupilumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 31. Tornado plot (nemolizumab versus abrocitinib 200 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 32. Tornado plot (nemolizumab versus upadacitinib 15 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 33. Tornado plot (nemolizumab versus upadacitinib 30 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 34. Tornado plot (nemolizumab versus baricitinib in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 35. Tornado plot (nemolizumab versus tralokinumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 36. Tornado plot (nemolizumab versus lebrikizumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 37. Tornado plot (nemolizumab versus abrocitinib 100 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 38. Tornado plot (nemolizumab versus abrocitinib 200 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 39. Tornado plot (nemolizumab versus upadacitinib 15 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 40. Tornado plot (nemolizumab versus lebrikizumab in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

B.3.10.3. Scenario analysis

A number of scenario analyses were performed, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and model parameters. Results of the scenario analyses (with PAS) for the adult and adolescent populations are presented in Table 75 to Table 85. The results of all scenario analyses were comparable to the base-case cost-effectiveness estimates, with nemolizumab remaining cost-effective versus all comparators in all scenarios in both the adult and adolescent populations. Therefore, these results demonstrate that the base-case cost-effectiveness estimates were robust to alternate model assumptions and parameters.

Table 75. Scenario analyses results (dupilumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 76. Scenario analyses results (abrocitinib 200 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	£705,531 (CE)
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 77. Scenario analyses results (upadacitinib 15 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 78. Scenario analyses results (upadacitinib 30 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	£231,335 (CE)
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 79. Scenario analyses results (baricitinib in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 80. Scenario analyses results (tralokinumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 81. Scenario analyses results (lebrikizumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 82. Scenario analyses results (abrocitinib 100 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 83. Scenario analyses results (abrocitinib 200 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 84. Scenario analyses results (upadacitinib 15 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 85. Scenario analyses results (lebrikizumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£133,492 (CE)

Abbreviations: AE. Adverse event; CE, cost-effective; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

B.3.11. Subgroup analysis

No economic subgroup analysis was conducted as part of this submission.

B.3.12. Benefits not captured in the QALY calculation

There are several potential value components that may not be captured fully in the QALY calculations detailed above.

Persistent itching impacts patient sleeping habits, with sleep problems noted to interfere with daily function to some degree in 86.4% of patients with uncontrolled moderate-to-severe AD.[14] Sleep disruption in adults with AD is associated with impaired overall health;[77] sleep disorders carry numerous personal consequences, with research documenting that poor sleep is linked to development of depression, suicide, anxiety, and disability.[196] The impact of nemolizumab therapy on SD NRS does not form part of the reference case, and hence the QoL benefits of decreased sleep disturbances may not be appropriately captured.

Patients with AD experience significant out-of-pocket costs as a result of the disease; the total out-of-pocket costs related to AD across Europe is estimated to be €4.7 billion.[20] In addition to the out-of-pocket costs in AD, there are significant indirect societal costs, related to productivity loss due to sleep deprivation, absenteeism, and presenteeism. The impact of indirect costs to patients with moderate-to-severe AD has been explored in the scenario analysis but is not included in the base-case analysis.

Adults with AD are almost three-times as likely to develop an infection than adults without AD,[67] causing significant morbidity and requiring additional healthcare resource use.[68] Our QALY calculation does not capture the benefits associated with avoided secondary infections, both on a patient-level and on a societal level where there is an emphasis on the importance of good antibiotic stewardship, to which reducing upstream need would be expected to have a valuable contribution.

Nemolizumab benefits from a less intensive dosing schedule than other biologic treatments currently available to patients (e.g. dupilumab, tralokinumab, lebrikizumab). Nemolizumab is administered initially at Q4W, decreasing to Q8W as

a maintenance regime. In contrast, dupilumab is administered Q2W, lebrikizumab is administered at Q4W, and tralokinumab is typically Q2W but may decrease to Q4W if the physician deems this appropriate. Where long-term effectiveness has been shown to be comparable, the less intensive dosing schedule for nemolizumab confers additional benefits for patients through reduced treatment burden, which is particularly beneficial in patients who may have a fear of injections, who travel frequently, and who may have difficulties remembering to take more frequent doses e.g. once-daily JAK inhibitor. The less intensive dosing frequency of nemolizumab has the potential to decrease the number of missed doses and improve adherence. Benefits of reduced dosing in the maintenance period are not an element captured by EQ-5D and have not been captured in the QALY calculation.

In addition to patient level benefits, reducing the number of injections, and the attendant waste created, would be expected to have a significant environmental impact. The healthcare sector accounts for up to 5% of the UK national carbon footprint, and in response NHS England have committed to a target of net zero by 2045. Part of achieving this target will require working with suppliers to minimise emissions at each step, for example through low-carbon substitutions and product innovation.[197,198] Carbon emissions are associated with the raw material extraction, production, distribution, and disposal of treatments and devices, and it may be assumed that for technologies like nemolizumab emissions per syringe/pen may be similar. However, nemolizumab may be predicted to be associated with a reduction in attributable emissions and plastic waste compared to other technologies, primarily due to lower dosing frequency at both the initial and maintenance phases of treatment.

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

Following the Professional Society for Health Economics and Outcomes Research Good Research practice guidelines on model validation and transparency, the following aspects of model validation were assessed:

- Model verification – the major spreadsheet calculations and VBA subroutines were assessed for accuracy, and to ensure they operate as intended. Model parameters were reviewed against their source, to ensure that there are no transcription errors. Input derivation and implementation were reviewed, to ensure that the inputs were derived and implemented correctly. Sensitivity and extreme value analysis were conducted to ensure model output is internally consistent and that the direction and magnitude of model outputs behave as expected.
- Model face validity – the model structure, key model assumptions and inputs have been validated by health economics and clinical experts specialising in the treatment of AD in a modified Delphi panel and two rounds of expert interviews.[120,173]
- Model external validity – different models were identified that addressed the same problem and compared similar predicted outcomes. The model outcomes for the comparator arms were validated against outcomes reported in TA816 (for the comparators that were reported).[3]

B.3.14. Interpretation and conclusions of economic evidence

B.3.14.1. Interpretation of economic evidence

Long-term cost-effectiveness analyses were conducted using data from ARCADIA 1 & 2, ARCADIA-CYCLO and the LTE study to compare nemolizumab (with BSC) versus all relevant comparators (with BSC) in adult and adolescent (≥ 12 years) patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.[127-130] The cost-effectiveness analyses showed that:

- Nemolizumab was associated with greater QALYs compared with all comparators in both the adult and adolescent populations. The greater QALY gain for nemolizumab versus the comparators was driven [redacted], which resulted in patients receiving nemolizumab [redacted].

- In both the adult and adolescent populations, nemolizumab was associated with cost savings versus all comparator treatments. Lower total costs were driven by the [redacted].

- Nemolizumab was dominant versus all comparators in both the adult and adolescent populations. Therefore, nemolizumab can be considered a cost-effective use of NHS resources in both adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.

Extensive sensitivity analyses were conducted, representing a key strength of the economic analyses, which has showed that the cost-effectiveness results are robust to changes in the input parameters and assumptions:

- The PSA results were comparable to the base-case deterministic results in both the adult and adolescent populations. Based on the PSA, the probability that nemolizumab is cost-effective at a WTP threshold of £30,000 per QALY gained is [redacted] versus all comparators in both the adult and adolescent populations.

- The DSA results demonstrate that overall, the cost-effectiveness results were robust to parameter uncertainty.

- Scenario analysis results showed that the cost-effectiveness results were robust to changes in the data sources and model assumptions. In all scenarios, nemolizumab remained cost-effective versus all comparators in both the adult and adolescent populations based on a WTP threshold of £30,000 per QALY gained.

B.3.14.2. Strengths and limitations of economic evidence

The economic analyses are supported by extensive clinical trial data from the 2 phase 3 trials ARCADIA 1 & 2, the phase 3b ARCADIA-CYCLO trial (for adult population only) and the ongoing LTE study.[127-130] These trials include long-term

efficacy and safety data for nemolizumab (with BSC) in both adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated. These trials are well designed, high quality RCT with appropriate sample sizes which were conducted in relevant European, US and UK settings and can therefore be considered generalisable to a UK population and the most suitable evidence to support these economic analyses.

The hybrid model structure was designed to accurately capture the short-term benefits in the first year of treatment and the long-term treatment benefits from year 2 onwards in patients with moderate-to-severe AD. This model structure is aligned with the structure used in TA814[3] and TA986[4] and has been further validated by UK health economic and clinical experts.[173] Furthermore, the economic model has incorporated previous NICE committee and clinical expert feedback by including treatment sequencing for patients who do not respond to treatment, where a proportion of patients will switch to receive subsequent biologic or JAK inhibitor treatment. Therefore, the model structure used in the economic analyses can be considered to accurately reflect UK clinical practice for patients with moderate-to-severe AD.

A limitation of the economic analyses was the requirement to make long-term projections for the patient's lifetime based on relatively short-term clinical data. This is a common limitation of health economic models, which remains an essential principle of health economic modelling in the absence of long-term data. However, the economic analyses are supported by the ongoing LTE study which provides long-term clinical data for nemolizumab for an additional 56 weeks based on the currently available interim data cut.[130] During the development of an economic model, it is also necessary to make assumptions. Where appropriate, assumptions used in the economic analyses were aligned with TA814[3] and TA986.[4] Furthermore, to account for the uncertainty related to these assumptions, extensive sensitivity and scenario analyses were conducted to demonstrate that the base-case cost-effectiveness results were robust to changes in model assumptions and input parameters.

There are no RCTs that provide direct head-to-head comparison of nemolizumab with any of the relevant comparators. In the absence of this evidence, an NMA was conducted to estimate the relative efficacy of nemolizumab versus the comparators included in the decision problem. To minimise the uncertainty related to the NMA results, sensitivity analyses were conducted which are presented in Appendix M. A limitation of the NMA was the availability of clinical data for all comparators. Indirect comparison versus abrocitinib 100 mg in the adult population was not feasible based on the lack of clinical data available to support this comparison. Therefore, it was not considered appropriate for abrocitinib 100 mg to be included in the economic analysis in the adult population based on the significant uncertainty that would be associated with the cost-effectiveness estimates. There was also a lack of data available for the comparators in a second-line moderate-to-severe AD adolescent population. Therefore, in the absence of second-line adolescent data, indirect comparison in a first-line moderate-to-severe AD adolescent population was considered the most appropriate approach to determine response rate at Week 16.

B.3.14.3. Conclusions

AD is a complex disease characterised by heterogeneity in clinical presentation,[38] with patients responding differently to currently available treatments.[104] AD is difficult to clinically manage, especially for patients with moderate-to-severe disease.[63,105-108] Both biologics and JAK inhibitors are associated with AEs, with biologics targeting IL-4/IL-13 immune signalling (dupilumab, tralokinumab, lebrikizumab) characterised by ocular surface disease and conjunctivitis and JAK inhibitors associated with safety concerns at the class level. Therefore, there remains an unmet need for increased therapeutic diversity and choice available to patients with moderate-to-severe AD. This is supported by previous NICE committee conclusions that increased therapeutic diversity and a choice of effective treatments are important to patients with AD.[3]

Clinical trial data from the ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study have demonstrated that nemolizumab is a safe and effective treatment.[127-130] The use of this clinical data in the economic analyses has demonstrated that in both the adult and adolescent populations nemolizumab was considered dominant versus all comparators. Therefore, nemolizumab can be considered a cost-effective use of

NHS resources in both adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated. Comprehensive sensitivity and scenario analyses have shown that overall, the cost-effectiveness estimates are robust to changes in the input parameters and model assumptions limiting the uncertainty in the conclusions of the economic analysis.

Nemolizumab offers patients with moderate-to-severe AD with a novel, safe, and effective treatment with a mechanism of action that is distinct from the currently available licenced biologics that target IL-4/IL-13 signalling. Furthermore, nemolizumab represents an alternative treatment option, with a reduced risk of conjunctivitis and ocular surface disease complications associated with other biologic therapies, and without the safety concerns of the JAK inhibitors. Overall, nemolizumab can be considered a clinically and cost-effective use of NHS resources that addressed the unmet need for increased therapeutic diversity to patients with moderate-to-severe AD.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nemolizumab for treating moderate-to-severe atopic dermatitis in people 12 and over [ID6221]

Summary of Information for Patients

October 2024

File name	Version	Contains confidential information	Date
[ID6221] Nemolizumab SIP 151124 [noCON]	2.0	No	15/11/2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Nemolizumab (Nemluvio®)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Nemolizumab will be used by patients aged 12 years or older who have been diagnosed with moderate-to-severe atopic dermatitis (AD) and are candidates for systemic therapy (drugs that work throughout the whole body) but who have not responded adequately to at least one systemic therapy, or for those whom these are not suitable. This population is similar to previous National Institute for Health and Care Excellence (NICE) appraisals for currently available systemic treatments in AD.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

A marketing authorisation application was submitted via Access Consortium NASWSI for nemolizumab for the treatment of AD. An opinion from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the organisation that gives companies legal permission to sell a medicine in the UK, is anticipated. Additional detail of the anticipated regulatory timelines is presented in section B.1.1. of the main company submission.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

No collaborations or conflicts of interest require disclosure. Note: for transparency, Galderma work with patient groups and healthcare professionals in a variety of ways, including, as examples, global awareness campaigns, and training/education programmes.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is AD?

Atopic dermatitis (AD), also known as 'atopic eczema', is a common, chronic (long-lasting) inflammatory (biologic response to external stimuli) skin disease. AD can flare (get worse) from time to time and then get better. The exact cause of AD is unknown but it is believed to be triggered by environmental factors (e.g., food allergens, living in an urban setting) in people whose genes increase their risk of AD.[1] Atopic dermatitis commonly occurs in children below five years old but can continue into, or start during, adulthood.[2]

Atopic dermatitis is characterised by persistent, severe itch (pruritis) and painful, inflamed eczema-like blisters/sores (lesions).[1]

Moderate-to-severe AD may be diagnosed when one or more of the following features are present: at least 10% of the body surface area is affected, individual lesions with moderate-to-severe features, highly visible or functionally important areas affected, or significantly impaired quality of life.[3]

How many people are living with AD in the UK?

It is estimated that approximately 1 in 40 (2.4%) adults (aged 18 years old or over) had AD in the UK (2015–2019).[4] Between 7.5%–8.3% of these individuals had moderate-to-severe AD (5,988–9,098 adults), and of these, approximately 60% received some form of systemic therapy.[4]

Another study which looked at adults and children in England reported similar findings,[5] approximately 1 in 10 (9.6%) children and 1 in 23 (4.3%) adults had AD.[5]

How does AD affect patients and their families?

Itch is reported to be the most burdensome symptom associated with AD,[6,7] and itch relief is the primary goal for patients with moderate-to-severe AD.[8,9] Approximately 42% of adults with moderate-to-severe AD report itching for more than 18 hours per day and 14% describe itching as 'unbearable'.[10] Persistent itching contributes to:

- Poor mental health: adults with AD are 14% more likely to be diagnosed with depression than adults without AD,[11] with the likelihood being higher for patients with more severe AD. Similar results were noted for anxiety

(17% more likely than non-AD adults).[9] Patients with AD are more likely to have suicidal thoughts and to carry out suicidal acts.[12]

- Sleep disruption: the majority (86.4%) of patients with uncontrolled moderate-to-severe AD report sleep problems interfere with their daily lives to some degree.[13] Sleep disruption is associated with worse overall health, tiredness, daytime sleepiness, missed workdays and additional doctor visits.[14]

- Decreased quality of life:[8,15] on average, people with AD have a 22% reduction in quality of life compared to someone who is in 'perfect health';[16] among UK patients, 72–85% of patients with moderate-to-severe AD stated it interfered with their ability to do regular daily activities and most (73–80%) patients report that they have tried to hide their AD from someone in their lives.[17]

- Chronic (long-lasting) itching drives persistent, repetitive scratching, creating a vicious circle: the 'itch-scratch cycle'.[18] As well as physical pain,[19] damage to the skin barrier from scratching enables harmful bacteria and viruses to enter the body; consequently, patients with moderate-to-severe AD are at high risk of skin infections.[20]

- Patients with AD have a tendency to develop additional allergy-related diseases (e.g., asthma, hay fever),[21] high blood pressure, high blood cholesterol, diabetes, and obesity.[2] Additionally, over an 18-year period, patients with severe AD had a 62% increased risk of death.[22]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

There are no new diagnostic tests required for the treatment of AD using nemolizumab. The diagnosis of AD is based on a doctor or skin care specialist's assessment of disease symptoms, severity, and patient-reported history;[23] patients are diagnosed with 'moderate-to-severe' AD when one or more of the following features are present:[3]

- more than 10% of their body surface area is affected by AD

- individual AD-related sores with moderate-to-severe features

- AD is affecting highly visible or important areas (e.g., neck, face, genitals, palms, soles)

- the patient's quality of life is significantly worsened by their AD

The itching and discomfort experienced by patients with moderate-to-severe AD disrupts their lives and significantly impacts sleep,[13] mental health,[8,11,15,17,19,24] and quality of life.[25]

The most commonly used clinical assessment measures of symptoms, severity, and patients quality of life include: Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), Dermatology Life Quality Index (DLQI) and Peak Pruritus Numerical Rating Scale (PP NRS).[26]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.

  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current treatment in the UK

In the UK, neither NICE nor the British Association of Dermatologists have published guidelines on the diagnosis and management of moderate-to-severe AD in adults or adolescents.

The aims when treating AD are to reduce itch,[1] improve skin barrier function,[27] and establish lasting disease control that allows patients to enjoy a higher quality of life and higher function in their work-, school- and social-lives.[1]

International guidelines, relevant to the UK, recommend a stepwise approach to treatment (Figure 1).[28-33] Patients begin with non-drug options (emollients, moisturisers, and educational programmes); if these are insufficient to relieve the symptoms of AD, patients escalate to topical therapies (applied directly to the skin) aimed at reducing inflammation, and finally systemic treatments (first-line systemic immuno-suppressants then second-line Janus kinase [JAK] inhibitors, and biologics).[28-33]

Best supportive care

Best supportive care (BSC) is the foundation of therapy upon which systemic treatments are added, based on response to therapy or disease flaring. Emollients and moisturisers protect and restore the skin barrier, relieve dryness and reduce itch.[30,33] When not able to achieve adequate disease control, topical therapies can be introduced including corticosteroids or calcineurin inhibitors.[30,33]

Systemic immunosuppressants

When topical therapies are not able to relieve symptoms, patients receive systemic immunosuppressants like ciclosporin, methotrexate, azathioprine and mycophenolate mofetil (referred to as first-line systemic therapies). Ciclosporin is the only first-line systemic therapy licensed for use in adults; while the others are all used 'off-label' (an unapproved use; see glossary).[34] Despite being used off-label, methotrexate is the preferred systemic immunosuppressant in UK practice.[35] All of the previously mentioned immunosuppressants have relatively poor safety profiles, and require patients to have frequent (~3 monthly) blood tests even when well tolerated.[36,37]

Biologics

When first-line systemic therapies are not able to treat a patient's symptoms, or they are unable to take them, subsequent second-line systemic therapies include biologics and JAK inhibitors.[29,32]

Biologic treatments are a type of medicine that is produced in living cells in a laboratory and are designed to target a specific target within the body. There are three biologic treatments currently available to patients in the UK. Dupilumab and tralokinumab are approved for adult patients with moderate-to-severe AD whose disease did not respond adequately to at least one other systemic therapy or for whom other therapies are not suitable.[38,39] NHS England will commission dupilumab and tralokinumab treatment for patients aged less than 18 years where specific commissioning conditions within a NICE technology assessment or NHS England policy are met. In addition, lebrikizumab has recently been approved by NICE for patients 12 years and over with moderate-to-severe AD whose disease did not respond adequately to at least one other systemic therapy or for whom other therapies are not suitable.[40]

JAK inhibitors

JAK inhibitors, abrocitinib, baricitinib and upadacitinib are approved for use in adult patients with moderate-to-severe AD who have not responded to at least one systemic immunosuppressant or for whom other therapies are not suitable.[41-43] Abrocitinib and upadacitinib are also recommended as options for adolescents aged ≥ 12 years.[39,44]

JAK inhibitors are associated with safety concerns related to an increased risk of major adverse cardiovascular events (like stroke and heart attack), cancer, venous thromboembolism (dangerous blood clots), serious infections, and death.[45-47] UK government guidance advises against prescribing these medicines unless there

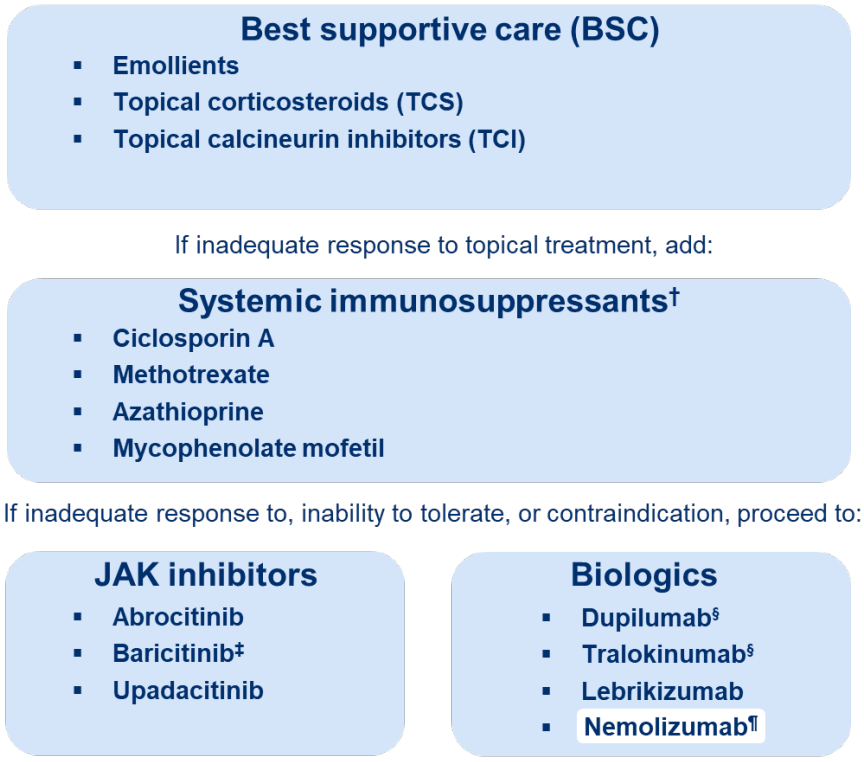
are no suitable alternatives in adults aged ≥ 65 years, patients with current or past long-time smoking, and other risk factors for cardiovascular disease or cancer.[46]

Proposed positioning of nemolizumab

Nemolizumab is a novel biologic treatment that offers a new option to patients; nemolizumab works in a different way to dupilumab, tralokinumab and lebrikizumab to improve patient's itch and disease control by targeting a different pathway in the body.[48]

The proposed positioning of nemolizumab is for adult and adolescent patients with moderate-to-severe AD whose disease is not adequately treated by first-line systemic therapy or for whom other therapies are not suitable. Therefore, nemolizumab would be a direct alternative to the other biologics and JAK inhibitor treatments (Figure 1).

Figure 1. Atopic dermatitis treatment pathway, with proposed positioning of nemolizumab in the current UK treatment pathway as a second-line systemic treatment



Abbreviations: BSC, best supportive care; JAK, janus kinase; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors.
†First line systemic therapies are conventional immunosuppressants; all use in AD is off-license except ciclosporin A in persons over 16 years
‡Baricitinib is only approved for treating moderate-to-severe AD in adults only
§Subsequent to the NICE recommendations for dupilumab and tralokinumab in adult patients; NHS England will commission treatments for patients aged less than 18 years where specific commissioning conditions within a NICE technology assessment (TA) or NHS England policy are met.[49,50]
¶Aspirational positioning of nemolizumab in the treatment pathway.
Note: phototherapy is not shown as it is not universally available and is used variably across the UK.[35]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Although the goals of AD therapy are to improve skin barrier function,[27] reduce itch and establish lasting disease control, the rationale is that achieving these allows patients to enjoy a higher quality of life and higher function in their work-, school- and social-lives.[1] Itch is the most burdensome symptom to patients,[6,7] and itch relief is the main goal for most patients with moderate-to-severe AD.[8,9] In booklets published by the UK National Eczema Society, itching is identified as the 'worst and most uncomfortable symptom'; a patient is quoted as saying *'Once I started scratching, I found it was impossible to stop.'*[51] Another patient reported: '*I was so distracted by the eczema that I only narrowly avoided being run over when crossing the road. The most frightening thing about this was that I wished I had been.'*[52]

In the report 'Eczema Unmasked: revealing the true impact of life with eczema',[17] there are multiple examples of how patients experience life with AD:

- 72–85% of patients with moderate-to-severe AD noted that AD interfered with their ability to do regular daily activities and most (73–80%) patients report that they have tried to hide their condition from someone in their lives.[17]

- 92–95% of patients with moderate-to-severe AD feel self-conscious or embarrassed about their condition.[17] The impact of AD on mental health is not always appreciated; as one patient reported: *'I have lived with severe eczema [AD] for decades and, over what is perhaps now hundreds of consultations, have rarely been asked "how are you feeling?" In my experience the health impact of eczema is not well understood or addressed.'* [17]

- 25–33% of patients with moderate-to-severe AD say that their close friends and family don't fully understand how difficult and painful their condition can be.[17]

- The majority of patients with moderate-to-severe AD report that their disease has negatively affected their school-, work-, social-, family-lives and their sexual intimacy.[17]

Section 3: The treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Nemolizumab is a new biologic therapy that targets a substance called IL-31,[53-55] which is part of the pathway that drives itch and contributes to inflammation, and skin barrier disruption in AD.[53,56] Higher levels of IL-31 are present in skin lesions and the blood of patient with AD, and is associated with disease severity and itch.[57-59]

The itch experienced by patients with AD is a result of an irregularity in the communication between the skin, the immune system, and the nervous system.[56] Immune cells release IL-31, which interact with nerves to cause the feeling of itch, leading to the patient scratching.[56] Scratching causes the skin to become inflamed and results in immune cells producing more IL-31, and so the cycle continues.[56] Separately, IL-31 encourages other cells to drive sustained inflammation and disruption to the skin barrier.[54,56,59-63]

Nemolizumab works by preventing IL-31 from interacting with nerves, relieving itch, inflammation, and improving the skin barrier.[53-55] Nemolizumab is the first biologic therapy to target this specific process which drives itch,[53,56] while other biologic therapies all target a different process within AD.[48] Nemolizumab addresses an unmet need for additional effective, safe, and targeted treatment options that address the burdensome symptoms such as itch and control the underlying inflammation in patients with AD.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☒Yes

☐No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

It is anticipated that nemolizumab will be used with BSC (which can include emollients, topical corticosteroids, and topical calcineurin inhibitors) for patients with moderate-to-severe AD, as seen for the other biologics dupilumab, tralokinumab, and lebrikizumab.[35,38,40] Moisturizer, emollients, topical corticosteroids, and topical calcineurin inhibitors provide local relief to affected areas, while nemolizumab provides a systemic effect on the processes that contribute to itch, inflammation, and dysfunction of the skin barrier.[54,56,59-63]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Nemolizumab is administered as an injection beneath the skin; patients/carers who are to use/administer nemolizumab will need to be taught the proper technique by a healthcare professional before they are able to administer this drug.[55] Patients receive an initial dose of **60 mg** followed by **30 mg every four weeks** for 16 weeks.[55] Patients who achieve a response to treatment then switch to a less frequent, 'maintenance' dose of **30 mg every eight weeks**.[55]

Treatment will continue for as long as patients respond positively to treatment; if at any point a patient notices that the drug has become less effective or completely stops working, they should reach out to their doctor or prescriber.[55]

Nemolizumab needs to be administered less frequently than the other biologics,[55] dupilumab,[38] tralokinumab[39] or lebrikizumab,[40] which are every two weeks until Week 16. Patients who respond well to tralokinumab and lebrikizumab may be allowed to transition to administration every four weeks if their doctors think it is appropriate.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and

completion dates etc. Please provide references to further information about the trials or publications from the trials.

The safety and clinical efficacy (i.e., how well the drug works) of nemolizumab in patients with AD has been tested in four main studies (a full description of the studies can be found in section B.2 of the company submission):

- **ARCADIA 1 & ARCADIA 2**:[64] these studies compared the safety and efficacy of nemolizumab with BSC versus placebo (i.e., an inactive substance used to compare to an active medication) with BSC in adult and adolescent participants with moderate-to-severe AD not adequately controlled with topical treatments. The studies ran over 48 weeks.

  The **severity of disease** was measured by:

  - *Investigator's Global Assessment (IGA):* An assessment by an investigator/doctor to rate the severity of the disease based upon the number of lesions that are present on the patient's skin.
  - *Eczema Area and Severity Index (EASI):* An assessment by an investigator/doctor to rate the severity and extent of disease in four body areas of the patient.

  ARCADIA 1 included 161 sites across 14 countries in Europe, North America, and Asia-Pacific, and enrolled 941 participants. ARCADIA 2 included 120 sites across 11 countries in Europe (including the UK), North America, and Asia-Pacific (Singapore only), enrolling a total of 787 patients. To take part, patients had to:

  - Be aged 12 years old and over
  - Have chronic AD for over 2 years
  - Have has inadequate response to topical corticosteroids
  - Have AD involvement for 10% of body surface area
  - Clinical assessment scores indicating moderate-to-severe disease: IGA score ≥ 3, EASI score ≥ 16, and Peak Pruritis Numeric Rating Scale PP NRS score ≥ 4

- **ARCADIA-CYCLO**:[65] this study compared the safety and efficacy of nemolizumab with BSC versus placebo with BSC in adult participants with moderate-to-severe AD who were not adequately controlled with/not advised to use first-line systemic treatment, ciclosporin, for medical reasons. The study ran over 16 weeks.

  The **severity of disease** was measured by:

  - Eczema Area and Severity Index (EASI)

  The severity of **itch** was measured by:

- *Peak Pruritis Numeric Rating Scale (PP NRS).* This scale considers the most intense itch experienced in the last 24-hours as reported by the patient themselves from 0 to 10.

ARCADIA-CYCLO included 58 centres across 6 countries in Europe (excluding the UK) and enrolled 273 participants. To take part, patients had to:

- Be aged 18 years old or over
- Have chronic AD for over 2 years
- Have had inadequate response to topical corticosteroids
- Had inadequate response to, or be medically inadvisable to take ciclosporin
- Have AD involvement for 10% of body surface area
- Clinical assessment scores indicating moderate-to-severe disease: IGA score ≥ 3, EASI score ≥ 20, and PP NRS score ≥ 4

- **ARCADIA Long-term Extension (LTE) study**:[66] this long-term trial is still ongoing and is mainly testing the safety of nemolizumab over 200 weeks. Most participants in this study have already taken part in other studies where nemolizumab was being investigated. No placebo arm was included in this trial; however, some patients enrolled from previous trials may have received placebo in those trials.

  The aim was to determine:

  - **Safety** of nemolizumab over the course of this study, investigators noted the different side effects that happened, as well as how severe they were, and if/how these effects resolved.

  The ARCADIA LTE study has a total of 1751 participants and is currently being held at 343 sites across Europe [including the UK], North America, and Asia Pacific.

Information can also be found at the clinical trials.gov website:

- ARCADIA 1: https://clinicaltrials.gov/study/NCT03985943
- ARCADIA 2: https://clinicaltrials.gov/study/NCT03989349
- ARCADIA-CYCLO: https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results
- ARCADIA LTE: https://clinicaltrials.gov/study/NCT03989206

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Understanding the ARCADIA clinical trials

The key measures used to show how well nemolizumab works in the clinical trials:

- Eczema Area and Severity Index (EASI): whether a participant had a 75% improvement in their condition over the trial period from baseline, referred to as 'achieving EASI-75'
- Investigator's Global Assessment (IGA): whether participants had a score of 0 or 1 (corresponds to clear or almost clear skin) or an improvement on the same scale of more than two points
- Peak Pruritis Numerical Rating Scale (PP NRS): whether a participant had an improvement in their itch of more than four points

The clinical trials also included secondary measures (further details on these are given in section B.2 in the main company submission)

ARCADIA 1 & 2

In both ARCADIA 1 & 2 trials, nemolizumab treatment resulted in a clinically meaningful and statistically significant (unlikely to be explained by chance) improvement in disease severity in adult and adolescent participants with moderate-to-severe AD not adequately controlled with topical treatments (further detail can be found in section B.2 of the company submission):[64]

- A greater proportion of participants demonstrated IGA success with nemolizumab (with BSC) treatment compared to those who received placebo (with BSC) at Week 16 (ARCADIA 1: 36% versus 25%, respectively; ARCADIA 2: 38% versus 26%, respectively).
- A greater proportion of participants achieved an EASI-75 with nemolizumab (with BSC) treatment compared with placebo (with BSC) at Week 16

(ARCADIA 1: 44% versus 29%, respectively; ARCADIA 2: 42% versus 30%, respectively).

ARCADIA-CYCLO

Nemolizumab treatment resulted in a clinically and statistically significant improvement in disease severity and reduction in itch in adult participants with moderate-to-severe AD who were not adequately controlled with/not advised to use first-line systemic treatment, ciclosporin, for medical reasons (further detail can be found in section B.2 of the company submission):[65]

- A greater proportion of participants achieved an EASI-75 with nemolizumab (with BSC) treatment compared to those who received placebo (with BSC) at Week 16.
- Similarly, a greater proportion of participants achieved an improvement in PP NRS of more than 4 points with nemolizumab (with BSC) treatment compared to those who received placebo (with BSC) at Week 16.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient quality of life is a key consideration. Numerous measures either of quality of life or factors believed to be crucial to improved quality of life were included in the ARCADIA trials:

- The Dermatology Life Quality Index (DLQI) is a 10-question questionnaire that asks patients how their skin condition has affected certain aspects of their daily lives over the past week on a scale of 0–3.[67] The questions cover various topics, including symptoms, shopping, wardrobe selection, social activities, work/education and relationships. The total score, out of a maximum of 30, indicates how much of an impact AD has on patients' quality of life; a score of 0 would mean that AD has had no effect on someone's quality of life, whereas a score of 30 would indicate a very severe impact.
    - When overall quality of life was assessed using the DLQI scale (where a lower score indicates a higher quality of life), patients in ARCADIA 1[68] and 2[69] who were treated with nemolizumab (with BSC) demonstrated a greater improvement in quality of life at Week 16 than patients treated with placebo (with BSC). Further detail can be found in Section B.2 of the company submission.
- The EuroQoL 5-Dimension (EQ-5D) scale also measures patient quality of life. It is a 5-item questionnaire where patients describe the impact of AD on their mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Impact is scored between 1 and 5, where 1 is 'no problems' or 'no pain/discomfort/anxiety/depression' and 5 is 'unable to/extreme problems'. Patients also rate their 'health today' out of 100, with 0 being the worse imaginable health state, and 100 being the best imaginable health state (a 'visual analogue scale').[70]
    - When quality of life was assessed using the EQ-5D visual analogue scale, patients in ARCADIA 1[68] and 2[69] who were treated with nemolizumab (BSC) demonstrated a greater improvement in quality

of life at Week 16 than patients treated with placebo (BSC). Further detail can be found in Section B.2 of the company submission.

- The Sleep Disturbance Numerical Rating Scale (SD NRS) asks patients to rate their sleep the night before on a scale of 0 to 10, with 0 being 'no sleep loss related to signs/symptoms of AD' and 10 being 'I did not sleep at all due to the symptoms of AD.'[71] Patients in ARCADIA 1, 2 and CYCLO rated their sleep disturbance with SD NRS daily in the morning.[68,69,72] Further detail can be found in Section B.2 of the company submission.
    - Across ARCADIA 1,[68] 2,[69] and CYCLO,[72] more patients treated with nemolizumab (BSC) reported decreased sleep disturbance (≥ 4-point improvement in a sleep disturbance numerical rating scale, SD NRS) compared with patients who received placebo (BSC).
- A detailed survey to assess the preferences of patients and physicians in the UK and Germany found patients prioritise reducing sleep disturbance first, and itch reduction second. Physicians also prioritised these outcomes, with itch reduction prioritised over the reduction in sleep disturbance. Time to itch relief was third most important for both groups, and more important to patients. Risk of eye problems was the most important safety concern for both patients and physicians. These preferences affect treatment choice from the perspective of both groups, emphasising the importance of addressing sleep issues, and itch.[73]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Nemolizumab was generally well tolerated and had a safety profile comparable to that of placebo in the ARCADIA 1, 2, and CYCLO trials.[64,65] The number of reported treatment emergent adverse events (TEAE; defined as a side-effect [adverse event] that began after starting a medical treatment) were similar between participants treated with nemolizumab and placebo in all three trials. For example, in ARCADIA 1, 50% of participants treated with nemolizumab and 45% who received placebo had at least one TEAE.[64,65] The majority of TEAE were mild or moderate in severity and easily managed.[64,65] Treatment emergent adverse events leading to treatment withdrawal or study discontinuation were low in all

three trials, e.g., in ARCADIA 1 less than 4% and 3%, respectively.[64,65] No participants died in the trials.[64,65]

The most common TEAE experienced by participants were dermatitis atopic (a worsening of skin condition), asthma, upper respiratory tract infection, headache, and nasopharyngitis (inflammation of the nose and throat); all were easily resolved with routine clinical practice.[64,65]

In the ARCADIA LTE study, an interim analysis at Week 56 demonstrates the safety profile of nemolizumab aligns with the pivotal ARCADIA 1 & 2, and ARCADIA-CYCLO trials, and supports its safe use in participants with moderate-to-severe AD.[66]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of nemolizumab compared to current treatments:

- **Efficacy**: nemolizumab has proven efficacy, and patients may expect rapid improvement in their disease symptoms. Across all trials, nemolizumab treatment resulted in a clinically and statistically significant improvement in disease severity[64] and reduction in itch.[65] Further detail can be found in section B.2 of the company submission.

- **Therapeutic diversity:** nemolizumab works in a different way to the other currently available biologics and JAK inhibitors; it has a different target within the body and specifically targets the molecular pathway that drives itch. There is an unmet need for more safe and effective treatments for patients with moderate-to-severe AD.

- **Safety:** nemolizumab is not associated with any safety concerns, and has marked benefits when compared with JAK inhibitors, all of which have been associated with safety concerns and must display additional safety warnings. This means JAK inhibitors may not be suitable for many patients.

- **Convenient dosing schedule:** nemolizumab is administered every four weeks initially, but patients who respond to treatment will receive nemolizumab every eight weeks. Other biologics are typically used every two weeks (although tralokinumab may be used every four weeks if deemed appropriate, and lebrikizumab is used every four weeks once response has been achieved). JAK inhibitors are taken daily, and patients may occasionally forget to take a dose. Nemolizumab is therefore likely to represent a more convenient option for some patients that could potentially result in reduced missed doses.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Before starting nemolizumab treatment for AD, patients will need to undergo a consultation with doctor or skin care specialist. As nemolizumab is administered by an injection underneath the skin, patients will be required to receive training to do so correctly by a nurse or other healthcare professional, which generally takes 30–60 minutes. This mode of administration may be difficult for patients or care partners with limited mobility. Lastly, some patients may feel some anxiety due to a fear of needles. However, these disadvantages are shared with the other current biologics.

As with all medications, patients taking nemolizumab may experience some side effects following their treatment (refer to section 3g). The side effects experienced by patients taking nemolizumab are generally tolerable, mild, or moderate in severity, and easily managed.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How does the model reflect AD

An economic model has been developed to assess the value of nemolizumab with BSC to the NHS in patients with moderate-to-severe AD. The economic model can estimate the long-term clinical and cost benefits (cost-effectiveness) of nemolizumab treatment compared to the current standard of care for patients with moderate-to-severe AD who have not responded to at least one other systemic therapy, or for whom these are not suitable and inform whether it offers value for the healthcare system (further detail can be found in Section B.3 of the company submission).

The cost-effectiveness of nemolizumab is assessed separately in the adult and adolescent populations. In the adult population nemolizumab is compared against dupilumab, baricitinib, upadacitinib, abrocitinib, tralokinumab and lebrikizumab. In the adolescent population, nemolizumab is compared against lebrikizumab, upadacitinib and abrocitinib. In both the adult and adolescent populations, nemolizumab and the comparators are used with BSC (including emollients, topical corticosteroids and topical calcineurin inhibitors); non-responders to treatment go on to receive subsequent therapy consisting of BSC, biologics or JAK inhibitors.

The economic model includes two distinct phases, reflecting the treatment and monitoring that a patient will undergo in the short- and long-term when starting a new treatment for AD: an initial evaluation over the first year of treatment and then long-term follow-up for the remainder of the patient's life.

In the first phase of the model, after 16 weeks on treatment, response to treatment is checked. Patients who respond to treatment continue their initial treatment. Patients who do not respond stop treatment and receive subsequent therapy. At 52 weeks, patients are assessed again; based on their response they may continue with their treatment or stop treatment.

In the second phase of the model, after 52 weeks of treatment all patients enter the 'long-term follow-up' period. Patients are assigned to one of three groups (health states): 'Maintained response', 'No response', or 'Death'. Patients who responded at Week 16 and continue to respond at Week 52, join the 'Maintained response' health state, where they stay until they stop taking the treatment for any reason. Patients who do not respond to treatment at Week 16 or have stopped treatment at Week 52, move to the 'No response' health state, in which they can switch to subsequent therapy, and stay there until death (move to 'Dead' health state). At any time, patients can move to the 'Dead' health state.

The effect of treatment for nemolizumab is based on the ARCADIA 1 & 2, and ARCADIA-CYCLO clinical trials, which include patients with moderate-to-severe AD receiving nemolizumab. The response to treatment with nemolizumab is based on EASI-75, which is considered by UK clinical experts as an appropriate measure to capture disease response in AD.

Modelling how much treatment extends life

In patients with moderate-to-severe AD, the disease is not expected to have a significant impact on the risk of death, which is reflected in the clinical trials informing this and similar appraisals. Therefore, in the economic model patients with moderate-to-severe AD had mortality rates in line with the general population.

Modelling how much treatment improves quality of life

The economic model measured the impact of moderate-to-severe AD and treatment on patients' quality of life. In the economic model, quality of life (as measured by EQ-5D) was dependent on response to treatment and the total time patients remained responders to treatment. The quality of life is based on data from the ARCADIA 1, ARCADIA 2, ARCADIA-CYCLO trials and LTE study for the adult population, and the ARCADIA 1, ARCADIA 2 and LTE study for the adolescent population. Please refer to Section 3f above.

In addition, the reduced quality of life from flares and adverse events were included in the economic model.

Modelling how much the costs of treatment differ with the new treatment

The economic model estimates the costs associated with treatment, which includes nemolizumab, comparator treatments (other biologics and JAK inhibitors), BSC and drug administration. In addition, costs associated with disease management and monitoring, adverse events and flares are included in the model.

Cost-effectiveness results

The economic model produces outcomes for patients as quality-adjusted life years (QALYs), a measure of how well a treatment improves and/or lengthens a patient's life. One QALY is worth one year of life in perfect health. For example, if a patient gained one QALY because of a new therapy compared to an existing therapy, it would be equivalent to them gaining one year of life in perfect health. Further details on the cost-effectiveness results of nemolizumab can be found in Section B.3.9 of the Company evidence submission.

Uncertainty

As part of the development of an economic model, it is necessary to make assumptions where there is a lack of direct evidence. These assumptions and other impactful elements of the model were tested through sensitivity analysis, where alternate assumptions or values were applied in the economic model to determine how they impact the cost-effectiveness outcomes.

Benefits not captured in the modelling

There are a number of benefits of nemolizumab for patients, their carers and the wider healthcare system that may not be captured in the economic model based on how response to treatment is assessed and the components that are routinely incorporated into economic models for NICE appraisals.

The persistent itching associated with AD impacts patient sleeping habits. Sleep disruption in adults with AD is associated with overall health impairment;[14] sleep disorders also carry numerous personal consequences, with research documenting that poor sleep is linked to development of depression, suicidal thoughts, anxiety, and disability.[9,12] The impacts of sleep disturbance may not be fully captured in the economic model.

Patients with AD experience significant out-of-pocket costs (costs to patients directly in addition to those paid by the NHS) as a result of the disease which are not captured in the model.[74] In addition to these out-of-pocket costs, there are also impacts to society as a result of reduced productivity and missed work time for patients with AD as a result of their sleep disruptions.[75]

Treatment with nemolizumab requires a reduced number of injections compared to the other biologic treatments which may be used for AD. The less frequent injections with nemolizumab represent an additional benefit for patients that is not captured in the model, which is particularly beneficial in patients who may have a fear of injections, who travel frequently, and who may have difficulties remembering to take more frequent doses. As a result, the reduced number of injections with nemolizumab may also result in fewer missed doses, which is not also captured in the economic.

