NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

Contents:

Any information supplied to NICE which has been marked as confidential, has been

redacted. All personal information has also been redacted.

Pre-meeting briefing

Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues for consideration
Clinical effectiveness

- How should severity of atopic dermatitis be defined?
- How should treatment response be assessed?
  - Which outcome measures are used routinely in clinical practice?
    - What are the associated minimum clinically important differences for these measures?
- Is the treatment pathway the same for moderate and severe atopic dermatitis?
  - Do patients with moderate atopic dermatitis receive systemic immunosuppressants in the same way as patients with severe atopic dermatitis?
  - Is phototherapy used in clinical practice?
  - What is usually included in ‘best supportive care’?
- How would dupilumab be used in clinical practice?
  - For moderate and/or severe atopic dermatitis?
  - Is dupilumab likely to be used as monotherapy or in addition to topical corticosteroids?
- Is dupilumab a clinically effective treatment?

Key issues for consideration
Cost effectiveness

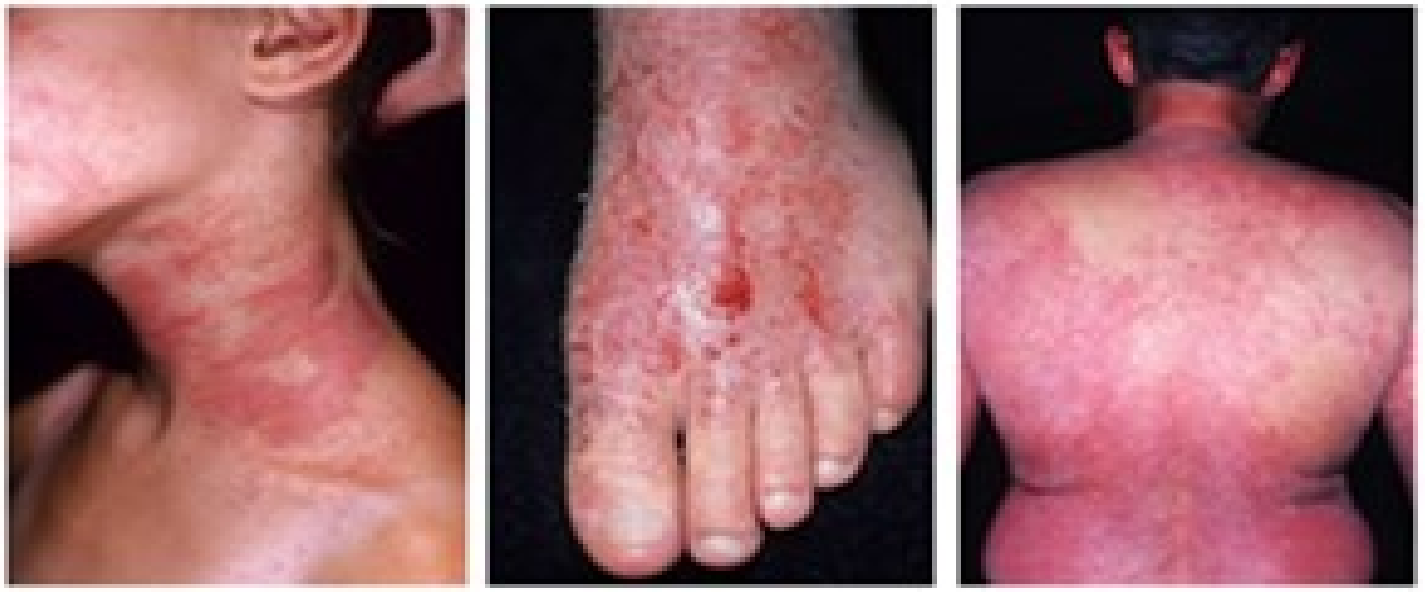
- How should treatment response be extrapolated after the 1 year trial period?
- How should quality of life be modelled, in particular after the 1 year trial period?
- Are resource use and cost estimates for dupilumab and best supportive care credible?
- What stopping rule should be applied?
- Innovation
- Are there any equality issues to consider, such as issues of assessing severity of atopic dermatitis in people with darker skin tones?

Atopic dermatitis (also called atopic eczema)

Chronic, remitting-relapsing, pruritic, inflammatory, immune-mediated skin condition

- Skin may be red and inflamed (erythema), thickened and leathery (lichenification) and dry (xerosis) with scaly plaques, bleeding, oozing, cracking and flaking
- Itching (pruritus) is the most disruptive symptom (may be unrelenting, frequent and intense; affecting sleep and causing anxiety or depression)

Examples of moderate to severe atopic dermatitis



Epidemiology

- Prevalence of atopic dermatitis in adults in UK is 2.5% (company submission) or 5% in industrialised countries (professional feedback)

- Estimates for prevalence of moderate to severe atopic dermatitis
  - Company: 7%
  - ERG: 53-67% depending on assessment tool used
  - Professional feedback: 15-23%

Definition of severity

- Large number of instruments assessing severity
  - systematic review of 18 instruments identified 5 with highest quality (based on COSMIN quality checklist): paediatric ISS, POEM, PO-SCORAD, SA-EASI and adapted SA-EASI (Gerbens *et al* 2017)
- No NICE guideline on atopic dermatitis in adults, only in children under 12s
  - NICE Clinical Guideline 57 (Atopic eczema in under 12s) recommends:
    - a holistic approach considering severity and quality of life
    - the following tools: VAS (severity, itch, sleep loss in previous 3 days), POEM (severity), CDLQI/IDLQI/DFI (quality of life)
- Company:
  - no consensus on most appropriate tool; no tool captures all key aspects of the disease; advisory board suggests clinicians' judgement and treatment response are used in UK practice
  - a single measurement may over- or under-estimate severity because of relapsing-remitting nature of condition
  - used IGA to stratify groups in its trials into moderate (IGA = 3) or severe (IGA = 4); also defined moderate to severe disease based on EASI scores at 2 levels (≥16 in CHRONOS trial and ≥20 in CAFÉ trial)
  - key outcomes in its trials: EASI, pruritus NRS, POEM, DLQI

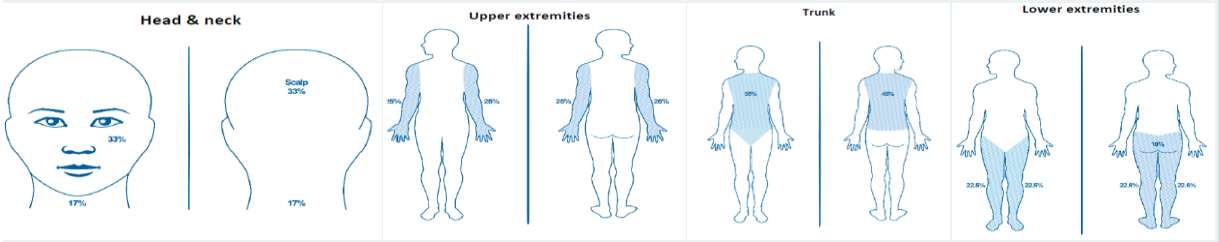
COSMIN, COnsensus-based Standards for the selection of health Measurement Instruments; DFI, Dermatitis Family Impact; (C/I)DLQI, (Children's/Infants') Dermatology Life Quality Index; (SA-)EASI, (self-administered) Eczema Area and Severity Index; IGA, Investigators' Global Assessment; ISS, Itch Severity Scale; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; PO-SCORAD, Patient-Oriented SCOring Atopic Dermatitis; VAS, Visual Analogue Scale

Measuring clinical effectiveness – clinician assessed

Eczema Area and Severity Index (EASI); 0 to 72

- Weighted score (0 to 72) of 4 affected areas
  - ❖ 0 (no eczema); 7.1-21 (moderate); 21.1-50 (severe); 50.1-72 (very severe)
- Response considered as EASI 50, EASI 75 or absolute reduction from baseline
  - ❖ EASI 50: ≥50% reduction in EASI score from baseline
  - ❖ Different perspectives on minimum clinically important difference
    - ➢ European Medicines Agency: co-primary outcomes in dupilumab trials at 16 weeks, EASI 75 and IGA 0/1 & ≥2 point improvement from baseline
    - ➢ British Association of Dermatologists: at 16 weeks, EASI 50 or 6-point improvement from baseline
    - ➢ Research studies: 6.6-point improvement from baseline

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							____ (0-72)



Investigator's Global Assessment (IGA); 0 to 4 or 5

- Clinician's impression of patient's eczema based on severity of erythema, infiltration, papulation and oozing/crusting
- Score: 0 (clear), 1 (almost clear), 3 (moderate) to 4 (severe for 5-point scale) or 5 (very severe for 6-point scale)

Measuring clinical effectiveness

Scoring Atopic Dermatitis Index (SCORAD); 0 to 103

- Combined score of A, B and C (0 to 103)
  - ❖ Estimates total body surface area affected [A]
  - ❖ Evaluates severity based on erythema, oedema/papulation, oozing/crusts, excoriation, lichenification and dryness (in areas of no inflammation) on a scale from 0 (mild) to 3 (severe) [B]
  - ❖ Includes patient-reported pruritus and sleep loss on a visual analogue scale, each symptom scored from 0 to 10 [C]
- 0-25 (mild); 26-50 (moderate); 51-103 (severe)
- Research studies suggest minimum clinically important differences to be:
  - ❖ 8.7 points for SCORAD (A, B and C)
  - ❖ 8.2 for objective SCORAD (A and B)

Measuring clinical effectiveness – patient reported

Patient Oriented Eczema Measure (POEM); 0 to 28

- 7 questions scored 0 (no days) to 4 (every day) on the presence of itch, sleep disturbance, bleeding, weeping/oozing, cracked, flaking and dry/rough skin
- 0-2 (clear or almost clear), 8-16 (moderate), 17-24 (severe), 25-28 (very severe)
- Response considered as POEM 25 (≥25% reduction in POEM score from baseline) or absolute reduction from baseline
  - ❖ Different perspectives on minimum clinically important difference
    - ➢ British Association of Dermatologists: at 16 weeks, POEM 25
    - ➢ Research studies: 3.4-point reduction from baseline

Pruritus Numerical Rating Scale (NRS); 0 to 10

- Patients rate intensity of itch from 0 (“no itch”) to 10 (“worst imaginable itch”)
- ≥4 to <7 (moderate); ≥7 to <9 (severe); ≥9 (very severe)

Dermatology Life Quality Index (DLQI); 0 to 30

- 10 questions scored 0 (no impact) to 3 (worst impact): symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment
- 0-1 (no effect at all); 6-10 (moderate effect); 11-20 (very large effect)
- ≥4 point improvement (clinically important difference)

Dupilumab
(Dupixent)
Sanofi Genzyme

Marketing authorisation
"moderate to severe atopic dermatitis in adults who are candidates for systemic therapy"

Mechanism of action

- Fully human monoclonal antibody
- Binds to interleukin-4 and -13 receptors (key mediators in atopic dermatitis)
- Inhibits inflammation

Administration and dose

- Subcutaneous injection (thigh or stomach)
- Initial 600 mg dose, followed by 300 mg once every 2 weeks (no dose adjustments are recommended)
  - ❖ If no response after 16 weeks, stop treatment
  - ❖ If partial response after 16 weeks, some patients may improve with continued treatment
- Can be used with or without topical corticosteroids
- Can be used with topical calcineurin inhibitors but only applied for problem areas (such as, the face, neck, intertriginous and genital areas)

Clinical perspective

Clinicians consider dupilumab a step change in managing atopic dermatitis

- Atopic dermatitis is heterogenous
  - severe disease linked to depression and suicide
- Limited systemic treatment options
  - significant side effects of current immunosuppressants
    - irreversible nephrotoxicity with ciclosporin
    - skin malignancy with azathioprine
- Dupilumab is a step change in management
  - first targeted biologic
  - not an immunosuppressant
  - associated with fewer side effects
  - effective in disease that has not responded to systemic therapy
- Clinicians routinely use validated tools (such as EASI, DLQI, POEM), so using dupliumab would not require additional assessment

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure

Treatment pathway and company's positioning of dupilumab adapted from International Eczema Council guidance

1st **Emollients and topical corticosteroids (TA81)**

2nd **Topical calcineurin inhibitors (tacrolimus; TA82)**

3rd **Phototherapy**
narrowband ultraviolet B (UVB) light

4th **Systemic immunosuppressants**
oral corticosteroids, ciclosporin (licensed), *methotrexate, azathioprine, mycophenolate mofetil*

5th Dupilumab for moderate to severe atopic dermatitis?