Adults with AD are almost three-times as likely to develop an infection than adults without AD, causing significant impacts to patient health and requiring additional treatment and often hospital admissions.[20,76] The model does not capture the impacts of treatment upon avoiding infections, so may be considered an additional benefit of effective treatment for AD.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Novel mechanism of action

Nemolizumab has a novel mechanism of action and offers an alternative treatment for patients with moderate-to-severe AD. Nemolizumab is distinct from the current biologics (dupilumab, tralokinumab, lebrikizumab) that all target the 'IL-4/IL-13' pathway.[48] Nemolizumab is the first biologic to target the separate and different 'IL-31' pathway which drives itch and contributes to inflammation and skin barrier disruption in AD.[77,78] Nemolizumab has been demonstrated to significantly reduce in itch and skin lesions, and improve the quality of life in patients with AD.[64]

Significantly fewer injections

Nemolizumab requires fewer injections than the currently approved biologics. In a year, a patient who responds to treatment with nemolizumab would be expected to receive nine injections, which compares to 26 injections for dupilumab. This is convenient for patients and may help with adherence (the extent a person follows the recommended treatment) and persistence (how long a person continues to use treatment), which may translate into improved patient outcomes.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

The use of nemolizumab is not expected to raise any equality issues in AD.

However, it is acknowledged there are significant differences in the prevalence of AD in the UK; it is more common in individuals who live in the most deprived areas of the country or who live in urban environments, and is more than twice as likely to affect Asian and Black compared with White individuals.[5] There are documented challenges in assessing AD in individuals with skin of colour,[79,80] which can lead to

an underestimation of disease severity.[79] Certain populations may therefore be more likely than others to receive inadequate treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

National Eczema Society: National Eczema Society

Allergy UK: Eczema (Atopic Dermatitis) | Allergy UK | National Charity

NHS: Atopic eczema - NHS (www.nhs.uk)

Clinical trials:

ARCADIA 1: https://clinicaltrials.gov/study/NCT03985943

ARCADIA 2: https://clinicaltrials.gov/study/NCT03989349

ARCADIA 1 & 2 publication: https://pubmed.ncbi.nlm.nih.gov/39067461/

ARCADIA CYCLO: https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results

ARCADIA LTE: https://clinicaltrials.gov/study/NCT03989206

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Adherence: adherence to treatment is the extent a person follows the recommended treatment regimen (including dose, dosing interval, duration of treatment, and any special instructions)

Atopic dermatitis (AD): also known as 'atopic eczema'; a common, chronic (long-lasting) inflammatory (biologic response to external stimuli) skin disease. characterised by persistent, severe itch (pruritis) and painful, inflamed eczema-like blisters/sores (lesions)

Biologic: a type of medicine that is produced in living cells in a laboratory; biologics are designed to block a specific target within the body, e.g. a particular part of the immune system

BSC: best supportive care

Contraindication: a condition or circumstance that means that a particular drug or therapy should not be used

Dermatology Life Quality Index (DLQI): a 10-question questionnaire used to assess a person's quality of life, specifically in the context of skin diseases

Eczema Area and Severity Index (EASI): an assessment by an investigator/doctor to rate the severity and extent of disease in four body areas of the patient

EuroQoL-5 Dimension (EQ-5D): a common scale used to measure a person's quality of life

Flare: a temporary worsening of AD that may last a long time and which may require additional medical advice and intensified treatment

Janus kinase (JAK): a family of enzymes within the body that are part of the immune system

Janus kinase inhibitors (JAKi): a type of drug that stops janus kinase enzymes from working properly, affecting the immune system

Interleukin-31 (IL-31): a chemical produced by immune cells to help regulating immune responses

Intensification: intensification of treatment is when patients escalate treatment to the next line of the atopic dermatitis treatment pathway

Investigator's Global Assessment (IGA): an assessment by an investigator/doctor to rate the severity of the disease based upon the number of lesions that are present on the patient's skin

Off-label: an unapproved use of an approved drug; drugs are licensed to treat specific conditions but may be effective in treating other conditions as well. In that case, a prescriber may use the drug outside the terms of its license 'off-label' in the best interests of the patient

Placebo: an inactive substance that looks identical to a real medication and is taken in the same way

Peak Pruritis Numeric Rating Scale (PP NRS): a scale that measures the most intense itch experienced in the last 24 hours as reported by the patient themselves. The scale ranges from 0 to 10

Quality adjusted life year (QALY): a measure of how well a treatment improves and/or lengthens a patient's life. One QALY is worth one year of life in perfect health

Subcutaneous: an injection route, whereby the needle penetrates and administers the drug directly into a specific layer of the skin

Systemic: throughout the whole body

Topical calcineurin inhibitors: a treatment applied to the skin to treat AD

Topical corticosteroids: a treatment applied to the skin to treat AD

Topical: a type of treatment that is applied to the skin, and normally only works locally on the area it is applied

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for treating moderate-to-severe atopic dermatitis in people 12 and over [ID6221]

Clarification questions

November 2024

File name	Version	Contains confidential information	Date
[ID6221] Nemolizumab CQ 240225 [Redacted]	2	Yes	24 February 2025

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

Clarification on search strategy

A1. The EAG notes that intervention terms for nemolizumab and its comparators were only searched in subject headings, titles and abstracts. Why did the company not search in other fields such as "name of substance" (MEDLINE) or the equivalent drug name fields in EMBASE? As shown in the example below, searching in other fields could have retrieved additional results:

Ovid MEDLINE(R) ALL <1946 to October 16, 2024>
1 nemolizumab.ti,ab,hw. 107
2 nemolizumab.nm. not nemolizumab.ti,ab,hw. 14
3 nemolizumab.mp. 143

Response – The company considers it to be unlikely that anything relevant was missed by not searching additional substance fields in the Ovid databases as CENTRAL and Global Resource for EczemA Trials (GREAT) were also searched, both of which include all trials from Embase and MEDLINE, as well as trials from other sources.

A2. CS states that for the clinical SLR "no language restrictions were applied in the search strategies, however, only studies that were published in English language were considered for inclusion". However, on closer inspection it appears that an

English language limit was applied to some of the searches (see CS appendix D table 1 line 21; table 2 line 15). Was this intentional? If not, please comment on possible implications for retrieval.

Response – This is a reporting error, as search results were restricted to English in the Ovid database searches. A recent meta-epidemiological study has found that the exclusion of non-English papers in systematic reviews does not impact on overall systematic review conclusions;[1] therefore, this restriction was considered to be acceptable.

A3. (Relevant to all SLRs): Please provide details of the source of the filters used to identify eligible study types (in appendices D, G, H and I respectively) including a citation to any relevant validation studies that demonstrate them to be effective.

Response – In Company submission (CS) Appendix D, to identify clinical studies, filters were adapted from the Scottish Intercollegiate Guidelines Network (SIGN).[2] In CS Appendices G and I, to identify economic studies, terms from two filters (Hubbard et al., 2022 and the Centre for Reviews and Dissemination [CRD])[3,4] were combined for comprehensiveness. In CS Appendix H, a filter was created for health-related quality of life (HRQoL) using established terms to identify what was most relevant for a submission to NICE.

Clarification on clinical effectiveness data

General

A4. Clinical advice to the EAG suggests that there is a benefit of having multiple treatments available for the treatment of AD as these work in different manners and may have benefits particularly when there are other comorbidities. Please provide a summary of the relative advantages of each intervention currently recommended by NICE and nemolizumab.

Response – The importance of therapeutic diversity to patients with moderate-to-severe AD has been noted in TA814.[5] The proposed positioning for nemolizumab in the current treatment pathway is for adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are

contraindicated or not tolerated, i.e., second-line treatment alongside other biologic treatments and the JAK inhibitors (refer to CS Section B.1.3.2).

Both biologics and JAK inhibitors have their advantages and disadvantages, and within each class individual treatments have certain benefits. At a class level, biologics and JAK inhibitors have markedly different mechanisms of action that provide mechanistic diversity. Patients who do not achieve disease control with one drug class can then switch to the other. The biologic treatments approved by NICE include dupilumab, tralokinumab, and lebrikizumab, and are administered via sub-cutaneous injection (Q2W/Q4W).[6-9] The JAK inhibitors approved by NICE include abrocitinib, baricitinib, and upadacitinib, and are orally administered daily tablets.[10-12] Biologic treatments offer a decreased pill burden versus the JAK inhibitors, while JAK inhibitors may be preferable for patients who have a phobia of injections, or for patients who feel that integrating a daily tablet into their current routines would be preferable to regular injections. In addition, JAK inhibitors are known to benefit from a rapid onset-of-action, particularly with respect to the reduction of itch, which would be expected to be of particular interest to patients in acute crisis who need fast control, while biologics have a slower onset of action.[13] However, compared with biologics at a class level, the JAK inhibitors have a major disadvantage due to their association with increased risk of major adverse cardiovascular events, malignancy, venous thromboembolism, serious infection and mortality.[14-16]

Comparing the biologic treatments currently approved by NICE, dupilumab targets interleukin (IL)-13 and IL-4 signalling,[17] while tralokinumab and lebrikizumab only target IL-13 signalling.[5,18] Dupilumab therefore provides a degree of mechanistic diversity compared with tralokinumab and lebrikizumab. The JAK inhibitors abrocitinib and upadacitinib are selective JAK1 inhibitors, while baricitinib is a JAK1 and JAK2 inhibitor.[10-12] However, there is currently limited evidence on the comparative efficacy of the different JAK inhibitors.[19] Nemolizumab is a novel biologic treatment and the only biologic treatment to target IL-31 signalling. Interleukin-31 is a neuroimmune cytokine that drives itch and contributes to inflammation and skin barrier disruption in moderate-to-severe AD. Nemolizumab is not associated with the same risk of conjunctivitis and ocular surface disease complications as other biologic therapies, nor does it raise the same safety concerns

as the JAK inhibitors. Nemolizumab provides an additional therapeutic option for patients with moderate-to-severe AD, with an alternative mechanism of action to the currently approved treatments.

Regarding frequency of administration, dupilumab is administered Q2W,[6] while both tralokinumab and lebrikizumab may be administered initially Q2W and subsequently Q4W at clinical discretion in patients who achieve a clinical response.[7,8] However, clinicians have indicated that this typically does not occur in practice for tralokinumab. In comparison, nemolizumab is administered Q4W (i.e., less frequently than the comparator biologics) decreasing to every eight weeks (Q8W) following response,[9] and would be expected to decrease healthcare resource use and treatment-associated environmental impact.[20,21]

A5. CS Appendix C.

[redacted]

Response – A popPK model was built and validated (accordingly to current guidelines) based on data from phase-1, phase-2 and phase-3 clinical studies to characterise the exposure and pharmacokinetic (PK) profile of nemolizumab after sub-cutaneous injections over the dose range of 0.3 to 3 mg/kg, 0.1 to 2 mg/kg for weight-based dosing, and over the range of 10 to 90 mg for flat dosing.[22]

Additionally, five pharmacokinetic/pharmacodynamic (PK/PD) models were also developed and validated based on data from phase-2 and phase-3 clinical trials to characterise the relationships between nemolizumab serum concentrations and the following clinical assessments: IGA, EASI, and weekly average PP NRS in adults and adolescents with moderate-to-severe AD,[22] and IGA and weekly average PP NRS in adults with PN.[23]

The popPK model showed that body weight (BW) had a significant impact on both nemolizumab clearance (Cl/F) and volume of distribution (V/F) and was a relevant predictor of nemolizumab exposure. The exposure of nemolizumab decreases with increasing BW. However, the difference in exposure between the upper- and lower-weight quartiles was < 2-fold, supporting the appropriateness of flat dosing (30 mg or 60 mg).

To investigate the impact of BW on the clinical endpoints, 3-arm virtual studies, with dosing scenarios either tested and untested during clinical studies, were simulated 100 times using the developed popPK and PK/PD models.

The drug serum concentrations, as well as EASI, IGA, and PP NRS scores, were simulated at baseline and at Week 16, when clinical endpoint of interest (i.e., the percentages of responders) were evaluated. Each arm included 1,000 virtual subjects and were defined as follows:

- Arm 1: Low BW subject population (BW < 90 kg) – nemolizumab dosing regimen: 30 mg, Q4W (with 60 mg loading dose [LD]) for 12 weeks
- Arm 2: High BW subject population (BW ≥ 90 kg) – nemolizumab dosing regimen: 30 mg, Q4W (with 60 mg LD) for 12 weeks
- Arm 3: High BW subject population (BW ≥ 90 kg) – nemolizumab dosing regimen: 60 mg, Q4W for 12 weeks

In patients with moderate-to-severe AD, the PK/PD simulations showed that variability in systemic exposure due to BW had no clinically meaningful impact on predicted EASI, IGA and PP NRS responders. A similar EASI, IGA and PP NRS responder rate was predicted when subjects in the high BW group (≥ 90 kg) were treated with either 30 mg Q4W (60 mg LD) or 60 mg Q4W.

In patients with PN, the PK/PD simulations also showed that BW had no clinically meaningful impact on predicted PP NRS responders. However, a 24% lower IGA success was predicted for subjects with BW ≥ 90 kg receiving the 30 mg dose Q4W (with 60 mg LD) compared to the subjects receiving the 60 mg Q4W dose regimen.

In conclusion, PK/PD simulations confirmed the necessity of a dose adjustment according to BW for subjects with PN, with a cutoff of 90 kg, while in subjects with moderate-to-severe AD and BW ≥ 90 kg no benefit was predicted when administering 60 mg of nemolizumab.

Systematic literature review

A6. CS Appendix D, Appendix G, Appendix M. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost sections. If not, please justify the approach undertaken.

Response – Galderma can confirm that two independent reviewers assessed records for eligibility at abstract and full text stage, with disagreements reconciled through discussion or involvement of the review lead. Data extraction and quality assessment was conducted by one reviewer and then thoroughly checked for accuracy by a second independent reviewer.

A7. CS Appendix D and Appendix M. For completeness, please comment on the limitations and generalisability of restricting the systematic review (including NMA) to English-language publications.

Response – As discussed in our response to A2, a recent meta-epidemiological study has found that the exclusion of non-English papers in systematic reviews does not impact on overall systematic review conclusions. Therefore, this restriction was considered to be acceptable.[1]

A8. CS Section B.2.3.3., Table 5 and B2.12.2, p116. In the LTE study, what was the clinical rationale of deliberately performing a Q4W dosing schedule, [redacted] how should the longer-term efficacy results from the LTE study be generalised and interpreted?

Response – The primary objective of the LTE study is to assess the long-term safety of nemolizumab in adult and adolescent participants with moderate-to-severe AD.[24] The decision to conduct the LTE using the 30mg Q4W dosing regimen [redacted], was made

to allow for the collection of comprehensive safety data. This higher dosing frequency ensures that any potential adverse effects are more likely to be detected, therefore providing a more-thorough safety profile.

The 30mg Q4W regimen represents a more frequent treatment schedule compared to the 30mg Q8W regiment, and exposes patients to a higher cumulative dose of nemolizumab over time. This was further confirmed by the 3.6-fold higher steady systemic exposure observed with the Q4W dosing interval compared to Q8W. At steady state, the PopPK mean (±SD) nemolizumab C_{trough} were 2.63±1.27 µg/mL for nemolizumab 30 mg administered Q4W, and 0.74±0.44 µg/mL for 30 mg administered Q8W. In demonstrating safety under these stringent (i.e., maximised frequency of application) conditions, we can infer that the less frequent 30mg Q8W regimen would be at least as safe as the 30mg Q4W regiment due to lower overall exposure. This strategy is aligned with section 7 of the ICH M3(R2) guideline,[25] specifying that the highest dose tested in long-term toxicity studies should generally correspond to the highest anticipated clinical dose to ensure that long-term safety data covers the exposure level patients might experience during chronic treatment.

Additionally, the LTE study commenced on 30/12/2019, prior to finalisation of the market authorisation and confirmation of the maintenance dosing schedule, which was submitted to the Access Consortium on 14/02/2024.

Finally, the efficacy data supporting the Company submission is derived from the pivotal ARCADIA 1 & 2 trials, with a 16-week initial treatment period, a 32-week maintenance period, and an 8-week follow-up,[26,27] whereas the LTE study provides valuable long-term safety data (interim data cut week-56).[28] The LTE study's EQ-5D-3L scores, in addition to those from ARCADIA 1 & 2, and ARCADIA-CYCLO were used to support the Company economic model. The long-term safety data is applied narratively in this submission and reflects a conservative estimation of adverse events as per study objectives.

A9. CS Section B.2.6 Please provide further details on whether there are any confounders that may influence treatment efficacy and its likely impact in the pivotal trials (ARCADIA 1 & 2) and ARCADIA-CYCLO e.g. race (skin colour), weight, age,

severity, area of the body (hands, for example), prior treatments, baseline IL-31, others?

Response – Race, ethnicity, weight, age, and disease severity (IGA [moderate/severe], EASI mean score, and PP NRS mean score) were generally well balanced between nemolizumab and placebo arms in ARCADIA 1 & 2, and ARCADIA-CYCLO (see CS Tables 11 and 13). Furthermore, the percentage of participants with at least 1 prior medication were similar in the nemolizumab and placebo arms in ARCADIA 1 (prior to informed consent signature – [redacted] vs. [redacted]; during the screening period – [redacted] vs. [redacted]),[26] ARCADIA 2 (prior to informed consent signature – [redacted] vs. [redacted]; during the screening period – [redacted] vs. [redacted]),[27] and ARCADIA-CYCLO (3 months prior to the date of the first dose of study drug – [redacted] vs. [redacted]).[29]

Patient baseline IL-31 cytokine levels were not measured in ARCADIA 1 & 2, and ARCADIA-CYCLO. Previous research has demonstrated IL-31 serum levels correlate with severity of disease and pruritic symptoms;[30,31] as stated above, severity was generally well balanced between nemolizumab and placebo arms in the three clinical trials.

As discussed in the decision problem (see CS, Table 1), people with AD affecting the hands are not considered a relevant subgroup in this submission. Atopic dermatitis affecting the hands is a distinct phenotype of the disease, whereas this submission focuses on a broader patient population. Information on affected areas of the body were not collected as part of the baseline characteristics in ARCADIA 1 & 2, or ARCADIA-CYCLO.[26,27,29]

A10. CS Section B.2.6.1.1, Table 10; B.2.6.1.2, Table 12 and B.2.6.1.3. If possible, provide further details on the primary reasons for discontinuation in Table 10, 12 and 14, particularly the type and severity of AE and the reasons, if collected, why participants requested to discontinue.

Response – CS Tables 10, 12, and 14 provide only a summary of the reasons for treatment and study discontinuation. Additional information on adverse events, protocol deviations, or physician decisions leading to treatment or study discontinuation are provided in the relevant clinical study reports.[26-29] However, the

adverse events identified as being the primary reason for treatment or study discontinuation are not presented separately to those which contributed to but were not the primary reason for discontinuation. Additional information on adverse events that led to treatment or study discontinuation are presented below.

In the initial treatment period of ARCADIA 1, [redacted] and [redacted] participants in the nemolizumab and placebo arms, respectively, experienced a treatment-emergent adverse event (TEAE) that led to study drug withdrawal.[26] The only TEAE experienced by more than one participant in either nemolizumab or placebo arm ([redacted] and [redacted], respectively) was dermatitis atopic. Most TEAEs were not considered study drug related. None of the study drug related TEAEs of dermatitis atopic leading to study drug withdrawal were serious. Except for one nemolizumab and two placebo participants, all dermatitis atopic TEAEs that led to study drug withdrawal also resulted in study discontinuation in the initial treatment period. [redacted] ([redacted]) nemolizumab and [redacted] ([redacted]) placebo participants experienced a TEAE leading to study discontinuation, with most not considered study drug related. All study drug related TEAEs leading to study discontinuation were dermatitis atopic events that also led to study drug withdrawal. In the maintenance period, [redacted] nemolizumab Q4W to Q4W, [redacted] nemolizumab Q4W to Q8W, [redacted] nemolizumab Q4W to placebo and [redacted] re-assigned to placebo participants experienced a TEAE leading to study drug withdrawal.[26] The only TEAE experienced by more than one subject in any treatment arm was dermatitis atopic ([redacted] nemolizumab Q4W to Q8W, and [redacted] reassigned to placebo). Most TEAEs were not considered study drug-related and were mild or moderate in severity. All study drug-related TEAEs that led to study discontinuation in the maintenance period were dermatitis atopic events that also resulted in study drug withdrawal.

In the initial treatment period of ARCADIA 2, [redacted] nemolizumab and [redacted] placebo arm participants experienced a TEAE that led to study drug withdrawal.[27] The only TEAEs experienced by more than one participant in either arm were dermatitis atopic ([redacted] nemolizumab, [redacted] placebo) and lymphadenopathy and oedema peripheral ([redacted] nemolizumab each). Most TEAEs were considered study drug related, and none were serious. Most participants who experienced study drug related TEAEs leading to study drug withdrawal had events that also led to study

discontinuation. [redacted] nemolizumab and [redacted] placebo participants experienced TEAEs leading to study discontinuation, with most considered study drug related. All study drug related TEAEs leading to study discontinuation also resulted in study drug withdrawal. In the maintenance period of ARCADIA 2, [redacted] nemolizumab Q4W to Q4W subject, [redacted] nemolizumab Q4W to Q8W subjects, [redacted] nemolizumab Q4W to placebo and [redacted] re-assigned to placebo participants experienced a TEAE leading to study drug withdrawal.[27] The only TEAE experienced by more than one subject in any treatment arm was dermatitis atopic ([redacted] nemolizumab Q4W to Q4W, [redacted] nemolizumab Q4W to Q8W, [redacted] nemolizumab Q4W to placebo and [redacted] reassigned to placebo). Most TEAEs were considered study drug-related, with [redacted] participants who experienced a serious TEAE (gastroenteritis in [redacted] nemolizumab Q4W to Q4W subject, and pulmonary embolism in [redacted] nemolizumab Q4W to placebo subject). All study drug-related TEAEs that led to study discontinuation in the maintenance period also resulted in study drug withdrawal.[27]

In ARCADIA CYCLO, [redacted] nemolizumab and [redacted] placebo participants experienced a TEAE leading to study drug withdrawal, but none were experienced by more than one participant in either arm.[29] Most TEAEs were considered mild or moderate in severity, related to the study drug, and led to study discontinuation. [redacted] ([redacted]) nemolizumab and [redacted] ([redacted]) placebo participants experienced a TEAE leading to study discontinuation; dermatitis atopic and drug hypersensitivity were experienced in [redacted] nemolizumab participant each and dermatitis atopic, thrombocytosis, and psychotic symptom were experienced by [redacted] placebo participant each. The event of psychotic symptom was considered severe; all other events were considered moderate in severity. All TEAEs leading to study discontinuation also led to study drug withdrawal.

In the LTE study, [redacted] participants experienced a TEAE leading to study drug withdrawal during the treatment period.[28] TEAEs leading to study drug withdrawal that were experienced by more than one participant were dermatitis atopic ([redacted] participants) and asthma and toxic skin eruption ([redacted] participants each), with most considered ([redacted]) study drug related. Most study drug related TEAEs leading to study drug withdrawal were mild or moderate in severity, with only [redacted]

participants who experienced serious study drug related TEAEs leading to study drug withdrawal (multiple sclerosis, lichen planus, dermatitis atopic, dermatitis infected). All participants who experienced study drug-related TEAEs leading to study drug withdrawal also discontinued the study.

Reasons for participants requesting discontinuation (i.e., consent withdrawal) were not independently collated across the trials, beyond those in the LTE study who discontinued treatment or study due to COVID-19.[28] Company submission Tables 10, 12 and 14 list the primary reason given for discontinuation of treatment or study; contributing factors, such as AEs that led to but which were not the primary reason for discontinuation, are not presented.

A11. CS Section B.2.12.2. Please provide further details on how the pivotal trials (ARCADIA 1 & 2) and ARCADIA-CYCLO are representative of and generalisable to the target population in UK clinical practice? For example, treatment pathway, patient selection, patient characteristics

Response – The populations of ARCADIA 1 & 2 were predominantly European (51% and 73%, respectively) or North American (33% and 24%, respectively), including [redacted] participants in the UK (ARCADIA 1).[26,27] ARCADIA-CYCLO was conducted solely in Europe.[29] Although only a small proportion of the ARCADIA trial programme participants were from the UK, participants from Europe have comparable healthcare systems, and populations that are generalisable to the UK. Furthermore, the trial populations are similar, i.e., predominantly European and North American, to previous submissions in this indication that have received positive recommendations by NICE.[5,18,32,33]

The proposed positioning for nemolizumab in the current treatment pathway is for adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated, i.e., second-line treatment, alongside biologic treatments and the JAK inhibitors (see CS, Section B.1.3.2). It is anticipated that nemolizumab will be used with best supportive care (BSC), which can include emollients, topical corticosteroids

(TCSs), and topical calcineurin inhibitors (TCIs). This positioning is considered appropriate by UK clinical experts via a modified Delphi process.[34]

ARCADIA 1 & 2, and ARCADIA-CYCLO all included BSC (refer to CS, Table 5 for permitted concomitant medication) in the nemolizumab and placebo arms and reflect the UK clinical pathway.[26,27,29]

ARCADIA 1 & 2 included both first-line (systemic immunosuppressive therapy naïve) and second-line patients (who previously received at least one systemic immunosuppressive therapy), which does not fully align with the second-line population in the decision problem and nemolizumab's proposed position in the UK clinical pathway. However, these trials were sufficiently powered to enable sub-population analysis for first- and second-line patients separately. A pre-planned subgroup analysis of the co-primary endpoints to estimate the treatment difference, corresponding two-sided 95% CI and strata-adjusted p-values for between-group comparisons was performed on pooled data from ARCADIA 1 & 2.[35] The results show that nemolizumab resulted in a statistically significant number of participants with EASI-75, regardless of previous use of any systemic therapy, immunosuppressive or immunomodulatory drug, and ciclosporin (i.e., analysis for first- and second-line patients separately) (CS, Section B.2.7).

In addition, the results of ARCADIA 1 & 2 are supported by ARCADIA-CYCLO, where nemolizumab was used exclusively as a second-line therapy. In ARCADIA-CYCLO, nemolizumab demonstrated comparable efficacy in second-line patients, and with respect to this, is representative and generalisable to the UK clinical pathway.[29] Although ARCADIA-CYCLO included adult patients only, NICE have previously concluded that evidence from adult patients with moderate-to-severe AD is sufficiently generalisable to paediatric and adolescent patients as to support use of a therapy in the latter population.[36] Therefore, Galderma considers that evidence from ARCADIA CYCLO's adult population would be generalisable to adolescent patients aged 12–18 years. Furthermore, the evidence from ARCADIA-CYCLO is supported by the ARCADIA 1 & 2 trials, which included both adult and adolescent patients.

Network meta-analysis

A12. Priority question: CS Appendix M Section 1.13.5 states that CS Appendix M Section 1.15.5 states that a sensitivity analysis was performed modelling EASI-50, EASI-75 and EASI-90 altogether in an NMA ordinal model. Please provide results of this analysis for both second-line adult and first-line adolescent population.

Response – This text in CS Appendix M is a reporting error. The option of performing an ordinal model sensitivity analysis on EASI outcomes was initially considered but was not conducted for any population as it was uncertain that the analysis was feasible for these outcomes.

A13. Priority question: Please provide the assessment of the distribution of effect modifiers across the included studies.

Response – Randomised controlled trials (RCTs) were assessed in a feasibility analysis (FA) to confirm if they were clinically and methodologically similar.[37] The FA examined heterogeneity between trials and was conducted according to the principles of Cope et al., 2014.[38] Study characteristics, patient characteristics, treatment characteristics, outcome definitions and data timepoints were evaluated. The RCTs included are relatively comparable in terms of study design, patient characteristics, treatment regimens and outcome measures, but with sensitivity analyses recommended to assess the impact of heterogeneity.

A14. Priority question: CS Appendix M Section 1.18 - 1.20, please clarify the following discrepancies in the input data for the NMA:

A. **Please clarify from where the EASI-75 response at week 16 data for adult 1L (Section 1.18.1, table 10), adult 2L (Section 1.19.1 table 43) and adolescent 1L (Section 1.20.1, Table 76) populations in the AD UP trial have been obtained; the values found in Appendix M do not match any found in Silverberg et al. 2022 or NCT03568318.**

B. **Please clarify from where the EASI-75 response at week 16 data for adult 1L (Section 1.18.1, Table 10) and adult 2L (Section 1.19.1, Table 43) populations in the ARCADIA 1 & 2 trials have been obtained; the values**

found in Appendix M do not match any found in ARCADIA 1 & 2 CSRs. Furthermore, please clarify whether or not the entire adolescent population in the ARCADIA 1 & 2 trials was ciclosporin-naïve.

C. **Please clarify why the EASI-75 response at week 16 data for adult 2L (Section 1.19.1, Table 43) population in the ADhere trial does not match the reported outcomes found in Simpson et al. 2023 or NCT04250337; please clarify if the NMA data corresponds to the adolescents and adults mixed ciclosporin-naïve/experienced population.**

D. **Please clarify from where the EASI-75 response at week 16 data for adolescent 1L (Section 1.20.1, Table 76) population in the ADhere trial has been obtained; the values found in Appendix M do not match any found in Simpson et al. 2023 or NCT04250337.**

E. **Please clarify why EASI-75 response at week 12 data from the JADE TEEN trial was included with EASI-75 response at week 16 data for the adolescent 1L (Section 1.20.1, Table 76) population; if this data were included erroneously please remove it and update the adolescent 1L NMA.**

Response – Data from the SLR may be from multiple sources for each RCT. The references included in CS Appendix M are based on the primary sources for each RCT and are not necessarily where the data was sourced. As agreed with the EAG during the clarification call, data pertaining to the adult first-line population is not relevant for this submission; therefore, updated references have only been provided for the adult second-line and adolescent first-line populations.

A – The EASI-75 response at week 16 for the adult second-line (Appendix M Section 1.19.1 table 43) and adolescent first-line (CS Appendix M Section 1.20.1, Table 76) populations in the AD UP trial were obtained from eTable 2 in Thyssen et al., 2022.[39]

B – The EASI-75 response at week 16 data for the adult second-line populations in the ARCADIA 1 & 2 trials were sourced from patient-level data (PLD) specific for adult patients who are ciclosporin-experienced. EASI-75 response at week 16 is not available for this population in the CSRs for ARCADIA 1 & 2. For EASI-75 response

in the adolescent population, the NMA used data from the SLR that included a mixed ciclosporin-naïve/experienced population but recorded the population as ciclosporin-naive. The ARCADIA 1 & 2 trials included a mixed ciclosporin-naïve/experienced population. In ARCADIA 1, there were [redacted] ciclosporin-experienced adolescent patients in the nemolizumab arm and [redacted] ciclosporin-experienced adolescent patients in the placebo arm. In ARCADIA 2, there were [redacted] ciclosporin-experienced adolescent patients in the nemolizumab arm and [redacted] ciclosporin-experienced adolescent patients in the placebo arm.

C – The EASI-75 response at week 16 data for the adult second-line (CS Appendix M Section 1.19.1, Table 43) population in the ADhere trial was sourced from eTable 2 in supplement 2 of Simpson et al., 2023.[40] The NMA data corresponds to the adolescents and adults mixed ciclosporin-naïve/experienced population.

D – The EASI-75 response at week 16 data for adolescent first-line (CS Appendix M Section 1.20.1, Table 76) population in the ADhere trial was obtained from Hebert et al., 2023.[41]

E – This is not an error in the analysis; EASI-75 response at week 12 data from the JADE TEEN trial was included with EASI-75 response at week 16 data for the adolescent first-line (CS Appendix M Section 1.20.1, Table 76) population as a surrogate for week 16 data.[42] This was considered the best available data for abrocitinib as the treatment duration for JADE TEEN was 12 weeks. This may underestimate the effect of abrocitinib at week 16; however, this approach is in line with TA814, where week 12 data for abrocitinib was included in the NMA networks for the second-line adult and adolescents populations.[5] Similarly, in Drucker et al., studies of 8 to 16 weeks of treatment were pooled using extracted outcome data at the latest reported time point during active treatment.[43]

A15. The NMA for the second line adult population for EASI-75 responders at 16 weeks included studies that have both adolescents and adults populations (CS Appendix M Table 43). Please comment on the potential impact on including adolescents in this analysis.

Response – In TA814, the Committee concluded that there are likely similarity between young people and adults in AD and that the results for adults who have

tried systematic therapy would likely be generalisable to young people.[5] Therefore, it can be assumed that the inclusion of studies with mixed adult and adolescent populations will have minimal impact on the analysis. The approach to use data from mixed adult and adolescent studies in analyses of adult data is in line with the approach used in Drucker et al.[43]

In addition, as stated in the clarification question B4, clinical experts have advised that dupilumab and tralokinumab are used adolescents despite NICE technology appraisals only being conducted in adult populations.[5,32] This further supports that results for adults would be generalisable to young people with AD and the inclusion of studies with mixed adult and adolescent populations will have minimal impact on the analysis.

A16. The NMA for the second line adult population for EASI-75 responders at 16 weeks also included studies that have mixed cyclosporine use (cyclosporine naïve and cyclosporine experienced) (CS Appendix M Table 43). Please comment on the potential impact on including cyclosporine naïve patients in this analysis.

Response – In the second-line adult population NMA for EASI-75 responders at 16 weeks, data from RCTs with mixed ciclosporin use were included in the analysis where there was no subgroup data available. These RCTs were included for abrocitinib, baricitinib and lebrikizumab as they were considered the best available evidence to support the NMA and allow comparison versus all relevant comparators. However, in the FA these studies were identified as "heterogenous but assumed comparable; with sensitivity analyses recommended" to maximise the available comparators.[37]

Sensitivity analysis was conducted excluding the heterogeneous data (CS Appendix M Section 1.21.2.1). The results of this sensitivity analysis demonstrated that removing the heterogenous trials showed similar results for the remaining comparators (Figure 1). A difference to note for this sensitivity analysis is that in the base-case analysis, nemolizumab has a statistically significantly lower odds than upadacitinib 30mg at achieving EASI-75 at week 16. whereas in the sensitivity analysis nemolizumab has a non-statistically significant difference versus upadacitinib 30mg. Therefore, the results for nemolizumab in the sensitivity analysis

are either similar or improved versus the base-case, which supports the use of the base-case results in the economic model.

Furthermore, in CS Figure 12 subgroup analysis for the pooled ARCADIA 1 & 2 trials supports that nemolizumab resulted in a statistically significant number of participants with EASI-75 regardless of previous use of any systemic therapy, immunosuppressive or immunomodulatory drug, and ciclosporin (i.e., analysis for first- and second-line patients separately). Therefore, this data further supports that the inclusion of ciclosporin-naive patients would have a minimal impact on the adult second-line analysis.

Figure 1. Forest plot of relative effects versus nemolizumab for EASI-75 responders at 16 weeks in adult 2L population for random effects model with informative priors, with heterogenous trials removed

Abbreviations: CrI, credible interval; OR, odds ratio; QD, once daily; Q2W, once every 2 weeks

A17. CS Section B.2.9.1.3 states that data for an adolescent population who had previously failed ciclosporin were not available for any comparators and the analysis was restricted to a first-line, ciclosporin-naïve adolescent population. Please comment on the reliability of using the NMA results for the first-line adolescent population as a surrogate for the second-line adolescent population.

Response – Based on the lack of data for the second-line adolescent population to conduct an NMA; Galderma considers the NMA in the first-line adolescent population as the most appropriate and generalisable data for the second-line adolescent population.

The reliability of using the NMA results for the first-line adolescent population as a surrogate for the second-line adolescent population is supported by the NMA for the second-line adult NMA. As presented in the CS, Section B.2.9.1, for the comparators included in the first-line adolescent NMA, (abrocitinib, lebrikizumab, and upadacitinib 15mg) the results are comparable to the adult second-line NMA, with there being no statistically significant difference versus nemolizumab in achieving EASI-75, with an odds ratio of 1 being applied. As discussed in response to A15, Committee conclusions from TA814 support the generalisability of findings from the adult to adolescent populations in AD.[5] Therefore, the comparable results between the

adolescent first-line and adult second-line populations supports the assumption that the adolescent first-line population is an appropriate proxy for the adolescent second-line population given the paucity second-line specific data.

A18. CS Section B.2.9.1. Please provide the informative prior used for each of the analyses presented in this section.

Response – The R package "gemtc", gemtc::mtc.hy.empirical.lor ("subjective", "pharma-control") was used.[44] This adds the random effects variance parameter to the JAGS model, using the distribution values given in Table 4 of Turner et al., 2012 for Pharmacological vs Placebo/Control comparison for subjective outcome type, i.e. with distribution log-normal ($\mu = -2.13$, $\sigma 2 = 1.5822$) (where μ and σ are the mean and SD on the log scale).[45]

A19. Please provide the R code and input data for the NMA analyses presented in CS Section B.2.9.1 to enable the EAG to reproduce the results

Response – The R code and input data have been provided in addition to the clarification question responses.

A20. Please provide the estimated between-study standard deviation for the analyses presented in CS Section B.2.9.1

Response – The estimated between-study standard deviation for the analyses presented in CS Section B.2.9.1 are:

- EASI-75 second-line adults: 1.246 (95% CRI 1.061, 1.980)
- EASI-75 adolescents: 1.311 (95% CRI 1.068, 2.617)

A21. Please comments on how the company's SLR and NMA compares with other similar reviews such as the living SLR and NMA by Drucker et al. (https://pubmed.ncbi.nlm.nih.gov/35293977/)

Response – The Company's SLR can be considered similar to the Drucker review, as both review studies in a population with moderate-to-severe AD treated with immunomodulatory therapies in combination with topical therapies.[43] However, a difference to note is that Drucker et al. includes children, whereas the CS focuses on patients who are adolescent and older (≥ 12 years).[43]

In the Drucker et al. NMA, change in continuous outcome scale for EASI and other outcomes was assessed, while noting that in future updates dichotomous responses rate would be included.[43] This is consistent with other NMAs which mostly assess these outcomes.[43] In terms of the size of the treatment effect, the relative order of the comparators in Drucker et al. is similar to the Company NMA.[43] In addition, and in line with the Company's NMA, the adult analysis in Drucker et al. includes studies where the population includes both adult and adolescent patients where data stratified by age is not available.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide an updated model, documentation describing how the model was changed and updated results based on any changes made following clarification.

Response – The updated economic model has been provided along with Appendix A, which includes the updated base-case, sensitivity analysis and scenarios, and a description of the updates to the base-case following the response to clarification questions. Please note that the PAS price for nemolizumab has been updated to [redacted] per pack.

B2. Priority question: Provide results in terms of net monetary benefit or net health benefit in addition to ICERs. These could be more meaningful than ICERs in the EAG's confidential appendix to the EAG where the confidential PASs are included.

Response – Both net monetary benefit and net health benefit are available in the economic model and are reported in Appendix A.

Population

B3. Clarify why the baseline characteristics for modelled patients were taken from TA814 rather than the nemolizumab studies. Provide a sensitivity analysis using data from the nemolizumab studies.

Response – Baseline characteristics have been updated in the base-case model to reflect the values from the ARCADIA trials. Values for adults were calculated based on relevant patients from the ARCADIA 1, ARCADIA 2 and ARCADIA-CYCLO trials,

and values for adolescents were based on ARCADIA 1 and ARCADIA 2. The updated baseline characteristics are presented in Table 1 and the updated base-case results are presented in Appendix A.

Table 1. Updated baseline characteristics in adult and adolescent population

Parameter	Adults	Adolescents
Age, years	[redacted]	[redacted]
Proportion of cohort male, %	[redacted]	[redacted]
Weight, kg	[redacted]	[redacted]
Source	ARCADIA 1,[26] ARCADIA 2[27] and ARCADIA-CYCLO[29]	ARCADIA 1[26] and ARCADIA 2[27]

Comparators

B4. Clinical advice to the EAG states that both dupilimab and tralokinumab are used in the adolescent population and therefore should be comparators in this group. Update the cost-effectiveness results to include these interventions using the results from the NMA.

Response – Dupilumab (TA534),[32] and tralokinumab (TA814),[5] are recommended by NICE in the adult AD population only. Since the publications of TA534 and TA814,[5,32] the marketing authorisations for dupilumab and tralokinumab have been extended to include people aged 12 to 17 years, and these treatments are commissioned by NHS England for this population. However, NICE confirmed via email communication that tralokinumab would likely be considered as a comparator in the adult AD population only. Therefore, based on equivalent recommendations between dupilumab and tralokinumab, both treatments were considered as comparators for nemolizumab in the adult population only. Furthermore, there was a lack of data for dupilumab and tralokinumab in the adolescent AD population to support an economic analysis.

However, at the request of the EAG the economic model has been updated to include comparison versus dupilumab and tralokinumab in the adolescent population, with the results presented in Appendix A. Based on the limited adolescent data for dupilumab and tralokinumab, inputs for these comparators in the economic model are based on inputs from the adult population.

Model structure

B5. Priority question: CS Section B.3.8.2, Table 70 and Executable model, worksheet "Costs calculations". The model assumes that for patients who enter the "*No response*" health state, 47.2% receive a form of biologics ([redacted] Dupilumab and [redacted] Tralokinumab) and 46.3% receive a JAKi ([redacted] Upadacitinib 30mg, [redacted] Abrocitinib 200mg and [redacted] Baricitinib). Treatment with a biologic/JAKi will be continued indefinitely until death, with utility estimated based on the weighted average of responders and non-responders at year 3+.

A. **Clarify why patients who are non-responders to biologic/JAKi treatment are assumed to remain on treatment. This notably inflates the costs of subsequent treatment whilst providing no (or little) clinical benefit and it is possible/likely that this treatment would be stopped (as happens with first line treatment). Amend the model to discontinue expensive**

treatment in those who do not respond or justify that this treatment would continue in clinical practice.

B. **In addition to (A) clarify the reasons for assuming zero discontinuation rate of biologic/JAKi treatment in those that respond as is assumed in first-line treatment options .**

C. **Clarify why AEs associated with biologic/JAKi treatment in the BSC basket were not included. Amend the model to include AEs associated with biologic/JAKi treatment.**

D. **Clarify why patients receiving biologic/JAKi treatment in the BSC basket have the same flare rates as non-responders. Amend the model to reduce the flare rates associated with biologic/JAKi treatment.**

E. **Clarify why baricitinib is in the basket of BSC for adolescents.**

F. **Clarify why the response rate/effectiveness of TCIs, TCSs and emollients are not considered for patients who did not respond to active treatment in the BSC basket.**

G. **Clarify why patients are allowed to receive the same drug used as a first line as part of the basket of subsequent treatments. Approximately 28% (47.2% * 59.2%) of patients using dupilimab first line would have this as a subsequent treatment.**

Response –

A – UK clinical experts have supported that patients with moderate-to-severe AD would remain on active treatment and not receive BSC alone after treatment failure in real-world clinical practice.[34] The clinical experts stated that if a biologic or JAK inhibitor treatment was not effective or discontinued then the patient would switch to another active treatment.[34] As patients would not receive BSC alone, this process would continue where patients are rechallenged with active treatments. Therefore, it was assumed that non-responders would remain in the basket of subsequent biologics and JAK inhibitors until death.

B – In line with the response to question B5A, as UK clinical experts supported that patients would remain on active treatment rather than receive BSC alone,[34] it was assumed that patients would switch between different biologics and JAK inhibitors, as there are multiple alternative treatments available. Therefore, zero discontinuation was assumed.

C – The base-case economic model has been updated to include adverse events associated with biologics and JAK inhibitors in non-responders. Updated base-case results are presented in Appendix A.

D – The base-case economic model has been updated to include flares for biologic and JAK inhibitors in non-responders. Updated base-case results are presented in Appendix A.

E – The base-case economic model has been updated to exclude baricitinib from the BSC basket for non-responders in the adolescent population. Updated base-case results are presented in Appendix A.

F – In UK clinical practice, biologics and JAK inhibitors are only administered to patients after they have had an inadequate response to emollients, TCSs and TCIs. Therefore, in line with the assumption accepted by the Committee in TA814, it was assumed that patients do not respond to emollients, TCSs and TCIs if they have not responded to active treatment.

G – The proportion of biologic and JAK inhibitors in the subsequent treatment basket were provided by UK clinical experts.[34] The UK clinical experts stated that the treatments are used in sequence following treatment failure and that patients can be rechallenged with active treatments that they have already received previously.[34] Therefore, it was assumed that patients could receive the same drug as at first-line.

B6. Priority question: Given the potential limitations associated with the modelling of subsequent treatments, provide an exploratory analysis where no

biogic/JAKi treatment is assumed and limit the time horizon to a period of three years.

Response – A scenario analysis which includes no treatment switching for non-responders to subsequent biologic and JAK inhibitors with a time horizon set to three years is presented in Appendix A.

B7. CS Section B.3.2.3.2 and Figure 16. A hybrid model (a decision tree followed by a Markov model) is used with the decision tree estimating patients response over the first year of treatment. However, no deaths are assumed to occur within the first 52 weeks. Please amend the model to account for death during the first year of treatment.

Response – The base-case economic model has been updated to include mortality within the first year of treatment. Updated base-case results are presented in Appendix A.

B8. Clarify why patients who enter the 'No response' health state remain there until death. Provide evidence to show that there would be no natural remission for these patients beyond the modelled response in the subsequent basket of care (Table 48 of the CS).

Response - Patients in the 'No response' health state remain in the health state until death to align with the model structures of TA814[5] and TA986.[18] No previous NICE submission in moderate-to-severe AD has modelled a natural remission for non-responders; therefore, Galderma does not consider it appropriate to include this in the economic model. Furthermore, the model structure with patients remaining in the 'No response' health state until death was validated by UK clinical experts as generalisable to UK clinical practice.[46]

AD has a fluctuating pattern of remission and flare,[47,48] which is modelled in the economic model via rates of flares which are associated with additional costs and utility decrements. During periods of remission, despite an absence of visible signs of inflammation, the underlying inflammation of the skin can still be present.[49] This therefore supports Galderma's view that it would not be appropriate to update the model structure to include a natural remission for non-responders.

B9. CS Section B.1.3.1.3 states that "Hazards for all-cause and cause-specific mortality are modestly increased across all patients with AD compared with patients without AD". However, CS Section B.3.3.6 states that "Moderate-to-severe AD is not expected to have any significant impact on mortality; thus, the mortality rates within the moderate-to-severe AD population are equivalent to those of the general population". Provide an exploratory analysis exploring the impact of applying a standardised mortality rate to general population mortality.

Response – In the economic model, the approach for modelling mortality is aligned with TA814 and TA986.[5,18] As requested, a scenario analysis was conducted where a hazard ratio (HR) is applied to general population mortality to reflect AD-specific mortality. Silverwood et al., 2021 presented limited evidence of increased hazard for all-cause mortality in adults with atopic eczema in the UK (HR = 1.04; 99%CI = 1.03–1.06).[50] However, the subpopulation of patients with severe atopic eczema demonstrates an increased hazard for mortality (HR = 1.62; 99%CI = 1.54–1.71) compared with those without atopic eczema. Scenario analysis using a HR of 1.62 applied to the general population mortality, which reflects the value for severe population, is presented in appendix A.

Response rate at Week 16 / 24

B10. Priority question: CS Table 17, states that EASI75 improvement was 43.5% in ARCADIA 1, 42.1% in ARCADIA 2 and [redacted] for patients in ARCADIA-CYCLO. However, Table 50 provides values of [redacted] and [redacted], for adults and adolescents respectively using pooled data from ARCADIA 1, ARCADIA 2 and ARCADIA CYCLO. Please explain in detail how the company calculated the EASI-75 response rates at Week 16 providing the total number of responders and randomised patients for those calculations.

Response – CS Table 17 provides the proportion of EASI-75 improvement for the ITT population of the ARCADIA 1 and 2 trials which includes adults/adolescents and first-line/second-line patients. This differs from Table 2 below, which presents the total number of EASI-75 responders and randomised patients used to calculate the final values of CS Table 50 based on second-line patients only, stratified into adults

and adolescents. The rate was calculated as the proportion of patients who respond at week 16:

$$\text{Response rate} = \frac{Number\ of\ responders}{Number\ of\ randomised\ patients}$$

Table 2. EASI-75 response rate at Week 16 for nemolizumab in adult and adolescent 2nd line populations

Treatment	EASI-75	
	Adults (2L)	Adolescents (2L)
Nemolizumab (responders/randomised)	[redacted]	[redacted]
Source	ARCADIA 1,[26] ARCADIA 2[27] and ARCADIA-CYCLO[29]	ARCADIA 1[26] and ARCADIA 2[27]

Abbreviations: EASI, Eczema Area and Severity

B11. Provide exploratory analyses using a criteria of EASI-50 and DLQI ≥ 4 to estimate the response for nemolizumab and then apply the ORs from EASI -75 assuming that these are transferable to EASI-50 and DLQI ≥ 4.

Response – Scenario analysis in the adult population using EASI-50 and DLQI ≥ 4 at week 16 for nemolizumab response applying the ORs from EASI-75 is presented in Appendix A. The response rate using EASI-50 and DLQI ≥ 4 at week 16 in the adult second-line population is presented in Table 3 below.

Scenario analysis in the adolescent population using EASI-50 and DLQI ≥ 4 at week 16 for nemolizumab response has not been presented based on uncertainty in the response value. In the adolescent second-line population, EASI-50 and DLQI ≥ 4 response at week 16 was [redacted]. This value is significantly different to the EASI-75 value at week 16 for the adolescent second-line population ([redacted]) and the EASI-50 and DLQI ≥ 4 value at week 16 for the adult second-line population ([redacted]). In TA814, the Committee concluded that results for adults who have tried systematic therapy would likely be generalisable to young people. Therefore, based on the significant difference versus the adult second-line population and the low patient numbers in the adolescent second-line population, Galderma does not consider it appropriate to present scenario analysis using EASI-50 and DLQI ≥ 4 in the adolescent population.

In addition, other measures of response are comparable between the adult second-line and adolescent second-line populations based on PLD from the ARCADIA trials[26,27,29] (IGA: [redacted] and [redacted]; PP NRS: [redacted] and [redacted], respectively). Therefore, this further supports that it would be inappropriate to model a significant difference in response between the adult and adolescent populations using EASI-50 and DLQI ≥ 4.

Table 3. EASI-50 and DLQI ≥ 4 response rate at Week 16 for nemolizumab in adult population

Treatment	EASI-50 and DLQI ≥ 4
	Adults (2L)
Nemolizumab	[redacted]
Source	ARCADIA 1,[26] ARCADIA 2[27] and ARCADIA-CYCLO[29]

Abbreviations: DLQI, dermatology life quality index; EASI, Eczema Area and Severity Index

B12. Clarify why elongated treatment for lebrikizumab patients who obtained a partial response is not included in the model. The CS, page 32 states that "*response to lebrikizumab may further improve with continued treatment every other week up to week 24*"

Response – In TA986, it is stated that for lebrikizumab 'consideration should be given to stopping treatment in patients who do not respond after 16 weeks. Some patients with initial partial response may further improve with continued treatment every other week up to Week 24'.[18] However, in the economic model in TA986, response for lebrikizumab was determined at 16 weeks.[18] Therefore, in order to align with the economic model structure in TA986, Galderma does not consider it appropriate to add an additional measure of response at week 24. Furthermore, the economic model structure has been validated by UK clinical experts as generalisable to UK clinical practice,[46] which supports the exclusion of an additional measure of response at week 24.

Discontinuation probabilities

B13. Priority question: CS Section B.3.3.3, Table 52. Please explain in detail how the company calculated the conditional discontinuation probability of nemolizumab at week 52 using the pooled data from ARCADIA 1 and 2. Please also clarify whether it was calculated based on the data from both nemolizumab 30mg Q4W to Q4W arm and nemolizumab 30mg Q4W to Q8W

arms or just nemolizumab 30mg Q4W to Q4W arm. Table 4 of the CSR states that [redacted] discontinued in nemolizumab 30mg Q4W to Q8W arm during the maintenance period using pooled ARCADIA 1 and 2 data.

Response - The conditional discontinuation for nemolizumab included in the CS Table 52 included a calculation error and the value did not represent discontinuation for the full weeks 16–48 period. The updated conditional discontinuation rate for nemolizumab based on pooled data from ARCADIA 1 and 2 is [redacted]. This value is based on PLD from the nemolizumab 30mg Q4W to Q8W arm of the ARCADIA 1[26] and 2[27] trials and all-cause discontinuation for patients who responded at week 16 based on EASI-75 and discontinued by week 48 in the maintenance period.

However, in TA986, clinical experts stated that discontinuation rates for treatments within a specific treatment class should be similar and the Committee concluded that, based on clinical expert opinion, discontinuation rates should be applied according to treatment class (3.9% for biologics and 10% for JAK inhibitors).[18] Furthermore, UK clinical experts consulted during the development of the current appraisal supported this assumption, stating that significant differences in discontinuation rates for biologics would not be observed in UK clinical practice for AD.[46]

However, the updated week 52 conditional discontinuation rates for nemolizumab show a relatively large discrepancy between discontinuation rates reported for other biologics, which does not align with the experiences and expectations of UK clinical experts. To explain these findings, further details were sought on the approaches to calculating conditional discontinuation from comparator appraisals; upon review, it appears that there is considerable uncertainty around the actual derivation of conditional discontinuation rates based on trial design, definitions of 'all-cause' discontinuation, and study time points from which 'week-52' discontinuation rates are derived. For example:

- In the CHRONOS trial informing dupilumab discontinuation rates,[51] re-randomisation for week-16 responders is not conducted, whereas, re-randomisation of all week-16 responders from the nemolizumab arm onto

further active treatment (Q4W or Q8W) or placebo is conducted in ARCADIA trials.

- In TA986,[18] week-52 conditional discontinuation for lebrikizumab combination therapy in the CS is derived based on the 16-week ADhere trial.[40] It is not clear whether discontinuation data is derived from subsequent cross-over to longer term studies, from which patients this data is derived and from which time points.

It is apparent that heterogeneity in study design and exact derivation of conditional discontinuation exists, which may present a substantial impact on the discontinuation rates derived for each treatment and make direct comparison between discontinuation rates uncertain. In addition, it should be noted that the [redacted] discontinuation rate calculated above for nemolizumab reflects the maximum conditional discontinuation rate on treatment, based on all patients in the nemolizumab 30mg Q4W to Q8W arm with week-16 response discontinuing treatment at any point until week 48 and for any reason. Therefore, based on the uncertainty in conditional discontinuation derivation for comparators, it is likely that this discontinuation rate calculated for nemolizumab is an overestimate. As noted above, the disparity in discontinuation rates between nemolizumab and other biologics is contrary to UK clinical expert opinion, reinforcing that there is likely to be some discrepancy in how these rates are derived, which makes the assumption that these conditional discontinuation rates are comparable highly uncertain. As a result, Galderma does not consider it appropriate to use the discontinuation rate from the ARCADIA 1 & 2 trials and instead assume parity to other biologics as is preferred by the Committee in TA986.[18] The updated conditional discontinuation rate for nemolizumab at week 52 and year 2 onwards is presented in Table 4. The updated base-case results are presented in Appendix A.

Table 4. Conditional discontinuation rate for nemolizumab at Week 52 and year 2 onwards in adult and adolescent populations

Treatment	Adults	Adolescents	Source / assumption
Nemolizumab	3.9%	3.9%	TA986[18]

B14. Priority question: CS Section B.3.3.4. Please clarify how the company defined the conditional discontinuation probability at Week 52; was it the discontinuation probability from Week 16-52 or the probability from Week 0-52? The model assumes that the long-term discontinuation probabilities are equal to the conditional discontinuation probabilities at Week 52. In the model, the conditional discontinuation probabilities at Week 52 ([redacted] for nemolizumab, 10% for JAKi and 3.9% for biologics) were not converted to annual probabilities with the same values used for long-term discontinuation probabilities. If the "conditional discontinuation probabilities at Week 52" were considered to reflect 36 weeks duration (from Week 16-52), then provide an analysis converting these values to annual probabilities, as the EAG believes happened in TA986.

Response – Conditional discontinuation were those patients that responded at week 16 and then discontinued at week 52. As requested, scenario analyses have been presented in Appendix A where the conditional discontinuation probabilities are converted to annual probabilities for long-term discontinuation. The annual long-term discontinuation values are presented in Table 5.

Table 5. Annual long-term discontinuation rates used in scenario analysis

Treatment	Adults	Adolescents*	Source / assumption
Nemolizumab	5.58%	5.58%	NICE TA986[18]
Upadacitinib 15 mg	14.12%	14.12%	
Upadacitinib 30 mg	14.12%	N/A	
Lebrikizumab	5.58%	5.58%	
Dupilumab	5.58%	5.58%	
Tralokinumab	5.58%	5.58%	
Baricitinib	14.12%	N/A	
Abrocitinib 100 mg	N/A	14.12%	
Abrocitinib 200 mg	14.12%	14.12%	

B15. Priority question: Table 10 of the CS states that approximately [redacted] of patients discontinued nemolizumab treatment in the initial treatment period of ARCADIA 1 and 2. Table 14 of the CS states that [redacted] in the continuous nemolizumab arm discontinued treatment at Week 56 in the LTE study. These

values are markedly different from the [redacted] assumed in the model; please clarify the reason for this difference. Please provide scenario analyses using the following assumptions:

- **Nemolizumab having the same discontinuation probability as the other biologic comparators (in both conditional discontinuation probability at week 52 and long-term annual discontinuation probability).**
- **Nemolizumab having the long-term discontinuation probability based on the data from the LTE study (interim data cut Week 56)**

Response – As discussed in our response to question B13, the discontinuation rate for nemolizumab included in CS Table 52 was an error. The conditional discontinuation rate for nemolizumab at week 52 and year 2 onwards in the updated base-case economic model (Table 4) has been updated based on the Committee's preferred assumptions in TA986.[18] This assumption is supported by UK clinical expert opinion, which stated that significant differences in discontinuation rates for biologics would not be observed in UK clinical practice for AD.[46] The updated base-case is in line with the first scenario requested by the EAG; which is presented in Appendix A.

In the week 56 interim data cut of the LTE study, patients in the continuous nemolizumab arm have been on nemolizumab treatment for longer than 56 weeks, with less than a 12-week interval between lead in study last dose and LTE first dose. Therefore, the discontinuation rate in the continuous nemolizumab arm of the 56-week interim data cut of the LTE does not reflect conditional discontinuation at week 52. Furthermore, using a significantly different rate of long-term discontinuation for nemolizumab compared to the other biologics would not align with UK clinical expert opinion[46] and the Committee's conclusions from TA986,[18] who concluded that there would not be a significantly different rate of discontinuation between treatments in the same class. Therefore, Galderma does not consider it appropriate to present scenario analysis using the discontinuation rate based on data from the LTE 56-week interim data cut that is significantly different to the other biologic treatments.

B16. In Table 10 of the CS, clarify the relationship between 'Discontinued treatment' and 'Discontinued from the study during initial treatment

period/maintenance treatment'. Clarify how the number in the latter group can be lower than the former group for the placebo arm in ARCADIA 1.

Response – First, CS Table 10 contained a reporting error in the row headings that indicated the patient disposition was for both the initial and maintenance periods of ARCADIA 1 & 2, when in fact it was only reflective of patient disposition in the initial treatment period. We have provided separate tables below (Table 6, Table 7) for the patient dispositions in the initial treatment and maintenance periods of ARCADIA 1 & 2.[26,27]

Regarding 'discontinuation from the study' and 'discontinuation from treatment', these terms are not equivalent. Participants may have 1) discontinued from the study or 2) discontinued treatment only but continued to participate in the study. For example, a trial participant who received systemic rescue therapy would discontinue study drug treatment but would be encouraged to complete the scheduled visits and remain in the study.[52,53] Hence the number of participants who discontinued the study can be lower than those who discontinued treatment.

Table 6. Patient disposition: ARCADIA 1 and 2, initial treatment period

	ARCADIA 1		ARCADIA 2	
	Initial treatment period		Initial treatment period	
	ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]	[redacted]	[redacted]
Randomised, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Re-randomised, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Treated, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation of treatment, n (%)				
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]

Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Physician/principle investigator decision	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Completed/exited the study after initial treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from the study during initial treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation from the study, n (%)				
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Proceeded to LTE study after initial treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Completed follow-up after initial treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ITT, intention to treat; LTE, long term extension; n, number; NA, not applicable, Q4W, every 4 weeks; Q8W, every 8 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[26,27]

Table 7. Patient disposition: ARCADIA 1 and 2, maintenance period

	ARCADIA 1				ARCADIA 2			
	Maintenance period				Maintenance period			
	ITT population				ITT population			
	Nemolizumab 30 mg Q4W to Q4W	Nemolizumab 30 mg Q4W to Q8W	Nemolizumab 30 mg Q4W to placebo	Reassigned to placebo†	Nemolizumab 30 mg Q4W to Q4W	Nemolizumab 30 mg Q4W to Q8W	Nemolizumab 30 mg Q4W to placebo	Reassigned to placebo†
Total, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Re-randomised, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation of treatment, n (%)								
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician/principle investigator decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed/exited the study after maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Discontinued from the study during maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation from the study, n (%)								
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proceeded to LTE study after maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed follow-up after maintenance period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Participants in placebo group are not part of ITT population. Placebo group in maintenance period is for all placebo-treated participants who were randomised and responded to placebo during initial treatment period and continued to receive placebo during the maintenance periods.
Abbreviations: AE, adverse event; ITT, intention to treat; LTE, long term extension; n, number; NA, not applicable, Q4W, every 4 weeks; Q8W, every 8 weeks
Source: Galderma data on file ARCADIA 1 & 2 CSR[26,27]

Flare rates and TEAEs

B17. CS Section B.3.3.7, Table 53, Executable model, worksheet "Flares". The treatment-specific flare rates of nemolizumab at Week 16 are 0.0% in both adults and adolescents. However, Table 51 of the CSR states that [redacted] received any topical rescue therapy during the maintenance period using pooled ARCADIA 1 & 2 data. Clarify why the value from the CSR was not used

Response – The flare rate for nemolizumab was updated in the model to reflect pooled data from ARCADIA 1 & 2 trials ([redacted]). The value observed over 32 weeks (weeks 16–48) was converted to a 16-week value ([redacted]). The same value was used for both adults and adolescents. Updated base-case results are presented in Appendix A.

B18. CS Section B.3.3.7, Table 53, Executable model, worksheet "Flares". The EAG cannot validate the Week 16 flare rates of dupilumab, abrocitinib 100 mg and abrocitinib 200 mg. Please clarify how the company calculated the rate for those treatments. In addition, the Week 0-16 flare rate data of lebrikizumab from the ADhere trial was reported to be 4.1% in TA986, please clarify why 0.0% was used for lebrikizumab in the model.

Response – Flare rates in the economic model have been updated for abrocitinib 100 mg, abrocitinib 200 mg, dupilumab and lebrikizumab, and are presented in Table 8. These values were recalculated to 16-week values. Updated base-case results are presented in Appendix A.

Table 8. Treatment-specific flares at week 16

Treatment	Adults	Adolescents	Source / assumption
Nemolizumab	[redacted]	[redacted]	ARCADIA 1& 2[26,27]
Upadacitinib 15 mg	5.30%	10.23%	Reich (2021) (adults);[54] Pooled Measure UP 1 and 2 (adolescents)[55]
Upadacitinib 30 mg	5.40%	N/A	Reich (2021)[54]
Lebrikizumab	1.80%	1.80%	NICE TA986[18]

Dupilumab	5.30%	20.73%	NICE TA814[5]
Tralokinumab	2.80%	2.80%	Silverberg (2021)[56]
Baricitinib	5.41%	N/A	NICE TA814[5]
Abrocitinib 100 mg	15.68%	15.68%	NICE TA814[5]
Abrocitinib 200 mg	6.21%	6.21%	

B19. CS Section B.3.3.8, Table 54 and 55. The CS states that TEAE rates of nemolizumab are based on data from ARCADIA 1, ARCADIA 2 and Kabashima 2022. The EAG cannot validate the values used in the model. For example, the upper respiratory tract infection rate was [redacted] in ARCADIA 1, [redacted] in ARCADIA [CSR Table 121] and 1.7% in Kabashima 2022. However, the rate is 0.0% in the model. Please clarify how the company calculated the rate for each event.

Response – For nemolizumab, study-drug related TEAEs were included in the economic model. The values included in the economic model for nemolizumab have been updated to include ARCADIA 1 & 2 as a source of data and are presented in Table 9. The same values were used for the adults and adolescent populations. In addition, the rates of TEAEs for lebrikizumab have been updated based on TA986 and are presented in Table 9. Updated base-case results incorporating these updated TEAE rates are presented in Appendix A.

Table 9. TEAE rates at week 16 in adult and adolescent population

Treatment	ISR	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Asthma	Source / assumption
Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ARCADIA 1 & 2[26,27]
Lebrikizumab	0.00%	8.20%	8.00%	5.00%	10.40%	0.00%	6.90%	TA986[18]

B20. The NMA for TEAEs (Section 1.18.10 of Appendix M) indicates that dupilimab has a better midpoint value for TEAEs compared with nemolizumab (Figure 33 in Appendix M). However, the sum of the 7 selected TEAEs considered in the model is [redacted] for nemolizumab and 28.11% for dupilimab (for

nemolizumab this was D11, F11, H11, J11, L11, N11 and P11). Please explain this apparent contradiction.

Response – Please note that Figure 33 in Appendix M to the CS is for the adult first-line population which is not considered relevant to this submission. The relevant figure in Appendix M for the adult second-line population is Figure 65. In the adult second-line population, when nemolizumab is considered as the reference treatment, odds of TEAEs for nemolizumab 30 mg were numerically lower but not significantly different than dupilumab 300 mg Q2W ([redacted]).

In addition, in the NMA, TEAE data is based on the number of subjects with at least 1 TEAE of any type, not on a subset of event types, whereas the economic model incudes adverse events that occurred in at least 5% of patients and is aligned with the TEAEs included in TA986.[18]

HRQoL

B21. Priority question: CS Section B.3.4.3, Table 58. For adults, the utility value for non-responders (0.753) is higher than in the first 8 weeks of treatment (0.648). Please explain the potential reason for this - is it regression to the mean or a placebo response? We note that this isn't the case for adolescents (Table 59).

Response – Heath state utility values used in the economic model were based on PLD from ARCADIA 1, ARCADIA 2, ARCADIA-CYCLO and LTE study for the adult population, and ARCADIA 1, ARCADIA 2 and LTE study for the adolescent population. No regression analysis was conducted and direct values observed within the clinical trial were used.

It may be expected that the utility value for non-responders would be higher than baseline values due to partial responders to treatment. While not meeting the threshold required to be considered 'responders', these patients may still receive some positive treatment effect which would increase their quality of life (QoL). To align the relationship between baseline and non-responder utility values between adolescents and adults, a scenario was conducted that assumes adolescents'

baseline utility value equal to the value for adults (0.648). This scenario analysis is presented in Appendix A.

B22. Clarify why the utility estimated in year 1 does not take into account both the utility at week 16 and week 48 from ARCADIA?

Response – Based on data availability and to reflect increasing utility over time from treatment initiation, the economic model used the utility value at week 16 in the clinical trials to reflect QoL in year 1, the utility value at week 48 for QoL year 2, and the utility value at week 104 for QoL in year 3. This is a conservative assumption that pushes back increased utility already observed at week 48 for responders to year 2. The assumption that utility values increase over time was validated by UK clinical experts who confirmed that HRQoL increases over time for responders, as although itch relief is observed shortly after treatment is initiated, it takes longer for skin lesions to heal.[46]

B23. Executable model, worksheet "Utilities". Utility values are adjusted using Ara and Brazier (2011). Please provide an updated version of the model which uses age-and sex-adjusted utility values from Hernandez Alava et al. (https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d)

Response – The base-case economic model has been updated to use general population utility values based on Hernandez Alava et al.[57] The updated base-case results are presented in Appendix A.

Productivity loss

B24. CS Section B.3.5.4, Table 68. The proportions of responders and non-responders for sleep duration from Table 68 are different from the values used in the model, working sheet "Costs calculations" cells U147:U149 and U153:U155. Please confirm which values are correct. The EAG cannot validate those proportions from ARCADIA 1 and 2. Please clarify how the company calculated those values.

Response – The values reported in CS Table 68 are a reporting error; the correct values are the values in the "Costs calculations" sheet and presented in Table 10 below.

These values were based on the second-line adult population of ARCADIA 1 & 2 and calculated as proportions by taking the total number of responders and non-responders based on the EASI-75 outcome at week 16 as the denominator where the numerator was the total number in a sleep duration category.

Table 10. Sleep duration and work impairment for responders and non-responders

Sleep duration	Responders	Non-responders	Work impairment
< 6 hours	[redacted]	[redacted]	2.36%
6-7 hours	[redacted]	[redacted]	1.47%
> 7 hours	[redacted]	[redacted]	0.00%

Executable model

B25. Priority question: It is assumed that treatments have identical efficacy when there is no statistically significant difference in the results from the NMA. However, in the PSA, there is uncertainty in the ORs which violates the assumption of equal efficacy. Please amend this, so that it is always 1, when this assumption is being used. Where the results are statistically significant, use the CODA samples from the NMA instead of a standard error (see next question)

Response – The PSA in the economic model has been updated so that an OR of 1 is used when there is no statistically significant difference in the NMA, and that CODA samples are used when there is a statically significant difference. Updated PSA results are presented in Appendix A.

B26. Priority question: Clarify why the CODA samples are not being used in the PSA for when the distributions from the NMA are used. The CODA samples ensure that correlation between the estimates will be explicitly incorporated

which is lost when independent distributions (using standard errors) are used. Amend the model to use CODA samples

Response – The PSA in the economic model has been updated so that CODA values are used in the PSA when there are non-statistically significant results from the NMA. Updated PSA results are presented in Appendix A.

B27. Priority question: Executable model, worksheets "Parameter Sampling". The CS states that utilities are treatment independent and the treatment discontinuation rates are the same in each drug-class for the comparators. However, within the PSA, utility and discontinuation rates are sampled independently for each treatment. Please confirm this is an error and provide a corrected version of the model.

Response – In the PSA in the economic model, formulas in the Parameter Sampling sheet have updated to reflect the assumption that utilities are not treatment-specific, and discontinuation rates are equal within drug class for comparators. The updated PSA results are presented in Appendix A.

B28. Priority question: Provide evidence that the random number seed does not influence the PSA results by repeating the PSA with a different seed and comparing results. If these are not sufficiently close in terms of incremental costs and QALYs then run further PSA iterations.

Response – The PSA was repeated with different seed numbers. The results for nemolizumab versus dupilumab in the adult population are presented in Table 11. Overall, the results it can be considered sufficiently close and that the random number seed does not influence the PSA results.

Table 11. Results of PSA for different seed numbers

Seed	Incremental costs	Incremental QALYs	ICER
7	[redacted]	[redacted]	-£311,814
2	[redacted]	[redacted]	-£310,281
5	[redacted]	[redacted]	-£311,369

B29. Executable model, worksheet "Mortality", cell F10:F110. The formulae in this cell range assume that the proportionate split of men and women remains constant at every age, yet the life table probabilities indicate that men and women have different age-specific risks of death. Both of these cannot be simultaneously true. Please amend the model to use a weighted survival model, based on separate survival models for men and women, with the weighting applied at baseline.

Response – Treatments for moderate-to-severe AD are not expected to impact mortality, thus survival is not a key driver in the economic model. In addition, the approach to model survival used in the economic model is in line with both TA814 and TA986.[5,18] Galderma does not consider that proportion of males will have any significant impact on the cost-effectiveness results. Therefore, the inclusion of a weighted survival model, separately for men and women, would add additional and unnecessary complexity to the cost-effectiveness calculations.

B30. Executable model, worksheets starting with "Markov Traces", columns Z to AE. The half-cycle correction ignored the patients in cycle 0 (year 1) and only started from cycle 1 (year 2). Please confirm that these are errors and provide a corrected version of the model.

Response – The base-case economic model has been updated to include patients in cycle 0. Updated base-case results are presented in Appendix A.

B31. Executable model, worksheets starting with "Markov Traces", column N, columns BN to BQ. The calculations in column N apply the age-and sex-adjusted general population mortality and those in columns BN to BQ include the age-and sex-adjustments of general population utility. Regarding the lookup function for the cycle-specific age in those calculations, ROUND(E15+baseDemAgeUsed,0) and ROUNDDOWN(baseDemAgeUsed,0)+E16 are used for age-and sex-adjusted mortality and age-and-sex adjusted general population utility, respectively. Please explain why these formulae are not consistent with respect to the age

used, and provide a model where the age used for mortality and for utility is the same.

Response – The age that was used in both formulas was equal for the same cycle; the only difference was in the ROUND/ROUNDDOWN function. The mortality formula has been updated in the base-case economic model to include the ROUNDDOWN function. The updated base-case results are presented in Appendix A.

B32. Executable model. In the first year (decision tree), the model allocates the same costs and QALYs for patients who responded at week 16 but discontinued at week 52, as patients who did not respond and discontinued at week 16. For example, in the nemolizumab arm, [redacted] of patients responded at week 16 but discontinued at week 52; these received the same costs and QALYs (per patient) as the [redacted] of patients who never responded to treatment. Please amend the model (within the Markov Traces sheets) to consider the likely improved outcomes of patients who responded.

Response – Patients who discontinued from week 52 onwards move to the 'No response' health state with the same outcomes as non-responders. However, this may not be fully true in the first year, where patients who discontinue at week 52 experience initial response for a few weeks and then discontinue. As most patients who discontinue switch to subsequent biologic or JAK inhibitors, the treatment effect and costs of these treatments will be assigned to them. In the case of nemolizumab, only [redacted] (responders to initial therapy [redacted] who discontinued at week 52 [3.9%]) of 6.6% (patients who do not switch to subsequent biologics or JAK inhibitors after failure or discontinuation of initial treatment) may have the effect underestimated in the first year. Therefore, this is expected to have a negligible impact on the economic model results.

B33. Executable model, worksheet "Markov Traces - Lebrikizumab", cell AX15. The calculations apply the treatment costs for responders of lebrikizumab at cycle 0 (Year 1). Please explain why the acquisition cost of lebrikizumab induction was applied for 14 weeks instead of 16 weeks.

Response – Lebrikizumab dosing is 2 × 250 mg at weeks 0 and 2, followed by 250 mg every other week. In the cost calculations, we included separate cost inputs for

loading dose and induction. For loading dose, we included 4 doses which captures both week 0 and 2, which means that in induction phase only 14 weeks are left.

B34. Executable model, worksheets starting with "Markov Traces", cell BO15. The calculations estimate the QALYs for non-responders at cycle 0 (Year 1). From Week 0-8, the baseline utility was applied to all patients regardless of response status. From Week 8-52, the weighted utility of second line biologic/JAKi was applied to patients who received biologics/JAKi in the BSC basket, and the utility of non-responders was applied to the rest. However, response status was measured at Week 16 and therefore non-responders would switch treatment only after that. The weighted utility of second line biologic/JAKi should be applied only after Week 16, rather than Week 8. Please confirm that this is an error and provide a corrected version of the model.

Response – The base-case economic model has been updated to include second-line specific utility starting from week 16, instead of from week 8. Updated base-case results are presented in Appendix A.

B35. Clarify why concomitant medication costs for non-responders were not included in the PSA.

Response – In the economic model, the concomitant medication cost for non-responders has been added to the PSA. The updated PSA results are presented in Appendix A

B36. Executable model, worksheet "Home", cell D15. Clarify why the lifetime horizon is 60 years in the base-case, which assumes that all patients are dead at ~ 95 years of age. If appropriate, increase the time horizon of the model.

Response – In the economic model, after 60 years approximately 90% of the cohort are dead, with all patients in the model dead in year 67. Scenario analysis has been conducted to extend the modelled time horizon to 67 years to test the impact of this parameter on model results. The results of this scenario are presented in Appendix A.

B37. Executable model, worksheet starting with "Markov Trace", cell AN15:AT15. Only those who respond to treatment at week 52 are assumed to have AEs. Allow AEs to occur in all patients.

Response – In the base-case economic model, traces have been updated to include adverse events in all patients. Updated base-case results are presented in Appendix A.

B38. Executable model, worksheet "Markov Traces - Nemolizumab", column AT. The calculations estimate the number of asthma events in each cycle.The model appears to be erroneously using the Week 16 asthma rate (cell J99) instead of using the adjusted annual rate (cell M99) from the working sheet "Parameter Sampling". The other working sheets starting with "Markov Traces" for comparators appear to have the same error in column AT (no impact on the results of comparators as the asthma rate is 0 for all comparators). Please amend these formulae if appropriate.

Response – The base-case economic model has been updated to include annual asthma rates for the intervention and all comparators. The updated base-case results are presented in Appendix A.

B39. Executable model, worksheets starting with "Markov Traces", columns G and H. The calculations apply the discount rate formulas for costs and QALYs. The formula "1/((1+disc_costs)^$E16)" appears to be erroneously used in the model. The formula should be "1/((1+disc_costs)^(t-1)) where t is the current year. Please confirm this is an error and provide an updated model.

Response – Galderma considers the discounting formula that is applied in the economic model to be correct. Based on Severens et al.,[58] in the formula the power should be 't' instead of suggested 't-1'.

B40. Executable model, worksheet "Costs calculations", cells G23:G24 and G30:G31. The calculations use the total units of drugs per week during the induction and maintenance period. We believe that: the total units per week for dupilumab for both induction and maintenance should be 1 instead of 0.5 (one unit of dupilumab has 150 mg); and that the total units per week for lebrikizumab should be 1 and 0.50 instead of 0.5 and 0.25 for induction and

maintenance treatment, respectively (one unit of lebrikizumab has 125 mg). Please amend the model if it is agreed these are errors.

Response – The EAG confirmed that this clarification question includes an error, and a response is not required.

B41. Executable model, worksheet "Costs calculations", cell E184:E192. The unit costs of dermatological nurse visits and psychological support are lower than the costs reported in TA986 (2021 price year). Please update those costs. Additionally, clarify why the day case unit cost of £765 was used instead of the total unit cost of £157 for phototherapy.

Response – A different approach to calculate unit costs of each medical service was used in the economic model compared with TA986.[18] Dermatological nurse visit cost was taken from PSSRU, 2022/23.[59] One-hour cost was £58 and for the purpose of the model, 0.5 hours was applied, i.e., £29. In TA986, 15 minutes of a band 6 hospital-based nurse was used (£51 per working hour) and additionally it was assumed that each hour spent with a client requires 2.5 paid hours (£32).[18]

For psychological support the economic model used service code 656, clinical psychology, WF01A, weighted average between consultant–led and non-consultant–led from NHS reference costs 2022/23.[60] The value was £257.46 per unit. In TA986 only consultant–led visits were included and weighted average from WF01A-WF01D, WF02A, WF02B (£321).[18]

Phototherapy cost was calculated based on code JC47Z, acute day case (£765; NHS reference costs 2022/23),[60] while in TA986 total HRG cost was used (£157).[18] As the difference between these two costs is significant, a scenario analysis was conducted to check the impact on decreased phototherapy costs on model results. The results of this scenario are presented in Appendix A.

B42. Comment on why the Life Years accrued in the PSA (45.186 in Table 73 of the CS) are greater than in the base case results (44.859 in Table 71 of the CS).

Response – The PSA in the economic model has been updated with results presented in Appendix A. In the updated PSA results, life years are now lower in PSA compared with base-case (46.792 vs 46.981, respectively).

Section C: Textual clarification and additional points

No additional questions

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nemolizumab for treating moderate-to-severe atopic dermatitis in people 12 and over [ID6221]

Clarification questions Appendix A: Updated base-case results

November 2024

File name	Version	Contains confidential information	Date
[ID6221] Nemolizumab CQ Appendix A 271124 [Redacted]	2	Yes	27 November 2024

Contents

Tables and figures

Tables

Figures

1 Summary of cost-effectiveness results

Table 1 and Table 2 present the updated base-case results at the Clarification Questions stage of the NICE process in the adult and adolescent populations, respectively. These results supersede those presented in the original Company Submission. A summary of the updates made to the base-case are presented in Table 3.

Table 1. Summary the updated base-case result (adult population)

Technology	ICER (cost/QALY)
NICE submission base-case	
Nemolizumab	-
Dupilumab	Dominant
Abrocitinib 200 mg	Dominant
Upadacitinib 15 mg	Dominant
Upadacitinib 30 mg	Dominant
Baricitinib	Dominant
Tralokinumab	Dominant
Lebrikizumab	Dominant
Updated base-case post-clarification questions	
Nemolizumab	-
Dupilumab	Dominant
Abrocitinib 200 mg	Dominant
Upadacitinib 15 mg	Dominant
Upadacitinib 30 mg	£673,855 (CE)
Baricitinib	Dominant
Tralokinumab	Dominant
Lebrikizumab	Dominant

Table 2. Summary the updated base-case results (adolescent population)

Technologies	ICER (cost/QALY)
NICE submission base-case	
Nemolizumab	-
Abrocitinib 100 mg	Dominant
Abrocitinib 200 mg	Dominant
Upadacitinib 15 mg	Dominant
Lebrikizumab	Dominant
Updated base-case post-clarification questions	
Nemolizumab	-
Abrocitinib 100 mg	Dominant
Abrocitinib 200 mg	Dominant
Upadacitinib 15 mg	Dominant
Lebrikizumab	Dominant
Dupilumab	Dominant
Tralokinumab	Dominant

Table 3. Summary of updates to the base-case economic model

Changes to base-case economic model	
Adult and adolescent population	
1	PAS updated to [redacted] per pack
2	Baseline characteristics updated to be based on ARCADIA 1, 2, and ARCADIA CYCLO for adult population and ARCADIA 1 and 2 for adolescent population (CQ B3)
3	TEAEs for biologics and JAK inhibitors used for non-responders at week 16 added (CQ B5C)
4	Flares for biologics used for non-responders at week 16 added (CQ B5D)
5	Mortality in the first year of the analysis added (CQ B7)
6	Conditional discontinuation at week 52 and year 2 onwards for nemolizumab updated to 3.9% equal to other biologics (CQ B13)
7	Nemolizumab flares rates updated (CQ B17)
8	Abrocitinib 100 mg, abrocitinib 200 mg, dupilumab and lebrikizumab flare rates updated (CQ B18)
9	Nemolizumab TEAEs updated (CQ B19)
10	Lebrikizumab TEAEs updated (CQ B19)
11	Source for general population utilities was updated to be Hernandez Alava et al. (2022)[1] (CQ B23)
12	Half-cycle correction implementation was updated to include value in cycle 0 (CQ B30)
13	General population mortality formula updated to use ROUNDDOWN instead of ROUND function (CQ B31)
14	Utilities for second-line biologics applied from week 16 instead of week 8 (CQ B34)
15	Trace updated to include TEAEs for all patients (CQ B37)
16	Formula updated to use annual asthma rate (CQ B38)
17	PSA updated to include CODA sampling for statistically significant ORs (CQ B25)
18	PSA updated so that ORs equal 1 for non-statistically significant ORs (CQ B25)
19	PSA modified to ensure that utilities are not treatment-specific and discontinuations are equal within drug classification (CQ B27)
20	Concomitant medication cost included in PSA (CQ B35)
21	Discounting calculations updated to avoid overestimation (Additional CQ)
22	Lebrikizumab flare rates updated to 4% based on TA986 (Additional CQ)
23	Lebrikizumab TEAEs updated based on TA986 (Additional CQ)
Adolescent population only	
21	Tralokinumab and dupilumab added as comparators to the adolescent population (CQ B4)
22	Baricitinib excluded as a subsequent treatment for non-responders in adolescent population (CQ B5E)

Abbreviations: CODA, convergence diagnosis and output analysis; OR, odds ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; TEAE, treatment-emergent adverse events

1.1. Base-case results

1.1.1. Base-case incremental cost-effectiveness analysis results

The updated base-case cost-effectiveness analysis results for nemolizumab versus all comparator treatments in patients with moderate-to-severe AD, are presented in Table 4 and Table 5 for the adult and adolescent populations, respectively. The cost-effectiveness analysis results for nemolizumab are presented with the PAS price applied.

In the adolescent population, nemolizumab was associated with improved QALYs versus all comparators with the incremental discounted QALYs ranging from [redacted] to [redacted]. In the adult population, nemolizumab was associated with improved QALYs versus all comparators with the incremental discounted QALYs ranging from [redacted] to [redacted], with exception of upadacitinib 30mg which was associated with [redacted] incremental discounted QALYs. In both the adult and adolescent populations there were no incremental differences in total LYs for nemolizumab versus the comparators.

In both the adult and adolescent populations, nemolizumab with PAS was associated with reduced costs versus all of the comparator treatments, with incremental discounted costs ranging from [redacted] to [redacted] in the adult population and from [redacted] to [redacted] in the adolescent population.

Nemolizumab was dominant versus all comparators in both the adult and adolescent populations, with the exception of upadacitinib 30mg, where nemolizumab was less costly and less effective resulting in a cost-effective ICER in the southwest (SW) quadrant based on a willingness-to-pay (WTP) threshold of £30,000 per QALY gained. Therefore, nemolizumab can be considered a cost-effective use of NHS resources in both adult and adolescent patients with moderate-to-severe AD who are candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.

In addition, the net monetary benefits and net health benefits are presented in Table 6 and Table 8 for the adult population and Table 7 and Table 9 for the adolescent populations.

Table 4. Updated base-case results (adult population) with PAS

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	46.981	[redacted]	N/A	N/A	N/A	N/A
Dupilumab	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 30 mg	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	£673,855 (CE)
Baricitinib	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant
Tralokinumab	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	46.981	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: CE, cost-effective; ICER, incremental cost-effectiveness ratio; LYs, life years; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 5. Base-case results (adolescent population) with PAS

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	57.160	[redacted]	N/A	N/A	N/A	N/A
Abrocitinib 100 mg	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant
Dupilumab	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant
Tralokinumab	[redacted]	57.160	[redacted]	[redacted]	0.000	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; PAS, patient access scheme; QALYs, quality-adjusted life year

Table 6. Base-case net monetary benefits (adult population) with PAS

Technologies	Net monetary benefit	Incremental
Nemolizumab	[redacted]	N/A
Dupilumab	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]
Baricitinib	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Lebrikizumab	[redacted]	[redacted]

Abbreviations: N/A, not applicable

Table 7. Base-case net monetary benefits (adolescent population) with PAS

Technologies	Net monetary benefit	Incremental
Nemolizumab	[redacted]	N/A
Abrocitinib 100 mg	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]
Lebrikizumab	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]

Abbreviations: N/A, not applicable

Table 8. Base-case net health benefits (adult population) with PAS

Technologies	Net health benefit	Incremental
Nemolizumab	[redacted]	N/A
Dupilumab	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]
Baricitinib	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Lebrikizumab	[redacted]	[redacted]

Abbreviations: N/A, not applicable

Table 9. Base-case net health benefits (adolescent population) with PAS

Technologies	Net health benefit	Incremental
Nemolizumab	[redacted]	N/A
Abrocitinib 100 mg	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]
Lebrikizumab	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]

Abbreviations: N/A, not applicable

1.2. Sensitivity analysis

1.2.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of input parameters. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution:

- costs, age, and AEs and flare duration: gamma
- ORs, normal; response rate, safety, and utilities parameters: beta

These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters. Reproducibility of results was achieved via the inclusion of a random number seed.

Several inputs are derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 10% of the mean value for the purposes of the PSA.

Results of PSA for the adult and adolescent populations are summarised in Table 12 and Table 13, respectively. Scatterplots for the base-case analyses (with PAS) for the adult and adolescent populations, arising from 1,000 simulations of the model with all parameters sampled are presented in [redacted]

Figure 1 to Figure 7 or the adult population and Figure 9 to Figure 12 for the adolescent population. Cost-effectiveness acceptability curves (CEACs) appraising nemolizumab versus all comparators are depicted in Figure 8 and Figure 15 for adults and adolescents, respectively.

Based on PSA, the probability that nemolizumab is cost-effective at a WTP threshold of £30,000 per QALY gained is estimated at between [redacted] to [redacted] in the adult population and [redacted] to [redacted] in the adolescent population across their relevant comparators.