BSC **Best supportive care**

Education
avoidance of triggers, adherence to treatment, optimise topical therapy, address steroid phobia, structured education

Decision problem – population and comparator

Company focused on narrower population compared with NICE scope and marketing authorisation to reflect likely position of dupilumab in NHS clinical practice

NICE scope:
Population: adults with moderate to severe atopic dermatitis who are candidates for systemic therapy

Comparators: phototherapy, immunosuppressive therapy, oral steroids, best supportive care, alitretinoin for hands

Company's decision problem: those who are candidates for systemic therapy and for whom topical and systemic immunosuppressant treatments (ciclosporin) are inadequately effective, not tolerated or contraindicated

Comparator in company's base case: best supportive care (emollients, low-to-mid potency topical corticosteroids, and rescue therapy of higher potency topical or oral corticosteroids or topical calcineurin inhibitors)

ERG: company's decision problem appropriate and reflects likely position of dupilumab in NHS clinical practice and treatment options at that stage; but:

- only 1 of the 4 key trials was stratified at randomisation for previous exposure to or inadequate control by ciclosporin
- in clinical practice, other systemic immunosuppressants such as azathioprine and methotrexate are used off-label if ciclosporin is inadequately effective; best supportive care also includes phototherapy and systemic therapy

Decision problem – outcomes and subgroups

Company submission included all outcomes as in NICE scope and relevant subgroup

NICE scope	Company submission and ERG comments
Outcomes • measures of disease severity • measures of symptom control • disease free period/maintenance of remission • time to relapse/prevention of relapse • adverse effects of treatment • health-related quality of life	**Company:** outcomes are included as per NICE scope **ERG:** dupilumab trials report time to first rescue treatment, not disease free period/maintenance of remission or time to relapse/prevention of relapse; but the ERG's clinical advisor considers these outcomes to be equivalent
Subgroups • people with atopic dermatitis affecting the hands • people for whom therapies have been inadequately effective, not tolerated or contraindicated • people with different skin colour	**Company:** dupilumab trials did not include outcomes associated with hand eczema. Base case is 2nd subgroup. Trials suggest there is no evidence that outcomes for people with various skin colour are different. **ERG:** considered company's rationale appropriate

Key clinical evidence and company's base case

4 phase III trials

'Monotherapy' trials
(dupilumab *vs* placebo)
SOLO 1 & SOLO 2

'Combination' therapy trials
(dupilumab + TCS *vs* placebo + TCS)
CAFÉ & CHRONOS

Primary endpoints of trials at 16 weeks

SOLO 1 & 2 and CHRONOS: EASI 75 and IGA 0/1 & ≥2-point improvement from baseline
CAFÉ: EASI 75

Company's base case

- ✓ **Subgroup**: history of ciclosporin failure or contraindication
- ✓ **2 separate analyses**: 'monotherapy and 'combination'; using 'all observed' data that include patients who had rescue therapy or stopped study treatment
- ✓ **Comparison**: dupilumab (licensed dose) *vs* best supportive care (data from placebo groups)
- ✓ **Endpoint**: EASI 50 & DLQI ≥4 (**different** to trials' primary endpoints)
- ✓ **Other outcomes**: EQ-5D, adverse events

Company: included matching-adjusted indirect comparison (MAIC) of dupilumab and ciclosporin in a scenario analysis (assumed same efficacy in groups over common treatment period)
ERG: MAIC not robust and not relevant given the anticipated positioning of dupilumab

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment; TCS, topical corticosteroids

Key phase III trials – design

DESIGN: international (UK sites), randomised, stratified (IGA 3 or 4), double-blind, parallel-group, 16-week treatment

- **SOLO 1 & 2:** stratified (Japan or rest of world); responders (EASI 75 or IGA 0/1) re-randomised to 36 week dupilumab at 4 different doses or placebo (**SOLO-CONTINUE study**); non-responders 12 week follow up
- **CAFÉ:** stratified (ciclosporin naïve or not), 12 week follow up
- **CHRONOS:** stratified (Japan or rest of world), 36 week maintenance; 12 week follow up

COMPARISON: dupilumab (600 mg loading dose on day 1, then 300 mg every week or every other week) ± topical corticosteroids *vs* placebo ± topical corticosteroids for 16 weeks

Rescue therapy

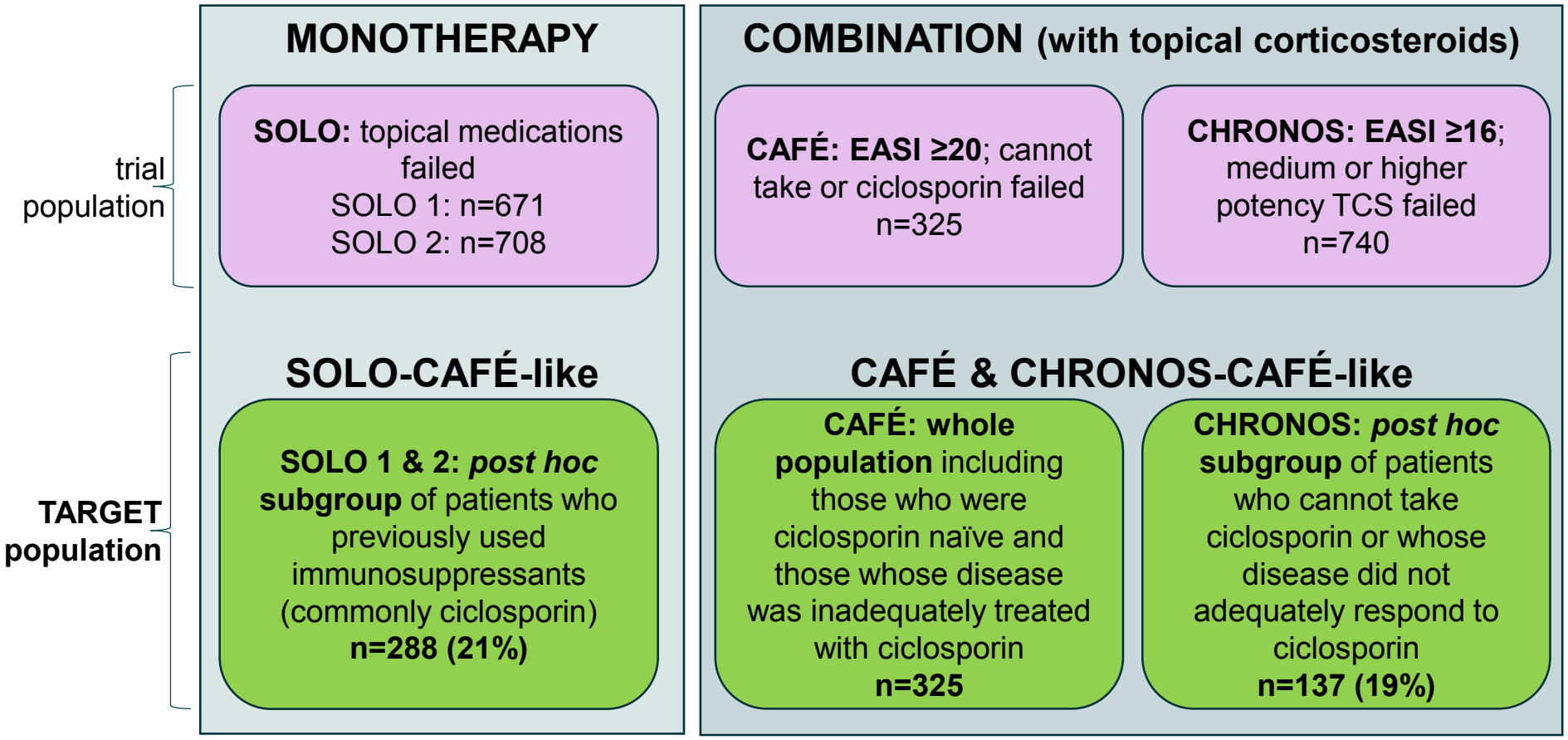
- Before 2 weeks: patients stop study treatment
- After 2 weeks: if patients take topical medications as rescue therapy, they continue study treatment. If patients take systemic drugs as rescue therapy, they stop study treatment and resume after >5 half lives of last dose of rescue drug
- Patients stopping study treatment complete all visits and assessments **(analyses all observed)**

ERG: only 1 of 4 trials was stratified at randomisation for previous use of immunosuppressant therapy (ciclosporin)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment

Key phase III trials – target population

POPULATION: adults with chronic moderate to severe atopic dermatitis (≥3 years; IGA ≥3, BSA ≥10%, **pruritus NRS ≥3**), inadequate treatment in ≥6 months with topical medications



BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment; n, number of patients; NRS, Numerical Rating Scale; TCS, topical corticosteroids

Baseline characteristics of target population

ERG: EASI and pruritus scores are slightly higher while DLQI and EQ-5D scores are slightly lower than respective values in individual trials indicating subgroups have more severe disease