Table 10. PSA results (adults) with PAS

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	46.792	[redacted]	N/A	N/A	N/A	N/A
Dupilumab	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	£10,636,326 (CE)
Abrocitinib 200 mg	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 30 mg	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	£539,787 (CE)
Baricitinib	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	Dominant
Tralokinumab	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	£10,853,756 (CE)
Lebrikizumab	[redacted]	46.792	[redacted]	[redacted]	0.000	[redacted]	£14,532,407 (CE)

Abbreviations: CE, cost-effective; ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; PAS, patient access scheme; QALY, quality-adjusted life year

Figure 1. ICER scatterplot (nemolizumab versus dupilumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 2. ICER scatterplot (nemolizumab versus abrocitinib 200 mg in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 3. ICER scatterplot (nemolizumab versus upadacitinib 15 mg in adult population, in adults) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 4. ICER scatterplot (nemolizumab versus upadacitinib 30 mg in adult population, in adults) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 5. ICER scatterplot (nemolizumab versus baricitinib in adult population, in adults) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 6. ICER scatterplot (nemolizumab versus tralokinumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 7. ICER scatterplot (nemolizumab versus lebrikizumab in adult population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 8. Cost-effectiveness acceptability curve (nemolizumab versus all comparators in adult population) with PAS

Abbreviations: WTP, willingness to pay

Table 11. PSA results (adolescents with PAS)

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Nemolizumab	[redacted]	57.188	[redacted]	N/A	N/A	N/A	N/A
Abrocitinib 100 mg	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	Dominant
Abrocitinib 200 mg	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	Dominant
Upadacitinib 15 mg	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	Dominant
Lebrikizumab	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	£50,215,444 (CE)
Dupilumab	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	£13,139,542 (CE)
Tralokinumab	[redacted]	57.188	[redacted]	[redacted]	0.000	[redacted]	£39,553,385 (CE)

Abbreviations: CE, cost-effective ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; PAS, patient access scheme; QALYs, quality-adjusted life year

Figure 9. ICER scatterplot (nemolizumab versus abrocitinib 100 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 10. ICER scatterplot (nemolizumab versus abrocitinib 200 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 11. ICER scatterplot (nemolizumab versus upadacitinib 15 mg in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 12. ICER scatterplot (nemolizumab versus lebrikizumab in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 13. ICER scatterplot (nemolizumab versus dupilumab in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 14. ICER scatterplot (nemolizumab versus tralokinumab in adolescent population) with PAS

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay

Figure 15. Cost-effectiveness acceptability curve (nemolizumab versus all comparators in adolescent population) with PAS

Abbreviations: WTP, willingness to pay

1.2.2. Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs and ICER. Each parameter is allocated a 'high' value and a 'low' value; for all parameters apart from discount rates, the high value and low value is +/- 20% of the mean value. By adjusting each parameter one at a time, the DSA assesses the impact of uncertainty around individual input parameters on the model outcomes. Results are presented in tornado plots, which clearly present the parameters that have the greatest effect on the relevant model outcomes. The ten most influential parameters are presented.

Results of the DSA (with PAS) in the adult and adolescent populations are presented (Figure 16 through Figure 28) and demonstrate the impact of specific parameters on ICER estimates. Overall, the cost-effectiveness results for the adult and adolescent populations were mostly robust to parameter uncertainty. A variety of parameters were observed to impact model results, with the utility values for the 'Maintained response health' state and 'BSC health state', and QALY discounting frequently being amongst the most influential comparators in both the adult and adolescent populations across all comparators.

[redacted]

Figure 16. Tornado plot (nemolizumab versus dupilumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

[redacted]

Figure 17. Tornado plot (nemolizumab versus abrocitinib 200 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

[redacted]

Figure 18. Tornado plot (nemolizumab versus upadacitinib 15 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 19. Tornado plot (nemolizumab versus upadacitinib 30 mg in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 20. Tornado plot (nemolizumab versus baricitinib in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 21. Tornado plot (nemolizumab versus tralokinumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 22. Tornado plot (nemolizumab versus lebrikizumab in adult population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 23. Tornado plot (nemolizumab versus abrocitinib 100 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 24. Tornado plot (nemolizumab versus abrocitinib 200 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 25. Tornado plot (nemolizumab versus upadacitinib 15 mg in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 26. Tornado plot (nemolizumab versus lebrikizumab in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 27. Tornado plot (nemolizumab versus dupilumab in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

Figure 28. Tornado plot (nemolizumab versus tralokinumab in adolescent population) with PAS

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, standard of care

1.2.3. Scenario analysis

A number of scenario analyses were performed, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and model parameters. Results of the scenario analyses (with PAS) for the adult and adolescent populations are presented in Table 12 to Table 24. The results of most of the scenario analyses were comparable to the base-case cost-effectiveness estimates, with nemolizumab remaining cost-effective versus all comparators in all scenarios in both the adult and adolescent populations. For the scenario analysis where disutilities due to TRAEs and flares were excluded an ICER calculation was not feasible versus dupilumab, tralokinumab and lebrikizumab in both the adult and adolescent populations as there were [redacted]. However, in all of these scenarios nemolizumab was cost saving. Overall, the scenario analysis results demonstrate that the base-case cost-effectiveness estimates were robust to alternate model assumptions and parameters.

Table 12. Scenario analyses results (dupilumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£577,367 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life ye

Table 13. Scenario analyses results (abrocitinib 200 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	£93,035 (CE)
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 14. Scenario analyses results (upadacitinib 15 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£981,574 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 15. Scenario analyses results (upadacitinib 30 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	£673,855 (CE)
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	£565,902 (CE)
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	£138,738 (CE)
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	£665,514 (CE)
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	£718,718 (CE)
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	£599,768 (CE)
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£773,895 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 16. Scenario analyses results (baricitinib in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 17. Scenario analyses results (tralokinumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 18. Scenario analyses results (lebrikizumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Utilities based on ARCADIA 1, 2 and CYCLO	Utilities based on ARCADIA 1 and 2	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£1,343,791 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 19. Scenario analyses results (abrocitinib 100 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 20. Scenario analyses results (abrocitinib 200 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£863,234 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 21. Scenario analyses results (upadacitinib 15 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	Dominant
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£591,041 (CE)

Abbreviations: AE. Adverse event; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 22. Scenario analyses results (lebrikizumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£124,305 (CE)

Abbreviations: AE. Adverse event; CE, cost-effective; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 23. Scenario analyses results (dupilumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	£424,275 (CE)

Abbreviations: AE. Adverse event; CE, cost-effective; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

Table 24. Scenario analyses results (tralokinumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on PP-NRS	[redacted]	0.000	[redacted]	Dominant
Response at week 16 based on EASI-75	Response at week 16 based on IGA	[redacted]	0.000	[redacted]	Dominant
No indirect costs included	Inclusion of Indirect costs	[redacted]	0.000	[redacted]	Dominant
Disutilities due to AEs and flares included	Exclude disutilities due to AEs and flares	[redacted]	0.000	[redacted]	N/A
Treatment effect waning included	No treatment effect waning	[redacted]	0.000	[redacted]	Dominant
OR of 1 assumed for comparators with no statistically significant difference in response at week 16	Point estimates for ORs	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AE. Adverse event; CE, cost-effective; LY, life year; ICER: incremental cost-effectiveness ratio; IGA, Investigator Global Assessment; OR, odds ratio; PAS, patient access scheme; PP-NRS, Peak Pruritus Numerical Rating Scale; QALY, quality-adjusted life year

1.2.4. Additional Scenario analysis

A number of scenario analyses were performed following response to the clarification questions, which explored the robustness of the base-case cost-effectiveness estimates to the key model assumptions and model parameters. Results of the scenario analyses (with PAS) for the adult and adolescent populations are presented in Table 25 to Table 37 The results of all scenario analyses were comparable to the base-case cost-effectiveness estimates, with nemolizumab remaining cost-effective versus all comparators in all scenarios in both the adult and adolescent populations. Therefore, these results demonstrate that the base-case cost-effectiveness estimates were robust to alternate model assumptions and parameters.

Table 25. Additional scenario analyses results (dupilumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£1,141,133 (CE)
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 26. Additional scenario analyses results (abrocitinib 200 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 27. Additional scenario analyses results (upadacitinib 15 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 28. Additional scenario analyses results (upadacitinib 30 mg in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	£673,855 (CE)
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	£194,873 (CE)
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	£952,238 (CE)
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£391,057 (CE)
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	£673,914 (CE)
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	£674,308 (CE)
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	£661,454 (CE)

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 29. Additional scenario analyses results (baricitinib in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 30. Additional scenario analyses results (tralokinumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£808,101 (CE)
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 31. Additional scenario analyses results (lebrikizumab in adult population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Nemolizumab response based on EASI-75	Nemolizumab response based on EASI-50 + DLQI (CQ B11)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£1,139,968 (CE)
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LY, life year; ICER: incremental cost-effectiveness ratio; JAK; Janus kinase; PAS, patient access scheme; QALY, quality-adjusted life year

Table 32. Additional scenario analyses results (abrocitinib 100 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Table 33. Additional scenario analyses results (abrocitinib 200 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Table 34. Additional scenario analyses results (upadacitinib 15 mg in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	Dominant
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Table 35. Additional scenario analyses results (lebrikizumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£929,992 (CE)
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Table 36. Additional scenario analyses results (dupilumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£935,051 (CE)
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

Table 37. Additional scenario analyses results (tralokinumab in adolescent population) with PAS

Base-case assumption	Scenario	Incremental costs	Incremental LYs	Incremental QALYs	Incremental ICER (£/QALY)
Base-case		[redacted]	0.000	[redacted]	Dominant
Patients receive subsequent JAK inhibitors or biologic therapy after treatment, 60-year time horizon	Patients receive no subsequent JAK inhibitors or biologic therapy after treatment, 3-year time horizon (CQ B6)	[redacted]	0.000	[redacted]	Dominant
Long-term discontinuation based on conditional discontinuation values	Long-term discontinuation recalculated to annual values (CQ B14)	[redacted]	0.000	[redacted]	£641,201 (CE)
Baseline utility based on adolescents in ARCADIA 1 & 2 (0.842)	Baseline utility equal to adult population (0.648) (CQ B21)	[redacted]	0.000	[redacted]	Dominant
Time horizon of 60 years	Time horizon of 67 years (CQ B36)	[redacted]	0.000	[redacted]	Dominant
Phototherapy costs of £765	Phototherapy costs of £157 (B41)	[redacted]	0.000	[redacted]	Dominant
Mortality driven only by general population all-cause death	Hazard ratio of 1.6 for AD patients applied to general population mortality (CQ B9)	[redacted]	0.000	[redacted]	Dominant

Abbreviations: AD, atopic dermatitis; LY, life year; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year

References

1. Hernández Alava M. PS, Wailoo A. Estimating EQ-5D by age and sex for the UK. National Institute for Clinical Excellence. 2022;Decision Support Unit Report.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 and over [ID6221]

Patient Organisation Submission

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	Eczema Outreach Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Eczema Outreach Support provides tailored support to children and young people with eczema and their families across the UK. We have 4,606 member families. We: 1. Support and empower families through the provision of tailored information, 1-1 practical and emotional support, specialist resources and support for children at school/nursery. 2. Increase the confidence and self-management skills of children & young people through our virtual clubs: the High 5 Club (age 3-10) and by providing tailored support for teenagers. 3. Offer families opportunities to meet and share experiences with a programme of events and an online community. 4. Shape services, encourage research and influence policy by being the voice of our members at national and international levels. 5. Improve understanding of eczema and reduce isolation & exclusion by increasing the understanding of the condition within local communities and with healthcare professionals. We are funded through a mix of: - Charitable trusts and foundations - Donations from our community and the wider public - Grants from medical industry partners - Support from corporate partners and businesses.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	• One-to-one conversations by our team of Family Workers providing support on the phone to young people and parents/carers caring for a child with eczema • Consultation with parents/carers via our closed Facebook peer support group where members share challenges faced, exchange solutions, problem-solve and provide peer support. • Insights gathered from our EOS Youth Panel (young people with eczema aged 16 -25) who are dealing with eczema every day and are connected with the broader needs of young people with the condition • Consultation with patient members of our volunteer Advisory Panel who either live with eczema and/or care for a child with the condition • Insights gathered from our wider networks of healthcare professionals and education professionals working with children and young people with eczema.

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?	One in five children in the UK has atopic eczema (National Eczema Society, website accessed September 2024) but every child and young person's experience is different. No single treatment or approach works for all, and families go through a frustrating and often unsuccessful process or trial and error to get their child/adolescent's needs met. There is no cure for eczema, only the management of symptoms. Young people often spend significant amounts of time visiting their GP or dermatology clinic trying to find treatments that can alleviate symptoms and improve their quality of life. These frequent visits result in time off school or college, exhaustion and loss of hope which all have damaging impacts on children/young people's wellbeing, their education, relationships, social life and the family unit's ability to take part in daily life. In EOS's 2024 annual survey, 60% of carers said their child also deals with another condition (e.g. allergies, asthma and autism) adding another layer of stress and anxiety. As one carer describes it, “Eczema effects all fields of life ... its [sic] like a cloud going with all of you always.” The unpredictability of eczema and lack of understanding around it often leads to anxiety and low confidence reducing a child’s ability to form positive relationships. Children as young as four share that they are bullied because of their skin and that they feel lonely. Our direct support team talks to parents/carers every day who tell us how helpless they feel to support their child and how isolated they have become. One told us: ‘*The toll it’s taken on my mental health. The times I’ve cried because I feel I am failing my child. I would literally do anything to take it all away.’* EOS Parent Member, email feedback Caring for a child with eczema can push parents/carers to burnout. Through EOS’s peer support services, they share their mental exhaustion, how they’ve lost their identity and feel alone. Many parents/carers have left careers to care for their child, which has personal and financial impacts on family relationships. Siblings direct anger towards their sister/brother for taking their parents’ attention, whilst also feeling sadness for their suffering. 60% of parents/carers told us that the impact of eczema on their whole family is a significant worry (EOS Annual Survey, 2024). *“There is a huge psychological burden of not knowing day to day the condition your skin will be in. I think as humans we are highly adaptable and even in poor health conditions we can learn to live with our "new normal", however this is not the case with eczema as your symptoms fluctuate dramatically day to day or even hour to hour. Leaving you permanently anxious as you anticipate the next flare.”* EOS member and volunteer with eczema, email feedback

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our member families share the long process of trial and error they experience to try to find a treatment that works and/or one that they/their child will tolerate. Often, they tell us that when they do find a treatment that can manage their symptoms, it may stop working after months or even weeks of being effective. 1. **Emollients:** Families describe them as messy to use. Trial and error to find one that the child will tolerate. They can sting for some children which can prevent use. Young people can feel reluctant to use an ointment on the face due to it being visible. However, there are a range of emollients available to meet differing preferences. 2. **Steroids:** Increasing fears exist across our community about the side effects of steroid use including skin thinning and topical steroid withdrawal which is a significant concern amongst many young people due to the influence of social media. Steroids can successfully treat eczema flares, however the skin frequently flares once steroid use ceases. Willingness to use steroids can depend on how much information a parent/child has been given by their healthcare professional and how much they have been influenced by social media content. 3. **Calcineurin Inhibitors:** Some children/young people have described a burning sensation when using them which causes them to stop treatment. However, if they can overcome the burning, some families say that the treatment can be very effective and many families are relieved to use a TCI instead of a steroid. 4. **Immunosuppressants:** Some families find immunosuppressants work well giving complete skin clearance. Some describe others a temporary change and others report little to no change in the eczema. The required blood tests can be challenging for children frightened of needles, those who live far away from hospital or have limited transport options. Some families can be worried about their child having a lowered immune system but others express that less frequent infections occur due to more controlled eczema. 5. **Phototherapy:** Accessing phototherapy is a significant commitment due to regular hospital trips and those without transport, who have inflexible jobs or live far from hospital can struggle to make appointments. The treatment can offer some relief, however many families report the eczema flares again at the end of treatment. 6. **Biologics- Monoclonal Antibodies:** Many families that have accessed Dupilumab share how effective it has been improving the skin and itch. Some have seen skin clearance, but the itch remained. Side effects have included problems with the eyes which has caused some people to stop using them. 7. **Janus Inhibitors:** Families have reported a reduction in itch and the severity of the eczema when using upadacitinib or abrocitinib. For some, taking the treatment in tablet form is positive as it gives flexibility, however it has put some young people off using the treatment if they struggle with swallowing tablets. Concerns around side effects, especially cancer, are off-putting for some parents/carers considering the treatment for their child.

8. Is there an unmet need for patients with this condition?	Atopic eczema is a widely underestimated and misunderstood condition. Because it is a complex and heterogenous disease, there remains a significant unmet need for new and effective treatment options. Our member families tell us that they often go through a long process of trial and error to find a treatment that works and if they do find one, it can become ineffective after weeks or months with no identifiable reason or that the "itch" remains, despite reduction in visibility of the condition. The importance of having access to a range of treatment options for moderate to severe eczema must not be underestimated; it can significantly enhance the wellbeing of a parent/carer and help them to keep going to be the vital support and champion that their child needs. One parent said, "Please do not underestimate the need for hope when dealing with eczema. Hope for better treatments brings hope for a better life for my child" (online discussion). Many adolescents describe the struggle of their teenage years being made impossible by the additional burden of eczema. For this age group (12+), the impact of their eczema on their mental health can be severe causing withdrawal from daily life, isolation and despair, all which have long term impacts on their education and future life chances. New and effective treatments for this age group are vital to ensure that their condition does not stifle and restrict their futures. *"I am about to start my fourth systemic treatment after the previous 3 showed good results initially before wearing off. The psychological impact of eczema is profound and for me personally the way I deal with this is with the hope that one day that right treatment will be created… If we as eczema sufferers are only provided with one or few potential treatments this creates a dangerous situation where after exhausting these few possibilities we are at the end of the road and it would be far too easy to fall into despair."* Person with eczema, email feedback

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Nemolizumab will provide another systemic treatment option for people with moderate to severe eczema aged 12+ giving vital alternative options if other treatments fail. Adolescents and their families welcome the reduced risk of ocular issues that Nemolizumab has so far offered. Ocular issues are a common reason for people ceasing to use some of the other biologics due to the additional distress it adds to managing their eczema. As noted above, families have concerns about the risks of using JAK Inhibitors, especially the cancer risk. They welcome that Nemolizumab does not have the same risks giving them more confidence in the treatment. Nemolizumab has a reduced dosing frequency compared with other available biologic treatments. This is significant particularly for young people who tell us that they often struggle to comply with their eczema treatment regime due to the range of priorities, concerns and challenges they face, especially in their teenage years. We would therefore expect treatment compliance to be higher in the child/young people population using Nemolizumab compared to other treatment options. Whilst we don't have access to further specific information on the Nemolizumab treatment regime, if it is simple and requires limited engagement with healthcare professionals, we would expect it to be regarded as more tolerable by children/young people allowing them to take more control of their eczema management and their parent/carer being able to "step back". As Nemolizumab is administered via injection, there is no tablet form which will be welcomed by young people who struggle to swallow pills and/or find it challenging to remember to take them regularly.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Based on the limited information we have access to, the main potential disadvantage is that Nemolizumab is administered via injection. This may prevent some children/young people from accessing it where they have needle phobia or are worried about needles hurting them. We do not have access to information on potential effects of this treatment however any side effects must always be clearly discussed with the child/young person and parent/carer so they understand the risks and known likelihood before making treatment decisions.

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.	Many families are not aware of the treatment options available for eczema outside of emollients and topical steroids. Families who are more likely to experience health inequalities, e.g. those living in poverty, may not know they can ask for a referral to secondary care or may not feel able to fight for a referral, which many families say has to happen before a referral is made. Consideration must be made on how treatment option awareness will be carried out to ensure that everyone who needs it has access to this treatment if approved.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Depending on the required number of hospital visits and treatment storage conditions, this treatment may not be suitable for people with less flexibility or who are unable to store their treatment safely and in the right conditions e.g. if they live in communal accommodation (such as students) or travel a lot.

Other issues

13. Are there any other issues that you would like the committee to consider?	Atopic eczema remains an enormous challenge for people across the UK, yet it is still widely underestimated and dismissed as "a bit of itchy skin". The investment in new treatment options, such as Nemolizumab, bring renewed hope to families who face this condition every day. For young people with eczema, an effective treatment can mean the difference between one future or another and we therefore must all invest in ensuring that every child/young person has access to treatment options that work. Further feedback from people with eczema: *"Eczema brings a lack of control which is a huge factor in eczema. Our lives are often dominated by treatments, routines, medications, dietary needs, lifestyle adjustments, the list goes on and you question whether the time/energy investment is even worth it. These routines often make us feel even more different and isolated and stop us from doing the things that many people take for granted e.g. example sleepovers and school trips."* Person with eczema, email feedback.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Eczema is a complex and heterogenous disease and there remains a significant unmet need for new and effective treatment options. Adolescents with eczema and their families greatly welcome a new systemic treatment option being made available. • Eczema affects every part of a child/young person's life and those of their family members. Everyone's experience of the condition is different. No single treatment or approach works for all, and families go through a frustrating and often unsuccessful process or trial and error to get their child/adolescent's needs met • Nemolizumab offers a new treatment option for children/young people aged 12 plus with moderate to severe eczema with key benefits including: reduced chance of ocular issues; reduced dosing frequency; and an alternative treatment option that reduces the possibility of there being no options if all other treatments fail and the subsequent despair and devastation that occurs.

Your privacy

Please select YES if you would like to receive information about other NICE topics - YES or NO

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 and over [ID6221]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

1. Your name	[redacted] on behalf of the British Association of Dermatologists
2. Name of organisation	British Association of Dermatologists (BAD)
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes** Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. 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.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To successfully treat the skin of people living with moderate-to-severe atopic dermatitis (AD).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In accordance with NICE TA814, an adequate response would be defined as at least a 50% reduction in the Eczema Activity and Severity Index (EASI) and a reduction in Dermatology Life Quality Index (DLQI) score of at least 4 points. An ideal treatment response might be reduction of EASI by 75% to 90%, Investigators' Global Assessment (IGA) score of 0 or 1 which represents clear or nearly clear skin, or a Patient-Oriented Eczema Measure (POEM) score of 0 to 2 which represents clear or nearly clear skin. All of the above would be considered clinically significant treatment responses.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need, as there are people who do not respond adequately to or are unable to tolerate existing treatments including topical corticosteroids, phototherapy and conventional systemic treatments such as ciclosporin, methotrexate and azathioprine, biologics such as dupilumab, tralokinumab, lebrikizumab and Janus kinase (JAK) inhibitors such as baricitinib, abrocitinib and upadacitinib as outlined above. They will need to have access to a range of safe and effective systemic treatments.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is a treatment ladder or stepped-care approach to managing people with AD. 1. Emollients +/- topical corticosteroids +/- topical calcineurin inhibitors would be advised in virtually all patients. The following steps are used to reduce the need for topical corticosteroids; calcineurin inhibitors must be withdrawn before phototherapy: 2. Phototherapy (UVA and/or UVB). 3. Conventional systemic therapy such as ciclosporin, methotrexate. 4. Systemic therapy that has become available more recently such as biologics (dupilumab, tralokinumab and lebrikizumab) or Janus kinase inhibitors (baricitinib, abrocitinib and upadacitinib).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	• The European guideline on atopic eczema published in 2022 (https://doi.org/10.1111/jdv.18345) might be most relevant currently and includes systemic therapy appraised by NICE from 2018 to 2022 such as dupilumab, baricitinib, abrocitinib, tralokinumab and upadacitinib. • There is a NICE guideline on the diagnosis and management of eczema for under 12s published in 2007 and Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of atopic eczema in primary care published in 2011. • Previous NICE technology appraisal guidance publications mean that the pathway for systemic treatment is defined to some extent. There is no current NICE guidance on the management of atopic eczema in adults and adolescents.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	There is some variation in the pathway of care across England, but the variation is more marked in Scotland where Health Boards define their own policies. Therefore, according to NICE recommendations, people with moderate-to-severe AD are eligible to have treatment with newer systemic treatment options such as dupilumab, baricitinib, abrocitinib, tralokinumab, lebrikizumab and upadacitinib if their disease has not responded to at least one systemic immunosuppressant, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil,

experience is from outside England.)	or if these are not suitable. However, in some regions of Scotland, these patients need to have failed to respond to or be unsuitable to have at least *two* immunosuppressive treatments.
9c. What impact would the technology have on the current pathway of care?	This technology would add to the treatments available for people who require biological treatment to manage their moderate-to-severe AD. It will be especially important as an alternative to other biologics available for managing people with moderate-to-severe AD and may be used in primary or secondary failure to the previously available biologics and Janus kinase inhibitors used in the management of these patients. Primary and secondary failures are well recognised to occur.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
10a. How does healthcare resource use differ between the technology and current care?	No significant difference – nemolizumab would be used as an alternative to previously NICE-approved biologics for managing people with moderate-to-severe AD.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary and tertiary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant investment as other similar drugs are already being used for AD.
11. Do you expect the technology to provide clinically meaningful	Having a variety of drugs will be useful because AD is a complex and diverse disease with different pathogenic mechanisms in different individuals. This is reflected in unpredictable inter-individual variation between people's

benefits compared with current care?	responses to dupilumab, tralokinumab and lebrikizumab. Nemolizumab will extend this choice and provide benefit for a greater diversity of patients.
11a. Do you expect the technology to increase length of life more than current care?	No.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, for people who experience primary or secondary failure to previously available biologics and Janus kinase inhibitors used in the management of moderate-to-severe AD.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Evidence is not yet available to know this, but with the advent of personalised medicine and better prediction algorithms we may find such patient groups.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	Same as current care.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that dermatologists will adopt a process of identifying and managing people on nemolizumab that is similar to the processes identified in the NICE TA guidance published so far on dupilumab, tralokinumab and lebrikizumab such as measuring adequate EASI and DLQI responses at 16 weeks.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, there is emerging evidence that nemolizumab may improve health-related quality of life outcomes (e.g. itch and sleep disturbance) in people living with moderate-to-severe AD. https://pubmed.ncbi.nlm.nih.gov/39067461/ https://pubmed.ncbi.nlm.nih.gov/31449914/ https://pubmed.ncbi.nlm.nih.gov/37522351/ https://pubmed.ncbi.nlm.nih.gov/32640132/ https://pubmed.ncbi.nlm.nih.gov/36779675/ https://pubmed.ncbi.nlm.nih.gov/29753033/
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is one of several innovative novel biologic treatments for AD.
16a. Is the technology a 'step-change' in the management of the condition?	This technology will be used alongside previously identified biologics and Janus kinase inhibitors used for managing people with moderate-to-severe AD.
16b. Does the use of the technology address any	Yes, those whose AD is not controlled by other drugs.

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is evidence that this new technology may have fewer and milder side effects (especially with reference to the ocular side effects of dupilumab) compared to some other agents identified above https://pubmed.ncbi.nlm.nih.gov/35412530/..

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	EASI and DLQI; HOME initiative (a global initiative of patients, healthcare professionals, journal editors, regulatory authorities and the pharmaceutical industry): EASI, POEM, NRS-11, RECAP or ADCT, DLQI.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No.
18d. Are there any adverse effects that were not apparent in clinical	No.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA534, TA681, TA814 or TA986]?	No.
21. How do data on real-world experience compare with the trial data?	Not known yet.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Please note, the erythema component in assessing disease severity (e.g. EASI) may be underestimated in darker skin tones. Thus, such measures may not be representative in such skin tones. Additionally, inflammatory skin disorders such as AD may have an increased impact on some people with darker skin tones due to their ethnicity – this is due to the inflammation potentially leading to longer-term effects on skin pigmentation following resolution of the inflammation. Quality of life measures such as the DLQI may not adequately capture impact in older people (question about work, studying, sport) or those who are not in a relationship (question about sexual activity). It is also known to capture anxiety and depression poorly across all groups (two parameters that are commonly negatively influenced by AD).
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• This treatment which adds to systemic treatment options available for managing people with moderate-to-severe atopic dermatitis, especially for people do not respond adequately to or are unable to tolerate existing treatments. • Useful because of the heterogeneity in atopic dermatitis which is a complex disease. • Useful because of the multiple comorbidities associated with the AD population, in whom targeted biologics may be safer than other systemic immunosuppressants.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221]

Clinical expert statement

Information on completing this form

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In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating severe atopic dermatitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew Pink
2. Name of organisation	Guy's & St. Thomas' NHS Foundation Trust
3. Job title or position	Consultant Dermatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with severe atopic dermatitis ? ☒ A specialist in the clinical evidence base for severe atopic dermatitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for severe atopic dermatitis ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	- To reduce and ideally eliminate debilitating symptoms – e.g. itch, pain - To reduce inflammation and improve/ normalise skin appearance - To improve sleep and ability to cope

	- To improve quality of life/ enable daily function - To improve disease-associated psychological burden e.g. low mood - To enable patients to feel in control of their eczema (achieve disease control)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Objective severity: - To achieve at least a 50% improvement in Eczema Area and Severity Index (EASI50), optimally ≥ 75% improvement (EASI75) Patient reported outcomes: - To achieve a clinically meaningful improvement in itch (e.g. peak pruritis NRS ≥4 point improvement) - To achieve a clinically meaningful improvement in quality of life (e.g. ≥ 4 point improvement in Dermatology Life Quality Index, DLQI)
10. In your view, is there an unmet need for patients and healthcare professionals in severe atopic dermatitis ?	Systemic therapy for atopic dermatitis (eczema) has evolved over the last decade with the advent of novel targeted therapies (e.g. dupilumab, tralokinumab, lebrikizumab and JAK inhibitors) in addition to the traditional conventional systemics (e.g. methotrexate and ciclosporin). This has been hugely important for what is a devastating, life-impacting, phenotypically heterogeneous condition that frequently requires trials of multiple different therapies to gain control. There are broadly 3 current therapeutic targets - IL4/13 (e.g. dupilumab, lebrikizumab, tralokinumab), Janus kinase (JAK) (e.g. upadacitinib, abrocitinib and baricitinib) and broad immunomodulation/ immunosuppression (e.g. ciclosporin, methotrexate), all of which have their own unique side effect profiles. As a result of primary inefficacy or poor tolerability, there is still a significant proportion of poorly controlled patients, often requiring intensive and high cost interventions (e.g. dermatology day care services) and affecting employment, social life and daily function. Treatment switching remains common and the need for new therapies with a different mechanism of action/ safety profile is still very

	high. Nemolizumab offers both a novel mechanism of action (anti-IL31) and different tolerability profile (no association with e.g. conjunctivitis/ facial flares/ arthritis seen with anti-IL4/13 drugs, no association with e.g. HSV/ VZV/ thromboemobolism seen with JAK inhibitors). A further unmet need in many eczema patients, even when their disease can seem objectively controlled, is profound and debilitating itch, for which the anti-IL31 (IL31 is a key itch cytokine) effect of nemolizumab could prove highly valuable. Having the option of another targeted and well tolerated treatment is important for all patients, especially adolescent populations. Outside of available treatment within secondary care settings (as described above), other key ongoing areas of unmet need include patient access to specialist services and re-engaging people who have previously lost hope. The capacity for multi-disciplinary holistic care for more complex cases is very limited (patients have often had eczema all of their lives, it impacts on every element of their life, very often needing support beyond just therapeutics). The emergence of new and more targeted treatments is helping to re-connect some of these populations. In skin of colour, inflammation can leave areas of very significant hyperpigmentation and hypopigmentation (post-inflammatory pigmentary change). This can improve slowly over time but is often permanent, conferring a a profound and lasting effect on some patients. There is no proven treatment to aid resolution in this context, thus early aggressive and effective therapy for AD is needed.
11. How is severe atopic dermatitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	The broad UK approach to AD management is as follows: 1. Topical therapy – topical steroids/ calcineurin inhibitors 2. (Oral prednisolone/ antibiotics – short term flare use only) 3. Phototherapy - where practically possible/ appropriate, often no access

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	4. Conventional systemic therapy – e.g. methotrexate/ ciclosporin 5. Novel targeted therapies – e.g. dupilumab, tralokinumab, lebrikizumab, abrocitinib, upadacitinib, baricitinib (as per NICE criteria) There are no UK guidelines for management of adult eczema outside of the technology appraisals for the above recent medicines. Outside of the UK guidelines include the European and American Academy Guidelines for management of AD (doi: 10.1111/jdv.18345, https://www.aad.org/member/clinical-quality/guidelines/atopic-dermatitis) updated in 2022 and 2014 respectively. Nemolizumab would offer a novel targeted therapy option with a different mode of action/ efficacy/ tolerabillity profile, complementing the existing options.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Nemolizumab could be used at step (4 or) 5 in the above example treatment ladder within the existing clinic infrastructure. Given the safety profile, nemolizumab would require significantly less clinical input and monitoring than conventional systemics. Requirements would be similar to the current biologic options (e.g. no or few bloods, reduced follow up requirements with perhaps 12-18 monthly follow up etc.). This technology should be used in secondary care. No specific investment is required in terms of specific infrastructure or training.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The trial data (phase 3, Arcadia 1 and 2 trials) demonstrated that of those with moderate-severe AD that received nemolizumab +TCS around 43% achieved EASI75, 35% clear or almost clear skin, 46% a clinically meaningful improvement in itch (peak pruritis NRS change of 4 points or more) over 16 weeks (statistical significance versus TCS alone). 35% were itch free or almost itch free (peak pruritic NRS <2) by 16 weeks with very rapid improvement in itch

	demonstrated over first 2 weeks. Interim analysis would infer (with usual caveats) potential incremental further benefit up to 52 weeks, which reflects my trial experience and experience with the existing biologic therapies (which take > 24 weeks to reach optimal impact, unlike the more rapidly acting JAKi). I think this innovative first in class technology has the clear potential to therefore significantly benefit adults with moderate-severe AD, both in terms of offering sustained objective improvement and a class specific effect of rapid and potent itch suppression. Itch is recurrently identified as the number one most bothersome symptom for patients with eczema (Silverberg JI et al. *Dermatitis* 2023;34:135-44), thus this is highly relevant. There was a clear impact of nemolizumab + TCS versus TCS alone on Dermatology Life Quality Index in the Arcadia trials.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I am not aware of any specific evidence supporting greater impact in particular phenotypes. A pre-defined subgroup analysis in the ARCADIA trials sought to identify whether there was a difference in the objective primary outcomes between the high itch burden group (PP-NRS ≥7) and the full trial population (PP NRS ≥4) and there was no clear difference – i.e. this medication appears to work irrespective of baseline itch severity.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Compared to phototherapy and conventional systemics, nemolizumab is much easier to use as it is a once monthly (or 8 weekly) injection, that can be self-administered by the patient at home. Biologic prescribing and homecare is very standard practice now in the NHS. The 4-8 weekly dosing makes this practically easier for patients than any of the existing biologic options. The safety profile of this medication, with no reported impact on bloods means that there is no clear rationale for frequent follow up or monitoring blood tests, both of which could help the current capacity issues that we face (methotrexate and ciclosporin require intense 2 weekly visits at outset then 3 monthly visits when stable, nemolizumab may require annual follow up at most when effective and patient stable).

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Outside of potential NICE criteria for access/ continuation, none specifically. In terms of screening for nemolizumab clinicians would follow SmPC advice around need for infection screening (if any required). As clinicians we always try to have a patient on the minimal immune modulation required to control their disease. It is therefore likely that over time, and following doctor-patient discussion, a dose reduction (or dose frequency reduction) or trial off the medication may be considered.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The QoL measures (e.g. the skin -specific DLQI) utilised in the trials are not specific to AD. Whilst DLQI (and other measures e.g. EQ5D) will capture some key consequences of the itch, sleep disturbance and skin appearance in AD, the true impact of eczema on all facets of life will not be fully captured. On a practical level, nemolizumab is a well tolerated infrequent (4-8 weekly) injection, versus the more regularly administered phototherapy (3x weekly), ciclosporin and JAK inhibitors (daily), methotrexate (weekly) or dupilumab, lebrikizumab or tralokinumab (2 weekly). It is also well tolerated. Stability on a 4-8 weekly injection with potentially annual follow up would enable patients to forget about their disease more than some existing options.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is an innovative highly targeted first in class monoclonal antibody therapy targeting the key itch cytokine, IL-31. IL-31 has long been known to be a key itch signal in atopic dermatitis and the trial data for nemolizumab in AD supports that, demonstrating a rapid and meaningful improvement in itch. Furthermore, the trial data demonstrate the ability of nemolizumab to significantly improve/ clear the objective skin signs in AD. This therapy could address the significant remaining unmet need in those patients who for example have failed to adequately respond to or tolerate existing mechanistic classes, those who are contraindicated to existing mechanistic classes or those with very high itch burden.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This appears to be a very well tolerated treatment with few side effects. There were some rare cases of oedema. I do not foresee associated side effects frequently detrimentally impacting QoL but as with any new targeted therapy these will need to be monitored and carefully characterised in real world practice.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The population studied in the pivotal phase III trials (Arcadia 1 and 2) is frequently encountered in secondary care dermatology and can prove extremely challenging to manage. It doesn't represent all patients seen in the NHS, whether that be because of the requirement for EASI ≥ 16 or a pp-NRS ≥ 4 at trial outset or other inclusion/ exclusion criteria, but I do think it represents a significant proportion. UK patients were enrolled in the Arcadia trials. As mentioned in the above sections, I feel the most important outcomes were captured in the ARCADIA trials, following the international Harmonising Outcome Measures for Eczema initiative suggestions (HOME, https://www.homeforeczema.org/). These include objective skin severity (EASI), itch (pp-NRS, which is the most accepted validated measure), patient symptoms (POEM) and quality of life (DLQI). Important downstream endpoints were assessed including impact on sleep and anxiety and depression. I am not aware of any side effects that were not apparent in trials but have materialised subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not
23. How do data on real-world experience compare with the trial data?	There is no real world UK data. There is limited real world data, one real world retrospective analysis of a small subset of Japanese patients on nemolizumab for atopic dermatitis demonstrated benefit and no new adverse events (doi:10.1684/ejd.2023.4551).
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any	Inflammation is often under-scored in more pigmented skin types (as redness can be less apparent). This is well recognised in atopic dermatitis, where it can

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	falsely reduce objective outcome measures such as the EASI. Education and emphasis on this is very important to prevent patients missing required access criteria for high cost medications due to inaccurate severity assessments. In skin of colour inflammation can leave very significant post-inflammatory pigmentation (darker and lighter). This can slowly improve over time but can also be permanent and have a devastating impact on patients. There are no effective treatments to help resolve this and thus prompt and effective treatment of eczema (inflammation) in this context is very important to reduce this downstream morbidity.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There remains a high unmet need in atopic dermatitis – including access to and variety, effectiveness and tolerability of treatments

Nemolizumab is an innovative first in class monoclonal antibody blocking IL-31 signalling – a key itch signal in eczema

Nemolizumab offers a new mechanism of action with a different efficacy profile and seemingly good tolerability

Targeting IL-31 confers a rapid and significant reduction in itch (most bothersome symptoms for patients) and objective skin signs

This treatment would require no infra-structural changes to integrate into practice – infrequent follow up and no monitoring

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with severe atopic dermatitis or caring for a patient with severe atopic dermatitis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **18 February 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Patient expert statement

Part 1: Living with this condition or caring for a patient with severe atopic dermatitis

Table 1 About you, severe atopic dermatitis, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with severe atopic dermatitis ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with severe atopic dermatitis ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Eczema Outreach Support
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with severe atopic dermatitis ? **If you are a carer (for someone with severe atopic dermatitis) please share your experience of caring for them**	I have lived with severe atopic dermatitis my whole life. I have tried and failed on many systemic/biologic treatments. I am currently taking an immunosuppressant combined with a newly available biologic under the care of St John's Institute of dermatology at Guy's Hospital London. This is a condition which has had a profound negative impact on every area of my life. When the organ which covers the entire surface area of your body is in pain, damaged and broken you therefore feel as a being in your entirety, in pain, damaged and broken. Atopic dermatitis, like many conditions, is on a scale and unfortunately the people who are chronically suffering often feel dismissed or feel they are being grouped together with the people who have much more minor symptoms. This results in not receiving the urgent and comprehensive care they so desperately need. As horrendous as the physical symptoms are; constant mind-bending itch, open sores, covered in painful rashes, weeping sores, flaking skin, poor sleep it is the psychological effect which is particularly catastrophic. This all-encompassing condition can all too often destroy feelings of self-worth, confidence, ability to form and maintain relationships, your ability to focus and be productive, your sex life and generally can result in you becoming a shadow of what would have been your full potential.
7a. What do you think of the current treatments and care available for severe atopic dermatitis on the NHS?	**7a)** I feel very fortunate to live in a country which provides the latest breakthrough medications to severe AD sufferers and also in a time where the pipeline is so strong. Having multiple treatment options is crucial to providing hope and

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	reassurance to those who continue to have to live with the physical and mental toll of what is a cruel and all-consuming disease. I do believe the locations for high quality/specialised care are limited however the care at these specific locations are excellent. **7b)** While the current treatments are in many ways groundbreaking and delivering life changing results to many, unfortunately this has not been the case for me. I often experience very good results for a few months and the effect then wears off. There is no one size fits all medication as of yet which is why it's so important that they continue to be approved.
8. If there are disadvantages for patients of current NHS treatments for severe atopic dermatitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The biggest disadvantage for myself and others is that these treatments keep failing. However, there's also the burden of regular injections, sometimes blood tests and potential side effects such as eye issues. I personally experienced these eye issues and have had to take Ciclosporin eye drops to counter this.
9a. If there are advantages of nemolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nemolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a)** Nemolizumab targets the itch-scratch cycle more effectively, a huge factor in reduced quality of life and control of symptoms in AD sufferers. It inhibits a different interleukin to other medications and therefore offers the chance of reduced symptoms to patients who have failed on other treatments. The injection frequency is a significant advantage as once per month injections greatly reduce the treatment burden when compared to many of the current treatments.

	There also appears to be reduced potential side effects such as eye issues which would again reduce the burden of treatment, medication and appointments. **9b)** The way in which it inhibits a different interleukin to other medications therefore provides the chance that it will provide relief to those who have failed on other treatments.
10. If there are disadvantages of nemolizumab over current treatments on the NHS please describe these. For example, are there any risks with nemolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	For those with a real phobia of injections they may opt for the Jaks inhibitors as a less daunting option.
11. Are there any groups of patients who might benefit more from nemolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who have been unable to tolerate other treatment options due to the side effects. For example, some patients may not be able to get the eye issues under control and therefore would have no choice but to stop treatment.
12. Are there any potential equality issues that should be taken into account when considering severe atopic dermatitis and nemolizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	I have found that access to these treatments can be difficult to receive outside of the major cities/hospitals. This could affect those who find travel more difficult such as those living with a disability.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Whilst there is still no one size fits all treatment for every AD sufferer, new and promising medications should be approved to give people the opportunity for potential relief of symptoms.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There are many who have failed on the current treatments and continue to suffer, new medications give the potential opportunity for relief
- The way in which the itch-scratch cycle if specifically targeted could drastically improve the physical and mental symptoms of many
- The reduced side effects could improve patient safety and tolerability
- There is a huge psychological benefit to those who continue to fail treatments in the knowledge that NICE are open to the approval of new medications

Thank you for your time.

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Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221] A Single Technology Appraisal

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Matt Stevenson provided advice to a comparator company, Leo, for an unrelated treatment in an unrelated disease area (delgocitinib for chronic hand eczema). Shijie Ren provided statistical methodology consultancy service to a possible comparator company, Pfizer, for an unrelated treatment in an unrelated disease area (tofacitinib for Moderate-to-Severe Ulcerative Colitis). Carsten Flohr has received investigator-led funding/consultancy and meeting support from Apogee, Bioderma, Almirall, Pfizer, and Sanofi. None of the remaining authors have any conflicts of interest to declare.

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Rider on responsibility for report

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Contributions of authors

Mark Clowes critiqued the company's search strategy. Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren and George Daly critiqued the statistical aspects of the submission. Matt Stevenson and Mon Mon Yee critiqued the health economic analysis submitted by the company and performed the exploratory and sensitivity analyses. Carsten Flohr, Miriam Wittmann, and Zenas You provided clinical advice. Matt Stevenson led the team. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AD	Atopic dermatitis
AEs	Adverse events
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CODA	Convergence diagnosis and output
CrI	Credible Intervals
CS	Company submission
DAE	Discontinuations due to adverse events
DIC	Deviance information criterion
DLQI	Dermatology life quality index
EA	Exploratory analysis / analyses
EAG	External assessment group
EASI	Eczema Area and Severity Index
eMIT	Electronic market information tool
FE	Fixed effects
HCRU	Health care resource use
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IGA	Investigator's global assessment
iNMB	Incremental net monetary benefit
JAKi	Janus kinase inhibitors
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
OR	Odds Ratio
PP-NRS	Peak pruritus numerical rating scales
PSS	Personal social services
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QALY	Quality-adjusted life years
RE	Random effects
SA	Sensitivity analysis / analyses
SLR	Systematic literature review
TCI	Topical calcineurin inhibitors

TCS	Topical corticosteroids
TEAE	Treatment emergent adverse event

1. EXECUTIVE SUMMARY

The company provided a submission to the National Institute for Health and Care Excellence (NICE) detailing the clinical-effectiveness, and the cost-effectiveness, of nemolizumab alongside best supportive care compared with other treatments recommended by NICE to treat people aged 12 years or over with moderate-to-severe atopic dermatitis (AD). Incremental cost effectiveness ratios (ICERs) were provided expressed in terms of additional cost per additional quality-adjusted life years (QALYs) gained and incremental net monetary benefit (iNMB).

Section 1.1 provides an overview of the key issues identified by the External Assessment Group (EAG) in the company submission (CS). Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 provides the EAG's base case ICER. These values presented in this report do not incorporate the commercial-in-confidence Patient Access Scheme (PAS) discounts for interventions other than nemolizumab; the results which include these discounts are contained in a confidential appendix to this report. All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: The EAG's key issues

Issue Number	Summary of issue	Report section
1	Would a cost-comparison approach comparing nemolizumab with other biologics be more appropriate?	4.5.2.1
2	Uncertainty in the relative efficacy of nemolizumab compared with the comparators	4.5.2.3
3	Uncertainty in the discontinuation probability of nemolizumab	4.5.2.4

Three key issues were identified by the EAG. The first was whether the appraisal would have been better suited as a cost-comparison against other biologic treatments (dupilumab, lebrikizumab and tralokinumab) rather than a cost-utility analysis, given that clinical advice provided to the EAG, and the company's model following the clarification round suggests similar efficacy and similar costs excluding drug acquisition costs between the biologic treatments.

The second key issue was that the company had decided to assume that if the credible intervals from the network meta-analysis (NMA) were not statistically significant, then the relative efficacy compared with nemolizumab was set to unity (that is, assumed to have the exact same efficacy as nemolizumab).

The third key issue was the discontinuation rate of nemolizumab compared with other biologics. In the company's revised submission, it assumed that discontinuation probabilities were equal for all biologic

treatments (a stance that the clinical experts providing advice to the EAG agreed with). However, the actual discontinuation probabilities observed in the ARCADIA 1 and ARCADIA 2 studies (pivotal nemolizumab studies) were considerably higher than the single value assumed for all biologics, which was based on data from a previous appraisal, and the impact of using a higher discontinuation probability on the ICER has been explored should the appraisal committee prefer this ICER.

Additionally, the EAG corrected what it believed to be errors and limitations within the company's model, but these did not materially affect the iNMB.

The EAG has provided two base cases.

The EAG's preferred assumptions for base case 1 are:

- To undertake a cost-comparison approach assuming that the efficacies and costs except drug acquisition for the biologic treatment are identical and comparing only the acquisition costs of nemolizumab, dupilumab, lebrikizumab and tralokinumab.

The EAG's preferred assumptions for base case 2 are:

- Correction of errors and amendment of the company's model to improve minor issues
- Using the odds ratios for treatment response directly from the EAG's NMA rather than assume there is no difference in efficacy when the credible interval crosses unity.

Scenario analyses have been run for EAG base case 2 exploring the impact on the ICER when: a different metric for response is used (Eczema Area and Severity Index [EASI]-50 and Dermatology life quality index [DLQI] ≥ 4 rather than EASI-75); and the discontinuation probability for nemolizumab is taken from the ARCADIA 1 and ARCADIA 2 studies, rather than being assumed to equal that of all biologics.

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology changes the length of life and the quality of life using the change in QALYs.

The company's model assumes that nemolizumab (compared with other biologic treatments) affects QALYs by:

[redacted]

The company's model assumes that nemolizumab affects costs by:

[redacted]

1.3 Summary of EAG's preferred assumptions and resulting ICER

For base case 1, the EAG simply compares the prices of biologic treatments assuming that efficacies of all biologics including nemolizumab are identical. These are shown in Table 2, in this analysis, nemolizumab has the lowest cost of all biologic treatments, although this was using the PAS price of nemolizumab and the list price of the comparators.

Table 2: Costs for drug acquisition per patient for nemolizumab and biologic comparators

Cost per patient	Nemolizumab (including PAS)	Lebrikizumab (list price)	Dupilumab (list price)	Tralokinumab with Q2W maintenance dosing schedule (list price)	Tralokinumab with Q4W maintenance dosing schedule (list price)
Total acquisition costs in year 1*	[redacted]	£22,713	£17,708	£14,980	£10,165
Total acquisition costs per year (year 2 onwards)	[redacted]	£14,814	£16,500	£13,958	£6,979

PAS: Patient Access Scheme; Q2W: Every 2 weeks; Q4W: Every 4 weeks
*including loading, induction and maintenance doses

For EAG base case 2, the results are shown in Table 3 for adult patients and Table 4 for adolescents. Exploratory sensitivity analysis results did not noticeably change the base case, except for an exploration of a higher discontinuation rate for nemolizumab than for other biologics, that was not favoured by the clinical advisors to the EAG but has been presented should the Appraisal Committee wish to consider these results.

The company does not make a claim for a QALY weighting based on disease severity, a stance with which the EAG agrees.

Table 3: EAG's exploratory analysis, full incremental analysis results, adult population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£673,855	[redacted]	£673,855
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA1: correction of model errors							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£1,108,189	[redacted]	£1,108,189
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA2: Applying ORs for response at 16 weeks from the NMA for all comparators instead of setting the ORs to unity when credible interval crosses unity							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£810,681
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£741,096
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,274,424
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£581,640	[redacted]	£581,640
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,203,560
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£553,553	[redacted]	£553,553
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,189,283
EAG's base case 2: combined EA1 and EA2, probabilistic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,592,848
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£542,618	[redacted]	£542,618
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,213,886

EA: exploratory analysis; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 4: EAG's exploratory analysis, full incremental analysis results, adolescents population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA1: Correction of model errors							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA2: Applying ORs for response at 16 weeks from the NMA for all comparators instead of setting the ORs to unity when credible interval crosses unity							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£423,236
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£868,590
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£118,524	[redacted]	£118,524
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£426,020
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,832,902
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£416,634
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£119,625	[redacted]	£119,625
EAG's base case 2: combined EA1 and EA2, probabilistic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£10,674,435
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£396,158
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£132,056	[redacted]	£132,056

EA: exploratory analysis: ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

1.4 ICERs incorporating confidential comparator patient access schemes

All comparators: abrocitinib, baricitinib, dupilumab, lebrikizumab, tralokinumab and upadacitinib have confidential discounts on their list prices. Results incorporating these prices are provided to the NICE Appraisal Committee as a confidential appendix.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company provides a good description of atopic dermatitis (AD) in Section B.1.3 of the company submission (CS).[1] In brief, AD is a common, chronic skin disorders characterised by painful eczematous lesions and pruritus (severe itch). Itch relief is the primary aim for the majority of patients with moderate-to-severe AD,[2, 3] as this, along with painful lesions, can have a large negative impact on a patient's quality of life.[4]

The company cites prevalence values in England / UK of AD of 1.86% / 2.4% for adults[5, 6] and in the UK of 4.99% for adolescents,[5] although both citations are abstracts only. These values compare with an age-standardised value of 4.6% in Western Europe.[7] It was reported that approximately 8% of UK patients with AD had moderate-to-severe AD, and that 60% of these patients had received systemic therapy (treatments that work throughout the whole body).[6]

2.2 Critique of company's overview of current service provision

The company summarises relevant treatment guidelines in Table 3 of the CS, noting that neither NICE nor the British Association of Dermatologists have "*published guidelines or quality standards on the diagnosis and management of moderate-to-severe AD in adults or adolescents.*" Section B.1.3.2.2 of the CS provides a detailed description of current treatments for AD, which have been categorised into 4 groups: best supportive care (BSC) (emollients, topical corticosteroids [TCS], and topical calcineurin inhibitors [TCI]); systemic immunosuppressants, of which ciclosporin is the only licensed treatment (in adults only) with others used off-label; Janus kinase inhibitors (JAKi), with three recommended by NICE (abrocitinib,[8] baricitinib[9] and upadacitinib[8]); and biologics, with three recommended by NICE (dupilumab,[10] tralokinumab[8] and lebrikizumab[11]).

Figure 1 (the company's representation of the current clinical pathway) reproduces Figure 1 of the CS. Clinical advice to the EAG states that the proposed positioning of nemolizumab alongside both JAKi and other biologics, and after BSC and systemic immunosuppressants is appropriate. Clinical advice to the EAG has suggested that the most appropriate treatment may be based on an individual patient's characteristics and that adding nemolizumab as a treatment option would be beneficial.

Figure 1: The company's representation of the current clinical pathway (reproduced from CS, Figure 1)

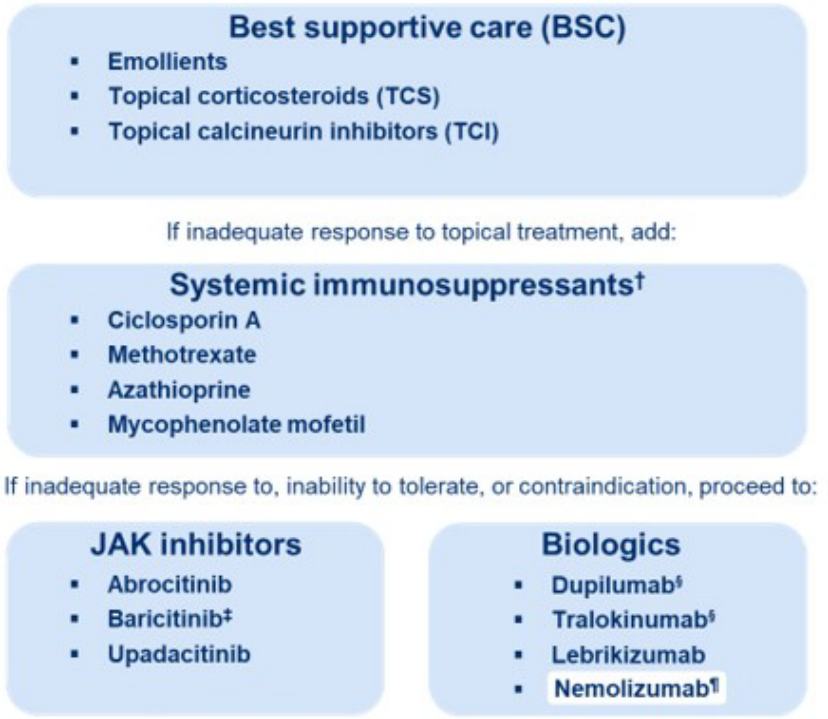


Figure 1. Atopic dermatitis treatment pathway in adolescents and adults
Note: Based on the EuroGuiDerm Guideline for Atopic Eczema and review of NICE committee papers.[1-3,24,89-91] Phototherapy is not shown as it is not universally available and is used variably across the UK.[61]
†First line systemic therapies are conventional immunosuppressants; all use in AD is off-license except ciclosporin in persons over 16 years.
‡ Baricitinib is only approved for treating moderate-to-severe atopic dermatitis in adults.[2]
§ Subsequent to the NICE recommendations for dupilumab and tralokinumab in adult patients; NHS England will commission treatments for patients aged less than 18 years where specific commissioning conditions within a NICE technology assessment (TA) or NHS England policy are met.[98,99]
¶ Aspirational positioning of nemolizumab in the treatment pathway.
Abbreviations: BSC, best supportive care; JAK, Janus Kinase; TCS, topical corticosteroid; TCI, topical calcineurin inhibitor

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The marketing authorisation for nemolizumab is for both adolescents and adults (which in combination covers people aged 12 years and over) with moderate-to-severe AD who are "*candidates for systemic therapy and who have not responded to at least one systemic immunosuppressive treatment, or where these treatments are contraindicated or not tolerated.*" The positioning of nemolizumab in the CS is narrower than the full marketing authorisation with the company anticipating that "*nemolizumab would be used as second-line systemic treatment, in line with the current positioning of the other biologic and Janus kinase (JAK) inhibitor therapies within UK clinical practice*." Clinical advice provided to the EAG supports the company's decision regarding positioning of nemolizumab.

2.3.2 Intervention

Nemolizumab is a humanised monoclonal antibody that inhibits interleukin-31; further details are provided in the CS. Nemolizumab is delivered subcutaneously with an initial loading dose of 60mg followed by 30mg every 4 weeks (Q4W) for a period of 16 weeks (induction phase). For patients judged to be responding to nemolizumab, the frequency of treatment is reduced, moving to a regimen of 30mg every 8 weeks (Q8W) (maintenance phase). The dosing schedule is the same for both adults and adolescents. Nemolizumab can be used alongside BSC, although for readability this has been henceforth referred to as just nemolizumab.

2.3.3 Comparators

The comparators are interventions that would also be used as second line systemic treatment. These are JAKi (abrocitinib, baricitinib and upadacitinib) and biologics (dupilumab, tralokinumab, and lebrikizumab). Abrocitinib, upadacitinib and lebrikizumab have been given positive NICE recommendations for the entire 12 years and over population.[8, 11] Baricitinib, dupilumab and tralokinumab were recommended only in adults,[8-10] although the marketing authorisations for dupilumab and tralokinumab have since been extended (to six months and above for dupilumab and 12 years and over for tralokinumab). Clinical advice to the EAG states that both dupilumab and tralokinumab are used in adolescents.

The dosing schedule is the same for both adults and adolescents for each comparator. Dupilumab and tralokinumab have the same schedule, with a loading does of 600mg followed by 300mg every 2 weeks (Q2W). Lebrikizumab has loading doses of 500mg at weeks 0 and 2, then 250mg Q2W until week 16, followed by 250mg Q4W. The JAKi are daily pills with no loading doses. Upadacitinib has two strengths (15mg and 30mg) with the recommended dose for adolescents weighing at least 40 kg is 15 mg, as does abrocitinib (100mg and 200mg) whereas baricitinib comes only in 4mg tablets.

All comparators can be used alongside BSC, but, as with nemolizumab, this treatment strategy has been described as the intervention name to improve readability.

2.3.4 Outcomes

The company includes the following outcomes: measures of disease severity and symptom control (for example, Eczema Area and Severity Index [EASI] response, Investigator's Global Assessment [IGA], Peak Pruritus Numeric Rating Scale [PP NRS]); measures of symptom control including improvement in itch; disease flares; treatment-emergent adverse effects (TEAEs) and health-related quality of life (HRQoL).

2.3.5 Economic analysis

The company follows the NICE reference case.[12]

3 CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company as part of the CS, its appendices and the company's clarification response comprise a:

- Systematic literature review (SLR),
- Summary and results of three clinical trials and an ongoing long-term extension study of nemolizumab.

This chapter summarises and critiques the company's review methods and clinical effectiveness evidence of nemolizumab for the treatment of adults and adolescents with moderate-to-severe AD. Full details are presented in the CS Section B.2 and the CS Appendix D and Appendix M.

3.1 Critique of the methods of review(s)

3.1.1 Searches

Section D of the CS appendices reports the searches for evidence of the clinical effectiveness of nemolizumab in atopic dermatitis used in the company's systematic literature review (SLR).

Searches covered all the core databases required by NICE (MEDLINE, Embase, CENTRAL) plus a specialist source (Global Resource for EczemA Trials) from database inception to October 2023, followed by an update from 2023 to May 2024. In addition, several trials registries, conference proceedings and HTA agency websites were searched by hand at both stages.

The search strategies combine subject headings with free text terms in titles and abstracts. For optimal sensitivity, it might have been preferable to extend the free text searches for the intervention terms to cover other fields (e.g., "name of substance" word in MEDLINE; drug name in EMBASE) however the company argued that this was unnecessary as they had also searched trials registers and conference proceedings (see clarification response A1). While the EAG is not entirely convinced by this defence, it has not discovered any relevant studies missed by the company.

Filters were used to limit the searches to the study types eligible for inclusion. While the company claims these are "*adapted from*" those designed by the Scottish Intercollegiate Guidelines Network, it did not provide details of what modifications were made and their anticipated benefit.

The EAG was surprised to see that in the CENTRAL search (CS Appendix D, Tables 3 and 4) the company actively excluded records for certain trials from registers which might have been in scope (e.g., including the World Health Organization International Clinical Trials Registry Platform) – presumably as they had searched these separately. When searching for evidence for a systematic review,

it is more conventional (and more transparent for reporting purposes) to search the included databases in full, before removing any duplicates using reference management software (e.g., EndNote).

Despite the limitations discussed, the searches appear to have mostly been conducted competently and are reported in full, albeit with some errors. For example, the company initially stated that no language limit had been applied, though on closer inspection it was apparent that the Ovid database searches had in fact been limited to English. In its defence, the company cites a recent publication which concluded that excluding non-English language studies did not affect the conclusions of systematic reviews (see clarification response A2), however the EAG would concur with a more recent letter published in the same journal that cautions against applying such limits at the searching stage.[13]

3.1.2 Inclusion criteria

The CS describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria to citations identified by the searches. Any disagreements were resolved through discussion or arbitration by a third reviewer (see CS, clarification response, question A6). A summary of the inclusion and exclusion criteria, as reported in the CS (Appendix D.1.7, Table 6), is reproduced (with minor changes) in Table 5.

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. While the SLR is comprehensive, its wider remit captures the entire evidence base and informs the company's NMA. Moreover, restricting the SLR (including NMA) to English-language publications may lead to language bias and undermine the core purpose of a SLR. Nevertheless, as noted in the company's clarification response (question A2 and A7), *'...a recent meta-epidemiological study has found that the exclusion of non-English papers in systematic reviews does not impact on overall systematic review conclusions. Therefore, this restriction was considered to be acceptable*'.[14]

Table 5: Inclusion/exclusion criteria used to select studies reporting clinical efficacy and safety for patients with moderate-to-severe atopic dermatitis in the CS (reproduced with minor changes from CS, Appendix D.1.7, Table 6)

PICOS element	Inclusion criteria	Exclusion criteria
Population	Adolescents (ages ≥12 years old) and adults with moderate-to-severe AD, including the following subgroups of interest: • Adolescents (ages 12 – 17 years) • Adults (ages ≥ 18 years) • Patients with an inadequate response to ciclosporin or for whom ciclosporin is not medically advisable • Disease severity (i.e., moderate vs. severe disease) • Patients who responded to treatment at 12 – 16 weeks (applicable to 48–52-week endpoints only)	• Children (<12 years old) with AD • Adolescents and adults with mild AD
Intervention(s)	Currently licensed systemic therapies in combination with topical corticosteroids (TCSs) and/or topical calcineurin inhibitors (TCIs; protocol amendment 1) for moderate-to-severe AD including[†]: • Abrocitinib • Azathioprine • Baricitinib • Ciclosporin • Dupilumab • Lebrikizumab • Methotrexate • Mycophenolate mofetil • Nemolizumab • Tralokinumab • Upadacitinib	• Topical interventions i.e., pimecrolimus and tacrolimus • Interventions with restricted licensing indications i.e., alitretinoin which is only indicated for the treatment of hand AD • Interventions that do not have FDA/EMA approval for the treatment of AD and were not previously considered to be relevant comparators in recent NICE and CADTH submissions i.e., mepolizumab, omalizumab, tezepelumab, ustekinumab
Comparator(s)	• Any of the interventions listed above (in combination with TCS/TCIs; protocol amendment 1) • Topical therapies alone • Placebo (in combination with TCS/TCIs; protocol amendment 1)	• Any other comparator

Outcomes	**Efficacy and HRQoL outcomes of interest include**: • IGA response • EASI response • PP-NRS response • Skin pain NRS • POEM response • Sleep disturbance NRS response • DLQI mean change and response • Composite EASI + DLQI response • Composite EASI + PP-NRS response • Composite IGA + PP-NRS response • Use of rescue medication • Days free from TCS use **Safety outcomes of interest include**: • TEAEs • Total moderate or severe AEs • Total grade 3 and 4 AEs • Total SAEs • Overall discontinuation rate • Discontinuation rate after an established treatment response • Discontinuations due to AEs • AEs of special interest: o Injection-related reactions (anaphylactic reactions, acute allergic reactions, severe injection site reaction) o Newly diagnosed or worsening of asthma o Severe infection o Peripheral oedema o Facial oedema o Elevated ALT or AST in combination with elevated bilirubin o Conjunctivitis (including both allergic and infectious conjunctivitis) o Oral herpes o Upper respiratory tract infection o Acne	• Any other outcomes§
Study design	• Phase 2/3/4 RCTs • Corresponding long-term, single-arm, or open-label extensions of included RCTs	• SLRs and MAs‡ • Phase 1 RCT • Trial protocols • Pharmacokinetic and pharmacodynamic studies • Animal/ *in vitro* studies • Editorials • Erratum • Case reports and case series • Narrative reviews • Observational studies
Language restrictions	English language	Non-English publications

†As per the original SLRs, the list of interventions of interest was informed by marketing authorisation status and recent HTA submissions. NICE TA814 stated that the following interventions were not considered relevant comparators, given that they are used outside their marketing authorisation: alitretinoin, azathioprine, methotrexate, and mycophenolate mofetil. However, recent CADTH submissions (Adtralza, Cibingo, Rinvoq) considered off-label use of azathioprine and mycophenolate mofetil to be relevant comparators in this landscape. Mepolizumab, omalizumab, ustekinumab, and tezepelumab are recommended for exclusion as these regimens are not approved in this indication and were not considered to be relevant in previous submissions.

‡SLRs and MAs will be used only to identify potentially relevant primary studies that have not been found through database searches, however no bibliography searching was performed.

§The CS, Appendix D.1.7, Table 6 reported that studies with 'Outcomes reported for a mixed adult and adolescent population, i.e., not reported by age subgroup' were excluded from the systematic review. However, the EAG notes that the CS includes data from mixed adult and adolescent population studies in the second-line adult NMA analysis. The EAG assumes this is an error and have deleted the text from the table.

Abbreviations: AD, atopic dermatitis; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; CADTH, Canadian Drugs and Health Technology Agency; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRQoL, health-related quality of life; IGA, Investigator's Global Assessment; MA, meta-analysis; NICE, National Institute for Health and Care Excellence; NRS, numerical rating scale; PICOS, Population, Interventions, Comparators, Outcomes and Study design; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritis Numerical Rating Scale; RCT, randomised controlled trial; SAE, serious adverse event; SLR, systematic literature review; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; TEAE, treatment-emergent adverse events

3.1.3 Critique of data extraction

The data extracted and presented in the CS for the SLR of clinical evidence appear to be appropriate and comprehensive (CS, Appendix D.1.9). As noted in the company's clarification response (question A6), all relevant data were extracted by a single reviewer and checked for accuracy by a second independent reviewer. Any discrepancies were resolved through discussion. Notwithstanding the issues raised Section 3.1.1 and 3.1.2, neither the EAG nor its clinical advisors are aware of any additional relevant completed studies within the scope of this appraisal.

3.1.4 Quality assessment

The CS (Appendix D.3) used the revised Cochrane risk of bias tool (RoB 2) to assess the risk of bias of included studies. In general, this tool is widely used in SLRs for assessing the risk of bias in randomised controlled trials (RCTs). In addition to using the RoB 2 tool, the company also appraised the included studies in the CS (Section B.2.5. Table 9) using the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs, as recommended in the current NICE user guide template for company evidence submissions.[15] Moreover, as noted in the CS (Appendix D.3), the quality assessment process was performed by a single reviewer and checked by a second with disagreements resolved

through discussion, or arbitration by a third reviewer. Furthermore, quality assessment was only performed on included full-text studies, whereas conference abstracts were not assessed as these may generally be considered at high risk of bias due to deficiencies in reporting.[16] The EAG considers this approach to be acceptable.

3.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence on nemolizumab for the treatment of moderate-to-severe AD; however, no explicit details were provided in the CS (including in Appendix D) on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e., describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[17, 18]

Due to the lack of head-to-head studies, the company undertook an NMA to evaluate the comparative efficacy of nemolizumab with other active systemic treatments for moderate-to-severe AD. Full details (see CS, Appendix M) and a critique of the methods and results are provided in Section 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

3.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches conforms to the PRISMA statement (http://www.prisma-statement.org/) and is a reasonable record of the full literature searching and screening process for the SLR of nemolizumab and its comparator treatments for patients with moderate-to-severe AD. Further details on the key studies involving nemolizumab can be found in Section 3.2.3, while information on the NMA is provided in Section 3.4.

3.2.2 Ongoing studies

The CS (Section B.2.11.1) does not cite any ongoing studies that will provide additional evidence for nemolizumab in the indication being appraised in the next 12 months. However, the CS does provide details of an ongoing long-term extension (LTE) study (NCT03989206) which is investigating the long-term safety of nemolizumab (with BSC) in adult and adolescent participants with moderate-to-severe AD. This study is expected to be completed by August 2026.[19]

3.2.3 Main studies included in the CS: ARCADIA 1, ARCADIA 2, and ARCADIA CYCLO with supporting evidence from an ongoing LTE study.

The company's SLR identified and included evidence supporting the effectiveness of nemolizumab for the treatment of moderate-to-severe AD from two pivotal phase 3 clinical trials (ARCADIA 1:

NCT03985943[20], ARCADIA 2: NCT03989349[21]), a phase 3b clinical trial (ARCADIA-CYCLO: 2021-002166-40[22]), and an ongoing long-term extension (LTE) study (NCT03989206).[19, 23]

The EAG notes that data from both the ARCADIA 1 and ARCADIA 2 trials were published in a peer-reviewed journal article.[24] Data from the ARCADIA-CYCLO and LTE study only appear to be publicly available on clinical trial registers.[19, 22] The CS seems to use a combination of data from the publication, clinical trial registers and the clinical study protocols/reports. A summary of the studies is provided in Table 6.

Table 6: Summary of the key studies (adapted from CS, Section B.2.2., Table 4; Section B.2.3., Tables 5; Appendix D.2.2, Tables 8-9)

Study	**ARCADIA 1 (NCT03985943)**	**ARCADIA 2 (NCT03989349)**	**ARCADIA-CYCLO (2021-002166-40)**	**LTE study (NCT03989206)**
Study design	Phase 3, multicentre randomised, double-blind, placebo-controlled trial	Phase 3, multicentre randomised, double-blind, placebo-controlled trial	Phase 3b, multicentre randomised, double-blind, placebo-controlled trial	Phase 3, prospective, multicentre, open-label, long-term extension study (ongoing)
Location	202 sites across 14 countries in Europe (including the UK), North America, and Asia Pacific	163 sites across 11 countries in Europe (excluding the UK), North America, and Asia Pacific (Singapore only)	58 sites across six countries in Europe (excluding the UK)	343 sites across 22 countries in Europe (including the UK), North America, and Asia Pacific
Duration	56 weeks		24 weeks	208 weeks
Population	Adults and adolescents (≥ 12 years) with moderate-to-severe AD		Adults (≥ 18 years) with moderate-to-severe AD and inadequate response to, or medically inadvisable to take ciclosporin	Adults and adolescents (≥ 12 years) with moderate-to-severe AD
Sample size	941	787 †	276 *	[redacted]
Intervention(s)	Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC including TCS-TCI) ‡ • Initial treatment period 16 weeks (Q4W) followed by • Maintenance period 32 weeks (Q4W/Q8W)		Nemolizumab 60 mg loading dose followed by 30 mg by subcutaneous injection (with BSC including TCS-TCI) ‡ • Treatment period 16 weeks (Q4W)	Nemolizumab (30 mg) by subcutaneous injection (with BSC including TCS-TCI) ‡ • Treatment period 200 weeks (Q4W)
Comparator(s)	Placebo (with BSC including TCS-TCI) ‡		Placebo (with BSC including TCS-TCI) ‡	NA
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16 • Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16		• Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16	• Incidence and severity of AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs

		• Proportion of participants with improvement of PP-NRS ≥ 4 at Week 16	
All other reported outcomes (used in economic model/specified in the scope)	• Proportion of participants with an improvement of PP-NRS ≥ 4 • Proportion of participants with PP-NRS < 2 • Proportion of participants with an improvement of SCORAD from baseline • Proportion of participants with an improvement of SD NRS ≥ 4 • Change in the DLQI/cDLQI total score from baseline • Change in POEM total score from baseline • Change in EQ-5D subscale scores from baseline • Incidence and severity AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs	• Proportion of participants with PP-NRS < 2 • Proportion of participants with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) • Proportion of participants with an improvement of SCORAD from baseline • Change in the DLQI total score from baseline • Change in POEM total score from baseline • Change in EQ-5D subscale scores from baseline • Incidence and severity of AEs, including AEs of special interest, treatment-emergent AEs, and serious AEs	• Proportion of participants with an IGA score = 0–1 • Proportion of participants reporting low disease activity (IGA score ≤ 2) • Proportion of participants with EASI-75 (≥ 75% improvement in EASI from baseline)

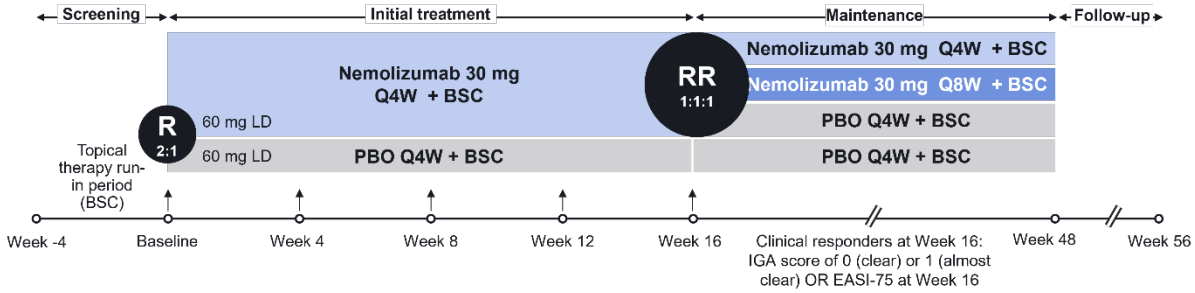
* Data publicly available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results
† Data from Silverberg et al.,[24] and NCT03989349[21]. However, CS (Section B.2.3., Tables 5) reports actual enrolment as n=788
‡ BSC strategies included basic skin care (cleansing and bathing), moisturisers, bleach baths, topical anaesthetics, and antihistamines without a sedative effect plus topical therapies (e.g. topical corticosteroids [TCS] with or without topical calcineurin inhibitors [TCI])

Abbreviations: AD, atopic dermatitis; AE, adverse events; BSC, best supportive care; cDLQI, children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index, EASI, Eczema Area and Severity Index, EQ-5D, EuroQol 5-Dimensions; IGA, Investigator's Global Assessment; LTE, long-term extension; PP-NRS, Peak Pruritus Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; SCORAD, SCORing Atopic Dermatitis; TCI, topical calcineurin inhibitor ; TCS, topical corticosteroids

ARCADIA 1 & 2 were similar in study design. Both studies were phase 3 randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational clinical trials developed to assess the efficacy and safety of nemolizumab in adult and adolescent participants (≥ 12 years) with moderate-to-severe AD not adequately controlled with topical treatments. ARCADIA 1 was conducted in 202 centres across 14 countries in Europe (Austria, Czechia, Germany Latvia, Lithuania, Netherlands, Poland, Spain, United Kingdom), North America (Canada United States) and Asia Pacific (Australia, Republic of Korea, New Zealand). ARCADIA 2 was conducted in 163 centres across 11 countries in Europe (Belgium, Bulgaria, Estonia, France, Georgia, Germany, Hungary, Italy, Poland), North

America (United States) and Asia Pacific (Singapore). Both studies included a 2- to 4-week screening (including run-in) period, a 16-week initial treatment period (baseline to week 16), a 32-week Maintenance Period (week 16 to week 48), and an 8-week follow-up period (Figure 2). As noted in the CS (section B.2.12.2., p115) '*The ARCADIA 1 & 2 trials included both first-line (who had not previously received at least one systemic immunosuppressive therapy) and second-line patients combined, which does not fully align with the second-line population in the decision problem. However, these trials were sufficiently powered to enable sub-population analysis for first- and second-line patients separately'.*

Figure 2: Study design: ARCADIA 1 & 2 (reproduced from CS, section B.2.3.1)



Abbreviations: BSC, best supportive care; LD, loading dose; PBO, placebo; R, randomisation; RR, re-randomisation Q4W, every 4 weeks; Q8W, every 8 weeks; W, week

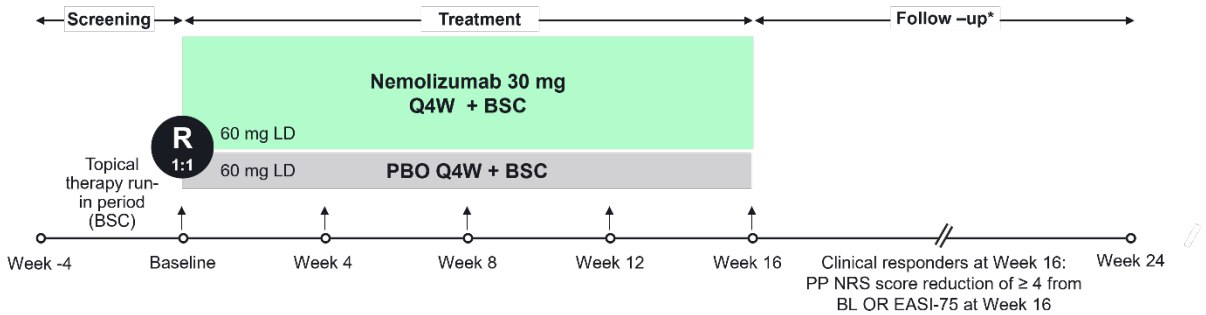
Note: Re-randomisation of treatment-arm participants was restricted to participants who had shown clinical response at Week 16.

Eligible participants in ARCADIA 1 (n= 941) & 2 (n=787) were initially randomised (2:1) to receive either nemolizumab 30 mg (60 mg loading dose at baseline) or placebo, which was given subcutaneously every 4 weeks along with BSC (includes emollients, moisturisers, topical corticosteroids [TCSs], and topical calcineurin inhibitors [TCIs]). Randomisation was stratified by disease severity (Investigator's Global Assessment [IGA] score = 3 [moderate], IGA = 4 [severe]) and itch severity (Peak Pruritus Numerical Rating Scale [PP-NRS] score ≥ 7 [severe], PP-NRS < 7 [moderate]). Participants who were randomised to nemolizumab in the initial treatment period and achieved clinical response (Eczema Area and Severity Index [EASI]-75 or IGA 0/1) at Week 16 were re-randomised (1:1:1) to receive either nemolizumab Q4W, nemolizumab Q8W, or placebo Q4W in the maintenance period (along with BSC and concomitant background TCS/TCI). In both trials, the demographic and baseline characteristics were generally similar between treatment groups (for further details see CS, Section B.2.6.1.1., Table 11 and Silverberg et al.,[24]). In ARCADIA 1, 53% were male, whereas in ARCADIA 2, 52% were female. The mean age of participants in ARCADIA 1 & 2 was 33 years and 35 years, respectively. In addition, most participants resided in Europe (ARCADIA 1: 51%; ARCADIA 2: 73%) or North America (ARCADIA 1: 33%; ARCADIA 2: 25%), and the majority identified as White (ARCADIA 1: 74%; ARCADIA 2: 87%[24]) and had moderate IGA scores (ARCADIA 1: 72%; ARCADIA 2: 68%). Across the individual treatment groups in both trials, mean

EASI and PP-NRS ranged from 27.1 to 27.8 and from 7.0 to 7.2, respectively. The co-primary endpoints were the proportion of patients with IGA success (defined as IGA score of 0 [clear skin] or 1 [almost clear skin], with ≥2-grade reduction from baseline) at week 16 and the proportion of patients with an EASI-75 response (≥75% improvement in EASI from baseline) at Week 16. Of note, in NICE TA814[25] and TA986[11] the committee noted that the use of EASI might not be appropriate for all people with AD as it may underestimate the severity of atopic dermatitis in people with brown or black skin, which could lead to undertreatment. Additionally, some key secondary endpoints included: evaluation of itch response (≥4-point improvement in PP-NRS score at week 16 and earlier time points), as well as improvement in sleep disturbance (≥4-point improvement in sleep disturbance numeric rating scale score [SD NRS]) at week 16 and patient-reported outcomes. Safety outcomes were the incidence and severity of treatment emergent adverse events (TEAE), including adverse events (AE) of special interest and serious adverse events (SAE)[24]. Both studies were funded by Galderma.[20, 21, 24]

ARCADIA-CYCLO was a phase 3b randomised, double-blind, placebo-controlled, parallel group, multicentre, multinational clinical trial designed to assess the efficacy and safety of nemolizumab in adult participants (≥ 18 years) with moderate-to-severe AD not adequately controlled with or who were advised not to use oral ciclosporin for medical reasons. However, as noted in the CS (section B.2.12.2., p115) '*The ARCADIA-CYCLO study included adult patients only, which does not fully align with the adult and adolescent population in the decision problem*'. ARCADIA-CYCLO was conducted in 58 centres across six countries in Europe (Czechia, Germany, Italy, Latvia, Poland and Spain).[22] The study included a 2- to 4-week screening (including run-in) period, a 16-week treatment period (baseline to week 16), and an 8-week follow-up period (Figure 3).

Figure 3: Study design: ARCADIA-CYCLO (reproduced from CS, section B.2.3.2)



Abbreviations: BL, baseline; BSC, best supportive care; EASI, Eczema Area Severity Index; LD, loading dose; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, every 4 weeks; W, week

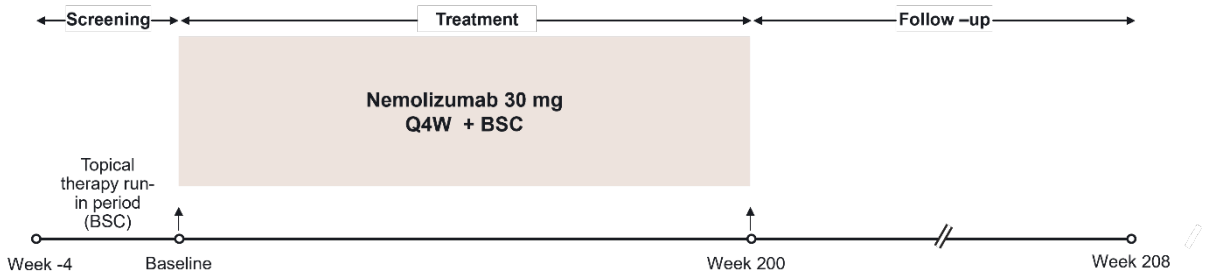
*Applicable for participants who did not participate in the LTE study only.

Eligible participants in ARCADIA-CYCLO (n=276) were randomised (1:1) to receive either nemolizumab 30 mg (60 mg loading dose at baseline) or placebo, via subcutaneous injection every 4

weeks along with BSC (includes emollients, moisturisers, topical corticosteroids [TCSs], and topical calcineurin inhibitors [TCIs]).[22] Randomisation was stratified by disease severity (IGA = 3 [moderate], IGA = 4 [severe]) and prior exposure to ciclosporin. The demographic and baseline characteristics were generally similar between treatment groups. In each group, most participants were male (52%),[22] identified as White [redacted] and had moderate IGA scores [redacted]. The mean age of participants in the nemolizumab group was 38.3 years[22] and 36.1 years[22] in the placebo group. Corresponding mean EASI scores were 29.5 and 31.3; and mean PP-NRS scores were 7.4 and 7.5, respectively.[22] The primary endpoints were (1) the proportion of patients with an EASI-75 response (≥75% improvement in EASI from baseline) at Week 16 and (2) improvement of PP-NRS (≥4-points from baseline) at Week 16. Some key secondary endpoints included: improvement in sleep disturbance (≥4-point improvement in SD NRS at week 16) and patient-reported outcomes. Safety outcomes were the incidence and severity of TEAEs, including AEs of special interest and SAEs. ARCADIA-CYCLO was funded by Galderma.

The LTE study is an ongoing phase 3, prospective, open-label, multicentre, multinational, single-arm long-term extension study, designed to assess the long-term safety and efficacy of nemolizumab in adult and adolescent participants (≥ 12 years) with moderate-to-severe AD.[22] The LTE study is being conducted in 343 centres across 22 countries in Europe (including the UK), North America, and Asia Pacific (no further details provided). The LTE study includes participants from prior nemolizumab AD phase 2b dose-ranging (NCT03100344), phase 2 adolescent pharmacokinetics/safety (NCT03921411), phase 2 vaccination safety (NCT04365387), phase 2 drug-drug interaction (DDI) (NCT04562116), phase 3b (ARCADIA-CYCLO, 2021-002166-40), and the phase 3 pivotal ARCADIA 1 & 2 clinical trials and adolescents from selected sites in Australia, Austria, Canada, and the US who had not previously participated in a nemolizumab study. The study includes a screening (including run-in) period of up to 4 weeks, a 200-week treatment period (baseline to week 200), and an 8-week follow-up period (Figure 4).

Figure 4: Study design: LTE study (reproduced from CS, section B.2.3.3)



Abbreviations: BSC, best supportive care; Q4W, every 4 weeks

Eligible participants in the LTE study (n=[redacted]) received nemolizumab (30 mg) via subcutaneous injection every 4 weeks (along with BSC and concomitant background TCS with or without TCI[23])

during the treatment period (200 weeks). As noted in the CS (section B.2.12.2., p116) '*the LTE study has been deliberately performed at a Q4W dosing schedule, and not the market authorisation maintenance dosing schedule of Q8W, to adopt a conservative approach to the safety evaluation*'. At baseline (interim data cut Week 56), the mean age of participants was [redacted], [redacted] were male, and [redacted] identified as White. In addition, [redacted]. The primary endpoints were the incidence and severity of AEs, including AEs of special interest, TEAEs, and SAEs at week 200. Some key secondary endpoints included: IGA and EASI-75 responses and patient reported outcomes. The LTE study is funded by Galderma.[23]

The company's assessment of the design, conduct and internal validity of the ARCADIA 1 & 2, ARCADIA-CYCLO, and the LTE study is summarised in Table 7 (for further details see CS, Section B.2.5, Table 9 and Appendix D.3.). Although, neither the CS nor its appendices provide a narrative assessment of the quality of the studies to inform the interpretation of the results of the nemolizumab studies, the EAG broadly agrees with the company's risk of bias assessments.

In general, based on the information available from various sources (a published article, clinical trials registers and the clinical study protocols/reports) the company and the EAG considered the ARCADIA trials (ARCADIA 1 & 2, and ARCADIA-CYCLO) to be at low risk of bias: randomisation and allocation concealment was conducted appropriately, groups were similar at baseline for prognostic factors; blinding (of care providers, participants and outcome assessors) was appropriate; no unexpected imbalances in drop-outs; no evidence of selective outcome reporting and appropriate use of intention-to-treat (ITT) analyses. Moreover, the generalisability of the results from trials to clinical practice in England is unclear. The patient population in the ARCADIA trials were predominantly young (mean age range between 33 to 38 years) and white (ARCADIA 1: 74%[24]; ARCADIA 2: 87%[24]; ARCADIA-CYCLO: [redacted]). As noted in the CS (Section B.1.3.1.2; p22) '*…in England…AD prevalence was found to have a bimodal distribution across the population, peaking in patients below one year of age and ≥ 80 years old'.*[26] These findings are generally supported by other UK-based sources.[27] In addition, *'There are statistically significant socio-economic and ethnicity differences in AD prevalence apparent in the UK. AD prevalence is increased in the most deprived quintile of UK patients and in patients living in an urban environment and is more than doubled in Asian and Black patients compared with White patients*'.[26] It is also important to note that the precise quantification of concomitant topical background therapy (TCS with or without TCI) was not measured in the ARCADIA trials; and this uncertainty may have affected the placebo or nemolizumab response.[24]

Table 7: Quality assessment of the ARCADIA trials (ARCADIA 1 & 2, and ARCADIA-CYCLO) and the LTE study, as assessed by the company (adapted from CS, Section B.2.5, Table 9)

Quality assessment criteria	ARCADIA 1		ARCADIA 2		ARCADIA-CYCLO		LTE study	
	Company's assessment	EAG's assessment	Company's assessment	EAG's assessment	Company's assessment	EAG's assessment	Company's assessment	EAG's assessment
Was randomisation carried out appropriately?	Y	Y	Y	Y	Y	Y	NA	N†
Was the concealment of treatment allocation adequate?	Y	Y	Y	Y	Y	Y	Y	N†
Were the groups similar at the outset of the study in terms of prognostic factors	Y	Y	Y	Y	Y	Y	NA	NA‡
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Y	Y	Y	Y	Y	Y	Y	N†
Were there any unexpected imbalances in dropouts between groups?	N	N	N	N	N	N	N	NA‡
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N	N	N	N	N	N	N	N
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y	Y	Y	Y	Y	Y	N	N

CS - company submission; EAG - External Assessment Group; N - no; NA – not applicable; Y – yes

† The LTE study was an open-label, single arm, long-term extension study of participants who rolled over from prior studies (n=7) and new adolescents from selected sites who had not previously participated in a nemolizumab study. All patients received open label nemolizumab on Day 1/baseline, except subjects from Phase 3 and Phase 3b studies who received blinded treatment on Day 1/baseline to maintain the blind of the lead-in (original) study. After Day 1/baseline, all participants received (open label) nemolizumab (30 mg).
‡ Single arm study

With regards to the LTE study, there is no consensus regarding whether an RCT extension is an observational study or an interventional study.[28] Some studies classify this type of research as observational due to the lack of appropriate randomisation at the start of the extension phase and the absence of new treatments being introduced.[28-30] In contrast, the LTE study has been registered as an interventional study on the EU Clinical Trials Register[23] and on ClinicalTrials.gov.[19] The EAG notes that the methodological qualities, as assessed using a quality assessment tool for RCTs, would generally result in a high risk of bias classification, due to the lack of randomisation, awareness of therapy by the assessors, missing data domain and lack of comparability in a single-arm study.[28] In addition, participants that enter the extension study are already a select group who can tolerate the study drug[31] and who have positively responded to treatment during the original trial.[32] Moreover, the LTE study was registered as an open-label study and included participants from seven different studies (four Phase II/IIb studies and three Phase 3/3b trials). However, as noted in the CS (Section B.2.5, Table 9), *'the LTE study was ongoing while phase 3 and phase 3b studies were still blinded, a blinded loading dose was required for applicable patients in order to maintain the blind of the previous study*'. As such, the LTE study may not truly be considered a fully open-label study. The extent of sample slippage in relation to the number randomised in the original RCT has also been noted as an important concern in long-term extension studies.[30] Due to poor reporting, the EAG could not fully determine the exact extent of sample slippage. Due to the noted limitations, the EAG considers the LTE study to be at high risk of bias. However, as noted by the company, the LTE data is only used to demonstrate the long-term safety profile of nemolizumab and provide additional utility inputs (EQ-5D-3L scores) to those derived from ARCADIA 1 & 2 trials for inclusion in the company's economic model.