	SOLO-CAFÉ-like		CAFÉ & CHRONOS-CAFÉ-like	
	dupilumab^ (n=104)	placebo (n=88)	dupilumab^ + TCS (n=130)	placebo + TCS (n=169)
Age in years*	38 (14)	39 (13)	38 (13)	38 (13)
Men, %	72	63	59	60
BMI in kg/m²*	25 (5)	26 (5)	25 (4)	26 (5)
Caucasian, % Asian, %	72 22	59 34	93 5	90 7
Years with AD*	29 (14)	30 (15)	30 (15)	29 (15)
Percent BSA with AD*	59 (22)	60 (24)	57 (19)	59 (22)
EASI [0-72, >20=severe]*	**37 (15)**	**36 (14)**	**34 (11)**	**35 (12)**
IGA [0-4, 4=severe]*	3.7 (0.5)	3.6 (0.5)	3.5 (0.5)	3.5 (0.5)
Weekly average of peak daily pruritus NRS [0-10, >6=severe]*	8 (2)	8 (2)	7 (2)	7 (2)
SCORAD [0-103, >50=severe]*	72 (14)	73 (13)	69 (13)	69 (13)
POEM [0-28, >24=severe]*	22 (5)	22 (6)	20 (6)	20 (6)
DLQI [0-30, >10=very large effect]*	**16 (7)**	**17 (8)**	**15 (8)**	**15 (8)**
HADS [0-42, 11 overt depression/anxiety]*	13 (8)	15 (9)	13 (8)	13 (8)
EQ-5D utility*	0.58 (0.32)	0.52 (0.38)	0.72 (0.25)	0.63 (0.32)

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; n, number of patients; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids

Key outcomes for target population – Monotherapy

Dupilumab significantly reduces disease severity and improves quality of life compared with placebo. Large proportion of patients in placebo group met criteria for treatment response (EASI 50 & DLQI ≥4 or EASI 75)

Outcomes at 16 weeks	SOLO-CAFÉ-like	
	dupilumab^ (n=104)	**placebo (n=88)**
Treatment response: proportion achieving EASI 50 & DLQI ≥ 4, %	59%	**24%**
Difference: % (95%CI)*	35% (20.7 to 48.8)	
EASI 75, %	45%	**17%**
Difference: % (95% CI)*	28% (14.7 to 41.6), *p*<0.0001	
Mean EASI change from baseline	-24 (1.2)	-12 (1.3)
Difference: LS mean (SE)*	-12 (1.6), *p*<0.0001	
Mean weekly average of pruritus NRS change from baseline	-3 (0.2)	-2 (0.3)
Difference: LS mean (SE)*	-1.3 (0.3), *p*<0.0001	
Mean EQ-5D change from baseline (SE)	0.28 (0.02)	0.16 (0.02)
Difference: LS mean (SE)*	0.12 (0.32), *p*=0.0002	

Analyses all observed, that is, includes patients who received rescue therapy

^licensed dose (300 mg every 2 weeks); *Difference is dupilumab minus placebo, CI calculated using normal approximation, †*p*-values derived by the Cochran-Mantel-Haenszel test; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; IGA, Investigator's Global Assessment; LS, least squares; n, number of patients; NRS, numerical rating scale; SE, standard error; TCS, topical corticosteroid

Key outcomes for target population – Combination

Dupilumab in combination with topical corticosteroids significantly reduces disease severity and improves quality of life compared with placebo in combination with topical corticosteroids. Large proportion of patients in placebo group met criteria for treatment response (EASI 50 & DLQI ≥4 or EASI 75)

Outcomes at 16 weeks	CAFÉ & CHRONOS-CAFÉ-like	
	dupilumab^ + TCS (n=130)	**placebo + TCS (n=169)**
Treatment response: proportion achieving EASI 50 & DLQI ≥ 4, %	73%	**28%**
Difference: % (95%CI)*	45% (34.4 to 56.1), *p*<0.0001	
EASI 75, %	67	**30%**
Difference: % (95% CI)*	37% (25.4 to 48.1), *p*<0.0001	
Mean EASI change from baseline	-26 (1.1)	-15 (1.0)
Difference: LS mean (SE)*	-12 (1.2), *p*<0.0001	
Mean weekly average of pruritus NRS change from baseline	-4 (0.2)	-2 (0.2)
Difference: LS mean (SE)*	-1.7 (0.2), *p*<0.0001	
Mean EQ-5D change from baseline (SE)	0.19 (0.02)	0.12 (0.02)
Difference: LS mean (SE)*	0.08 (0.02), *p*=0.0012	

Analyses all observed, that is, includes patients who received rescue therapy

^licensed dose (300 mg every 2 weeks); *Difference is dupilumab minus placebo, CI calculated using normal approximation, †*p*-values derived by the Cochran-Mantel-Haenszel test; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; IGA, Investigator's Global Assessment; n, number of patients; NRS, numerical rating scale; SE, standard error; TCS, topical corticosteroid

Adverse events – trial population

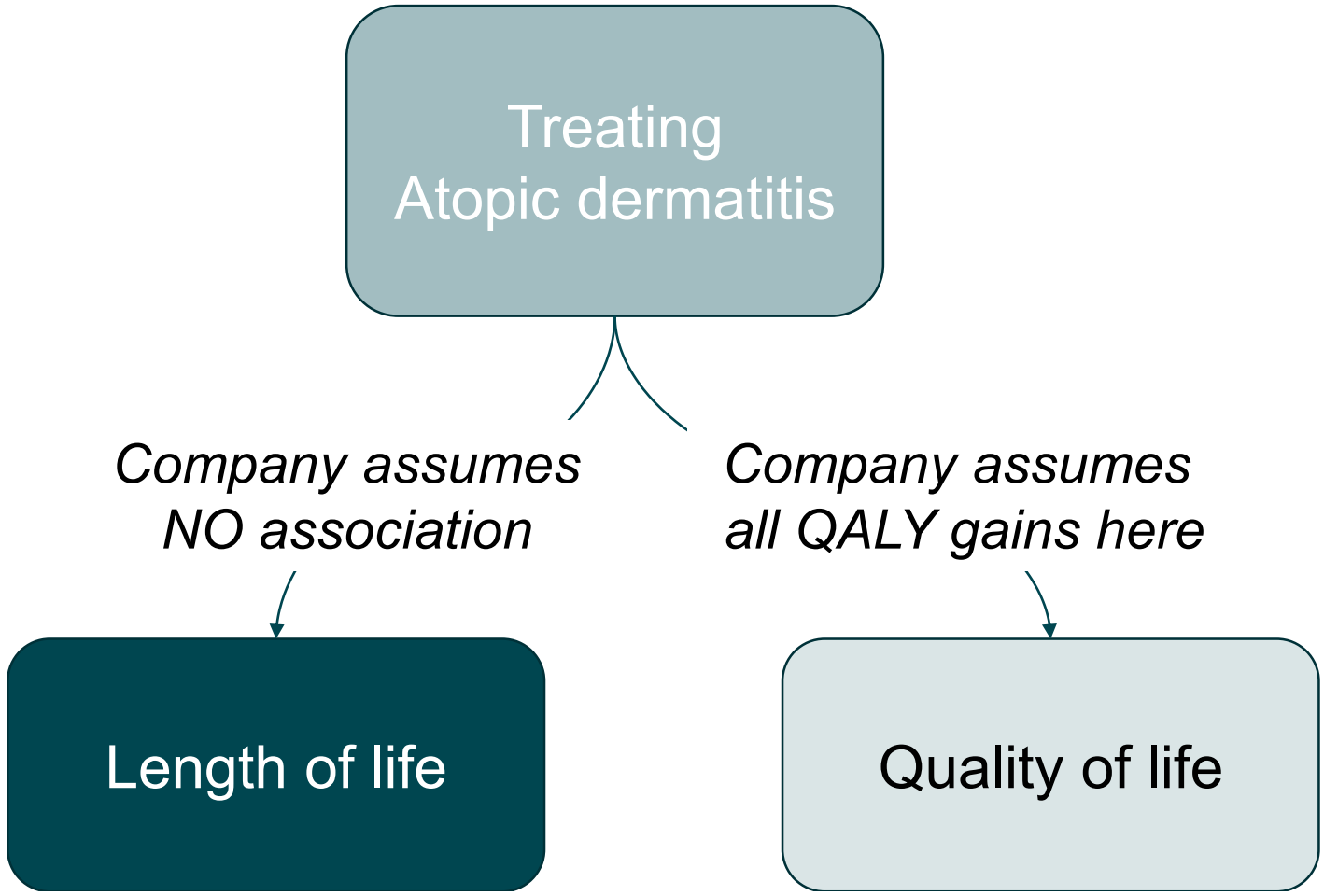
Adverse events leading to treatment discontinuation were generally low across all groups and trials. Generally, the number of patients in the placebo groups reporting flares is twice that of dupilumab groups. Injection site reactions were reported at 16 and 52 weeks and were generally higher in dupilumab groups

Event, %	SOLO 1 at 16 weeks			SOLO 2 at 16 weeks			CAFÉ at 16 weeks			CHRONOS at 16 weeks			CHRONOS at 52 weeks		
	P n=222	Q2W n=229	QW n=218	P n=234	Q2W n=236	QW n=237	P n=108	Q2W n=107	QW n=110	P n=315	Q2W n=110	QW n=315	P n=315	Q2W n=110	QW n=315
At least 1 AE[a]	65	73	69	72	65	66	69	72	69	68	74	72	85	88	84
At least 1 SAE[b]	5	3	1	6	2	3	2	2	2	2	3	1	5	4	3
Death	0	0	0	0	0.4	0.4	0	0	0	0	0	0	0	0	0.3
AE leading to treatment discontinuation[a]	1	2	2	2	**11**	1	1	0	2	5	1	3	8	2	3
Exacerbation of atopic dermatitis	30	13	10	35	14	16	15	8	8	27	11	8	47	20	18
Adverse events included in health economic model															
Injection site reaction[c]	6	8	19	6	14	13	0	1	4	6	10	16	8	15	19
Allergic conjunctivitis	1	5	3	11	11	1	7	15	9	3	6	6	5	11	15
Infectious conjunctivitis	1	5	3	0.4	4	4	3	11	7	0.6	0	1	2	1	3
Conjunctivitis bacterial	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.6	1	2	2	2	3
Oral herpes	2	4	2	2	3	4	0	3	5	2	3	3	3	4	5

[a]Labelled as treatment emergent adverse event in CAFÉ and CHRONOS; [b]Labelled as treatment emergent serious adverse event in CAFÉ and CHRONOS; [c]**Health economic model assumed injection site reactions only occurred as an initial one-time event;** n, number of patients; NR, not reported; P, placebo; Q2W, dupilumab every 2 weeks (licensed dose); QW, dupilumab every week