3.3 Clinical effectiveness results

Based on information reported in the CS and its appendices, this section briefly presents the main results from the ARCADIA trials (ARCADIA 1 & 2, and ARCADIA-CYCLO) which compared nemolizumab with placebo in people with moderate-to-severe AD. Due to the absence of head-to-head studies that compare the efficacy of nemolizumab with other active approved treatments (e.g. dupilumab, tralokinumab, lebrikizumab and the JAK inhibitors) for moderate-to-severe AD, an NMA is provided in the CS with further details, results and a critique of the NMA provided in Section 3.4 (Indirect and mixed treatment comparisons).

3.3.1. Disease severity (IGA success and EASI-75)

The key results from the ARCADIA 1 & 2 trials are summarised in Table 8 (initial treatment period) and Figure 5 (pooled maintenance period). During the initial treatment period, IGA success (IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-grade improvement from baseline) was significantly higher across both studies for nemolizumab Q4W compared with placebo at Week 16 (ARCADIA 1, 35.6% vs. 24.6%, strata-adjusted p = 0.0003; ARCADIA 2, 37.7% vs. 26.0%, strata-adjusted p = 0.0006). This

response was continued in the pooled maintenance period up to Week 48 (nemolizumab Q4W to Q4W compared to nemolizumab Q4W to placebo at Week 48, 61.5% vs. 49.7%, strata-adjusted p = 0.0290; nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 60.4% vs. 49.7%, strata-adjusted p = 0.0465).

During the initial treatment period a statistically significant greater proportion of participants achieved EASI-75 (a ≥ 75% improvement from baseline) at week 16 for nemolizumab Q4W compared with placebo (ARCADIA 1, 43.5% vs.29.0%, strata-adjusted p < 0.0001; ARCADIA 2, 42.1% vs. 30.2%, strata-adjusted p = 0.0006). This response was continued in the pooled maintenance period up to Week 48 (nemolizumab Q4W to Q4W compared to nemolizumab Q4W to placebo at Week 48, 76.3% vs. 63.9%, strata adjusted p = 0.0129; nemolizumab Q4W to Q8W compared to nemolizumab Q4W to placebo at Week 48, 75.7% vs. 63.9%, strata-adjusted p = 0.0179).

In the ARCADIA-CYCLO trial (Table 8), a statistically significant greater proportion of participants achieved EASI-75 (a ≥ 75% improvement from baseline) at week 16 for nemolizumab Q4W compared with placebo ([redacted] vs. [redacted], strata-adjusted [redacted])

Table 8: Summary of key results from the ARCADIA trials (adapted from CS, Tables 16-19, and Tables 26-28)

Outcomes	ARCADIA 1			ARCADIA 2			ARCADIA-CYCLO		
	Initial treatment period			Initial treatment period					
	ITT Population			ITT population			ITT population		
	Nemolizumab 30 mg Q4W (n=620)	Placebo Q4W (n=321)	Strata-adjusted p-value	Nemolizumab 30 mg Q4W (n=522)	Placebo Q4W (n=265)	Strata-adjusted p-value	Nemolizumab 30 mg Q4W [redacted]	Placebo Q4W [redacted]	Strata-adjusted p-value
IGA success† at week 16	221 (35.6%)	79 (24.6%)	0.0003	197 (37.7%)	69 (26.0%)	0.0006	[redacted]	[redacted]	[redacted]
EASI-75 response‡ week 16	270 (43.5%)	93 (29.0%)	<0.0001	220 (42.1%)	80 (30.2%)	0.0006	[redacted]	[redacted]	[redacted]
PP-NRS score reduction ≥4 at week 16	265 (42.7%)	57 (17.8%)	<0.0001	214 (41.0%)	48 (18.1%)	<0.0001	[redacted]	[redacted]	[redacted]
PP-NRS score <2 at week 16	190 (30.6%)	36 (11.2%)	<0.0001	148 (28.4%)	30 (11.3%)	<0.0001	[redacted]	[redacted]	[redacted]
SD-NRS score reduction ≥4 at week 16	235 (37.9%)	64 (19.9%)	<0.0001	175 (33.5%)	43 (16.2%)	<0.0001	[redacted]	[redacted]	[redacted]

† IGA success defined as a rating of 0 (clear skin) or 1 (almost clear skin) plus at least a 2-grade improvement from baseline. IGA scores range from 0 (clear skin) to 4 (severe disease)
‡ EASI-75 response defined as at least 75% improvement in EASI from baseline

Abbreviations: EASI, eczema area and severity index; IGA, Investigator's Global Assessment; ITT, intention-to-treat; PP-NRS, peak pruritus numerical rating scale; Q4W, every 4 weeks; SD NRS, sleep disturbance numerical rating scale

Figure 5: Summary of key results from the ARCADIA 1 & 2 trials - IGA success and EASI-75 from maintenance baseline through Week 48 (reproduced from CS, Figure 9)

Abbreviations: BSC, best supportive care; EASI, eczema area and severity index; IGA, Investigator's Global Assessment; Q4/8W, every 4/8 weeks

3.3.2. Itch response (PP-NRS)

In the ARCADIA 1 & 2 trials (Table 8), a substantially higher proportion of patients treated with nemolizumab reported a ≥4-point improvement from baseline in PP-NRS scores at week 16 compared with placebo (ARCADIA 1, 42.7% vs. 17.8%, strata-adjusted $p < 0.0001$; and ARCADIA 2, 41.0% vs. 18.1%, strata-adjusted $p < 0.0001$). In addition, a greater proportion of participants with a weekly average PP-NRS <2 was observed for nemolizumab compared with placebo at Week 16 in ARCADIA 1 (30.6% vs. 11.2%, strata-adjusted $p < 0.0001$) and ARCADIA 2 (28.4% vs. 11.3%, strata-adjusted $p < 0.0001$).

In the ARCADIA-CYCLO trial (Table 8), a higher proportion of participants reported an improvement of ≥4 from baseline in weekly average PP-NRS for nemolizumab Q4W compared with placebo at Week 16 (vs. respectively, strata-adjusted). In addition, a greater proportion of participants with a weekly average PP-NRS < 2 was observed for nemolizumab compared with placebo at Week 16 (vs. , strata-adjusted)

3.3.3. Sleep disturbance

In the ARCADIA 1 & 2 trials (Table 8), a higher proportion of participants reported improvements in sleep disturbance (reduction of ≥4 points from baseline in weekly average Sleep Disturbance Numerical Rating Scale [SD NRS] score) for nemolizumab compared with placebo at Week 16 (ARCADIA 1, 37.9% vs. 19.9%, strata-adjusted $p < 0.0001$; and ARCADIA 2, 33.5% vs. 16.2%, strata-adjusted $p < 0.0001$).

In the ARCADIA-CYCLO trial (Table 8), improvements in sleep disturbance (≥ 4 points from baseline in weekly average SD NRS) were also observed with nemolizumab at Week 16 (vs. , strata-adjusted). [33, 34 33, 3434]

3.3.4. Patient-reported outcome assessments

In the ARCADIA 1 & 2 trials, nemolizumab was more effective than placebo in reducing the Dermatology Life Quality Index total score (DLQI: ARCADIA 1, Least Squares [LS] mean difference -2.50; 95% CI -3.63, -1.37; ; ARCADIA 2: LS mean difference -2.44; 95% CI -3.58, -1.30;) and the Patient Oriented Eczema Measure total score (POEM: ARCADIA 1, LS mean difference -4.04; 95% CI -5.09, -2.99; ; ARCADIA 2, LS mean difference -3.93; 95% CI -5.07, -2.78;) compared with baseline at Week 16. In addition, nemolizumab was more effective than placebo in increasing the EuroQol 5-Dimensions (EQ-5D) Visual Analog Scale (VAS) score compared with baseline at Week 16 (ARCADIA 1, LS mean difference 2.56; 95% CI 0.16, 4.95; ; ARCADIA 2, LS mean difference 2.39; 95% CI -0.30, 5.09;). For further details, see CS, Section B.2.6.2.2., Tables 21-23.

In the ARCADIA-CYCLO trial, nemolizumab was also more effective than placebo in reducing the DLQI and POEM total scores and increasing EQ-5D VAS score compared with baseline at Week 16 (DLQI: LS mean difference ; 95% CI ; ; POEM: LS mean difference ; 95% CI ; and EQ-5D: LS mean difference ; 95% CI ;). For further details, see CS, Section B.2.6.2.2., Tables 30-32.

3.3.5. Additional analyses

Additional analyses presented by the company included data from the ARCADIA trials (ARCADIA 1, 2 and ARCADIA-CYCLO) on the extent and severity of AD using the SCORing Atopic Dermatitis (SCORAD) index. In general, nemolizumab was more effective than placebo in reducing the SCORAD compared with baseline at Week 16 in ARCADIA 1 (LS mean difference -9.17; 95% CI: -12.35, -5.99;), ARCADIA 2 (LS mean difference -8.10; 95% CI: -11.39, -4.82;) and ARCADIA-CYCLO (LS mean percent difference ; 95% CI: ;). For further details see CS, Section B.2.6.2.2., Table 20 and Table 29. Further, pre-planned subgroup analyses from the ARCADIA 1 & 2 trials were presented in the CS. Due to the limited population in each subgroup, a pooled analysis of ARCADIA 1 & 2 was conducted for the following pre-planned subgroups relevant to the submission (CS, section B.2.7.): race, previous use of any systemic therapy for AD, previous use of any immunosuppressive or immunomodulatory drugs for AD and previous use of ciclosporin for AD. . In general, a statistically significant greater proportion of participants achieved EASI-75 and

IGA success at week 16 for nemolizumab compared with placebo regardless of previous use of any systemic therapy, immunosuppressive or immunomodulatory drug, and ciclosporin. As noted in the CS (Section B.2.7), '*…Due to the small number of participants with available data in the Black or African-American, Asian, and other subgroups for race, these results are difficult to interpret any meaningful conclusions*'. For further details, see CS, Section B.2.7., Figure 12 and Figure 13.

3.3.6. Safety and tolerability

This section provides the main safety evidence from the ARCADIA trials (ARCADIA 1 & 2, and ARCADIA-CYCLO) and the LTE study, as reported by the company, for all patients who received at least one dose of study medication (Safety Population). In general, nemolizumab was shown to have an acceptable safety profile, with few SAEs reported, including in patients who had an inadequate response to, or for whom ciclosporin is not medically advised. The majority of TEAEs were mild or moderate in severity, with no concerning AEs being observed with longer exposure (up to 56 weeks).

The key safety results from the ARCADIA 1 & 2 trials are summarised in Tables 9-10 (initial treatment period) and Tables 11-12 (pooled maintenance period). In the safety population, 306 (49.7%) of 616 participants (ARCADIA 1) and 215 (41.4%) of 519 participants (ARCADIA 2) who received nemolizumab had at least one treatment-emergent adverse (TEAE) event during the initial treatment period (serious TEAEs in six [1%] and 13 [3%], respectively); and 146 (45.5%) of 321 (ARCADIA 1) and 117 (44.5%) of 263 (ARCADIA 2) who received placebo had at least one TEAE (serious TEAE in four [1%] and three [1%], respectively). TEAEs possibly related to nemolizumab were reported in five (1%) participants in ARCADIA 2 only. No deaths occurred in either trial. In ARCADIA 1, nine (1.5%) participants in the nemolizumab group experienced a TEAE leading to study discontinuation compared with three (0.9%) participants in the placebo group. Similarly, in ARCADIA 2, 15 (2.9%) nemolizumab and three (1.1%) placebo participants experienced a TEAE leading to study discontinuation. Although not explicitly reported in the CS, Silverberg *et al*[24] reported that during the initial treatment period, the use of rescue therapies in the ARCADIA 1 & 2 were marginally higher in the placebo group compared with the nemolizumab group (33/620 [5.3%] vs. 24/321 [7.5%] in ARCADIA 1 and 16/522 [3.1%] vs. 13/265 [4.9%] in ARCADIA 2). As shown in Table 10, the most common TEAEs (reported by ≥ 5.0% of participants in either group) were dermatitis atopic (12.2% nemolizumab, 10.6% placebo) and asthma (5.4% nemolizumab, 4.0% placebo) in ARCADIA 1, dermatitis atopic (7.1% nemolizumab, 5.7% placebo) in ARCADIA 2. In ARCADIA 1 & 2, the incidence of conjunctivitis in the initial treatment period was low and comparable across both treatment groups (ARCADIA 1: nemolizumab: [redacted]; placebo: [redacted]; ARCADIA 2: nemolizumab: [redacted]; placebo: [redacted]).

Table 9: Summary of TEAEs in the ARCADIA trials (adapted from CS, Table 37, and Table 41)

Participants with at least 1:	ARCADIA 1		ARCADIA 2		ARCADIA-CYCLO	
	Safety population		Safety population		Safety population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30mg Q4W	Placebo Q4W
Total participants, n	616	321	519	263	137*	137*
TEAE, n (%)	306 (49.7)	146 (45.5)	215 (41.4)	117 (44.5)	[redacted]	[redacted]
TEAE by maximum severity						
Mild, n (%)	168 (27.3)	89 (27.7)	113 (21.8)	66 (25.1)	[redacted]	[redacted]
Moderate, n (%)	120 (19.5)	49 (15.3)	81 (15.6)	44 (16.7)	[redacted]	[redacted]
Severe, n (%)	18 (2.9)	8 (2.5)	21 (4.0)	7 (2.7)	[redacted]	[redacted]
Study drug-related TEAE†, n (%)	123 (20.0)	42 (13.1)	67 (12.9)	29 (11.0)	[redacted]	[redacted]
Study drug-related TEAE by maximum severity†‡						
Mild, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Moderate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Severe, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
TEAE related to protocol procedure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE, n (%)	6 (1.0)	4 (1.2)	13 (2.5)	3 (1.1)	3 (2.2)*	2 (1.5)*
SAE related to study drug, n (%)	0	0	5 (1.0)	0	[redacted]	[redacted]
Severe TEAE, n (%)	18 (2.9)	8 (2.5)	21 (4.0)	7 (2.7)		
TEAE leading to study drug interruption, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
TEAE leading to study drug withdrawal, n (%)	11 (1.8)	13 (4.0)	18 (3.5)	3 (1.1)	[redacted]	[redacted]
TEAE leading to study discontinuation, n (%)	9 (1.5)	3 (0.9)	15 (2.9)	3 (1.1)	[redacted]	[redacted]
AESI, n (%)					[redacted]	[redacted]
Treatment-emergent AESIs by categories, n (%)	56 (9.1)	20 (6.2)	47 (9.1)	21 (8.0)		
Injection-related reactions, n (%)	1 (0.2)	0	0	0		

Newly diagnosed asthma or worsening of asthma, n (%)	32 (5.2)	11 (3.4)	15 (2.9)	8 (3.0)		
Infections, n (%)	20 (3.2)	10 (3.1)	20 (3.9)	12 (4.6)		
Peripheral oedema: limbs, bilateral; facial oedema, n (%)	7 (1.1)	1 (0.3)	12 (2.3)	1 (0.4)		
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN), n (%)	0	0	0	0		
TEAE leading to death, n (%)	0	0	0	0	[redacted]	[redacted]
TEAE related to study drug leading to death, n (%)	0	0	0	0	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.

* Data publicly available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results

† Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).

‡ If participants experienced multiple events, the participants were counted once at the event with maximum severity

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of participants in the treatment group; n, number of participants with available data; NR, not recorded Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

Table 10: TEAEs experienced by ≥ 1.0% (ARCADIA 1 & 2) or ≥ 2.0% (ARCADIA-CYCLO) of participants in either group by system organ class and preferred term (adapted from CS, Table 38, and Table 42)

	ARCADIA 1		ARCADIA 2		ARCADIA-CYCLO	
	Safety population		Safety population		Safety population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30mg Q4W	Placebo Q4W	Nemolizumab 30mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]	[redacted]	[redacted]	137*	137*
Participants with at least 1 TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Conjunctivitis allergic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Gastrointestinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Nausea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Abdominal pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
General disorders and administration site conditions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Oedema peripheral, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Fatigue, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Vaccination site pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Infections and Infestations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covid-19, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	7 (5.1)*	4 (2.9)*
Nasopharyngitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	13 (9.5)*	14 (10.2)*
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	5 (3.6)*	1 (0.7)*
Urinary tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.2)*	3 (2.2)*
Skin infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Folliculitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Herpes simplex, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Viral upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

Sinusitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Oral herpes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Conjunctivitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Rhinitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (2.9)*	1 (0.7)*
Gastroenteritis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Bronchitis, n (%)					0*	3 (2.2) *
Tonsillitis, n (%)					0*	3 (2.2) *
Investigations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	5 (3.6) *	1 (0.7) *
Peak expiratory flow rate decreased, n (%)	[redacted]		[redacted]	[redacted]	3 (2.2) *	1 (0.7) *
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	4 (2.9) *	1 (0.7) *
Arthralgia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Myalgia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Nervous system disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Headache, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	5 (3.6) *	2 (1.5) *
Cough, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Dyspnoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Rhinitis allergic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	10 (7.3) *	6 (4.4) *
Urticaria, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Pruritis , n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Alopecia areata, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

Vascular disorders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Hypertension, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.

*Data publicly available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results
†Data corrected by EAG

Abbreviations: N, number of participants in the treatment group; n, number of participants who experienced the events; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event

The safety data for the maintenance period in the ARCADIA 1 & 2 trials were pooled in the CS and summarised by treatment group (nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W, nemolizumab Q4W to placebo). In general, participants who experienced at least one TEAE was similar across the treatment groups ([redacted], [redacted] and [redacted], respectively) with serious TEAEs in [redacted] participants respectively (Table 11). SAEs considered study drug-related were experienced by [redacted] the nemolizumab Q4W to Q4W and the nemolizumab Q4W to placebo group. [redacted] TEAEs leading to study discontinuation were experienced by [redacted] participants in the nemolizumab Q4W to Q4W, nemolizumab Q4W to Q8W, and nemolizumab Q4W to placebo groups, respectively. As shown in Table 12, the most common TEAEs (reported by ≥ 5.0% of participants in any group) across treatment groups were COVID-19 (range: [redacted] to [redacted]), dermatitis atopic (range: [redacted] to [redacted]), nasopharyngitis (range: [redacted] to [redacted]), and upper respiratory tract infection (range: [redacted] to [redacted]). Conjunctivitis was not common across treatment groups (range: [redacted] to [redacted]).

Table 11: Summary of TEAEs in the maintenance period of the ARCADIA 1 & 2 trials (reproduced from CS, Table 39)

Participants with at least 1:	Safety population		
	Nemolizumab 30 mg Q4W to Q4W	**Nemolizumab 30 mg Q4W to Q8W**	**Nemolizumab 30 mg Q4W to placebo**
Total, n	[redacted]	[redacted]	[redacted]
TEAE, n (%)	[redacted]	[redacted]	[redacted]
Study drug-related TEAE†, n (%)	[redacted]	[redacted]	[redacted]
TEAE related to protocol procedure (including topical background therapy), n (%)	[redacted]	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]	[redacted]
SAE related to study drug, n (%)	[redacted]	[redacted]	[redacted]
Severe TEAE, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to temporary discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to permanent discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to permanent discontinuation from study discontinuation, n (%)	[redacted]	[redacted]	[redacted]
Treatment-emergent AESIs by categories, n (%)	[redacted]	[redacted]	[redacted]
Injection-related reactions, n (%)	[redacted]	[redacted]	[redacted]
Newly diagnosed asthma or worsening of asthma, n (%)	[redacted]	[redacted]	[redacted]
Infections, n (%)	[redacted]	[redacted]	[redacted]
Peripheral oedema: limbs, bilateral; facial oedema, n (%)	[redacted]	[redacted]	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN), n (%)	[redacted]	[redacted]	[redacted]
TEAE leading to death, n (%)	[redacted]	[redacted]	[redacted]
TEAE related to study drug leading to death, n (%)	[redacted]	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.

† Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of participants in the treatment group; n, number of participants who experienced the events; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

Table 12: TEAEs experienced by ≥ 1.0% of participants in the maintenance period of the ARCADIA 1 & 2 trials by system organ class and preferred term (reproduced from CS, Table 40)

	Safety population		
	Nemolizumab 30 mg Q4W to Q4W	**Nemolizumab 30 mg Q4W to Q8W**	**Nemolizumab 30 mg Q4W to placebo**
Total, n	[redacted]	[redacted]	[redacted]
Participants with at least 1 TEAE, n (%)	[redacted]	[redacted]	[redacted]
Blood and Lymphatic System Disorder, n (%)	[redacted]	[redacted]	[redacted]
Neutropenia, n (%)	[redacted]	[redacted]	[redacted]
Eye Disorders, n (%)	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic, n (%)	[redacted]	[redacted]	[redacted]
Dry eye, n (%)	[redacted]	[redacted]	[redacted]
Gastrointestinal Disorders, n (%)	[redacted]	[redacted]	[redacted]
Abdominal pain upper, n (%)	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]
Nausea, n (%)	[redacted]	[redacted]	[redacted]
Angular cheilitis, n (%)	[redacted]	[redacted]	[redacted]
Duodenal ulcer, n (%)	[redacted]	[redacted]	[redacted]
Gastrooesophageal reflux disease, n (%)	[redacted]	[redacted]	[redacted]
Vomiting, n (%)	[redacted]	[redacted]	[redacted]
Dyspepsia, n (%)	[redacted]	[redacted]	[redacted]
General Disorders and Administration Site Conditions, n (%)	[redacted]	[redacted]	[redacted]
Pyrexia, n (%)	[redacted]	[redacted]	[redacted]
Vaccination site pain, n (%)	[redacted]	[redacted]	[redacted]
Infections and Infestations, n (%)	[redacted]	[redacted]	[redacted]
Nasopharyngitis, n (%)	[redacted]	[redacted]	[redacted]
COVID-19, n (%)	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]
Gastroenteritis, n (%)	[redacted]	[redacted]	[redacted]
Herpes dermatitis, n (%)	[redacted]	[redacted]	[redacted]
Oral herpes, n (%)	[redacted]	[redacted]	[redacted]
Pharyngitis, n (%)	[redacted]	[redacted]	[redacted]
Urinary tract infection, n (%)	[redacted]	[redacted]	[redacted]
Asymptomatic COVID-19, n (%)	[redacted]	[redacted]	[redacted]
Influenza, n (%)	[redacted]	[redacted]	[redacted]
Tonsilitis, n (%)	[redacted]	[redacted]	[redacted]
Tooth abscess, n (%)	[redacted]	[redacted]	[redacted]
Folliculitis, n (%)	[redacted]	[redacted]	[redacted]
Gastrointestinal infection, n (%)	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection, n (%)	[redacted]	[redacted]	[redacted]
Cellulitis, n (%)	[redacted]	[redacted]	[redacted]

Rhinitis, n (%)	[redacted]	[redacted]	[redacted]
Sinusitis, n (%)	[redacted]	[redacted]	[redacted]
Sinusitis bacterial, n (%)	[redacted]	[redacted]	[redacted]
Injury, Poisoning and Procedural Complications, n (%)	[redacted]	[redacted]	[redacted]
Ligament sprain, n (%)	[redacted]	[redacted]	[redacted]
Investigations, n (%)	[redacted]	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]	[redacted]	[redacted]
Peak expiratory flow rate decreased, n (%)	[redacted]	[redacted]	[redacted]
Musculoskeletal and Connective Tissue Disorders, n (%)	[redacted]	[redacted]	[redacted]
Neck pain, n (%)	[redacted]	[redacted]	[redacted]
Arthralgia, n (%)	[redacted]	[redacted]	[redacted]
Arthritis, n (%)	[redacted]	[redacted]	[redacted]
Nervous System Disorders, n (%)	[redacted]	[redacted]	[redacted]
Headache, n (%)	[redacted]	[redacted]	[redacted]
Psychiatric Disorders, n (%)	[redacted]	[redacted]	[redacted]
Depression, n (%)	[redacted]	[redacted]	[redacted]
Reproductive System and Breast Disorders, n (%)	[redacted]	[redacted]	[redacted]
Pelvic pain, n (%)	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders, n (%)	[redacted]	[redacted]	[redacted]
Asthma, n (%)	[redacted]	[redacted]	[redacted]
Dyspnoea, n (%)	[redacted]	[redacted]	[redacted]
Cough, n (%)	[redacted]	[redacted]	[redacted]
Oropharyngeal pain, n (%)	[redacted]	[redacted]	[redacted]
Wheezing, n (%)	[redacted]	[redacted]	[redacted]
Rhinitis allergic, n (%)	[redacted]	[redacted]	[redacted]
Rhinorrhoea, n (%)	[redacted]	[redacted]	[redacted]
Skin and Subcutaneous Tissue Disorders, n (%)	[redacted]	[redacted]	[redacted]
Dermatitis atopic, n (%)	[redacted]	[redacted]	[redacted]
Urticaria, n (%)	[redacted]	[redacted]	[redacted]
Acne, n (%)	[redacted]	[redacted]	[redacted]
Pruritus, n (%)	[redacted]	[redacted]	[redacted]
Vascular Disorders, n (%)	[redacted]	[redacted]	[redacted]
Hypertension, n (%)	[redacted]	[redacted]	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.

Abbreviations: N, number of participants in the treatment group; n, number of participants who experienced the events; PT, Preferred Term; Q4W, every 4 weeks; SOC, System Organ Class; TEAE, treatment-emergent adverse event

In the ARCADIA-CYCLO trial, [redacted] of participants who received nemolizumab experienced at least one TEAE during the treatment period compared with [redacted] in the placebo group (Table 13) with SAEs experienced by three (2.2%) nemolizumab participants and two (1.5%) placebo participants. SAEs considered study drug-related were experienced by [redacted]

participant in each nemolizumab and placebo arms. TEAEs leading to study discontinuation were experienced by [redacted] participants in the nemolizumab group compared with [redacted] participants in the placebo group. The most common TEAEs (reported by ≥ 5.0% of participants in either group) were nasopharyngitis (9.5% nemolizumab, 10.2% placebo), dermatitis atopic (7.3% nemolizumab, 4.4% placebo), and COVID-19 (5.1% nemolizumab, 2.9% placebo). No TEAEs leading to death were recorded during the study period.

Table 13: Summary of TEAEs in the ARCADIA-CYCLO trial (adapted from CS, Table 41, and Table 42)

Participants with at least 1:	Safety population	
	Nemolizumab 30mg Q4W	Placebo 30mg Q4W
Total participants, n	137*	137*
TEAE, n (%)	[redacted]	[redacted]
TEAE by maximum severity†		
Mild, n (%)	[redacted]	[redacted]
Moderate, n (%)	[redacted]	[redacted]
Severe, n (%)	[redacted]	[redacted]
Study drug-related TEAE‡, n (%)	[redacted]	[redacted]
TEAE related to protocol procedure, n (%)	[redacted]	[redacted]
SAE, n (%)	[redacted]	[redacted]
SAE related to study drug, n (%)	[redacted]	[redacted]
TEAE leading to study drug withdrawal, n (%)	[redacted]	[redacted]
TEAE leading to study discontinuation, n (%)	[redacted]	[redacted]
AESI, n (%)	[redacted]	[redacted]
TEAE leading to death, n (%)	[redacted]	[redacted]
TEAE related to study drug leading to death, n (%)	[redacted]	[redacted]
TEAEs experienced by ≥ 2.0% of participants by system organ class and preferred term		
Infections and infestations, n (%)	[redacted]	[redacted]
Bronchitis, n (%)	0*	3 (2.2)*
COVID-19, n (%)	7 (5.1)*	4 (2.9)*
Nasopharyngitis, n (%)	13 (9.5)*	14 (10.2)*
Rhinitis, n (%)	4 (2.9)*	1 (0.7)*
Tonsillitis, n (%)	0*	3 (2.2)*
Upper respiratory tract infection, n (%)	5 (3.6)*	1 (0.7)*
Urinary tract infection, n (%)	3 (2.2)*	3 (2.2)*
Skin and subcutaneous tissue disorders, n (%)	[redacted]	[redacted]
Dermatitis atopic, n (%)	10 (7.3)*	6 (4.4)*
Investigations, n (%)	[redacted]	[redacted]
Blood creatine phosphokinase increased, n (%)	5 (3.6)*	1 (0.7)*

Peak expiratory flow rate decreased, n (%)	3 (2.2)*	1 (0.7)*
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]	[redacted]
Asthma, n (%)	5 (3.6)*	2 (1.5)*
Musculoskeletal and connective tissue disorders, n (%)	[redacted]	[redacted]
Back pain, n (%)	4 (2.9)*	1 (0.7)*

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
*Data publicly available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002166-40/results
† If the severity of an AE was missing, the AE was reported as 'Severe'.
‡ Study drug-related TEAEs were those for which a reasonable possibility of relationship was reported (or with a missing relationship).
Abbreviations: AE, adverse event; AESI, adverse event of special interest; N, number of participants in the population; n, number of participants who experienced the event; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event

In the ongoing LTE study, no new safety concerns were identified with nemolizumab treatment at the interim data cut (Week 56). A summary of the key safety results from the LTE study are summarised in Table 14. In the safety population, [redacted] of [redacted] participants treated with nemolizumab (30 mg Q4W) experienced at least one TEAE during the treatment period. The majority of TEAEs were considered mild or moderate in severity. Study drug-related TEAEs were experienced by [redacted] participants, with SAE considered drug-related by [redacted] participants. TEAEs leading to study discontinuation were experienced by [redacted] participants. Adverse events of special interest (defined by Investigator) were experienced by [redacted] participants. No subject died during the study. As shown in Table 15, the most common (reported by ≥ 5.0% of participants) TEAEs in the LTE study were COVID-19 ([redacted]), dermatitis atopic ([redacted]), nasopharyngitis ([redacted]), and upper respiratory tract infection ([redacted]).

Table 14: Summary of TEAEs in the LTE study (interim data cut Week 56) (reproduced from CS, Table 43)

Participants with at least 1:	**Safety population**
	Nemolizumab 30 mg Q4W
Total participants, n	[redacted]
TEAE	[redacted]
TEAE by maximum severity†	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
Study drug-related TEAE	[redacted]
Study drug-related TEAE by maximum severity†	
Mild	[redacted]
Moderate	[redacted]
Severe	[redacted]
TEAE related to protocol procedure	[redacted]

SAE	[redacted]
SAE related to study drug	[redacted]
Severe TEAE	[redacted]
TEAE leading to study drug interruption	[redacted]
TEAE leading to study drug withdrawal	[redacted]
TEAE leading to study discontinuation	[redacted]
AESIs by categories (by Investigator)	[redacted]
Injection-related reactions	[redacted]
Newly diagnosed asthma or worsening of asthma	[redacted]
Infections	[redacted]
Peripheral edema: limbs, bilateral; facial edema	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN)	[redacted]
AESIs by categories (MedDRA search)	[redacted]
Injection-related reactions	[redacted]
Newly diagnosed asthma or worsening of asthma	[redacted]
Infections	[redacted]
Peripheral edema: limbs, bilateral; facial edema	[redacted]
Elevated ALT or AST (>3×ULN) in combination with elevated bilirubin (>2×ULN)	[redacted]
TEAE leading to death	[redacted]
TEAE related to study drug leading to death	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.
† If participants experienced multiple events, the participants were counted once at the event with maximum severity

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in the population; n=number of participants who experienced the events; NA, not applicable Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

Table 15: TEAEs experienced by ≥ 1.0% of participants in the LTE study (interim data cut Week 56) by system organ class and preferred term (reproduced from CS, Table 44)

	Safety population
	Nemolizumab 30 mg Q4W
Total, n	[redacted]
Participants with at least 1 TEAE, n (%)	[redacted]
Eye disorders, n (%)	[redacted]
Conjunctivitis allergic, n (%)	[redacted]
Gastrointestinal disorders, n (%)	[redacted]
Diarrhoea, n (%)	[redacted]
General disorders and administrative site conditions, n (%)	[redacted]
Pyrexia, n (%)	[redacted]
Fatigue, n (%)	[redacted]
Infections and infestations, n (%)	[redacted]
COVID-19, n (%)	[redacted]
Nasopharyngitis, n (%)	[redacted]
Upper respiratory tract infection, n (%)	[redacted]
Urinary tract infection, n (%)	[redacted]
Asymptomatic COVID-19, n (%)	[redacted]
Impetigo, n (%)	[redacted]
Oral herpes, n (%)	[redacted]
Pharyngitis, n (%)	[redacted]
Rhinitis, n (%)	[redacted]
Sinusitis, n (%)	[redacted]
Bronchitis, n (%)	[redacted]
Respiratory tract infection, n (%)	[redacted]
Investigations, n (%)	[redacted]
Blood creatine phosphokinase increased, n (%)	[redacted]
Peak expiratory flow rate decreased, n (%)	[redacted]
Musculoskeletal and connective tissue disorders, n (%)	[redacted]
Back pain, n (%)	[redacted]
Arthralgia, n (%)	[redacted]
Nervous system disorders, n (%)	[redacted]
Headache, n (%)	[redacted]
Respiratory, thoracic, and mediastinal disorders, n (%)	[redacted]
Asthma, n (%)	[redacted]
Cough, n (%)	[redacted]
Dyspnoea, n (%)	[redacted]
Oropharyngeal pain, n (%)	[redacted]
Rhinorrhoea, n (%)	[redacted]
Skin and subcutaneous tissue disorders, n (%)	[redacted]

Dermatitis atopic, n (%)	[redacted]
Urticaria, n (%)	[redacted]
Acne, n (%)	[redacted]
Alopecia, n (%)	[redacted]
Vascular disorders, n (%)	[redacted]
Hypertension, n (%)	[redacted]

Note: Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 25.0.

Abbreviations: N, number of participants in the population; n, number of participants who experienced the events; Q4W, every 4 weeks; TEAE, treatment-emergent adverse event

3.3.7 Flares

In the company's clarification response, the probability of having a flare between week 16 and week 48 of nemolizumab treatment was reported to be [redacted] based on the pooled data from ARCADIA 1 and ARCADIA 2 studies using data where people move from nemolizumab 30mg Q4W to nemolizumab 30mg Q8W.[35]

3.4 Indirect and mixed treatment comparisons

In the absence of head-to-head data, the CS presented an NMA to compare the efficacy and safety of nemolizumab with other active treatments for moderate-to-severe AD, using published evidence identified from its clinical SLR. Separate NMAs were conducted for the following populations:

- Adults (≥ 18 years of age), second-line (ciclosporin-experienced),
- Adolescents (12–17 years of age), first-line (ciclosporin-naïve).

The outcomes evaluated in the NMAs include EASI-50 (≥ 50% improvement in EASI from baseline), EASI-75, EASI-90, PP-NRS, IGA, DLQI, TEAEs, discontinuations due to adverse events (DAEs), and a composite of EASI-50 and DLQI, all at week 16. Only the results for EASI-75 are presented in the CS, and the results for the remaining outcomes are presented in CS Appendix M.

3.4.1 Identification and selection of relevant studies for the network meta-analysis

The company's NMA has included all the relevant studies used in the two most recent NICE appraisals for this indication (TA814[25] and TA986[11]). The studies used in the company's NMA are summarised in Table 16. Given that there was no major criticism of the studies selected for the NMA in TA814[25] and TA986[11], and as the clinical advisors to the EAG did not identify any key studies that were omitted from the company's NMA, the EAG did not explicitly quality assess the studies that were included in the company's NMA.

Table 16: Summary of the trials used to carry out ITC for EASI-75 (modified from CS Table 33 and CS Appendix M Tables 10, 43, and 76)

Reference of trial	Phase	NMA	Patient Description	Intervention(s)	Comparator
ARCADIA 1[20]	3	Adult 1L	Adults CsA naïve	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
		Adult 2L	Adults CsA experienced		
		Adolescent 1L	Adolescents CsA naïve		
ARCADIA 2[21]	3	Adult 1L	Adults CsA naïve	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
		Adult 2L	Adults CsA experienced		
		Adolescent 1L	Adolescents CsA naïve		
ARCADIA-CYCLO[34]	3b	Adult 2L	Adults CsA experienced	Nemolizumab + TCS/TCI	Placebo + TCS/TCI
AD Up[36]	3	Adult 1L	Adolescents and adults CsA naïve	Upadacitinib + TCS/TCI	Placebo + TCS/TCI
		Adult 2L	Adolescents and adults CsA experienced		
		Adolescent 1L	Adolescents CsA naïve		
ADhere[37]	3	Adult 2L	Adolescents and adults mixed CsA naïve/experienced	Lebrikizumab + TCS/TCI	Placebo + TCS/TCI
		Adolescent 1L	Adolescents CsA naïve		
ADhere-J[38]	3	Adult 1L	Adolescents and adults CsA naïve	Lebrikizumab + TCS/TCI	Placebo + TCS/TCI
ADvantage[39]	3	Adult 2L	Adolescents and adults mixed CsA naïve/experienced	Lebrikizumab + TCS	Placebo + TCS
BREEZE AD-4[40]	3	Adult 2L	Adults mixed CsA naïve/experienced	Baricitinib + TCS	Placebo + TCS
BREEZE AD-7[41]	3	Adult 2L	Adults mixed CsA naïve/experienced	Baricitinib + TCS	Placebo + TCS
ECZTRA 7[42]	3	Adult 2L	Adults CsA experienced	Tralokinumab + TCS	Placebo + TCS
ECZTRA 8[43]	3	Adult 1L	Adults CsA naïve	Tralokinumab + TCS/TCI	Placebo + TCS/TCI
JADE COMPARE[44]	3	Adult 1L	Adults CsA naïve	Dupilumab + TCS/TCI Abrocitinib + TCS/TCI	Placebo + TCS/TCI
JADE DARE[45]	3	Adult 2L	Adults mixed CsA naïve/experienced	Abrocitinib + TCS/TCI	Dupilumab + TCS/TCI
JADE TEEN[46]	3	Adolescent 1L	Adolescents CsA naïve	Abrocitinib + TCS/TCI	Placebo + TCS/TCI
LIBERTY AD CAFÉ[47]	3	Adult 2L	Adults CsA experienced	Dupilumab + TCS/TCI	Placebo + TCS/TCI
Rising UP[48]	3	Adult 1L	Adolescents and adults CsA naïve	Upadacitinib + TCS/TCI	Placebo + TCS/TCI
		Adolescent 1L	Adolescents CsA naïve		

Abbreviations: RCT, randomised controlled trial; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

3.4.2 NMA methods and results

The company conducted a series of NMAs in a Bayesian framework using a normal likelihood with an identity link for binary endpoints (with the binary endpoints converted to log odds ratios [ORs]) and a

normal likelihood with an identity link for continuous endpoints. NMAs were performed for the ciclosporin-experienced (second-line) adult population and the ciclosporin-naïve (first-line) adolescent population separately. No analysis was conducted for second-line adolescent population because the company stated that data for an adolescent population who had previously failed ciclosporin were not available. The EAG notes that NMAs were also performed for the ciclosporin-naïve (first-line) adult population as the indirect treatment comparison was conducted from a global perspective, and the results from this NMA was not used in the economic model because the first-line adult population is outside of the NICE scope.

The company presented both fixed effects (FE) and random effects (RE) models. Vague prior distributions were used to allow the data to dominate. Where there were a small number of trials included in the network, an informative prior was used for the heterogeneity parameter in the RE model to help estimate the between-study standard deviation. This informative prior was informed by Turner *et al*. for pharmacological vs placebo/control comparison for subjective outcome type.[49] All NMAs were conducted in R using the geMTC package.[50]

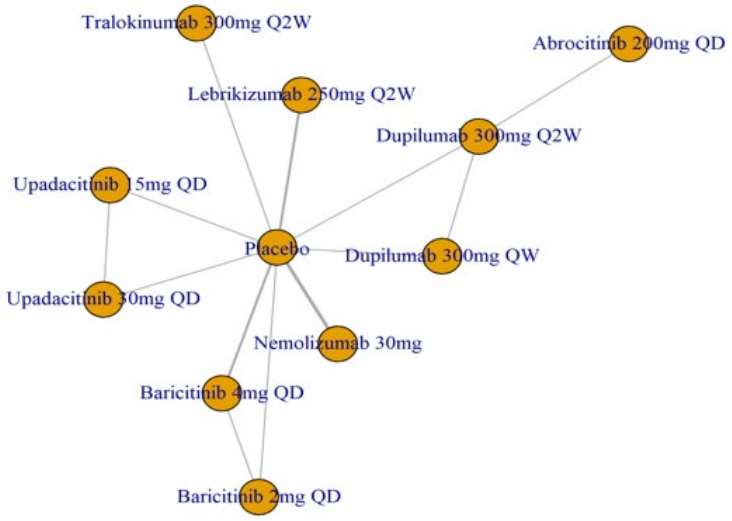
For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used with a further 50,000 iterations retained to estimate parameters. Convergence was assessed visually on the overlapping history plots of the chains. Absolute model fit was assessed by examining the total residual deviance. The fit of different models to the same data was assessed based on the deviance information criterion (DIC). Lower DIC values are favourable and the CS states that a difference in DIC between three and five suggests a meaningful difference in models. Model choice was also be determined by the presence of heterogeneity based on the I^2 statistic and model convergence.

Treatment effects are presented as ORs relative to nemolizumab for binary endpoints, with an OR less than one in favour of nemolizumab for efficacy outcomes and an OR greater than one in favour of nemolizumab for safety outcomes. Treatment effects are presented as mean differences for continuous endpoints, with a mean difference more than zero in favour of nemolizumab. The results used in economic modelling (i.e., EASI-75) are presented below. The results for other outcomes can be found in CS Appendix M.

3.4.2.1 Second-line adult population

The network diagram for EASI-75 at Week 16 in the second-line adult population is reproduced in Figure 6. FE and RE models with both vague and informative priors for the heterogeneity parameter were performed. All models had similar DIC with range of 3 points amongst the values. All models show low levels of heterogeneity based on the I^2 statistic. The CS presented results based on RE model with an informative prior, in line with the preference expressed in TA814.[25]

Figure 6: Network diagram for EASI-75 at Week 16 in second-line adult population (reproduced from CS Appendix M Figure 38)



Abbreviations: QD, once daily; Q2W, once every 2 weeks

Figure 7 shows the forest plot for the EASI-75 outcome in the second-line adult population. [redacted]

Figure 7: Forest plot of relative effects versus nemolizumab for EASI-75 responders at 16 weeks in second-line adult population for random effects model with informative priors (reproduced from CS Appendix M Figure 39)

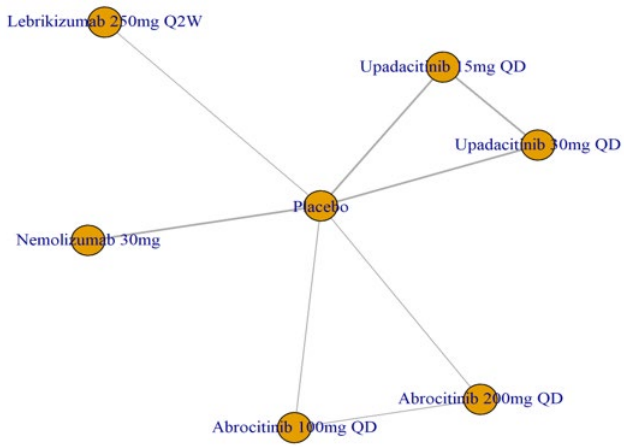
Abbreviations: CrI, credible interval; OR, odds ratio; QD, once daily; Q2W, once every 2 weeks

The company presented the results of NMAs for safety endpoints in CS Appendix M. The EAG summaries the results here.