Cost effectiveness

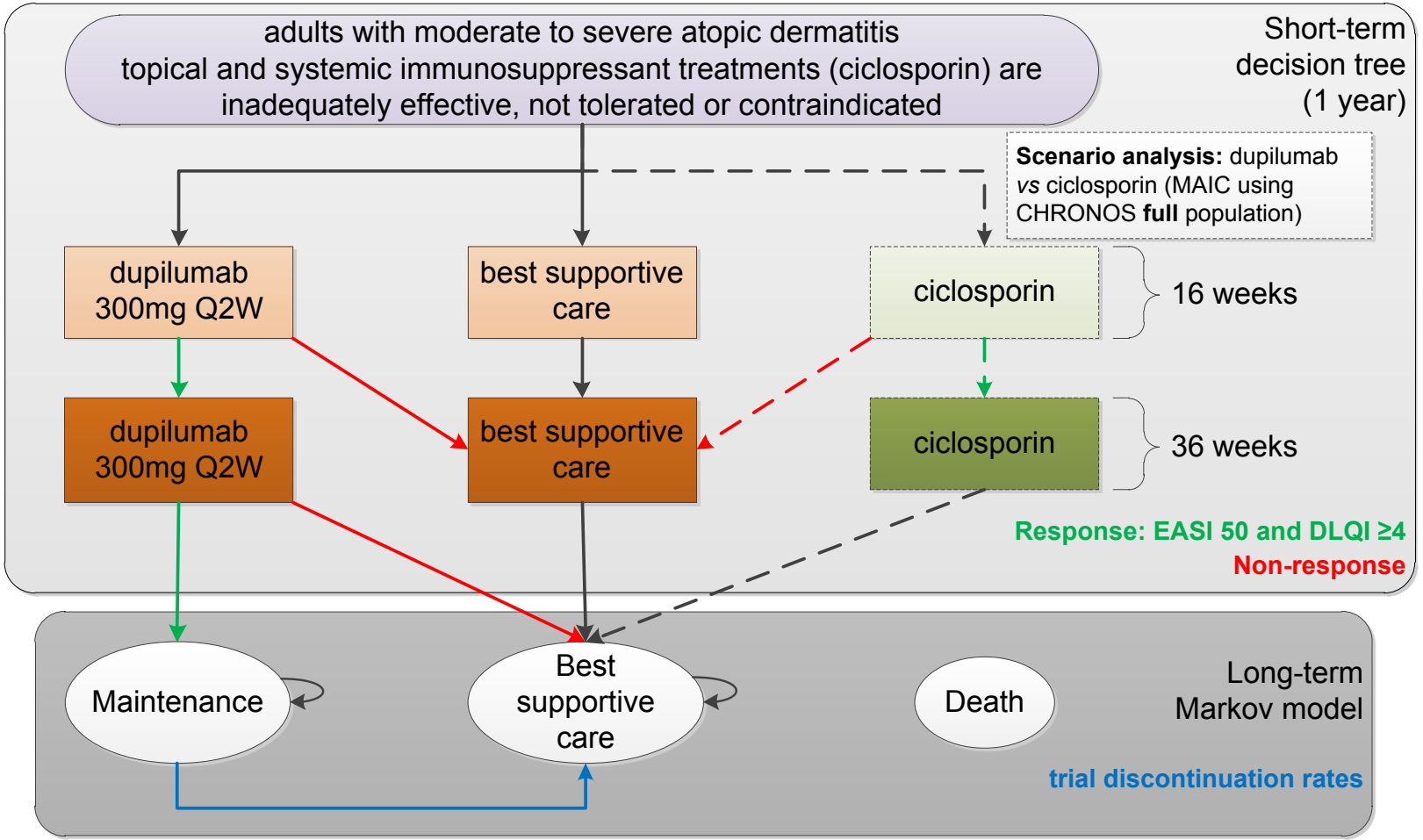
Where do the QALY gains come from?



Increase in QALYs comes only from improvement in quality of life, rather than increasing length of life

Company model

ERG: model largely meets requirements of NICE reference case. Uncertainty about extrapolation assumptions due to lack of existing longitudinal data on long-term quality and response status of moderate to severe atopic dermatitis patients



- Decision tree and Markov state transition model: lifetime horizon, annual cycle, adverse events included. Perspective from NHS only, 3.5% discount, dupilumab monotherapy (SOLO-CAFÉ-like) or with topical corticosteroids (CAFÉ & CHRONOS-CAFÉ-like) considered separately, data from trials' placebo groups used for best supportive care
- Baseline characteristics SOLO-CAFÉ-like: 38 years, 60% men, mean EASI 34, mean weekly pruritus NRS 6.8
- Baseline characteristics CAFÉ & CHRONOS-CAFÉ-like: 38 years, 65% men, mean EASI 36, mean weekly pruritus NRS 7.6

Q2W, every 2 weeks

Company key assumptions and rationale

ERG: model structure and assumptions lack flexibility to capture relapsing-remitting nature of disease

- Response starts during treatment at 8 weeks rather than at end of 16-week treatment period
- ❖ **Company**: trials → 50% responders showed response before 8 weeks
- ❖ **ERG**: reasonable correction; not applied to non-responders but likely to have little impact on results

decision tree (year 1)

- Dupilumab response at 52 weeks continued in *Maintenance* state
- Best supportive care:
  - ➢ retain 16 week utility weights in *Best supportive care* state
  - ➢ but quality of life gains during trials are not sustained indefinitely
- ❖ **Company**: simplify assumption; best supportive care quality of life gains unlikely to be maintained after input from trial ends

Markov (year 2+)

Resource use

- Best supportive care (responders and non-responders): based on dupilumab target patients
- Dupilumab responders: based on clinical opinion
- ❖ **Company**: best available evidence

Disutility from adverse events

- ❖ **Company**: frequency of EQ-5D data collection captured disutility → avoid double counting
- ❖ **ERG**: 2 weekly data collection may have missed full impact of short-lived adverse events

EQ-5D, European Quality of Life-5 Dimensions

Company model – base case

- **Decision tree component – half period correction (assumes responders at 16 weeks would have responded by week 8)**
  - patients receive either dupilumab (monotherapy or with topical corticosteroids) or best supportive care for 16 weeks
  - At the end of 16 weeks,
    - dupilumab responders (**EASI 50 & DLQI ≥4**) continue to receive treatment for further 36 weeks
    - non-responders receive best supportive care
- At the end of 52 weeks, patients enter the **Markov state transition component**
  - dupilumab responders with sustained response continue into the Maintenance health state. Patients in Maintenance state discontinue at an annual rate
  - dupilumab responders who lose response move into the Best Supportive Care health state
  - patients receiving best supportive care in decision tree component continue to Best Supportive Care health state
  - Death: patients can transition to this state at any time. All-cause mortality adjusted for age and sex based on UK National Life Tables with no adjustment for atopic dermatitis-specific mortality
- ERG: half period correction reasonable and although not applied to non-responders, unlikely to have a significant impact on results. Model structure and assumptions lack flexibility to capture relapsing-remitting nature of disease. Markov states are not defined by disease severity or staging, only on treatment received, with responders assumed to remain only on dupilumab, not best supportive care

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

Extrapolating treatment effectiveness up to 52 weeks (decision tree component)

- **All trials**: data on treatment up to 16 weeks
- **CHRONOS**: only trial with data up to 52 weeks
  - ❖ whole trial population data used to derive conditional probabilities of response at 52 weeks based on 16 week response for dupilumab and placebo groups
    - ➢ applied to target population for monotherapy and combination

	Proportion of patients achieving response (EASI 50 & DLQI ≥4)				Conditional probabilities derived from CHRONOS
	Monotherapy		Combination		
Time point	dupilumab^	BSC	dupilumab^	BSC	
Week 16	59	24	73	28	dupilumab^: 0.94
Week 52	55	18	69	21	BSC: 0.77

^licensed dose (300 mg every 2 weeks); BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

Extrapolating dupilumab effectiveness beyond 1 year trial period (Markov '*Maintenance*' health state)

ERG: *unclear rationale for adding probabilities of quality of life waning in addition to treatment stopping rates*

- Annual stopping rates of dupilumab
  - **Monotherapy**: annual stopping probability 0.063
    - patients who stopped SOLO-CONTINUE study at 52 weeks
      - SOLO-CONTINUE: SOLO 1 & 2 patients achieving treatment response (EASI 75 or IGA 0/1 at 16 weeks) re-randomised to 36 week dupilumab treatment at 4 doses or placebo
  - **Combination**: annual stopping probability 0.037
    - patients achieving treatment response (EASI 50 & DLQI ≥4) at 16 weeks who stopped CHRONOS study at 52 weeks
- Company additionally applied probability of sustained quality of life

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators' Global Assessment

Health-related quality of life

- Based on EQ-5D-3L trial data (collected every 2 weeks for first 16 weeks, then every 4 weeks up to 52 weeks for CHRONOS only) valued using UK tariff
- Mixed model regression estimated utility values on all observed data at trial level (CAFÉ, CHRONOS, SOLO 1 & 2) and not on target subgroup
  - Company: quality of life is dependent on EASI and pruritus reduction and differences in populations are adjusted for by taking into account baseline utility weight. Total EASI scores and weekly average of peak daily pruritus are used in regression to calculate utility weights specific to subgroup

Patient population	Parameter	dupilumab^	BSC*
Monotherapy	All patients at week 16	0.830	0.718
Baseline utility: 0.55	Week 16 EASI 50 +DLQI ≥4 responder	0.855	-
Combination	All patients at week 16	0.898	0.811
Baseline utility: 0.66	Week 16 EASI 50 +DLQI ≥4 responder	0.904	-

^licensed dose (300 mg every 2 weeks); ***Aggregate utility applied for all patients as they do not move health states according to response**; BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

How the utilities are applied

Treatment	From 0 to 8 weeks	From 8 to 16 weeks	From 16 to 52 weeks	Markov (Year 2+)
dupilumab	baseline utility	utility from all patients at 16 weeks	Responder: utility for responders at 16 weeks **Non-responder: utility from all BSC patients at 16 weeks**	
BSC	baseline utility	utility from **all patients** at 16 weeks*		

***High number of patients in placebo groups showed treatment response at 16 weeks**

Probability of sustained quality of life beyond 1 year trial period

ERG: company assumes utility gains in dupilumab responders are stable over time, but that short-term gains in BSC responders decrease rapidly over time. This creates a large difference in utility values and influences results (key model driver)

- Based on feedback from 5 dupilumab trial principal investigators

	Probability of sustained quality of life (%)	
	dupilumab^	best supportive care
Year 2	98	37
Year 3	95	9
Year 4	93	0
Years 5+	92	0

^licensed dose (300 mg every 2 weeks)
BSC, best supportive care: weighted average of utility for all BSC patients during trial period and baseline utility

- High number of patients receiving placebo showed treatment response but company used utility values for 'all patients' (responders and non-responders) from 8 weeks onwards
  - Company: adherence to topical regimens likely to vary after trial ends, so response unlikely to continue. Only applied to BSC based on clinical advice that dupilumab responders are likely to use less steroids and emollients (less burdensome)

Health-related quality of life – adjustments

- **Adverse events:** no adjustments
  - Company: EQ-5D data collected frequently and should capture any disutility from adverse events; excluded to avoid double-counting
  - ERG: 2 week schedule may have missed full impact of short lived adverse events
- **Utility adjustments based on age:** age-adjusted utility decrements derived from UK general population data (Ara *et al* 2011) and applied additively per cycle
  - ERG: QALY increment does not change because constant decrement is also applied to dupilumab and comparator group and has no impact on ICER
  - Company provided updated results using multiplicative method for age adjustment as per NICE DSU guidance

DSU, Decision Support Unit; EQ-5D, European Quality of Life-5 Dimensions; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Resource use estimates for responders and non-responders – data source (1)

- **Secondary care case notes review** used to estimate resource use for responders and non-responders
  - Observational, multicentre retrospective descriptive research study conducted in 5 secondary/tertiary NHS Hospital Trusts
  - Participants were uncontrolled on current systemic therapies and could be candidates for dupilumab

Secondary / tertiary care visit to:	Total visits	Number of patients	Mean number of visits (per patient)	Range
Clinician	211	30	7.03	1-16
Nurse	17	30	0.57	0-6

- ERG: Company only used 30 patients in year 3 of the secondary care case notes review study, but data are available for years 1 and 2
- Supplemented by **Salford Integrated Records Review** of 37 patients with atopic dermatitis on prescription medication

	Number of events	Mean per patient per year
Day case	5	0.17
Accident and emergency	3	0.1
Hospitalisation	7	0.23

Resource use estimates for responders and non-responders – data source (2)

- Resource use estimates adjusted based on 51 dermatologists' perceptions of resource use in 850 patients whose atopic dermatitis was well controlled (proxy for dupilumab responders) or not (proxy for dupilumab non-responders)
- Derived multipliers and used these on resource use data to adjust estimates for responders only

	Responding to systemic therapy	Not responding to systemic therapy/ intolerant/ contraindicated	Multiplier to adjust resource use data estimates
Total number of patients	560	290	-
OP visits to dermatologist (total patient visits/year)	3.53	4.92	0.72
OP visits to dermatology nurse (total patient visits/year)	1.84	2.39	0.77
Visits to the GP (total patient visits/year)	2.30	4.78	0.48
A&E attendance (total patient visits/year)	0.43	1.74	0.25
Hospital admissions (total patient admissions/year)	0.15	1.16	0.13

A&E, accident and emergency; GP, general practitioner; OP, outpatients

Adverse events rates

- Company estimated adverse event rates from individual trials
- Injection site reaction: company assumed to be one-time event
- All other adverse events: company assumed per cycle rates

	Monotherapy		Combination	
	dupilumab^	BSC	dupilumab^	BSC
Injection site reaction	0.881	0	0.091	0
Allergic conjunctivitis	0.114	0.03	0.401	0.188
Infectious conjunctivitis	0.163	0.022	0.255	0.033
Oral herpes	0.135	0.059	0.055	0.11

^licensed dose (300 mg every 2 weeks); BSC, best supportive care

ERG: company had little justification for assuming injection site reaction events are one-time event; more appropriate for company to apply injection site reaction rate on a cycle-by-cycle basis in the dupilumab *Maintenance* health state

Resource use

ERG: patients unlikely to be hospitalised; used estimates from data for all 3 years from secondary care case notes review, while company used data only from 1 year

Resource	Dupilumab				Best supportive care: Years 1, 2+	
	Year 1		Years 2+		Company	ERG
	Company	ERG	Company	ERG		
Dermatologist outpatient consultation (per patient per year)						
Responder	4	4.32	2	4.32	**2**	4.32
Non-responder	7.03	6	7.03	6	**7.03**	6
Dermatology related GP consultation (per patient per year)						
Responder	2	6.15	2	6.15	**2**	6.15
Non-responder	12.81	12.81	12.81	12.81	12.81	12.81
Dermatology Nurse visit (per patient per year)						
Responder[a]	1	1	0.44	0.35	**0.44**	0.35
Non-responder	1	1	0.57	0.46	**0.57**	0.46
Accident and emergency visit (per patient per year)						
Responder[b]	0.06	0.021	0.06	0.021	**0.06**	0.021
Non-responder	0.25	0.082	0.25	0.082	**0.25**	0.082
Hospitalisation (per patient per year)						
Responder[c]	0.03	0.017	0.03	0.017	**0.03**	0.017
Non-responder	0.23	0.13	0.23	0.13	**0.23**	0.13
Tests and investigations (per patient per year)						
Responder	0	0	0	0	4	4
Non-responder	4	4	4	4	4	4
Day case (per patient per year)						
Responder	0	0	0	0	0	0
Non-responder	0.17	0.2	0.17	0.2	**0.17**	0.2

Multipliers used to reduce number of visits for responders: [a](0.77), [b](0.25), [c](0.13)

Company costs

Parameter	Costs	
Background treatments	**Responder (assuming 50% reduction)**	**Non-responder**
• Bathing products	£1.36 per week	£2.48 per week
• Emollients	£2.38 per week	£5.73 per week
• Topical corticosteroid (mometasone)	£1.76 per week	£3.47 per week
• Topical calcineurin inhibitors (tacrolimus)	£0	£1.38 per week
Treatment of flares (based on rescue therapy in CHRONOS over 52 weeks)	Dupilumab: £10.41 per year	Best supportive care: £14.03 per year
Full blood count		£3.10
Consultant appointments (average of different types of attendance and multidisciplinary team)		[redacted]
Hospitalisations		£1,795
Accident and Emergency		£137.82
Adverse events		
• Injection site reactions		£104
• Allergic conjunctivitis		£36
• Infectious conjunctivitis		£45.41
• Oral herpes		£36

Company base case results

Monotherapy

	Total			Incremental			
	Costs (£)	Life years gained	QALYs	Costs (£)	Life years gained	QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,749

Combination

	Total			Incremental			
	Costs (£)	Life years gained	QALYs	Costs (£)	Life years gained	QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,419

*licensed dose (300 mg every 2 weeks); BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life year
Model: multiplicative adjustment for age

Company key one-way deterministic sensitivity analyses – monotherapy

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	**Base case**	[redacted]	[redacted]	[redacted]	**£25,749**
Assumption: sustained quality of life benefit post trial period					
3	Sustained QoL response does not decline after year 2 (37%)	[redacted]	[redacted]	[redacted]	£30,992
4	No decline in dupilumab patients	[redacted]	[redacted]	[redacted]	£25,148
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£27,308
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£26,184
7	No decline in dupilumab patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£33,127
Measure of response					
11	Efficacy evaluation at 16 weeks: EASI 75	[redacted]	[redacted]	[redacted]	£26,611
12	Efficacy evaluation at 16 weeks: EASI 50	[redacted]	[redacted]	[redacted]	£26,117
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£27,196

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

Company key one-way deterministic sensitivity analyses – combination

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	**Base case**	[redacted]	[redacted]	[redacted]	£30,419
Assumption: sustained quality of life benefit post trial period					
3	Sustained QoL response does not decline after year 2 (37%)	[redacted]	[redacted]	[redacted]	£38,267
4	No decline in dupilumab patients	[redacted]	[redacted]	[redacted]	£29,792
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£32,154
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£30,901
7	No decline in dupilumab patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£41,838
Measure of response					
11	Efficacy evaluation at 16 weeks: EASI 75	[redacted]	[redacted]	[redacted]	£32,350
12	Efficacy evaluation at 16 weeks: EASI 50	[redacted]	[redacted]	[redacted]	£31,843
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£30,492

BSC, best supportive care; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; QALY; quality-adjusted life year; QoL, quality of life
Model: multiplicative adjustment for age

ERG exploratory analyses

Key areas of concern

- Company's assumptions about waning of treatment response and health utilities (key model driver)
  - ERG applied different assumptions
- Method company used to derive resource use for responders and non-responders based on only 1 year of data from the 30 patients
  - ERG used data from additional 2 years
- Feasibility of defining non-response (EASI 50 & DLQI ≥4) and stopping treatment ('stopping rule')

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

ERG results – monotherapy

	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	**Company's Base Case**	[redacted]	[redacted]	[redacted]	**25,749**
Combination of waning effect assumptions and resource use calculation using all available patient data					
6	25% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	32,118
7	50% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	37,378
8	75% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	44,579
9	No waning assumptions. Probability of sustained QoL does not decline in either arm after trial ends	[redacted]	[redacted]	[redacted]	54,438
10	Exploring removal of stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	29,468

BSC, best supportive care; EASI, incremental cost-effectiveness ratio; LYG, life years gained; QALY; quality-adjusted life year

ERG results – combination

	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	**Company's Base Case**	[redacted]	[redacted]	[redacted]	**30,419**
Combination of waning effect assumptions and resource use calculation using all available patient data					
6	25% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	39,293
7	50% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	47,274
8	75% of responders in BSC will sustain QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	59,069
9	No waning assumptions. Probability of sustained QoL does not decline in either arm after trial ends	[redacted]	[redacted]	[redacted]	77,701
10	Exploring removal of stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	33,279

BSC, best supportive care; EASI, incremental cost-effectiveness ratio; LYG, life years gained; QALY; quality-adjusted life year

‘Stopping rule’

Treatment stops for ‘non-responders’

- Clinical trials 16 week induction treatment co-primary efficacy outcomes: EASI 75 and IGA 0/1 (+ ≥2 point improvement from baseline)
- Company base case and economic model treatment response: EASI 50 and DLQI ≥4
- Dupilumab summary of product characteristics: patients with partial response at 16 weeks may improve with continued treatment
- Professional feedback: patients starting at high absolute EASI score, disease involving extensive body surface area, and patients for whom atopic dermatitis mainly affects the head and face may take longer to achieve EASI 50; 24 weeks is a more realistic time frame to evaluate treatment response

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigators’ Global Assessment

Innovation

- Designations:
  - “breakthrough therapy” by US Food and Drug Administration
  - MHRA Promising Innovative Medicine
  - Early Access to Medicine Scheme for severe atopic dermatitis
- Interleukin (IL)-4/IL-13-targeted mechanism of action tackles underlying inflammation associated with T-helper type 2 (Th2) pathway
- Area of high disease burden and unmet need
- No current effective treatments for patients whose disease does not respond to current systemic therapy, or are intolerant, contraindicated or cannot take systemic immunosuppressant therapies
- No targeted biologic therapies
- Benefit to society, carers and family not included in quality-adjusted life year

MHRA, Medicines and Healthcare products Regulatory Agency

Equality issues

- Assessing atopic dermatitis in patients with darker skin tones is complicated
  - more scattered papular lesions, lichen planus-like lesions, prurigo nodularis, lichenification, post-inflammatory changes and extensor involvement in patients with darker skin tones
  - outcome measures may have poor reliability and validity in patients with darker skin tones, because of erythema perception. Eligibility and response criteria based solely on EASI or other such measures of severity may not be sensitive to people with darker skin tones
- Different ethnic groups have different cytokine pathways in atopic dermatitis, so dupilumab may be more effective in some groups. Th2 cytokines interleukin (IL)-4 and IL-13 predominate in most populations but some Asian populations IL-17 predominate

EASI, Eczema Area and Severity Index

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Additional information

COSMIN checklist

- Quality checklist for studies on outcome measures
- 12 sections
  - 10 sections assess quality of studies
    - measurement properties: internal consistency, reliability, measurement error, content validity, structural validity, hypotheses testing, cross-cultural validity, criterion validity, responsiveness
    - interpretability
  - 1 section on general requirements of methods
  - 1 section on generalisability of results