3.4.2.2 First-line adolescent population

The network diagram for EASI-75 at Week 16 in first-line adolescent population is reproduced in Figure 8. FE and RE models with both vague and informative priors for the heterogeneity parameter were performed. All models had similar DIC with range of 3 points between the values. All models show low levels of heterogeneity based on the I^2 statistic. The CS presented results based on RE model with an informative prior, in line with the preference expressed in TA814.[25]

Figure 8: Network diagram for EASI-75 at Week 16 in first-line adolescent population (reproduced from CS Appendix M Figure 70)



Abbreviations: QD, once daily; Q2W, once every 2 weeks

Figure 9 shows the forest plot for the EASI-75 outcome in the first-line adolescent population.

[redacted]

Figure 9: Forest plot of relative effects versus nemolizumab for EASI-75 responders at 16 weeks in first-line adolescent population for random effects model with informative priors (reproduced from CS Appendix M Figure 71)

[redacted]

Abbreviations: CrI, credible interval; OR, odds ratio; QD, once daily; Q2W, once every 2 weeks

The company presented the results of NMAs for safety endpoints in CS Appendix M. The EAG summaries the results here. [redacted]

3.4.3 Critique of the company's NMA

3.4.3.1 Data used in the NMA

The NMA for the second-line adult population for EASI-75 responders at 16 weeks included studies that have both adolescent and adult populations (see Table 16). In response to clarification question A15, the company highlights that in TA814[25] the committee concluded that there are likely similarity between young people and adults in AD and that the results for adults who have tried systemic therapy would likely be generalisable to young people. The approach of using mixed adult and adolescent studies to inform the analysis for the adult population is in line with the approach used in a living NMA by Drucker *et al*.[51] In addition, the company highlights that its clinical experts advised that dupilumab and tralokinumab are used in adolescents despite the fact that the NICE appraisals for these treatments were only conducted in adult populations. Based on the above arguments, the company believes that the impact on the analysis for the second-line adult population by including studies conducted in mixed populations of adults and adolescents would be minimal. The EAG is satisfied with the company's approach.

The NMA for the second-line adult population for EASI-75 at 16 weeks also included studies that have mixed ciclosporin use (ciclosporin-naïve and ciclosporin-experienced) (see Table 16). In response to clarification question A16, the company clarified that data from RCTs with mixed ciclosporin use were only included in the analysis where subgroup data were not available. The sensitivity analysis excluding studies with mixed ciclosporin use shows consistent results with the base case analysis. The company also highlights that the subgroup analysis for the pooled ARCADIA 1 & 2 trials (CS Figure 12) shows that nemolizumab resulted in a [redacted]. Based on these reasons, the company believes that the impact on including ciclosporin-naive patients on the results would be minimal. The EAG is satisfied with the company's approach.

The company presented an NMA in the ciclosporin-naïve (first-line) adolescent population instead in the ciclosporin- experienced (second-line) adolescent population of because data for an adolescent population who had previously failed ciclosporin were not available. The results from the NMA for EASI-75 in the first-line adolescent population were used in the company's economic model as a scenario analysis. The EAG notes that the NMA results in the first-line adolescent population are quite different to the second-line adult population (the point estimates are much more in favour of the comparators in NMA in the first-line adolescent population). Because the company also presented the NMA results in the first-line adult population in CS Appendix M, the EAG is able to compare the results in the first-line adolescent population to the first-line adult population. The EAG notes that the NMA results in the first-line adolescent population is much closer to the NMA results in the first-line adult population. The EAG believes that it is uncertain if the NMA results in the first-line adolescent population are generalisable to the second-line adolescent population and presents a scenario analysis in its economic model using the NMA results in the second-line adult population to inform the treatment effects for EASI-75 in the second-line adolescent population.

3.4.3.2 Model used in the NMA

The EASI outcomes EASI-50/75/90 were analysed in separate NMAs treating the outcome as a binary endpoint. CS Appendix M states that a sensitivity analysis was performed modelling EASI-50, EASI-75, and EASI-90 together in an NMA ordinal model. The EAG asked for the results of this sensitivity analysis (clarification question A12). In response to this question, the company clarifies that this was a reporting error. The analysis based on the ordinal model was initially considered but was not conducted because the company was uncertain that the analysis was feasible.

The EAG believes that the company's model choice is not the appropriate because the data are ordered categorical, and the most appropriate approach is an NMA ordinal model. The EAG is unclear why such an NMA ordinal model analysis is not feasible. However, the EAG is not expecting a large impact on the results by treating the outcome as a binary endpoint.

3.4.3.3 Assessment of clinical equivalence

The company concludes [redacted]

3.4.3.4 Summary statistics for the treatment effect

As described in Section 3.4.2, the company conducted an NMA in which binary endpoints were converted to log odds ratios (LORs). Treatment effects were subsequently presented as odds ratios (ORs) by exponentiating the mean of the LORs for each comparator intervention versus nemolizumab 30mg QD. The EAG notes that $E[f(.)] \neq f(E[.])$ when the function is not linear and prefers to use median of the ORs as the summary statistics. The EAG has re-run the company's NMAs for EASI-75 for both the adult and adolescent populations and presents median and 95%CrI (see Section 3.5). The EAG's NMA results, and the company's results were very similar. In the EAG's economic model, the EAG's NMA results were used.

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG was able to reproduce the results of the NMA undertaken by the company for EASI-75 response in the second-line adult population and first-line adolescent population separately, using R code provided by the company in response to clarification question A19. To validate the company's methodology, the EAG carried out its own NMA in a Bayesian framework using a binomial likelihood with a logit link function for binary endpoints, performed for EASI-75 in the second-line adult population and the first-line adolescent population separately.

The EAG used RE models. Vague prior distributions were used to allow the data to dominate. In the case where there are small number of trials included in the network, an informative prior (same as what the company used) was used for the heterogeneity parameter in the RE model to help estimate the between-study standard deviation. All NMAs were conducted in WinBUGS.[52] For all outcomes, a burn-in of 20,000 iterations of the Markov chain was used with a further 30,000 iterations retained to estimate parameters.

The differences between the EAG and company's approach are (i) the EAG's approach used a binomial likelihood without converting ORs to LORs vs. the company's approach converted ORs to LORs and used a normal likelihood; (ii) median of ORs was used as the summary measurement in the EAG's NMAs vs. the exponential of the mean of LORs was used in the company's NMAs.

Overall, the EAG's NMA results were similar to the company's in both the second-line adult population and first-line adolescent population (see Figure 10 and Figure 11).

Figure 10: Forest plot of relative effects versus nemolizumab for EASI-75 responders at 16 weeks in second-line adult population from EAG's NMA

Abbreviations: CrI, credible interval; OR, odds ratio; QD, once daily; Q2W, once every 2 weeks

Figure 11: Forest plot of relative effects versus nemolizumab for EASI-75 responders at 16 weeks in first-line adolescent population from EAG's NMA

Abbreviations: CrI, credible interval; OR, odds ratio; QD, once daily; Q2W, once every 2 weeks

3.5 Conclusions of the clinical effectiveness section

The clinical evidence base supporting nemolizumab generally demonstrated significant efficacy in comparison to placebo across all ARCADIA trials with improvements in disease severity (IGA success, EASI-75), itch response (PP-NRS), sleep disturbance (SD NRS) and patient-reported outcome assessments (DLQI, POEM, EQ-5D VAS). Nemolizumab was well tolerated with low rates of TEAEs, SAEs and AEs of special interest. Discontinuations rates due to TEAEs were generally low with no deaths recorded in the ARCADIA trials. In addition, there were no important differences in safety profiles between participants with moderate-to-severe AD and those who had an inadequate response to, or where it was medically inadvisable to take ciclosporin. With longer-term follow up in ARCADIA 1 and 2 (spanning 48 weeks) and the ongoing LTE study (up to 56 weeks), no new safety concerns were identified with nemolizumab treatment.

As there are no direct comparisons of nemolizumab with other active treatments for moderate-to-severe AD, the company conducted an NMA to evaluate the comparative efficacy and safety of nemolizumab with other active approved treatments such as biologics (dupilumab, lebrikizumab, tralokinumab), and

JAK inhibitors (abrocitinib, baricitinib, upadacitinib) using published evidence from RCTs identified in a SLR. The company conducted separate NMAs for the EASI outcomes EASI-50/75/90 treating the outcome as a binary endpoint in the second-line adult population and first-line adolescent population. Despite the data being ordered categorically, the company stated that conducting a categorical NMA using a probit link function was not feasible, but the reasons why, remain unclear to the EAG.

The results from the company's NMA for EASI-75 outcome in both the second-line adult population and the first-line adolescent population were reproduced by the EAG using the company's code and validated against the EAG's own binary NMA. [redacted].

[redacted]

As noted in Section 3.2.3, the generalisability of the results from the nemolizumab trials to clinical practice in England is unclear. The patient population in the ARCADIA trials were predominantly young (mean age ranges between 33 to 38 years) and white (ARCADIA 1: 74%; ARCADIA 2: 87%[24]; ARCADIA-CYCLO: [redacted]). As noted in the CS (Section B.1.3.1.2; p22) '*…in England…AD*

prevalence was found to have a bimodal distribution across the population, peaking in patients below one year of age and ≥ 80 years old'.[26] These findings are generally supported by other UK-based sources.[27] In addition, *'There are statistically significant socio-economic and ethnicity differences in AD prevalence apparent in the UK. AD prevalence is increased in the most deprived quintile of UK patients and in patients living in an urban environment and is more than doubled in Asian and Black patients compared with White patients*'.[26] It is also important to note that the precise quantification of concomitant topical background therapy (TCS with or without TCI) was not measured in the ARCADIA trials; as such, this may have affected the responses in the nemolizumab and placebo groups.[24] Moreover, as there multiple treatment options available for people 12 years and over with AD who are candidates for systemic therapy, the exact treatment sequence for second-line systemic treatments is unclear and could be influenced by patient characteristics.

4 COST EFFECTIVENESS

This chapter represents a summary and critique of the company's health economic analyses of nemolizumab for the treatment of moderate to severe atopic dermatitis in patients 12 years and older in England who are candidates for systemic therapy and who have not responded to at least one other systemic immunosuppressive therapy, or for whom these are not suitable. Section 4.1 presents the EAG's critique of the company's review of cost-effectiveness evidence. Section 4.2 presents the summary of the company's submitted economic evaluation. Section 4.3 presents the model validation undertaken by the company whilst Section 4.4 presents the cost-effectiveness results reported by the company. Section 4.5 presents a detailed critique of the model and Section 4.6 provides the additional exploratory analyses undertaken by the EAG. Section 4.7 contains a discussion of the differences between the company's and the EAG's preferred analyses and summarises key uncertainties around the cost-effectiveness of nemolizumab.

The two key components of the economic evidence presented in the CS are: (i) a report of the company's economic evaluation and (ii) a presentation of the incremental cost effectiveness ratio (ICER) in terms of costs per QALY gained. The company also submitted a fully executable model programmed in Microsoft Excel®. Following the clarification process, the company submitted two revised versions of the model, including changes related to the PAS discount, baseline characteristics, comparators for adolescents, discontinuation probability of nemolizumab, TEAE and flare probabilities, mortality within the first year of treatment, and corrections to model programming errors that had been identified at that point. Additional scenario analyses as requested by the EAG and revised estimates of cost-effectiveness of nemolizumab are also reported. For brevity, the report will only refer to the latest version of the model (and the results) received, unless explicitly stated otherwise. Limitations identified within the model which the EAG believed would make minimal (or zero) impact on the ICERs if amended have not been formally documented for brevity reasons, but some are mentioned in passing within this report. This allows the NICE Appraisal Committee to focus on key issues.

4.1 EAG's comment on company's review of cost-effectiveness evidence

Appendices G, H and I of the CS report the literature searches for the SLRs of economic, utility and cost-resource use evidence (respectively). The EAG would anticipate considerable overlap between these reviews and the results retrieved, and indeed many STA submissions use a common search for these three SLRs, but here they are reported separately.

As with the clinical SLR, searches were undertaken in two phases, in September 2023 and May 2024. All the key databases (MEDLINE, Embase, Cochrane Library) were searched, plus the relevant additional sources PsycINFO and EconLit. Supplementary searches were conducted of relevant

conference proceedings, plus the websites of international HTA organisations, and Tufts' Cost Effectiveness Analysis registry. Search terms include relevant subject headings and free text strings, and filters to identify study types eligible for inclusion. The original submission did not acknowledge the sources of the study filters used, but the company later provided some details about these in its clarification response (A3). Overall, the searches across the three reviews appear to have been conducted to the EAG's satisfaction.

There were 45 studies which met the eligibility criteria of the SLR, of which 24 included an economic evaluation and were summarised, and quality-assessed in the CS. None specifically addressed this decision problem however could guide the company on the most appropriate model structure. Having reviewed the included papers the company concluded that the cost-effectiveness model developed for the NICE appraisal of abrocitinib, upadacitinib, and tralokinumab[8] "*provided the most comprehensive cost-effectiveness analysis of biologic and JAK inhibitor treatments for adult and adolescent patients with moderate-to-severe AD in the UK*" and "*was considered appropriate for decision making by the NICE Committee*." This model structure, which was also used in the lebrikizumab submission to NICE,[11] was used to inform the *de novo* model submitted by the company.

4.2 Description of company's health economic analysis

4.2.1 Model scope

A summary of the company's base case model is provided in Table 17. The economic analysis was undertaken from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 60-year time horizon in the base case. Unit costs were valued at a 2022/23 price year. Health outcomes and costs were discounted at a rate of 3.5% per annum as recommended by NICE.[12]

Table 17: Summary of company's base case model

Population	Patients with moderate-to-severe atopic dermatitis, aged 12 years and older, who are candidates for systemic therapy and who have not responded to at least one other systemic immunosuppressive therapy or for whom these are not suitable The population is divided into two groups in the economic analysis: • Adults (≥ 18 years) • Adolescents (≥ 12 years and < 18 years)
Time horizon	60 years, assumed to represent a patient's lifetime
Intervention	Nemolizumab + BSC
Comparators	*Adult population (≥ 18 years)* Dupilumab + BSC Abrocitinib 200 mg + BSC Upadacitinib 15 mg + BSC Upadacitinib 30 mg + BSC Baricitinib + BSC Tralokinumab + BSC Lebrikizumab + BSC *Adolescent population (≥ 12 years and < 18 years)* Abrocitinib 100 mg + BSC Abrocitinib 200 mg + BSC Upadacitinib 15 mg + BSC Lebrikizumab + BSC Dupilumab + BSC (Scenario analysis) Tralokinumab + BSC (Scenario analysis)
Outcome	Incremental costs per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum for both health outcomes and costs
Price year	2022/23

QALY: quality-adjusted life year; NHS: National Health Services; PSS: Personal Social Services; BSC: Best Supportive Care

4.2.1.1 Population

The population included in the company's model relates to patients with moderate-to-severe atopic dermatitis, aged 12 years and older, who are candidates for systemic therapy and who have not responded to at least one other systemic immunosuppressive treatment, or for whom these are not suitable. The model population is narrower than the company's anticipated full marketing authorisation of nemolizumab. The CS states that the marketing authorisation of nemolizumab was submitted to the Access Consortium (New Active Substance Work Sharing Initiative) on [redacted] and an opinion from the MHRA is expected in [redacted].[1] The economic analysis was conducted separately for adults (≥ 18 years of age) and adolescents (≥12 years of age and <18 years of age) in the company's submission. The populations are consistent with the ones from ARCADIA 1,[53] ARCADIA 2,[54] ARCADIA CYCLO[34] and LTE[55] studies. At model entry, patients are assumed to have a mean age of 34.61 years with 32.6% female in the adult population, and to have a mean age of 15.54 years with 50% female in the adolescent population.

4.2.1.2 Intervention

The intervention under consideration is nemolizumab as described in Section 2.3.2.

4.2.1.3 Comparators

The comparators are described in Section 2.3.3.

4.2.1.4 Best supportive care

BSC is composed of three main treatments: TCIs, TCSs and emollients, which is in line with the approach undertaken in TA814[25] and TA986.[11] BSC is used alongside the intervention and comparators, and also used in patients who did not respond to these treatments (see Section 4.2.4.5).

4.2.2 Model structure and logic

The company's model adopts a hybrid approach with a 1-year decision tree followed by a state-transition model with 59 annual time cycles equating to a total time horizon of 60 years.

4.2.2.1 *One-year* d*ecision tree*

Patients who enter the decision tree model are assumed to receive treatment with the appropriate intervention and induction dose for 16 weeks. At this timepoint, response is determined by whether an EASI-75 (a 75% or greater improvement in Eczema Area and Severity Index (EASI) score from baseline) was obtained. Responders continue treatment using the maintenance dose until week 52, when there is a possibility that response has been lost or that patients discontinue treatment. Non-responders discontinue treatment and move to subsequent therapy although they remain classified as non-responders regardless of response to subsequent treatment. Death within the first year has been considered by applying age-and gender-adjusted general population mortality risks to all patients in the model using data from the Office of National Statistics (ONS) life tables for England (2020-2022).[56]

Patients alive at the end of the initial year enter the state transition model (Section 4.2.2.2) in one of two health states.

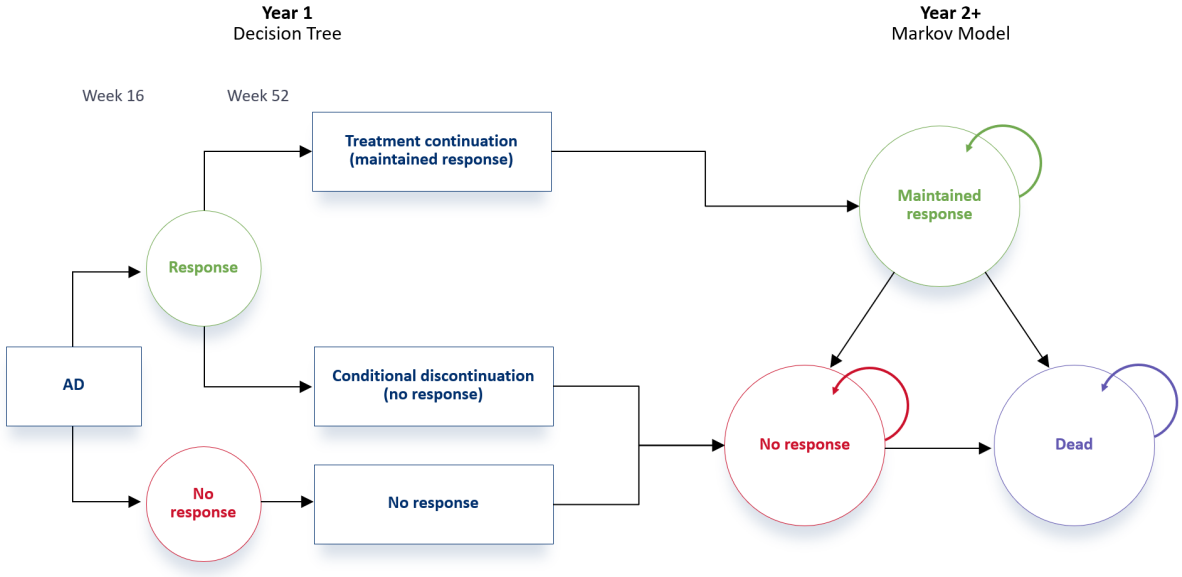
1) Maintained response – patients who responded to the initial treatment at week 16 and who neither lost response nor discontinued treatment at week 52.
2) No response – patients who did not meet the criteria for maintained response.

4.2.2.2 *State transition model*

The long-term Markov model includes three mutually exclusive and exhaustive health states: (i) maintained response, (ii) no response, and (iii) dead. The cycle length is 12 months, and a half-cycle correction is employed. The model simulates the progression of patients through these health states with

the move from maintained response to no response determined by probabilities of treatment waning and treatment discontinuation; the move from both maintained response and no response to dead being determined using general population life tables; and with dead being an absorbing health state. A schematic of the company's model is shown in Figure 12. Patients in the maintained response health state continue on initial treatment, whereas patients in the no response state are treated with a basket of subsequent therapies which is composed of BSC (TCIs, TCs and emollients), biologics and JAKi.

Figure 12: The company's model structure (reproduced from company's submission, Figure 16)



AD: atopic dermatitis

4.2.3 Key assumptions employed in the company's model

The company's base case model employs the following key assumptions:

- An agreed patient access scheme (PAS) discount of [redacted] was applied to the list price of nemolizumab.
- The Week 16 response rate for nemolizumab was informed by the proportion of patients achieving an EASI-75 at Week 16 in the ARCADIA 1 and ARCADIA 2 (for both adults and adolescents) and ARCADIA-CYCLO (for adults only).
- The Week 16 response rates for comparators were estimated based on the Week 16 response rate for nemolizumab and odds ratios (ORs) between each comparator and nemolizumab. A network meta-analysis (NMA) informs the ORs for each comparison, with the company assuming in its base case an OR of 1 when the credible intervals (CrI) crossed unity.

- At Week 16, responders remain on treatment whilst non-responders discontinue treatment and switch to a basket of subsequent treatments (which comprises biologics, JAKi and BSC) until death; those receiving subsequent treatment remain in the non-response state till death
- For responders, the probability of discontinuing treatment from all causes between week 16 and week 52 was calculated with the assumption that all non-responders discontinued at week 52. Based on TA986, these values were 3.9% for nemolizumab, dupilumab, lebrikizumab, tralokinumab and 10% for upadacitinib, baricitinib, and abrocitinib.
- In the long-term state transition model, the transition probability from the maintained response state to the no response state was based on both the annual discontinuation probability and the treatment waning probability. The EAG notes that annual discontinuation probabilities were the same as the treatment discontinuation probabilities between week 16 and week 52 in the base case. In the clarification response, the company conducted a scenario analysis in which those 36-week discontinuation probabilities were converted into 52-week probabilities to estimate the annual discontinuation probabilities.
- Based on TA814,[25] the following annual treatment waning probabilities were applied: 2% (year 2), 5% (year 3), 7% (year 4) and 8% (years 5 and later). Patients moving to the no response state would receive the subsequent therapy basket.
- The model assumed that patients with AD had the same life expectancy as the general population at the same age and sex composition.
- Utilities were independent of treatment received but were dependent on response status, time since treatment initiation and population. During the first 8 weeks of treatment the same utility value was applied to both responders and non-responders. For responders, utility increased from week 8 onward reaching a maximum value at 3 years. Non-responders had a constant utility value between week 8 and week 16 conditional on age. Following week 16, the utility for non-responders, conditional on age, was calculated depending on whether patients received additional biologics or JAKi or had BSC alone. Utilities were age-adjusted.
- The probability of flares was assumed to be treatment-dependent and age-dependent (adult or adolescent).
- Disutilities associated with treatment-emergent adverse events (TEAEs) and flares were included. Caregiver disutilities were not considered.

4.2.4 Evidence used to inform the company's model parameters

The sources of evidence used to inform the company's model parameters are summarised in Table **18**. These are discussed in detail in the subsequent sections.

Table 18: Summary of evidence used to inform the company's base case analysis

Parameter	Source
Patient characteristics (age, percentage of female and body weight)	Pooled data from the ARCADIA 1,[53] ARCADIA 2[54] for both adults and adolescents and the ARCADIA-CYCLO[34] only for adults.
Response rate at week 16	For nemolizumab: calculated using the proportion of patients achieving EASI-75 at Week 16 from the ARCADIA 1,[53] ARCADIA 2,[54] and ARCADIA-CYCLO[34] studies. For comparators: ORs were derived from an NMA conducted by the company.[1] In the base case, an OR of 1 was assumed where the CrI crossed unity.
Discontinuation of treatment in responders between week 16 and week 52.	The company used the NICE Committee's preferred assumptions in TA986,[11] which differed for biologics and JAKi.
Probability of long-term discontinuation	The company assumes that the annual long-term discontinuation probability is the same as the assumed probability of discontinuation between week 16 and week 52.
Probability of discontinuation due to treatment waning	The company used the values assumed in TA814[25]
Composition of subsequent therapy	The percentages of patients receiving BSC, biologics and JAKi were informed by clinician estimates.
Risk of death	General population life tables for England, 2020-2022[56]
TEAEs frequency	For nemolizumab: serious TEAEs from ARCADIA 1,[53] ARCADIA 2[54] studies were pooled . For comparators: based on data from clinical trials (ECZTRA 3,[57] ECZTRA 1+2[58]), published literature (Reich *et al*.,[41, 59] De Bruin-Weller *et al*.,[47] Boguniewicz *et al*.,[60] Bieber *et al*.[61] and Eichenfield *et al.*[62]) and a previous NICE TA (TA814[25]).
Probability of flares	For nemolizumab: pooled data taken from the ARCADIA 1,[53] ARCADIA 2,[54] For comparators: taken from the Measure UP 1 & 2 studies,[63] published literature (Kabashima *et al*.,[64] Reich *et al*.,[41, 59] Simpson *et al*.,[65] Silverberg *et al*.,[57] Bieber *et al*.[61]) and previous NICE TAs (TA534[10] and TA986[11])
Utilities	Health state utilities for responders (year 1 and 2) and non-responders were based on the EQ-5D-3L estimates from ARCADIA 1[53] and ARCADIA 2[54] studies (for both adults and adolescents) and ARCADIA-CYCLO[34] (for adults only). The health state utility for responders (year 3+) was based on the nemolizumab LTE study.[55] The decrements associated with disutilities were taken from an ICER report,[66] Sullivan *et al*. [67] and TA986[11]. General population utility was obtained from Hernandez Alava *et al*.[68]
Costs	NHS Reference Costs 2022/23,[69] PSSRU 2023,[70] BNF 2024[71] and TA814[25].

TA: Technology Appraisal; ITC: indirect treatment comparison; TEAE: treatment-emergent adverse event; BNF: British National Formulary; PSSRU: Personal Social Services Research Unit

4.2.4.1 Patient characteristics at model entry

The model assumes that on model entry, adult patients have a mean age of [redacted] years, a mean body weight of [redacted] kg, and that [redacted] are male. For adolescents, these values are [redacted] years, [redacted] kg, and [redacted] male, respectively. These characteristics were assumed to appropriately reflect the population of patients with moderate-to-severe AD and were taken from pooled data from the ARCADIA 1[53] and ARCADIA 2[54] (adults and adolescents) and ARCADIA-CYCLO[34] (adults only). The age of patients changes as time within the model progresses.

4.2.4.2 Response rate at Week 16

The probability of treatment response rate at Week 16 for nemolizumab was estimated based on the pooled data from ARCADIA 1[53] and ARCADIA 2[54] (adults and adolescents) and ARCADIA-CYCLO[34] (adults only). The observed proportion of nemolizumab-treated patients achieving EASI-75 at Week 16 was estimated to be [redacted] for adults and [redacted] for adolescents.

Given the absence of head-to-head RCTs comparing the effectiveness of nemolizumab versus comparators, the company conducted an NMA (See Section 3.5) with limited convergence diagnosis and output analysis (CODA) samples provided at clarification stage. The company assumed that if the CrI for the OR crossed unity, then the OR applied in the model would be fixed at 1. [redacted] All responders continue treatment whilst non-responders change to receive subsequent treatment.

4.2.4.3 Probability of responders discontinuing treatment between week 16 and week 52

The model includes the possibility that patients who respond at week 16 discontinue treatment at week 52 for any reason, including loss of response and adverse events (AEs) or any other reason. Presumably for simplicity, all such discontinuations were assumed to happen at week 52, and the probability was independent of whether patients were adults or adolescents.

The probabilities were based on the Committee's preferred assumptions in TA986[11] and was 3.9% for biologics (nemolizumab, dupilumab, tralokinumab and lebrikizumab) and 10.0% for JAKi (upadacitinib, abrocitinib and baricitinib).

4.2.4.4 Discontinuation probabilities within the state transition model

The total probability of discontinuation in the state transition model comprised of two probabilities which were applied multiplicatively. Initially, patients who discontinued treatment for all causes were

removed, and from the remaining patients, a proportion in whom treatment had waned were removed from treatment.

4.2.4.4.1 Annual discontinuation probability

The base case model applied annual discontinuation probabilities in the state transition model that were equal to the discontinuation probabilities applied between week 16 and week 52 in the decision-tree phase (3.9% for biologics and 10% for JAKi). The 36 week estimates from the decision-tree model were converted to annual probabilities in the scenario analysis and were 5.58% for biologics and 14.12% for JAKi.

4.2.4.4.2 Discontinuation due to treatment waning

Based on the approaches undertaken in TA814[25] and TA986[11], the model assumes that patients also discontinue treatment due to treatment effect waning starting from year 2. Treatment waning-related discontinuation probabilities of 2%, 5%, 7% and 8% were applied for years 2, 3, 4 and 5 and subsequent years, respectively, for all biologics and JAKi.

4.2.4.5 Best supportive care and subsequent therapies

The model assumes that all patients can receive BSC (a combination of TCI, TCS and emollients) although this is higher in responders, whereas some non-responders receive additional second-line treatment with either biologics or JAKi. These assumptions were based on clinician estimates and are presented in Table 19. These values apply regardless of the initial treatment.

Table 19: Proportion of patients receiving BSC and subsequent therapy

Concomitant medications	Responders	Non-responders
BSC		
TCIs	87.5%	77.5%
TCs	81.3%	76.3%
Emollients	91.3%	83.8%
Subsequent treatment		
Biologics (59.2% dupilumab, 40.8% tralokinumab)	0.0%	47.2%
JAKi for adult population (37.5% upadacitinib 30mg, 36.1% abrocitinib 200mg, 26.4% baricitinib)	0.0%	46.3%
JAKi for adolescent population (50.9% upadacitinib 30mg, 49.1% abrocitinib 200mg)	0.0%	46.3%

BSC: best supportive care; JAKi: Janus kinase inhibitors; TCI topical calcineurin inhibitors; TCS topical corticosteroids

4.2.4.6 Mortality

The model assumes that moderate-to-severe AD is not associated with additional mortality risk compared with the general population. Therefore, age-and gender-adjusted general population mortality

was applied to all patients in the model using data from the Office of National Statistics (ONS) life tables for England (2020-2022).[56]

4.2.4.7 Treatment-emergent adverse events

TEAEs occurring in at least 5% of patients in the intervention or comparator arm of relevant studies were included in the model. The rates of TEAEs for nemolizumab were informed by week 16 data of ARCADIA 1[53] and ARCADIA 2[54] and the rates for comparators were sourced from their respective clinical studies and the literature. See Table 20 and Table 21 for further details. The EAG notes that these are naïve indirect treatment comparisons and were not informed by the company's NMA and thus the relative differences should be treated with some caution.

The rate of TEAEs at week 16 were converted to annual rates and applied to responders continuing treatment and non-responders receiving the second-line biologics or JAKi in each model cycle. The TEAE rates are summarised in Table 20 and Table 21 for adults and adolescents, respectively. The rates of nemolizumab and lebrikizumab are similar between adults and adolescents. The EAG notes that the acne rate for tralokinumab was updated to be 0.2% for adults in the company's latest version of the model .

Table 20: TEAEs rates at Week 16 in adult population (reproduced from CS, Table 54)

Treatment	ISR	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Asthma	Source/assumption
Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54]
Upadacitinib 15 mg	0.00%	0.00%	1.15%	3.83%	7.66%	9.58%	0.00%	Reich *et al*.[23]
Upadacitinib 30 mg	0.00%	0.77%	0.77%	8.85%	7.31%	13.85%	0.00%	Reich *et al*.[23]
Lebrikizumab	2.80%	0.00%	4.80%	1.40%	0.70%	1.40%	0.00%	TA986[11]
Dupilumab	5.53%	10.60%	5.53%	2.76%	3.69%	0.00%	0.00%	De Bruin-Weller *et al*.,[47] Boguniewicz *et al*.[60]
Tralokinumab	6.70%	11.10%	0.00%	0.4%	1.50%	0.20%	0.00%	NICE TA814[25] ECZTRA 3,[57] ECZTRA 1+2[58]
Baricitinib	0.00%	0.00%	0.00%	3.60%	2.70%	3.60%	0.00%	Reich *et al*.[24]
Abrocitinib 200 mg	0.10%	1.30%	4.00%	1.80%	12.00%	6.60%	0.00%	NICE TA814,[25]Bieber *et al*.[61] (adjusted for 16 weeks)

ISR: injection site reaction; NICE: National Institute for Health and Care Excellence; TA: technology appraisal; TEAE: treatment-emergent adverse event

Table 21: TEAEs rates at Week 16 in adolescent population (reproduced from CS, Table 55)

Treatment	ISR	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Asthma	Source/assumption
Nemolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54]
Upadacitinib 15 mg	0.00%	1.33%	0.00%	0.00%	14.67%	13.33%	0.00%	Pooled Measure UP 1 & 2[63]
Lebrikizumab	2.80%	0.00%	4.80%	1.40%	0.70%	1.40%	0.00%	TA986[11]
Abrocitinib 100 mg	0.00%	0.00%	0.00%	1.10%	9.50%	3.20%	0.00%	Eichenfield *et al.*[62] (week 12 data)
Abrocitinib 200 mg	0.00%	0.00%	0.00%	2.10%	10.60%	5.30%	0.00%	Eichenfield *et al.*[62] (week 12 data)

BSC: best supportive care; ISR: injection site reaction; TEAE: treatment-emergent adverse event

4.2.4.8 Flares

Flares are a sudden worsening of symptoms. Table 22 summarises the probability of flares for each treatment at 16 weeks. These values are converted to annual probabilities applied in each model cycle and are correctly calculated for weeks 17 to 52 in the decision tree model. Responders received treatment-specific flare probabilities whilst non-responders received a probability calculated from the placebo arm in the ECZTRA 3 study.[57] The EAG notes that these are naïve indirect treatment comparisons and thus the relative differences should be treated with some caution.

Table 22: Treatment-specific flare probabilities at Week 16 in adult and adolescent populations (reproduced from CS, Table 53)

Treatment	Adults	Adolescents	Source / assumption
Nemolizumab	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54] , Kabashima *et al*.[72]
Upadacitinib 15 mg	5.30%	10.23%	Reich *et al*.,[23] Pooled Measure UP 1&2[63]
Upadacitinib 30 mg	5.40%	N/A	Reich *et al*.[23]
Lebrikizumab	4.00%	4.00%	NICE TA986[11] (ADhere week 0–16 data)
Dupilumab	5.30%	20.73%	NICE TA534[10] (adjusted for 16 weeks), Simpson *et al*.[65]
Tralokinumab	2.80%	2.80%	Silverberg *et al*.[57]
Baricitinib	5.41%	NA	Reich et al.[24]
Abrocitinib 100 mg	15.68%	15.68%	Bieber *et al*.[61] (adjusted for 16 weeks)
Abrocitinib 200 mg	6.21%	6.21%	
Placebo	10.20%	10.20%	ECZTRA 3[57]

BSC: best supportive care; TA: technology appraisal; NA: not applicable; NICE: National Institute for Health and Care Excellence

4.2.4.9 Health-related quality of life

4.2.4.9.1 Health-related quality of life associated with model health states

For adults, the company used health state utilities values based on EQ-5D-3L responses collected in the ARCADIA 1,[53] ARCADIA 2,[54] ARCADIA-CYCLO[34] and LTE[55] studies. For adolescents, values were based on responses from the ARCADIA 1, ARCADIA 2, and LTE studies. The utility values used in the company's model are summarised in Table 23.

Table 23: Summary of utility values for costs-effectiveness analysis for adult and adolescent populations (adapted from CS, Table 58, Table 59)

Health state	Utility value (adults)	Utility value (adolescents)	Reference
Baseline (weeks 0-8) all patients	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO*[34]
Maintained response health state			
Responders between weeks 9 and 52	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO*[34] (Week 16 data)
Responders in year 2	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO*[34] (Week 48 data)
Responders in year 3 and beyond	[redacted]	[redacted]	LTE[55] (Week 104 data)
No response health state			
Non-responders on BSC only (applied from week 8)	[redacted]	[redacted]	ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO*[34]
Non-responders on 2nd line biologics/JAKi	[redacted]	[redacted]	Weighted average of year 3 (and later) utility of responders and non-responders, by assuming the same efficacy as in the first line†
Weighted value for non-responders	[redacted]	[redacted]	Weighted average of utility of BSC and 2nd line biologics/JAKi treatments‡

BSC: best supportive care; JAKI: Janus kinase inhibitor
*only for adult population
†weighted across the utility of [redacted] for responders (48%) and [redacted] for non-responders (52%) among those receiving 2nd line active treatments
‡weighted across the utility of [redacted] for 93.5% (receiving active treatments) and utility of [redacted] for remaining patients (receiving BSC only)

The model assumes that utility values are not dependent on the type of treatment received but dependent on response status, time since treatment initiation and age. The model applied a constant utility to all patients between weeks 0 and 8 ([redacted] for adults and [redacted] for adolescents).

For responders, utility improved across time, reaching a maximum at 3 years. For non-responders, a constant utility value until death was applied for patients who only receive BSC ([redacted] for adults and [redacted] for adolescents). Following week 16, patients could additionally receive biologics/JAKi, for these patients, the company estimated a utility of [redacted] for adults and [redacted] for adolescents. These values are the weighted average of year 3 (and subsequent years) utility for responders and non-responders of 2nd line biologics/JAKi, assuming the efficacy of second-line biologics/JAKI is identical to first-line, and then weighting by the proportions receiving biologics / JAKi (see Table 19). All utility values were age-adjusted using Hernandez Alava *et al*.[68]

4.2.4.9.2 QALY losses due to TEAEs and flares

The company's model estimated QALY losses associated with TEAEs and flares in each model cycle using the disutility, the assumed duration of, and the proportion of patients experiencing each event. The disutilities and frequencies of these events (and source) are summarised in Table 24.

Table 24: Disutility and duration of each TEAE and flares

Event	Disutility (SE)	Event duration (years)	Source
Injection site reaction	0.004 (0.0004)	0.0055	ICER report[66]
Allergic conjunctivitis	0.03 (0.0030)	0.0192	
Infectious conjunctivitis	0.03 (0.003)	0.0192	
Oral herpes	0.05 (0.005)	0.0192	TA986[11]
Upper respiratory tract infection	0.037 (0.0037)	0.0383	
Acne	0.050 (0.0050)	0.0383	
Asthma	0.021 (0.0021)	0.0383	Sullivan *et al*. [67]
Flare	0.03 (0.003)	0.0192	TA986[11]

SE: standard error; TA: technology appraisal; ICER: Institute for Clinical and Economic Review

4.2.4.9.5 Caregiver disutility

No caregiver disutility was assumed in the model.

4.2.4.10 Costs

This section provides a description of the resource costs included in the company's model. The model included costs associated with: (i) drug acquisition and administration; (ii) subsequent therapy (BSC, with or without, second-line biologics and JAKi) (iii) disease management and monitoring and (iv) management of TEAEs and flares.

4.2.4.10.1 Acquisition and administration costs

Drug acquisition costs

The list price per pack of 1x 30 mg nemolizumab SC injection is [redacted], and the cost per pack with a PAS discount is [redacted]. The list prices of comparators were obtained from the NICE British National Formulary (BNF) 2024,[71] as recommended by NICE, are shown in Table 25.The EAG comments that there are PAS in place for the comparators which will be provided in a confidential appendix.

The dosing schedules of nemolizumab and comparators are based on the anticipated license for nemolizumab. The company assumes the same unit costs and dosing schedules between adults and adolescents, Summarised drug acquisition costs are provided in Table 25.

The EAG notes that tralokinumab may be provided with a Q4W schedule for the maintenance treatment at the prescriber's discretion, according to Summary of Product Characteristics. Therefore, the EAG provided costs for both the Q2W and Q4W regimens in EAG base case 1 allowing the Committee to form a weighted average if it desired. However, due to the uncertainty in the proportion of patients who would receive tralokinumab Q4W, the main analyses have maintained the company's Q2W schedule which will overestimate the costs of tralokinumab to an unknown degree.

Drug administration costs

For patients receiving subcutaneous therapies (nemolizumab, dupilumab, tralokinumab and lebrikizumab), the model applied a one-off administration cost of £58 in the first model cycle based on one-hour cost of a hospital-based Band 6 nurse reported in PSSRU 2023.[70] After the first training with a nurse, patients can self-administer SC injection and incur no longer administration costs. The model assumed zero administration costs for orally administered drugs (upadacitinib, abrocitinib and baricitinib).

Table 25: Drug acquisition costs per week

Treatment	Loading phase dosing	Induction phase dosing	Maintenance phase dosing	Units per pack*	Costs per pack	Loading costs (one-off costs)	Induction / maintenance average costs per week	Source
Biologics								
Nemolizumab (with PAS)	60mg x1	30mg Q4W	30mg Q8W	1	[redacted]	[redacted]	[redacted] (induction) (maintenance)	CS[1]
Dupilumab	600mg x1	300mg Q2W	300mg Q2W	2	£1,265	£1,265	£316	TA814,[25] BNF 2024[71]
Tralokinumab	600mg x1	300mg Q2W	300mg Q2W	4	£1,070	£1,070	£268	
Lebrikizumab	500mg at week 0 and 2	250mg Q2W	250mg Q4W	2	£2,271	£4,543	£568 (induction) £284 (maintenance)	
JAKi								
Upadacitinib 15mg	NA	15mg daily	15mg daily	28	£806	£0	£201	TA814,[25] BNF 2024[71]
Upadacitinib 30mg	NA	30mg daily	30mg daily	28	£1,282	£0	£320	
Baricitinib	NA	4mg daily	4mg daily	28	£806	£201	£201	
Abrocitinib 100mg	NA	100mg daily	100mg daily	28	£894	£223	£223	
Abrocitinib 200mg	NA	200mg daily	200mg daily	28	£894	£223	£223	

BNF: British National Formulary; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; TA: technology appraisal
* All units correspond to the appropriate maintenance phase dose (for example, 30mg for nemolizumab)

4.2.4.10.2 Costs of BSC and subsequent therapy

The resource use data of TCI, TCS and emollients were taken from the NICE TA814[25] and unit costs were based on BNF 2024.[71] Within the model, the BSC cost for responders was calculated as the weighted costs of TCI, TCS and emollients applied to the proportion of patients in the maintained response state taking each in each model cycle. This resulted in a BSC cost of £384 per year for responders and £750 for non-responders who were assumed to require higher drug does of TCI, TCS and emollients. More details on BSC costs are provided in Table 63 of the CS.

Responders, who have not discontinued treatment, remain on their initial treatments however, non-responders have the costs of biologics and JAKi as detailed in Table 19. These costs were estimated to be £13,426 per patient per year for adults and £13,880 per patient per year for adolescents, with patients remaining on these treatments independent of whether the patient responded to subsequent treatment.

Combining both the costs of BSC and subsequent therapy, responders remaining on treatment had additional costs of £384 per year whereas non-responders or patients who discontinued treatment had costs of £14,175 per year for adults and £14,629 for adolescents.

4.2.4.10.2 Background health state costs

Background health state costs for the maintained response and no response states include costs related to disease management and monitoring: medical appointments; accident and emergency visits; hospitalisations; phototherapy; blood tests; and psychological support. The model assumes the same costs for both adults and adolescents. Health care resource use (HCRU) data was extracted from NICE TA534[10] and TA681[9] and unit costs were from NHS Reference Costs 2022/23[69] and PSSRU 2023[70]. The frequencies of the HCRU and unit costs are summarised in Table 26. The total cost per model cycle was estimated to be £1,072 for the maintained response health state and £2,068 for the no response health state.

The EAG notes that the same annual cost for "no response" health state was applied to patients treated with subsequent therapy, regardless of their response to second-line biologics or JAKi. Whilst this assumption appears to lack face validity, the EAG believes that correction of this would have only a slight impact of the ICER for nemolizumab given the similarity of input parameters for nemolizumab compared with other biologics.

Table 26: HCRU and unit costs for disease management per year (adapted from CS, Table 64)

Resource use	Resource use per year		Unit cost	Source
	Responders	Non-responders		
Dermatologist outpatient consultation	4.320	6.000	£165	NICE TA534,[10] TA681,[9] NHS Reference Costs 2022/23, [69] and PSSRU 2023[70]
Dermatologist nurse visit	0.350	0.460	£29	
GP consultation	6.150	12.810	£49	
Accident and Emergency visit	0.021	0.082	£263	
Hospitalisation	0.017	0.130	£1,812	
Day case	0.000	0.200	£518	
Full blood count test	4.000	4.000	£3	
Phototherapy	0.000	0.060	£765	
Psychological support	0.000	0.070	£258	
Total cost per year	**£1,072**	**£2,068**	-	

GP: general practitioner; HCRU: healthcare resource use; TA: technology appraisal; PSSRU: Personal Social Services Research Unit

4.2.4.10.3 Costs of managing treatment-related adverse events and flares

Costs of TEAEs

The model includes the costs of managing TEAEs occurring in at least 5% of patients in either arm, as shown in Table 20 and Table 21. The unit costs for managing TEAEs were based on the NHS Reference Costs 2022/23,[69] PSSRU 2023[70] and BNF 2024,[71] and are summarised in Table 65 of the CS. These costs were applied to patients who remained in the maintained response health state and to those who received second-line biologics or JAKi. Table 27 provides the cost of managing TEAEs for each drug, although these are relatively small compared with drug acquisition costs.