Other outcome measures

Hospital Anxiety and Depression Scale (HADS)

- 14 questions; 7 for anxiety and 7 for depression, scored from 0 to 3
- Scores range from 0-42 (total) or 0-21 (sub-domain of anxiety or depression)
- Overt anxiety or depression = total ≥11 or individual subdomain ≥8

European Quality of Life-5 Dimensions (EQ-5D-3L)

- Measure generic health status on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)
- Respondents self-rate level of severity for each dimension using three-level (EQ-5D-3L) or five-level (EQ-5D-5L) scale
- Respondents also evaluate overall health status using the visual analogue scale (EQ-VAS) (0–100)

Use of rescue medication

- Proxy for flares/exacerbations

Baseline characteristics of full population – Monotherapy (SOLO 1 & 2)

	SOLO 1		SOLO 2	
	dupilumab^ (n=224)	placebo (n=224)	dupilumab^ (n=233)	placebo (n=236)
Age in years*	40 (15)	40 (14)	37 (14)	37 (14)
Men, n (%)	130 (58)	118 (53)	137 (59)	132 (56)
BMI in kg/m²*	26 (5)	26 (6)	26 (6)	27 (6)
Caucasian, n (%) Asian, n (%)	155 (69) 54 (24)	146 (65) 56 (25)	165 (71) 44 (19)	156 (66) 50 (21)
Years with AD	29 (16)	30 (14)	27 (14)	28 (14)
Percent BSA with AD*	55 (23)	58 (23)	53 (21)	54 (23)
EASI (0-72, >20=severe)*	33 (14)	35 (14)	32 (13)	34 (14)
IGA (0-4, 4=severe)*	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
IGA = 4, n (%)	108 (48)	110 (49)	115 (49)	115 (49)
Weekly average of peak daily pruritus NRS (0-10, >6=severe)*	7.2 (1.9)	7.4 (1.8)	7.6 (1.6)	7.5 (1.9)
SCORAD (0-103, >50=severe)*	70 (14)	68 (14)	67 (13)	69 (15)
POEM (0-28, >24=severe)*	20 (6.4)	20 (5.9)	21 (5.5)	21 (6)
DLQI (0-30, >10=very large effect)*	14 (7.4)	15 (7.2)	15 (7.1)	15 (7.7)
HADS (0-42, 11 overt depression/anxiety)*	12.2 (7.3)	12.6 (8.3)	13.7 (7.5)	13.7 (8.32
EQ-5D (0-1) utility*	0.65 (0.32)	0.60 (0.34)	0.61 (0.32)	0.61 (0.35)

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; n, number of patients; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis

Key clinical outcomes for full population – SOLO 1 & 2 at 16 weeks as observed and SOLO-CONTINUE at 36 weeks (patients having rescue therapy censored)

	SOLO 1		SOLO 2	
	dupilumab^ (n=224)	placebo (n=224)	dupilumab^ (n=233)	placebo (n=236)
EASI 75, n (%)	133 (59)	50 (22)	116 (50)	37 (16)
	37 (29, 46)		***34 (26, 42)***	
IGA 0/1 & ≥2 point improvement, n (%)	91 (41)	29 (13)	87 (37)	25 (11)
	28 (20, 35)		***27 (19, 34)***	
EASI 50, n (%)	185 (83)	94 (42)	172 (74)	80 (34)
	41 (32, 49)		***40 (32, 48)***	
DLQI ≥4, n (%)	170 (76)	132 (59)	184 (79)	125 (53)
	17 (8, 26)		***26 (17, 35)***	
Weekly average of peak daily pruritus NRS (0-10, >6=severe)*	−3.9 (0.2)	−2.2 (0.2)	−3.3 (0.2)	−1.5 (0.2)
	−1.8 (−2.2, −1.4)		***−1.9 (−2.3, −1.5)***	
POEM (0-28, >24=severe)*	−12 (0.5)	−6 (0.5)	−11 (0.5)	−4 (0.5)
	−7 (−7.9, −5.4)		***−6 (−7.5, −5.1)***	
POEM ≥4, n (%)	184 (82)	113 (50)	189 (81)	117 (50)
	32 (23, 40)		***32 (23, 40)***	
HADS (0-42, 11 clinically overt depression/anxiety)*	−5 (0.6)	−4 (0.6)	−5 (0.4)	−2 (0.4)
	−2 (−2.8, −0.6)		***−4 (−4.5, −2.5)***	
EQ-5D (0-1) utility*	0.26 (0.01)	0.15 (0.01)	0.23 (0.01)	0.11 (0.1)
	0.11 (0.07, 0.14)		***0.12 (0.08, 0.15)***	

SOLO-CONTINUE: Responders (EASI 75 or IGA 0/1 + ≥2 point improvement from baseline) from SOLO 1 & 2 were re-randomised to 36 week maintenance: more patients re-randomised to dupilumab 300 mg every week or every 2 weeks achieved EASI 50 (116/169 dupilumab vs 24/83 placebo) or maintained IGA 0/1 (68/169 dupilumab vs 9/83 placebo) at 36 weeks compared to placebo.

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); *Difference (95% confidence interval)* ***bold*** *= statistically significant*; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; n, number of patients; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure

Use of rescue therapy for full population – SOLO 1 & 2 at 16 weeks

Rescue therapy n (%)	SOLO 1		SOLO 2	
	dupilumab^ (n=224)	placebo (n=224)	dupilumab^ (n=233)	placebo (n=236)
Any rescue therapy	47 (21)	115 (51)	35 (15)	123 (52)
Systemic corticosteroids	2 (1)	17 (8)	3 (1)	30 (13)
Immunosuppressants	3 (1)	5 (2)	1 (0.4)	16 (7)
Oral calcineurin inhibitors	2 (1)	4 (2)	1 (0.4)	13 (6)
Systemic immunosuppressants	1 (0.4)	0	0	0
Other immunosuppressants	0	1 (0.4%)	0	4 (2)

^licensed dose (300 mg every 2 weeks); n, number of patients

Baseline characteristics of full population – Combination (CAFÉ and CHRONOS)

	CAFÉ		CHRONOS	
	dupilumab^ + TCS (n=107)	placebo + TCS (n=108)	dupilumab^ + TCS (n=106)	placebo + TCS (n=315)
Age in years*	38 (13)	39 (13)	40 (14)	37 (13)
Men, n (%)	65 (61)	68 (63)	62 (59)	193 (61)
BMI in kg/m²*	25 (4)	26 (5)	26 (6)	26 (6)
Caucasian, n (%) Asian, n (%)	104 (97) 2 (2)	104 (96) 2 (2)	74 (70) 29 (27)	208 (66) 83 (26)
Years with AD*	30 (16)	29 (15)	30 (16)	28 (14)
Percent BSA with AD*	56 (18)	55 (21)	60 (21)	60 (22)
EASI (0-72, >20=severe)*	33 (10)	33 (11)	34 (13)	33 (13)
IGA (0-4, 4=severe)*	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
IGA = 4, n (%)	50 (47)	52 (48)	53 (50)	147 (47)
Weekly average of peak daily pruritus NRS (0-10, >6=severe)*	6.6 (2.1)	6.4 (2.2)	7.4 (1.7)	7.3 (1.8)
SCORAD (0-103, >50=severe)*	69 (12)	67 (12)	69 (15)	66 (14)
POEM (0-28, >24=severe)*	19 (6)	19 (6)	20 (6)	20 (6)
DLQI (0-30, >10=very large effect)*	14.5 (7.6)	13.2 (7.6)	14.5 (7.3)	14.7 (7.4)
HADS (0-42, 11 clinically overt depression/anxiety)*	13 (8)	13 (8)	13 (8)	13 (8)
EQ-5D (0-1) utility*	0.72 (0.26)	0.68 (0.29)	0.65 (0.28)	0.63 (0.32)

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; n, number of patients; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid

Key clinical outcomes for full population – CAFÉ and CHRONOS as observed

	CAFÉ at 16 weeks		CHRONOS at 16 weeks		CHRONOS at 52 weeks	
	dupilumab^ (n=107)	placebo (n=108)	dupilumab^ (n=106)	placebo (n=315)	dupilumab^ (n=106)	placebo (n=315)
EASI 75, n (%)	69 (65)	35 (32)	78 (74)	102 (32)	72 (68)	127 (40)
	32 (19, 45)		***41 (31, 51)***		***28 (17, 38)***	
IGA 0/1 & ≥2 point improvement, n (%)	43 (40)	16 (15)	41 (39)	49 (16)	40 (38)	60 (19)
	25 (14, 37)		***23 (13, 33)***		***19 (9, 29)***	
EASI 50, n (%)	95 (89)	54 (50)	91 (86)	176 (56)	92 (87)	192 (61)
	39 (28, 50)		***30 (21, 39)***		***26 (17, 34)***	
DLQI ≥4, n (%)	88 (82)	51 (47)	86 (81)	193 (61)	91 (86)	187 (59)
	35 (22, 48)		***20 (10, 30)***		***27 (17, 36)***	
Weekly average of peak daily pruritus NRS (0-10, >6=severe)*	-3.5 (0.2)	-1.7 (0.2)	−4.3 (0.2)	−2.6 (0.1)	−4.4 (0.2)	−2.6 (0.1)
	-1.8 (-2.3, -1.2)		***−1.7 (−2.2, −1.2)***		***−1.9 (−2.4, −1.4)***	
POEM (0-28, >24=severe)*	-12 (0.6)	-4 (0.6)	-13 (0.6)	-6 (0.4)	-14 (0.7)	-7 (0.4)
	-7 (-9.2, -5.7)		***-7 (-8.1, -5.3)***		***-7 (-8.5, -5.6)***	
POEM ≥4, n (%)	92 (86)	54 (50)	89 (84)	176 (56)	91 (86)	167 (53)
	36 (25, 48)		***28 (19, 37)***		***33 (24, 42)***	
HADS (0-42, 11 clinically overt depression/anxiety)*	-6 (0.6)	-2 (0.6)	−5 (0.6)	−4 (0.3)	−6 (0.6)	−4 (0.4)
	-3.8 (-5.3, -2.3)		*−0.7 (−2.0, 0.6)*		*−1.1 (−2.4, 0.3)*	
EQ-5D (0-1) utility*	0.19 (0.02)	0.10 (0.02)	0.22 (0.02)	0.18 (0.01)	0.24 (0.02)	0.18 (0.01)
	0.09 (0.04, 0.13)		*0.05 (0.00, 0.09)*		***0.06 (0.02, 0.10)***	

*Mean (standard deviation); ^licensed dose (300 mg every 2 weeks); *Difference (95% confidence interval)* ***bold*** *= statistically significant*; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and

Use of rescue therapy for full population – CAFÉ (at 16 weeks) and CHRONOS (at 52 weeks)

Rescue therapy n (%)	CAFÉ at 16 weeks		CHRONOS at 52 weeks	
	dupilumab^ + TCS (n=107)	placebo + TCS (n=108)	dupilumab^ + TCS (n=106)	placebo + TCS (n=315)
Any rescue therapy	4 (4)	19 (18)	17 (16)	167 (53)
Topical corticosteroids	3 (3)	16 (15)	16 (15)	151 (48)
Systemic corticosteroids	0	2 (2)	7 (7)	32 (10)
Immunosuppressants	0	3 (3)	1 (1)	25 (8)
Oral calcineurin inhibitors	0	3 (3)	0	14 (4)
Selective immunosuppressants	0	0	0	7 (2)
Other immunosuppressants	0	0	1 (1)	7 (2)

^licensed dose (300 mg every 2 weeks); n, number of patients; TCS, topical corticosteroids

Comparison of baseline characteristics in target population and EAMS patients

EAMS patients generally had lower EASI scores and higher DLQI scores compared to target population on dupilumab

	EAMS		SOLO-CAFÉ-like dupilumab^ (n=104)	CAFÉ & CHRONOS-CAFÉ-like dupilumab^ (n=130)
Measure	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
EASI	160	23.5 (13.1)	36.9 (14.6)	33.6 (10.5)
IGA	156	3.5 (0.7)	3.7 (0.5)	3.5 (0.5)
DLQI	161	16.65 (7.54)	15.7 (6.8)	14.6 (7.5)

EAMS: dupilumab was made available to adults with severe atopic dermatitis whose disease failed to respond, or who are intolerant of or ineligible for all approved therapies

^licensed dose (300 mg every 2 weeks); DLQI, Dermatology Life Quality Index; EAMS, Early Access to Medicines Scheme; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients

NICE CG57 severity definition and stepped approach to management

MODERATE

Physical severity (moderate): areas of dry skin, frequent itching, redness (± excoriation and localised skin thickening)
Quality of life: moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep

- Emollients
- Moderate potency topical corticosteroids (TA81)
- Topical calcineurin inhibitors (tacrolimus, TA82)
- Bandages

SEVERE

Physical severity (severe): widespread areas of dry skin, incessant itching, redness (± excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)
Quality of life: severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

- Emollients
- Potent topical corticosteroids (TA81)
- Topical calcineurin inhibitors (tacrolimus, TA82)
- Bandages
- Phototherapy
- Systemic immunosuppressant therapy (including oral corticosteroids, ciclosporin [licensed], azathioprine, methotrexate, mycophenolate mofetil)
- Best supportive care

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating adults with moderate-to-severe atopic dermatitis [ID1048]

Document B

Company evidence submission

March 2018

File name	Version	Contains confidential information	Date
Document B_REDACTED	**V 4**	**No**	**15th March 2018**

Contents

Figures

Tables

Abbreviations

AAR	Accelerated Access Review
ADA	Anti-drug antibody
ACD	Appraisal Committee Determination
AAD	American Academy of Dermatology
AAR	Accelerated Access Review
AD	Atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike's information criterion
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BLA	Biologic Licence Application
BNF	British national Formulary
BSA	Body Surface Area
BSC	Best Supportive Care
BTD	Breakthrough Therapy Designation
CEAC	Cost-Effectiveness Acceptability Curve
CCL17	Chemokine (C-C motif) ligand 17
CCL	CHRONOS-CAFÉ-like
CDLQI	Children's Dermatology Life Quality Index
CG	Clinical Guideline
CHMP	Committee for Human Medicinal Products
CMQs	Customised MedDRA queries
Cr. Int.	Credible Interval
CSR	Clinical Study Report
CUP	Compassionate Use Programme
DALY	Disability-adjusted life year
DARE	Database of Abstracts of Reviews of Effects
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analysis
EADV	European Academy of Dermatology and Venereology
EAMS	Early Access to Medicines Scheme
EAP	Early Access Programme
EASI	Eczema Area Severity Index

EASI-50	Eczema Area Severity Index ≥50% response
EASI-75	Eczema Area Severity Index ≥75% response
EASI-90	Eczema Area Severity Index ≥90% response
EDF	European Dermatology Forum
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESDR	European Society for Dermatological Research
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
FDS	Formulated drug substance
GISS	Global Individual Signs Score
HRQoL	Health-Related Quality of Life
HADS	Hospital Anxiety and Depression Scale
HOME	Harmonising Outcomes Measures in Eczema
HTA	Health technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
IEC	International Eczema Council
IGA	Investigators' Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4	Interleukin-4
IL-13	Interleukin-13
IL-4 Rα	Interleukin-4 receptor α
ISR	Injection site reaction
ITT	Intention-to-Treat
IV	Intravenous
LOCF	Last observed carried forward
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAIC	Matching-adjusted indirect comparison
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
ml	Millilitre
MI	Multiple imputation
MRI	Magnetic resonance imaging
MMRM	Mixed models for repeated measures
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence

NMA	Network Meta-Analysis
NRS	Numeric Rating Scale
OCS	Oral Corticosteroids
OLE	Open-label extension
ONS	Office for National Statistics
OS	Overall Survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PASI	Psoriasis Area Severity Index
PASLU	Patient Access Scheme Liaison Unit
PICOS-T	Population, Intervention, Comparator, Outcomes,
PIM	Promising Innovative Medicine
PMDA	Pharmaceuticals and Medical Devices Agency
POEM	Patient-Oriented Eczema Measure
PRISMA	European Dermatology Forum
PRO	Patient Reported Outcomes
PT	Preferred Term
PSA	Probabilistic sensitivity analysis
PUVA	Psoralen and ultraviolet A
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QW	Every week
Q2W	Every two weeks
Q4W	Every four weeks
Q8W	Every eight weeks
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard error
SAE	Serious Adverse Events
SC	Subcutaneous
SCC	Squamous cell carcinoma
SCORAD	Severity Scoring of Atopic Dermatitis
SD	Standard deviation
S. aureus	Staphylococcus aureus
SG	Standard Gamble
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SO	Scientific Opinion
TARC	Thymus and activation-regulated chemokine
TEAE	Treatment-emergent adverse event
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid

TGA	Therapeutic Goods Administration
TTO	Time-trade-off
UK	United Kingdom
US	United States
UVB	Narrowband ultraviolet B
VAS	Visual analogue scale
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform
WTP	Willingness to pay

Glossary*

Atopic Dermatitis	Chronic, eczematous skin condition that primarily affects children, is marked especially by intense itching, inflammation, and xerosis, and occurs chiefly in those with a personal or familial history of atopy
Atopy	A probably hereditary allergy characterised by symptoms (such as asthma, hay fever, or hives) produced upon exposure especially by inhalation to the exciting environmental antigen
Eczematous	An inflammatory condition of the skin characterised by redness, itching, and oozing vesicular lesions which become scaly, crusted, or hardened
Erythema	Abnormal redness of the skin or mucous membranes due to capillary congestion (as in inflammation)
Excoriation	Raw and irritated lesions
Lichenification	Process by which the skin becomes hardened and leathery usually as a result of chronic irritation
Papule	A small solid usually conical elevation of the skin
Pathophysiology	The physiology of abnormal states; specifically the functional changes that accompany a particular syndrome or disease
Pruritus	Local or generalised itching
Xerosis	Abnormal dryness of a body part or tissue (as the skin or conjunctiva)

*Taken from Websters medical dictionary (https://www.merriam-webster.com/. *Accessed 18/08/2017*)

Definitions and key descriptions used in the submission

Term	**Definition**
FAS	The full analysis set (FAS) included all randomised patients. This was the primary analysis population for efficacy analysis.
Primary analysis	In the primary response analysis patients receiving rescue treatment were censored and set to non-responders. Missing data was inputed thereafter using a range of methods including last observation carried forward and multiple imputation.
All observed	The 'all observed' response method includes all patients regardless of rescue treatment. The base case analysis uses the all observed method.
SOLO CAFÉ-Like (SOLO-CL)	Subgroup of patients from SOLO 1 & 2 who showed an inadequate efficacy response to oral ciclosporin, inadequate efficacy response or were intolerant to oral ciclosporin or patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or otherwise medically inadvisable. In this submission we refer to this population as the SOLO CAFÉ-like population.
CHRONOS CAFÉ-like (CCL)	A subset of CHRONOS which includes all patients who showed an inadequate efficacy response to oral ciclosporin, patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or because treatment with oral ciclosporin was otherwise medically inadvisable.
CAFÉ + CHRONOS CAFÉ-like (CCL)	Pooled analysis which includes CAFÉ and CHRONOS CAFÉ-like (CCL) patients. As both CAFÉ and CHRONOS-CAFÉ-like subgroups evaluated dupilumab when used concomitantly with TCS these two subgroups were pooled and are referred to as the CAFÉ+CCL population in this submission.
EASI-xx	Response to treatment according to the reduction in absolute Eczema Area Severity Index score. For example EAS-75 is a reduction of 75% in baseline EASI score. (Absolute EASI scores range from 0 to 72, where EASI 72 is the most serious including total body surface area involvement).

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

- Atopic dermatitis (AD) is an immune-mediated skin disease. It is characterised by unsightly skin lesions that are often persistent or relapsing with pronounced erythema (redness), scaly plaques, bleeding, oozing, cracking, flaking and dry/rough skin[1, 2].
- AD often begins in infancy and affects 10-15% of children. The prevalence in adults is estimated to be 2.5% in the UK and for many patients is a chronic, lifelong condition[1].
- For the patient population addressed in this submission, that is moderate to severe AD, pruritus (itch) can be unrelenting, frequent, persistent and intense and can disrupt sleep and/or cause anxiety or depression, and is the most intrusive symptom reported by patients with moderate-to-severe AD[2, 3].
- Moderate to severe AD has a profound negative impact on patients' quality of life (QoL)[2, 4] demonstrated to be greater than other skin disorders such as psoriasis[2, 5, 6].
- QoL scores for moderate-to-severe patients as measured by EQ-5D at baseline in the LIBERTY trial programme reflect a QoL that is only around 60% (or less) of full health.
- Patients with more severe AD are more likely to report a higher impact of their disease on employment, study and career opportunities than patients with milder disease[2]. Patients with AD also report higher absenteeism and overall work impairment[5].
- A holistic approach to disease management is recommended. Tools exist to assess the severity of the clinical signs or the impact on quality of life of AD. However, no single tool captures all the elements of AD that are important to patients and their clinicians.
- Systemic immunosuppressants (of which only ciclosporin is licenced for AD in the EU) are used after non-responsiveness to topical treatments, but these do not specifically target the underlying mechanisms of the disease and their long-term use is limited by severe, and potentially life-threatening, adverse effects[7-10].
- There are currently no effective treatments for patients who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. For these patients there are no other options beyond Best Supportive Care (BSC).
- The marketing authorisation for dupilumab (Dupixent®) is for treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy[11].
- Sanofi Genzyme requests NICE's consideration of dupilumab for the treatment of adult patients with moderate-to-severe AD not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. This reflects the likely use of dupilumab in UK clinical practice.
- Dupilumab, designated a Promising Innovative Medicine (PIM) by the MHRA was the first medicine for a non-life threatening, chronic condition to be approved for the Early Access to Medicines Scheme (EAMS) in the UK. This acknowledgement highlights both the innovative nature of dupilumab, and the high unmet need for an effective treatment.