Table 27: TEAE costs associated with each drug

Drug	Cost per cycle per adult (£)	Cost per cycle per adolescent (£)
Nemolizumab	£8	£8
Dupilumab	£65	£75
Abrocitinib 100 mg	£57	£45
Abrocitinib 200 mg	£90	£67
Upadacitinib 15 mg	£103	£133
Upadacitinib 30 mg	£141	NA
Baricitinib	£43	NA
Tralokinumab	£54	£52
Lebrikizumab	£42	£42

NA: not applicable

Costs of flares

Within the model, both responders and non-responders incur flare-related costs in each cycle. These costs were estimated based on the unit cost per flare event and the treatment-specific flare rates

summarised in Table 22. The cost of managing flares was estimated to be £10.32 per event (see Table 66 in the CS for more details).

4.2.4.10.5 Indirect costs

The company presented a scenario analysis exploring the impact of productivity loss. The annual indirect costs for responders and non-responders due to workdays lost and sleep duration reduction were calculated based on the data from the De Bruin *et al*.,[73] ONS 2023,[74] ARCADIA 1,[53] ARCADIA 2[54] and Hafner *et al*.[75] The total annual indirect costs were [redacted] for responders and [redacted] for non-responders. The EAG notes that this is outside of NICE's reference case.[12]

4.3 The company's model validation and verification

The company stated that model verification was conducted by assessing the accuracy of the programming in the executable model including reference checking of model parameters. For model face validity, the company stated that *"the model structure, key model assumptions and inputs have been validated by health economics and clinical experts specialising in the treatment of AD in a modified Delphi panel and two rounds of expert interviews"*. To assess model external validity, the company stated that the outcomes from TA814[25] were compared against the model's predicted outcomes for comparator groups.

4.4 The company's cost-effectiveness results

The CS presents base case ICERs for nemolizumab versus comparators for both adults and adolescents. Deterministic results are presented in Table 28 and Table 29. No QALY weightings were applied in the model. The company performed one-way sensitivity analysis and scenario analyses, which are not presented in this section, although key ones are incorporated in the EAG's base case.

Probabilistic ICERs were based on 1000 Monte Carlo simulations by which point the ICER had largely stabilised. Sampled values were generated by the company using CODA samples where appropriate or by assuming that standard errors (SEs) were equal to 10% of the mean where distributions were unavailable.

The EAG believes the results of PSA including the cost-effectiveness acceptability curves (CEACs), presented in Figures 17-29 of the CS, are incorrect due to a coding issue (see Section 4.5.2.1). The EAG has run PSA within its exploratory analyses.

Table 28: The company's base case results for adult population, deterministic

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£673,855	[redacted]	£673,855
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated

ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years
*at £20,000 per QALY gained threshold
† incremental costs and QALYs vs next least costly non-dominated option

Table 29: The company's base case results for adolescent population, deterministic

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated

ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years
*at £20,000 per QALY gained threshold
† incremental costs and QALYs vs next least costly non-dominated option

4.5 EAG Critique of company's submitted economic evaluation

4.5.1 Adherence to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[12] (see Table 30). Each element is discussed in further detail within the EAG report.

Table 30: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	EAG comments
Defining decision problem	The scope developed by NICE	This is aligned with the NICE Reference Case.
Comparators	As listed in the scope developed by NICE	People who have not previously had a systemic therapy were not covered in this submission and thus immunosuppressive therapies were not included as comparators. Clinical advisors consulted by the company and the EAG agreed that the positioning of nemolizumab in the second-line population is appropriate. The EAG agrees with this omission. Comparators for the population who can receive systemic therapy and who have not responded to at least one systemic immunosuppressive therapy, or for whom these are not suitable, are aligned with the NICE Reference Case.
Perspective on outcomes	All direct health effects, whether for patients or , when relevant, carers	Direct health effects for patients were used. Caregivers effects were not included.
Perspective on costs	NHS and PSS	The perspective used was that of NHS and PSS.
Type of economic evaluation	Cost-utility analysis with full incremental analysis	The results of the analyses are presented in terms of incremental costs per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between technologies being compared	The model assumed a 60-year time horizon where approximately 89% of the cohort are dead. The company conducted a scenario analysis with a 67-year time horizon where all patients are dead.

Element	Reference case	EAG comments
Synthesis of evidence on health effects	Based on systematic review	The week 16 response rate of nemolizumab was obtained from the ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO[34] studies. The company conducted an NMA to estimate ORs for the comparators. The company used the NICE Committee's preferred assumptions in TA986[11] for both the treatment discontinuation probabilities between week 16 and week 52 and the annual long-term discontinuation probabilities.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	This is aligned with the NICE Reference Case. Health gains are valued in terms of QALYs. The EQ-5D-3L was used.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	This is aligned with the NICE Reference Case with utility values reported by responders and non-responders in the ARCADIA 1,[53] ARCADIA 2[54] and ARCADIA-CYCLO[34].
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	This is aligned with the NICE Reference Case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances.	No additional QALY weighting was applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Resource costs relate to NHS and PSS. Drug costs were valued at current prices. Other resource costs were valued using estimates from NHS Reference Costs 2022/23,[69] PSSRU 2023,[70] TA534,[10] TA681,[9] TA814[25] and TA986[11].
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	This is aligned with the NICE Reference Case.

EAG: external assessment group; EQ-5D: Euroqol 5-Dimensions; NICE: national institute for health and care excellence; PSS: personal social Services; QALY: quality-adjusted life year

4.5.2 The main issues identified by the critical appraisal

Box 1: Main issues identified within the critical appraisal undertaken by the EAG

(1) Would a cost-comparison approach comparing nemolizumab with other biologics be more appropriate?
(2) Model programming errors and other minor issues
(3) Uncertainty in the relative efficacy of nemolizumab (using an OR of 1, when the difference is not statistically significant)
(4) Uncertainty in the discontinuation probability of nemolizumab
(5) Uncertainty in the criteria for having a response
(6) Uncertainty in the relative efficacy of nemolizumab in adolescents
(7) Uncertainty in the utility to use for responders in year 1 and year 2.
(8) Uncertainty in subsequent active treatments (type of treatment, response, discontinuation) for non-responders
(9) Underestimation of the costs of treatment due to half-cycle correction

4.5.2.1 Would a cost-comparison approach comparing nemolizumab with other biologics be more appropriate?

Within the revised company model's base case the input parameters for all biologics including nemolizumab are similar. Clinical advice provided to the EAG suggests that the efficacies of the biologic treatments are likely to be similar and that there would not be a marked difference in other characteristics such as AEs and the incidence of flares. As such, the EAG considers that a cost-comparison approach may have been appropriate here.

4.5.2.2 Model programming errors and other minor issues

Model Errors

(a) Time horizon

The company's base case model uses a 60-year time horizon where approximately 11% of people are still alive. The company provided a scenario analysis using a 67-year time horizon in their clarification response. The EAG believes that it would be more appropriate to set the time horizon to 67 years in the base case in order to reflect a lifetime horizon.

(b) Miscalculation of costs within weeks 16 and 52

The company's model used the number of patients in the maintenance health state at the end of week 52 to estimate the costs of those receiving maintenance treatment (either nemolizumab or comparators) and the number in the non-responder health state at week 52 to estimate those receiving subsequent treatment. The EAG believes a better approach is to half-cycle correct the number of responders (and

non-responders) between week 16 and week 52 in order to calculate treatment costs. For simplicity, the EAG assumed no one died during the first 16 weeks with all deaths in year 1 being between week 16 and week 52. The EAG has amended the company's model in the EAG's base case 2 to implement this change. The same amendment has been made for monitoring costs.

(c) Annual discontinuation probability calculation

The company's base case model used the same values for both conditional discontinuation probability between week 16 and week 52 (the 36-week discontinuation probability) and annual discontinuation probability. In the clarification response, a scenario was provided where the 36-week probability is converted to annual value for use as the annual discontinuation probability. The EAG believes that the approach in the clarification response is better.

(d) Programming error leading to independent sampling of non-responders' utility values and costs in year 1, year 2, and year 3 (and subsequent years)

The CS states that the utility for non-responders remains the same in year 1 and after, and they receive the same subsequent treatments. However, in the PSA, the values for year 1, year 2 and year 3 and onwards were sampled independently resulting in different values. The same problem exists with subsequent treatment costs. The EAG believes that the intention of the company was to have dependent samples and have amended the company's model.

(e) *Programming error in VBA code of FncSampleCODA() leading to sampling error in ORs which are not fixed at unity*

The EAG notes that there is a formula error in the VBA code of *FncSampleCODA()* which results in returning the same value in each PSA iteration for the OR for any comparison where the OR was not fixed at unity. The EAG amended the company's model to allow CODA to be sampled appropriately.

(f) Programming errors in VBA code of psaModel() and FIApsaModel() leading to returning the same deterministic values of adjusted response rates of comparators, TEAEs and flares for all iterations

The EAG notes that there is a formula error in the VBA code of *FIApsaModel()*: the code called *"Sheets("Results").Calculate"* was erroneously used in the company's model which returned the same deterministic values for all iterations in the PSA FIA Output Sheet. The EAG amended this error to record the PSA results appropriately in the PSA FIA Output Sheet.

There are also formula errors in the VBA code of *psaModel()* and *FIApsaModel()*: the code named *"Sheets("Parameter Sampling").Range("baseDemAgeUsed").Offset(i - 1, 0).Calculate*. These errors result in the deterministic values for (i) the adjusted response rates of comparators, (ii) the adjusted

TEAEs and (iii) the adjusted flare proportions being used rather than the PSA sample as the values in Column M are not updated. The EAG amended this error to run PSA appropriately.

(g) Minor error in oral herpes calculation of nemolizumab

There are formulae errors in the calculation of oral herpes events related to second-line subsequent therapies in the nemolizumab group. In the "Markov Traces- Nemolizumab" worksheet, a blank column (column A) was erroneously used instead of the number of patients treated with second-line biologics/JAKi (column AA) leading to underestimation of oral herpes cases. The EAG amended this error in the EAG's base case 2.

Other minor issues

After submitting the clarification letter, the EAG notes that some drug costs on BNF 2024 have been recently updated in Oct 2024. It was also identified that the costs in the electronic market information tool (eMIT) are less expensive than used in the company's model. Updated prices are shown in Table 31. These values are updated in the EAG's base case.

Table 31: Updated unit costs in the EAG's base case

Medication	Unit costs (Company's model)	Updated unit costs (EAG base case)	Source
Protopic 0.1% ointment, 60g	£34.16	£28.10	BNF 2024
Oilatum cream, 1L*	£5.28	£16.58	BNF 2024
Mometasone 0.1% ointment, 100g	£10.97	£2.51	eMIT 2024
Hydromol ointment, 1kg**	£5.50	£7.04	eMIT 2024
White soft paraffin, 500 g	£4.57	£2.18	eMIT 2024

BNF: British National Formulary; eMIT: electronic market information tool
*Assumed double the price of a 500ml bottle
**Assumed double the price of a 500mg tube

4.5.2.3 Uncertainty in the relative efficacy of nemolizumab compared with the comparators

The company's base case model assumes an OR of 1 when the credible intervals crossed unity for week 16 response. The EAG considers it unconventional (unless the company are putting forward a cost-comparison case) to ignore ORs informed by the NMA and prefers to use the point estimates from NMA.

4.5.2.4 Uncertainty in the discontinuation probability of nemolizumab

In calculating the discontinuation probability of nemolizumab between week 16 and week 52, the company's original model used [redacted] with the intention of using the pooled data from ARCADIA 1 and ARCADIA 2 studies. In its clarification response, the company stated that there was a calculation error, and the corrected value was [redacted]. The company updated its assumption and used 3.9% as the discontinuation probability of nemolizumab in the clarification model arguing that the assumption was changed as there was "*a relatively large discrepancy between discontinuation rates reported for other*

biologics, which does not align with the experiences and expectations of UK clinical experts", that "*It is apparent that heterogeneity in study design and exact derivation of conditional discontinuation exists, which may present a substantial impact on the discontinuation rates derived for each treatment and make direct comparison between discontinuation rates uncertain.*" and that "*it is likely that this discontinuation rate calculated for nemolizumab is an overestimate."*

The EAG's clinical advisors agreed that nemolizumab discontinuation probabilities should be similar to other biologics. Therefore, the EAG used the same discontinuation probability of nemolizumab between week 16 and week 52 in the EAG's base case and explored the impact of applying [redacted] in the exploratory sensitivity analysis.

4.5.2.5 Uncertainty in the criteria for having a response

The EAG notes that in the TA814,[25] the criteria for response was an EASI-50 and 4 or more points improvement on the DLQI. The EAG used this value for nemolizumab assuming that the ORs associated with an EASI-75 were generalisable to responses defined as an EASI-50 and 4 or more points improvement on the DLQI.

4.5.2.6 Uncertainty in the relative efficacy of nemolizumab in adolescents

The EAG notes that the ORs calculated for adult patients include studies that recruited adolescents. Given the smaller amount of data in adolescents only, the EAG explored the impact of assuming that the ORs for adults were generalisable to adolescents.

4.5.2.7 Uncertainty in the utility to use for responders in year 1 and year 2

In the adolescent population, the company used observed utility at week 16 to represent utility within year 1 and used observed utility values at week 48 to represent utility within year 2 and used observed utility at week 104 for year 3 onwards. For adults, utility was based on week 16 data for year 1, week 104 for years 3 onwards and the average of week 16 and week 104 data for year 2. The EAG believes this may not correctly characterise the change in utility over time and preferred to use the average of the utility at weeks 16 and 48 for year 1, and the average between weeks 48 and 104 for year 2. As utility values were not collected for adults at week 48, this was estimated assuming that the ratios in utility between week 16 and week 48, and between week 48 and week 104 for adolescents were generalisable to adults.

Table 32: Utility values used in the EAG's base case 2

	Adult population		Adolescent population	
	Company's base case	**EAG's base case 2**	**Company's base case**	**EAG's base case 2**
Year 1 utility	[redacted]	[redacted]	[redacted]	[redacted]
Year 2 utility	[redacted]	[redacted]	[redacted]	[redacted]
Year 3 utility	[redacted]	[redacted]	[redacted]	[redacted]

4.5.2.8 Uncertainty in subsequent active treatments for non-responders

The company's base case model assumed 93% of non-responders receive either biologics or JAKi as subsequent therapy. The indefinite treatment was assumed over their lifetime regardless of treatment response, treatment discontinuation or potential treatment waning. The clarification response stated that based on clinical opinions received by the company, non-responders were assumed to switch between different active treatments (instead of receiving BSC alone, patients would remain on active treatment until death). The EAG notes that the company appears to be modelling steady state treatment of the cohort. Exploratory analyses undertaken by the EAG shows that changing the assumed costs and utility associated with subsequent treatments within plausible ranges only had a moderate impact on the incremental net monetary benefit (iNMB) and therefore any limitations in the methodology for modelling subsequent treatments have been ignored.

4.5.2.9 Slight underestimation of the costs of treatment due to half-cycle correction

In the company's model, half cycle correction was employed when calculating the acquisition costs of interventions. This will lead to a slight underestimation of these costs as they were based on the average number of the patients who begin the treatment cycle and the number who receive the next treatment cycle . For example, if 1000 patients receive treatment in cycle 1 and 800 patients receive treatment in cycle 2, the company's method would apply the costs of treatment to 900 patients in cycle 1, rather than 1000. However, due to the yearly time cycle, which incorporates many rounds of treatment, and the fact that this limitation applies to all interventions within the model, the EAG has not attempted to correct the methodology.

4.6 Exploratory analyses undertaken by the EAG

4.6.1 Overview of the EAG's exploratory analyses

All analyses presented in this section reflect the PAS price of nemolizumab and the list price of comparators; analyses using the PAS price for comparators are provided for the Appraisal Committee in a confidential appendix.

The EAG present two base cases. The first base case is assuming that the efficacies of the biologics (including nemolizumab) are identical, and that costs except drug acquisition costs are similar which allows an approach akin to NICE's cost-comparison route. This method is not dissimilar to the

company's base case where any non-statistically significant difference in ORs were assumed to have equal efficacy and where the costs of flares and AEs are of small magnitude compared with the costs of the interventions.

The second base case uses the more traditional approach of using the estimated ORs, rather than assuming that the value was unity if the difference was not statistically significant. The EAG undertook exploratory analyses (EA) to address the key points identified within the critical appraisal. The EAG has only made changes to the company's base case when it believes there is a strong justification to change the company's assumption or value. The EAG's base case 2 differs from the company's base case in only two aspects: (i) correction of model errors and amendments to improve upon minor issues and (ii) using the estimates of ORs for the week 16 response rate of comparators without setting the ORs for non-statistically significant credible intervals to unity. Exploratory sensitivity analyses (SA) using the EAG's base case 2 are provided for the NICE Appraisal Committee to consider. All SAs were undertaken using the deterministic version of the model, although probabilistic ICERs were also generated for the EAG's base case 2. The EAs and SAs are described in Section 4.6.2 with the results presented in Section 4.6.3.

4.6.2 EAG's exploratory analyses – methods

The following changes were made to the company's base case to inform EAG base case 2. Appendix 1 details how these can be implemented in the company's model.

EA1 Correction of errors and amendments to improve upon minor issues

The following corrections were applied to the company's updated base case within a single combined analysis.

a. The EAG set the model time horizon to 67 years instead of 60 years.
b. Half-cycle correction was applied within the first year of the treatment. The EAG made the amendment of formulas in the Markov traces sheets, cells Z15, AB15, AY15 and BA15, detailed in Appendix 1.
c. The EAG used the company's scenario analysis where annual discontinuation probabilities are calculated from the 36-week discontinuation probability between week 16 and week 52.
d. The EAG amended formulas in the Parameters Sampling sheet, J236:J237 and J370:J378, to ensure that the non-responders utilities in years 1 and later are the same in each PSA iteration and subsequent treatment costs are the same for both intervention and comparators in each PSA iteration, respectively.
e. The EAG amended the VBA code to ensure that the values are correctly drawn from the EAG's CODA samples in each PSA iteration where the ORs was not fixed at unity.
f. The EAG corrected the VBA code for *FIApsaModel()* to ensure that the values are correctly drawn from the PSA samples and saved in the PSA FIA Output sheet.

g. The EAG updated the unit costs of some BSC drugs, as shown in
h. Table 31.
i. The EAG used the average of the utility at weeks 16 and 48 for year 1, and the average between weeks 48 and 104 for year 2. The utility value for adults at week 48 was estimated assuming that the ratios in utility between week 16 and week 48, and between week 48 and week 104 for adolescents were generalisable to adults (see Table 32).
j. The EAG corrected the formulae in the "Markov Traces - Nemolizumab" sheet, cells AQ15:AQ114, to ensure that the number of patients treated with subsequent therapies were used to estimate the oral herpes events related to the second-line biologics/JAKi.

EA2 Using the ORs for the week 16 response rate of comparators without setting the ORs for non-statistically significant credible intervals to unity

The EAG use the treatment-specific estimates from the EAG's NMA for the ORs of comparators for the week 16 response rate. The values are summarised in Figure 10 and Figure 11 for adults and adolescents, respectively.

EAG base case 2 combines EA1 and EA2. Results are presented using both the deterministic and probabilistic versions of the model.

The following EAG's additional sensitivity analyses (SA) were undertaken using the EAG's base case 2. Appendix 1 details how these can be implemented in the company's model.

SA1 Uncertainty in the efficacy of nemolizumab

In this scenario, the EAG used the week 16 response rate of nemolizumab based on the EASI-50 and DLQI ≥ 4. Results are not presented for adolescents as the company provided response rates based on EASI-50 and DLQI ≥ 4 for adults only, which was [redacted] and therefore this analysis was only undertaken for adults. The relative efficacies of the comparators were assumed to be generalisable from the EASI-75 analysis (see Figure 10).

SA2 Uncertainty in the discontinuation probability of nemolizumab

The EAG set the conditional discontinuation probability of nemolizumab between week 16 and week 52 to [redacted] which is based on the pooled data from ARCADIA 1 and ARCADIA 2, whilst maintaining the discontinuation probability for other biologics at 3.9%. Whilst the clinical advice to the EAG suggests that assuming the same value for all biologics is reasonable, the EAG noted that the company preferred to use a nemolizumab-specific value in its initial base case, and only changed to the 3.9% value once the nemolizumab value was acknowledged to be higher than this.

SA3 Uncertainty in relative efficacy of nemolizumab in the adolescent population

The EAG set the ORs for the week 16 response rate of comparators in adolescents the same as in adults based on EAG's NMA (see Figure 10).

4.6.3 Results of the EAG's exploratory analyses

The results of the EAG's base case 1, a cost comparison analysis, are provided in Table 33. In this analysis, nemolizumab has the lowest cost of all biologic treatments.

Table 33: Costs for drug acquisition per patient for nemolizumab and biologic comparators

Cost per patient	Nemolizumab (including PAS)	Lebrikizumab (list price)	Dupilumab (list price)	Tralokinumab with Q2W maintenance dosing schedule (list price)	Tralokinumab with Q4W maintenance dosing schedule (list price)
Total acquisition costs in year 1*	[redacted]	£22,713	£17,708	£14,980	£10,165
Total acquisition costs per year (year 2 onwards)	[redacted]	£14,814	£16,500	£13,958	£6,979

PAS: Patient Access Scheme; Q2W: Every 2 weeks; Q4W: Every 4 weeks
*including loading, induction and maintenance doses

The results of EAG base case 2 are provided in Table 34 for adult patients and Table 35 for adolescent patients, although the costs of tralokinumab may be overestimated as detailed in Section 4.2.4.10.1. Sensitivity analyses are provided in Table 36 for adult patients and Table 37 for adolescent patients. The incremental NMB, assuming a cost per QALY threshold of £20,000 and ICERs for each comparator against nemolizumab are also presented.

The EAG's probabilistic analyses indicated the nemolizumab had a 98% chance, or greater, of being cost-effective at all willingness to pay values up to £55,000 per QALY gained in adults and had a 97% chance at £20,000 per QALY gained in adolescents (96% at £30,000 per QALY gained).

Table 34: EAG's exploratory analysis, full incremental analysis results, adult population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£673,855	[redacted]	£673,855
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA1: correction of model errors							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£1,108,189	[redacted]	£1,108,189
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA2: Applying ORs for response at 16 weeks from the NMA for all comparators instead of setting the ORs to unity when credible interval crosses unity							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£810,681
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£741,096
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,274,424
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£581,640	[redacted]	£581,640
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,203,560
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£553,553	[redacted]	£553,553
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,189,283
EAG's base case 2: combined EA1 and EA2, probabilistic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,592,848
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£542,618	[redacted]	£542,618
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,213,886

EA: exploratory analysis; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 35: EAG's exploratory analysis, full incremental analysis results, adolescent population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA1: Correction of model errors							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EA2: Applying ORs for response at 16 weeks from the NMA for all comparators instead of setting the ORs to unity when credible interval crosses unity							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£423,236
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£868,590
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£118,524	[redacted]	£118,524
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£426,020
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,832,902
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£416,634
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£119,625	[redacted]	£119,625
EAG's base case 2: combined EA1 and EA2, probabilistic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£10,674,435
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£396,158
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£132,056	[redacted]	£132,056

EA: exploratory analysis; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 36: EAG's exploratory sensitivity analysis, full incremental analysis results, adult population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,203,560
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£553,553	[redacted]	£553,553
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,189,283
SA1: the week 16 response rate of nemolizumab based on the EASI-50 and DLQI ≥ 4							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£2,637,323
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£632,372	[redacted]	£632,372
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,333,550
SA2: both short-term and annual discontinuation probabilities of nemolizumab based on ARCADIA 1 & 2							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£2,775	[redacted]	£2,775
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£39,973
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	£154,116
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£153,807
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£131,190
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£342,277	[redacted]	£112,352
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£136,976

EA: exploratory analysis; SA: sensitivity analysis; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 37: EAG's exploratory sensitivity analysis, full incremental analysis results, adolescent population

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 2: combined EA1 and EA2, deterministic							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,832,902
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£416,634
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£119,625	[redacted]	£119,625
SA2: both short-term and annual discontinuation probabilities of nemolizumab based on ARCADIA 1 & 2							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£21,637
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£30,319
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£134,611
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£89,090
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£80,027	[redacted]	£49,257
SA3: Applying the ORs for adults to adolescents							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£551,422
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£416,303	[redacted]	£416,303
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£908,679

EA: exploratory analysis; SA: sensitivity analysis; ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £20,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

4.7 Discussion

In terms of the clinical evidence submitted by the company, no major concerns were noted by the EAG. Other issues have been discussed throughout Section 3. Clinical advice to the EAG has suggested that the most appropriate treatment may be based on an individual patient's characteristics and that adding nemolizumab as a treatment option would be beneficial.

In terms of cost-effectiveness, the EAG believes that this appraisal may have been best undertaken via a cost-comparison approach and has provided in its base case 1 a simple comparison of the anticipated acquisitions costs of nemolizumab and biologic comparators over the first and subsequent years. In this analysis, nemolizumab has the lowest cost of all biologic treatments, although this was using the PAS price of nemolizumab and the list price of the comparators.

In base case 2, the EAG corrected errors and amended minor limitations in the company's model (which had a slight impact on the ICERs) and used the ORs from its NMA rather than maintain the company's preference that efficacy should be considered equal if the credible intervals crossed unity. The probabilistic results for the EAG base case for adult patients produced an efficiency frontier containing nemolizumab and dupilumab, with dupilumab having an ICER compared with nemolizumab of £542,618. For adolescent patients produced an efficiency frontier containing nemolizumab and lebrikizumab, with lebrikizumab having an ICER compared with nemolizumab of £132,056. The change in the drugs on the efficiency frontier is due to the different ORs generated by the EAG's NMA for adult and adolescent patients.

Scenario analyses undertaken by the EAG suggests that assumptions relating to the discontinuation probability for nemolizumab has a big impact on the ICERs. When the values observed in ARCADIA 1 and ARCADIA 2 are used, in SA2, rather than assuming the same value for all biologics as in base case 2, the efficiency frontier becomes nemolizumab, upadacitinib 15mg and dupilumab for adults, and becomes upadacitinib 15mg and lebrikizumab for adolescents. In adults, the ICER for upadacitinib 15mg was below £20,000 per QALY gained compared with nemolizumab, with the ICER for dupilumab compared to upadacitinib 15mg being above £340,000 per QALY. In adolescents, the efficiency frontier was upadacitinib 15mg and lebrikizumab, with the ICER for lebrikizumab being above £49,000 per QALY. However, clinical advisors to the EAG were content to assume the same discontinuation probability for all biologic treatments which would mean that SA2 is not relevant.

When the ORs assumed for adults were used in the adolescent population, SA3, the efficiency frontier becomes nemolizumab and dupilumab; the ICER for dupilumab compared with nemolizumab is greater than £400,000 per QALY gained.

5 SEVERITY MODIFIERS

The company states that nemolizumab does not meet the criteria for obtaining a severity weighting as neither the absolute QALY shortfall (of 12 or more) nor the proportionate QALY shortfall (of more than 0.85) are met. The EAG agrees with the company's assessment.

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7. APPENDICES

Appendix 1: Technical appendix – instructions for implementing the EAG's exploratory analyses within the company's model

Scenario		Instructions
EAG exploratory analysis	1	Set Z26:Z32 in the "Home" worksheet to "TRUE".
	2	Set Z33 in the "Home" worksheet to "TRUE", then run the macro called "EA2". To uncheck this scenario, set Z33 to "FALSE", then run the macro called "EA2" again.
EAG sensitivity analysis	1	Set Z36 in the "Home" worksheet to "TRUE"
	2	Set Z38 in the "Home" worksheet to "TRUE"
	3	Set Z40 in the "Home" worksheet to "TRUE", then run the macro called "EA2". To uncheck this scenario, set Z40 to "FALSE", then run the macro called "EA2" again.

Single Technology Appraisal

Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID6221]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 8 January 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.3, pages 11–12, Table 3 and 4 – the abbreviation 'EA' is not explained in the footnotes to the tables.	Explanation of this term (presumable exploratory analysis) should be added to the footnotes.	Unclear abbreviations may lead to misinterpretation of the table content.	The EAG has amended the text as suggested.
Section 2.3.4, page 16 – the report as written only states EASI as an included measure of disease severity and symptom control in the trials. This is incorrect.	We propose that the text be amended to indicate EASI and at least one other measure be given as examples: 'The company includes the following outcomes: measures of disease severity and symptom control (e.g., Eczema Area and Severity Index [EASI] response; Investigator's Global Assessment [IGA], Peak Pruritus Numeric Rating Scale [PP NRS]).	As written, this section would mislead the reader to think that only one measure of clinical efficacy is included within the company submission.	The EAG has amended the text as suggested.
Section 3.2.3, page 26, Figure 3 – the explanations for the abbreviations PP NRS and EASI 75 are missing from the footnote.	The following abbreviations should be added to the footnote: EASI, Eczema Area Severity Index; PP NRS, Peak Pruritus Numeric Rating Scale.	Unclear explanations of the used abbreviations (in this case clinical endpoints) may	The EAG has amended the text as suggested.

		prevent readers from interpreting the Figure accurately.	
Section 3.4.2, page 51 – “and as mean differences for continuous endpoints, with a mean difference more than one in favour of nemolizumab”.	Amend sentence to “and as mean differences for continuous endpoints, with a mean difference more than zero in favour of nemolizumab”.	Methodological error	The EAG has amended the text as suggested.
Section 3.4.2.2, Page 54, Figure 8 – The Figure heading contains a mistake	The heading should read (reproduced from CS Appendix M Figure 70).	By not indicating the figure was taken from Appendix M this may lead to confusion over which figure is being reproduced in the EAG report.	The EAG has amended the text as suggested.
Section 3.4.2.2, page 54 and section 3.5, page 59 – error in upadacitinib 30 mg QD upper CrI. ’24.07’	The value of ‘24.07’ should be amended to 25.07.	Typographical error	The EAG has amended the text as suggested.
Section 4, page 61 – ‘Section 4.1 presents the EAG’s critique of the company’s review of cost-effectiveness evidence. Section 4.2 presents the summary of the company’s submitted economic evaluation. Section 4.3 presents a	The text does not align with the navigation pane in the document. Therefore, the text should be updated to ‘Section 4.1 presents the EAG’s critique	Typographical error	The EAG has amended this text so that all sub-sections are listed, and has corrected the

detailed critique of the model and Section 4.4 provides the additional exploratory analyses undertaken by the EAG'	of the company's review of cost-effectiveness evidence. Section 4.2 presents the summary of the company's submitted economic evaluation. Section 4.5 presents a detailed critique of the model and Section 4.6 provides the additional exploratory analyses undertaken by the EAG.'		typographical errors identified by the company.
Section 4.2.1.1, page 63, line 7 and Table 17 – incorrect spelling 'systematic'	Change to 'systemic immunosuppressive therapy'.	Typographical error	The EAG has amended the text as suggested.
Section 3.4.3.2 and 3.4.3.3., page 56, lines 22 and 33 – incorrect abbreviation ERG	Change to 'EAG'.	Typographical error	The EAG has amended the text as suggested.
Section 4.5.1, page 80, Table 30, 'comparators' – incorrect spelling 'systematic'	Change to 'systemic therapy' and 'systemic immunosuppressive therapy' respectively.	Typographical error	The EAG has amended the text as suggested.
Section 4.5.2.2, (b), page 82 - 'at the end of the end of'	Change to 'at the end of'.	Typographical error	The EAG has amended the text as suggested.
Section 4.5.2.2, (f), page 83 - 'There are also formula errors in the VBA code of *psaModel()* and *FIApsaModel()*: the code	Text should be deleted	The values in column M are calculated based	The EAG does not agree with the company's comments.

named *“Sheets("Parameter Sampling").Range("baseDemAgeUsed").Offset(i - 1, 0).Calculate*. These errors result in the deterministic values for (i) the adjusted response rates of comparators, (ii) the adjusted TEAEs and (iii) the adjusted flare proportions being used rather than the PSA sample as the values in Column M are not updated’		on values in column J, which are varied within PSA. Therefore, the values in column M change simultaneously within PSA and there is no need to recalculate them separately.	Within the PSA, the values in column M of the “Parameter Sampling” sheet are not varied. The EAG suggests confirming this error by using the following approach. Set all parameters for PSA in the ‘Parameter Sampling’ sheet to “No” (column F) except for F200:F219. Set cells G419:G426 (second-line TEAEs and flares) to zero. Run the PSA macro. It can be seen that the values in PSA Output are identical for all PSA iterations. As an aside, the EAG notes that there is a calculation error in the ‘PSA results’ worksheet where cell

			D10 adds cells AG8:AJ8 from the 'PSA Output' worksheet, however the QALY impacts of AEs and flares should be subtracted. The same mistake is in E10 of 'PSA Results'. These calculations are conducted correctly in the 'PSA Output' worksheet.
Section 4.7, page 94 – 'The probabilistic results for the EAG base case for adult patients produced an efficiency frontier containing nemolizumab and dupilumab, with dupilumab having an ICER compared with nemolizumab of £627,390.'	The probabilistic ICER for dupilumab does not align with the probabilistic ICER presented in Table 3 and Table 34.	Typographical error	The EAG has amended the text so that the values presented are consistent.
Inconsistent spelling of ciclosporin throughout document	Amend document so that ciclosporin is spelled consistently.	Typographical error	All instances of 'cyclosporin' have been changed to 'ciclosporin' apart from in the references.

Issue 2 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.3, Table 3 and Table 4, pages 11-12 and Section 4.6.3, Table 34 and 35, pages 90 – 91 - Unable to replicate the EA1: Correction of model error results	In both the adult and adolescent populations, the Company are unable to replicate the results for EA1: Correction of model errors in the model shared by the EAG so want to confirm that there are no typographical errors in the results table.	Confirm model results reflect the model shared by the EAG.	The EAG can confirm that there are no typographical errors in the results table. The EAG is not clear why the Company could not replicate the results for EA1. The EAG believes that EA1 can be implemented as instructed in the technical appendix. If cells Z26:Z32 in the "Home" worksheet are set to "TRUE", it will return the same results as reported in tables. As was instructed for EA2, please ensure the macro called "EA2" is re-run when you want to uncheck EA2. As an aside, the EAG added additional instructions to run SA3 for clarity in the technical appendix.

Section 2.3.3, page 16 – 'Upadacitinib has two strengths (15mg and 30mg) as does abrocitinib (100mg and 200mg) whereas baricitinib comes only in 4mg tablets.'	Amend as follows – 'Upadacitinib has two strengths (15mg and 30mg) as does abrocitinib (100mg and 200mg) whereas baricitinib comes only in 4mg tablets. The recommended dose for upadacitinib in adolescents weighing at least 40 kg is 15 mg.'	The text should make clear that the 30mg dose of upadacitinib is recommended in adults only.	The EAG has amended the text for clarity. *"Upadacitinib has two strengths (15mg and 30mg) with the recommended dose for adolescents weighing at least 40 kg is 15 mg, as does abrocitinib (100mg and 200mg) whereas baricitinib comes only in 4mg tablets."*
Section 3.2.3, pages 25–27 – unclear description of best supportive care (BSC) permitted in the ARCADIA trials 'along with BSC and concomitant background TCS/TCI'.	Amend as follow – 'best supportive care (BSC) (includes emollients, moisturisers, TCSs, and TCIs)'	The EAG statement reads as if BSC does not include TCSs/TCIs. In the ARCADIA trials permitted medications included basic skin care, moisturisers, bleach baths, topical therapies (TCS/TCI), topical anaesthetics, and antihistamines. In the UK, BSC represents the foundational therapy options upon which	The EAG has amended the text as suggested for clarity.

		systemic treatment lines are added, based on response to therapy or disease flaring. Initially, emollients and moisturisers are used to protect and restore the skin barrier, relieve dryness and reduce itch.[1] They continue to be used at all disease severity stages. TCSs and/or TCIs are introduced when emollients are insufficient to achieve adequate disease control. They may be used as an acute response or proactively to prevent flares and retain disease control.[2,3] Clinicians may choose to use a maintenance	

		regimen of TCSs for long-term, proactive use, either step-down treatment or intermittent therapy.[4] TCIs are typically introduced after TCSs for UK patients who do not adequately respond, or may be introduced following emollients where TCS use is contraindicated.[3]	
Section 3.2.3, page 28, lines 30–32, and Section 3.5, page 60, lines 6–8 – clarification required on the following statement 'It is also important to note that the precise quantification of concomitant topical background therapy (TCS with or without TCI) was not measured in the ARCADIA trials; as such, this may have affected the placebo response or	Amend sentence as follows – 'It is also important to note that the precise quantification of concomitant topical background therapy (TCS with or without TCI) was not measured in the ARCADIA trials, and this uncertainty may have affected the placebo or nemolizumab response.'	The EAG statement does not make it clear that 'not precisely quantifying concomitant topical background therapy' is as likely to affect placebo as it is to affect nemolizumab responses. The EAG statement	The EAG has amended the text as suggested for clarity.

improved response in the nemolizumab group.’	.	implies that there may be a bias in favour of nemolizumab. At the beginning of the ARCADIA trial the participants applied moisturiser at least once daily and an authorised background topical therapy (including a medium-potency TCS for the body and a low-potency TCS or a TCI for sensitive areas such as the face, neck, and intertriginous areas) for use throughout the study. Higher potency TCS were used as rescue therapy. In ARCADIA 1 & 2 a key secondary endpoint included	

		‘Number of days free of topical AD therapy throughout the initial treatment period (day 1 to week 16)’. In both trials, a numerically greater mean number of days free of topical AD therapy was observed in the nemolizumab treatment group versus the placebo treatment group at each visit through Week 16. The data is available in the relevant clinical study reports, Section 11.4.1.3.9.[5,6]	
Section 3.2.3, page 30 – ‘EAG considers the LTE study to be at high risk of bias.’	Amend the sentence as follows – ‘Due to the noted limitations, the EAG considers the LTE study to be at high risk of bias. However, the LTE data is only used to demonstrate the long-term safety profile of nemolizumab	The company is aware of the limitation of the LTE study. The study was designed to address the	The EAG has amended the text as suggested for clarity.

	and provide additional utility inputs (EQ-5D-3L scores) to those from derived from ARCADIA 1 & 2 for inclusion in the CS economic model.'	primary objective – long-term safety of nemolizumab in adult and adolescent participants with moderate-to-severe AD. Inclusion of the additional text will make it clear that only relevant data from the LTE has been included in the CS e.g., safety and utility values, as opposed to efficacy data.	
Section 3.4.2, page 51, - 'Treatment effects are presented as ORs for binary endpoints with an OR less than one in favour of nemolizumab'.	Amend sentence to 'Treatment effects are presented as ORs relative to nemolizumab for binary endpoints with an OR less than one in favour of nemolizumab for efficacy outcomes and an OR greater than one in favour of nemolizumab for safety outcomes'	Clarification of interpretation of OR depending on whether increase in response is favourable (as for efficacy endpoints) or unfavourable (as for safety endpoints).	The EAG amended the text as suggested for clarity.

Section 4.4, page 78 - 'the cost-effectiveness acceptability curves (CEACs) reported were incorrect as these did not consider all options simultaneously and summed to more than 1.'	Amend the sentence as follows – 'The cost-effectiveness acceptability curves (CEACs) reported incorrect results due to programming errors in PSA module'.	The CEACs were aligned with PSA results and considered all options simultaneously. However, the probability of being cost-effective was 0% for all comparators, thus the lines for comparators were not visible (all lying at 0%) and the line for the intervention was at 100%	The EAG has amended the text for clarity. *"The EAG believes the results of PSA including the cost-effectiveness acceptability curves (CEACs), presented in Figures 17-29 of the CS, are incorrect due to a coding issue (see Section 4.5.2.1)."*
Section 4.5.2.2, (b), page 82 - 'The company's model used the values associated with the numbers in each health states at the end of the end of the decision tree (year 1). By using this number, the company has underestimated the costs associated with the maintenance state'	Text should be amended to state that costs are not underestimated within the company's approach. Although patients are split into health states for the first year of the model, for the first 16 weeks treatment the cost of initial treatment (biologic or JAK inhibitor) is assigned to all patients in both the maintained response and no response health states.	Based on the model structure, in year 1 patients are split into the maintained response or no response health states. However, in year 1 all patients received initial treatment and	<u>Section 4.5.2.2, (b)</u> The EAG agrees that the treatment costs during the induction period (first 16 weeks) are not underestimated. However, the EAG does not agree with the company's comments for the remaining 36 weeks of year 1. The EAG believes the best estimate of number of responders

Section 4.5.2.9, page 86 'In the company's model, half cycle correction was employed when calculating the acquisition costs of interventions. This will lead to an underestimation of these costs as all patients receiving treatment at the start of a treatment cycle would receive the drug, not the average of the patients who begin the treatment cycle and those who receive the next treatment cycle'		incurred treatment costs for the first 16 weeks, i.e., treatment cost was assigned to all alive patients. For the remaining 36 weeks of year 1, only responders continued the initial treatment and incurred these treatment costs. Whereas non-responders, receive subsequent treatment and incurred the relevant treatment costs. Therefore, the treatment costs for the maintained response health state are not underestimated.	during week 16 and week 52 should be the average of the number of responders at week 16 and at the end of the cycle. Therefore, the company's approach is still slightly underestimating the costs of responders beyond week 16 which were calculated based on the number of responders at the end of year 1. The EAG also spotted an error in half-cycle correction of EAG's EA1 leading to a slight overestimation of the costs in the maintenance phase, had fixed the error and updated the results. For clarity, the EAG had amended the text in Section 4.5.2.2, (b). <u>Section 4.5.2.9</u> The description in the Section 4.5.2.9 was intended to explain the acquisition costs of interventions (both maintenance and no response states) in every model cycle, not necessarily

			limited to specific health state or year 1 cost. Nevertheless, the EAG has edited the text for clarity as follows. *"This will lead to a slight underestimation of these costs as the costs were based on the average number of the patients who begin the treatment cycle and those who receive the next treatment cycle".* In checking the model, the EAG identified an additional error (that has a very small impact on the ICER) in the calculations of oral herpes events related to the second-line active subsequent treatments. This correction has been added to the EAG report, Section 4.5.2.2 (g), and included in the revised EAG base case 2.
Section 4.5.2.2, (e), page 83 - 'The EAG notes that there is a formula error in the VBA code of *FncSampleCODA()* which results in returning the	Should be stated that in base-case analysis ORs for all comparators except upadacitinib 30 mg were equal to 1 and returning the same values in PSA (equal 1) was intentional for	The intention was to keep ORs equal 1 in PSA for comparators for which OR of 1 was	The EAG does not agree with the company's comment. The EAG did not mention the name of the comparator (updacitinib 30 mg) in the report

same value in each PSA iteration for the OR for any comparison where the OR was not fixed at unity'	these comparators. OR for upadacitinib 30 mg (not equal to 1 in base case) was varied within PSA.	applied in base-case. This was the case for all comparators except upadacitinib 30 mg, where ORs were varied within PSA.	and instead used the term "*where the OR was not fixed at unity'* to preserve results marked as confidential. Thus, the model error description in Section 4.5.2.2, (e) was only applicable for upadacitinib 30mg. Within the PSA, the OR for updacitinib 30mg was not varied in each iteration. This can be demonstrated as follows. Set all values in column F of the "Parameter Sampling" sheet to "No", except for F26 which should be set to "Yes". Set the comparator to upadacitinib 30mg. Run the PSA Macro. It can be seen that the values in PSA Output are identical for all PSA iterations.
Section 4.5.2.7, page 85 'The company used observed utility at week 16 to represent utility within year 1 and used observed utility values at week 48 to represent utility	Amend the sentence as follows - 'The company used observed utility at week 16 to represent utility within year 1 and used observed utility values at week 104 to represent utility from year 3 onwards. The utility value at year 2 was calculated as an average from	The utility at year 1 was equal to the value observed in the ARCADIA clinical trials at week 16, while the year 3 onwards utility was equal to	The EAG notes the description in the EAG report was accurate for adolescents. The EAG agrees with the company's suggestions for the

within year 2, ignoring the value at week 104’	values at year 1 and 3+, due to data limitation.’	the value at week 104 from the LTE study. The utility value at week 48 was not available in ARCADIA clinical trials, thus the utility at year 2 was calculated as an average from values at year 1 and 3 onwards.	adult population, and therefore edited the text as follows: *“In the adolescent population, the company used observed utility at week 16 to represent utility within year 1 and used observed utility values at week 48 to represent utility within year 2 and used observed utility at week 104 for year 3 onwards. For adults, utility was based on week 16 data for year 1, week 104 for years 3 onwards and the average of week 16 and week 104 data for year 2.”.*

References

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