B 1.1 Decision problem

The marketing authorisation for dupilumab (Dupixent®) is for treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy[11].

The submission focuses on part of the technology's marketing authorisation. The expected population for dupilumab in UK clinical practice is moderate-to-severe patients previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. This is narrower than the marketing authorisation because:

- The marketing authorisation is for patients eligible for systemic therapy.
- This position is relevant to NHS clinical practice as we expect clinicians will use dupilumab after considering a systemic immunosuppressant agent.
- This position reflects where dupilumab provides the most clinical benefit for patients in England and Wales and the highest unmet need for effective treatment.

The company submission is broadly consistent with the final NICE scope and is consistent with the NICE reference case see table below.

Table 1.1 The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	The decision problem in the submission considers two populations: **1. Base case**: Adults with moderate-to-severe AD with a history of intolerance, inadequate response or contraindication to topical therapies (emollients, TCS, TCI) and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable **2. Scenario analysis:** full licence population for adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	The base case population is considered the most likely place in therapy for dupilumab as it reflects the highest unmet need in UK clinical practice. This patient population is a subgroup of the full licence population. A scenario analysis based on the full licence population as defined in the NICE decision problem is also presented. Hence the licence indication is broader than the expected position and usage of dupilumab in the real world.
Intervention	Dupilumab / Dupixent®	Dupilumab / Dupixent®	As per final scope
Comparator(s)	• Phototherapy including the one with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA) • Immunosuppressive therapies (azathioprine, ciclosporin, and methotrexate) • Oral steroids • Best supportive care (combination of emollients, low-to-mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors) • Alitretinoin (in people with atopic dermatitis affecting the hands)	Best supportive care (combination of emollients, low-to-mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors. In the real world BSC also includes systemic immunosupressant therapies). The evidence is sparse for comparison with the current systemic immunosupressant therapies and we believe that dupilumab would be positioned after them we do present a comparison with ciclosporin using a mixed adjusted indirect comparison (MAIC) in scenario analysis. .	Phototherapy, oral steroids are not valid comparators for dupilumab because these are short-term treatment options and would not be used as chronic/long term/continous treatment of AD. • Phototherapy is typically used after the failure of topical therapies and is considered to be useful for the intermittent control of active symptoms. The recently published treatment algorithm from the International Eczema Council places UV therapy higher in the pathway directly after the failure of topical therapies and before the use of immunosupressants[12]. It is not a long-term option due to the increased risk of skin cancer. Phototherapy is not universally available and not used by all clinicians • Oral steroids are not recommended as a long-term treatment option for patients with AD. European guidelines state that courses of systemic steroids should not exceed 2 weeks due

			to long-term side effects • Alitretinoin is also not a valid comparator to dupiliumab based on its licenced indication and place in therapy in treatment of severe chronic hand eczema Alitretinion is used for hand eczema. Atopic dermatitis affecting the hands and chronic hand eczema are not synonymous. The latter is a clinical umbrella term for a collection of conditions affecting hands that manifest in various forms and can have distinct and sometimes unknown causes. Importantly, in numerous studies, atopic dermatitis consistently accounts for only a low percentage of registered causes of hand eczema (13% to 23%)[13, 14] Regulatory authorities approved aliretinoin for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids whereas dupilumab is approved for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy • The dupilumab trial programme did not include measures of hand eczema and in one of the two pivotal alitreinoin Phase III studies patients with AD treated with prescription drugs were excluded. Hence we do not believe that alitretion is a valid comparitor for dupilumab and comparison with it is not feasible given the evidence base
Outcomes	• Measures of disease severity • Measures of symptom control • Disease-free period/maintenance of remission • Time to relapse/prevention of relapse	Clinical outcomes supported by evidence from the LIBERTY trial programme are reported addressing all the points raised in the scope. Outcomes used in the economic modelling are: • Measure of disease severity (for example according to absolute EASI or IGA scores)	As per final scope

	• Adverse effects of treatment • Health-related quality of life	• Measures of symptom control according to relative EASI scores (reduction in absolute score) • Adverse effects of treatment • Health-related quality of life	
Economic analysis	• Cost-effectiveness should be expressed in terms of incremental cost per quality-adjusted life year • Time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs from an NHS and Personal Social Services perspective	As per final scope.	As per final scope.
Subgroups to be considered	• People with atopic dermatitis affecting the hands • People for whom therapies have been inadequately effective, not tolerated or contraindicated • Skin colour subgroups.	As per the scope we present the following sub-group as our base case: People for whom therapies have been inadequately effective, not tolerated or contraindicated. This is more specifically defined, in line with the SmPC as: Adults with a history of intolerance, inadequate response or contraindication to topical therapies (emollients, TCS, TCI) and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.	The population included in this submission in the base case is the subgroup for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable This is the anticipated position for dupilumab in real world clinical practice in the UK. The clinical trial programme for dupilumab was not designed to measure the effect on localised areas of the body such as hand eczema. Although it is likely that dupilumab would have an effect on hand eczema there were no outcomes associated with hand eczema in the study against which this can be measured. There is no evidence in the trial programme to suggest that outcomes for people with various skin colour groups are different. However, the assessment of eligibility and efficacy for these

			patients is nuanced and clinicians should be aware of the way in which the disease presents for these groups.
Perspective for outcomes	[All direct health effects, whether for patients or, when relevant, carers]	As per final scope.	As per final scope.
Perspective for costs	[NHS and PSS]	As per final scope.	As per final scope.
Time horizon	[Long enough to reflect all important differences in costs or outcomes between the technologies being compared]	Phase III outcomes from the LIBERTY trial programme are limited to 1 year. These are extrapolated to a lifetime time horizon in accordance with NICE methods guide.	As per final scope.
Synthesis of evidence on health effects	[Based on systematic review]	Evidence is taken from the LIBERTY trial programme and supported by systematic review (SLR). For the comparisons with immunosuppressant agents a Matching-Adjusted Indirect Comparison (MAIC) was used also supported by an SLR.	As per final scope.
Measuring and valuing health effects	Expressed in QALYS using EQ-5D	As per final scope. EQ-5D was included in the LIBERTY trial programme.	As per final scope.
Source of data for measurement of health-related quality of life	[Reported directly by patients and/or carers]	Directly reported from patients in the LIBERTY trial programme. . In addition to EQ-5D, DLQI was included in the clinical trial programme to elicit health-related QoL from patients with AD.	As per final scope.
Source of preference data for valuation of changes in health-related quality of life	[Representative sample of the UK population]	As per final scope.	As per final scope.
Equity considerations	[An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit]	As per final scope.	As per final scope.
Evidence on resource use and	NHS & PSSRU	As per final scope.	As per final scope.

costs			
Discounting	[The same annual rate for both costs and health effects (currently 3.5%)]	As per final scope.	As per final scope.

B 1.2 Description of the technology being appraised

A description of dupilumab is provided in Table 1.2 below. Please refer to Appendix C for the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR).

Table 1.2 Key details of dupilumab

UK approved name and brand name	**Dupilumab/ Dupixent®**
Mechanism of action	Dupilumab is a fully human monoclonal antibody that specifically binds to the shared alpha chain subunit of the receptors for interleukin (IL)-4 and IL-13, inhibiting IL-4 and IL-13 signalling[15-18]. IL-4 and IL-13 are key inflammatory cytokines thought to be important drivers of atopic diseases, such as atopic dermatitis (AD). • T-helper type 2 (Th2) lymphocytes and the cytokines they produce, including IL-4 and IL-13, are elevated in patients with moderate-to-severe AD. These activate proinflammatory pathways, leading to chronic cutaneous inflammation. This type 2 response-mediated inflammation is recognised as the key underlying disease driver for AD • Inhibition of IL-4 and IL-13 signalling with dupilumab is associated with decreases in concentrations of type 2-associated biomarkers, such as thymus and activation-regulated chemokine/chemokine (C-C motif) ligand 17 (TARC/CCL17), total serum immunoglobulin E (IgE), and allergen-specific IgE in serum
Marketing authorisation/CE mark status	Committee for Human Medicinal Products (CHMP) opinion was received on the 20 July 2017 and Marketing Authorisation (MA) from the European Medicines Agency (EMA) was obtained on the 28 September 2017[19]. Dupilumab was granted Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA) on the 23 December 2015. Positive Scientific Opinion for the Early Access to Medicine Scheme (EAMS) was received on the 13 March 2017. See Section B 2.11.2 for more information about the dupilumab EAMS.
Indications and any restriction(s) as described in the summary of product	The indication for dupilumab is: *Dupilumab (Dupixent®) is indicated for treatment of moderate-to-severe atopic dermatitis in adult patients* who are candidates for systemic therapy. Dupilumab (Dupixent®) can be used with or without topical therapies.* Contraindications included in the draft Summary of Product Characteristics (SmPC) are:

characteristics (SmPC)	• Hypersensitivity to the active substance or any of the excipients: sucrose, L-arginine-hydrochloride, L-histidine, polysorbate 80, sodium acetate and acetic acid • The safety and efficacy of concurrent use of dupilumab with live vaccines has not been studied. Live vaccines should not be given concurrently with dupilumab. Patients with pre-existing helminth infections should be treated prior to initiating dupilumab. If a patient becomes infected while receiving treatment with dupilumab and does not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until infection is resolved. Limited data exist for the use of dupilumab in pregnant women. Dupilumab should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. *The efficacy and safety of dupilumab were evaluated in the clinical trial programme in patients 18 years of age and older.
Method of administration and dosage	**Administration** • 300 mg solution for injection in pre-filled syringes • Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis. • Self-administered by subcutaneous (SC) injection into the thigh or abdomen • Available with homecare delivery **Dosage** • Initial dose of 600 mg (two 300 mg injections), followed by 300 mg once every two weeks (Q2W) • No dose adjustments are recommended for dupilumab **Storage** • Dupilumab should be stored in a refrigerator and allowed to reach room temperature by waiting for 45 minutes before use • If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days
Additional tests or investigations	No additional tests or investigations are required for patients treated with dupilumab.
List price and average cost of a course of treatment	Annual cost at list price: £16,500 based on 26 injections per year of 300 mg solution in pre-filled syringe. An additional loading dose in required in year 1. Cost in year 1 is therefore £17,132.45. List price for a pack of two pre-filled syringes: £1,264.89.
Patient access scheme (if applicable)	A simple, confidential Patient Access Scheme (PAS) was approved on 15th November 2017 by the Department of Health. A discount to the list price of [redacted] The PAS adjusted price for a pack of two pre-filled syringes [redacted]

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

B 1.3.1 What is Atopic Dermatitis (AD)?

Atopic Dermatitis (AD) is an immune-mediated skin disease characterised by chronic or relapsing red and inflamed skin (erythema) and an intense and unrelenting itch. The clinical term for itch is pruritus. Clinical features of AD include skin dryness, erythema (redness), oozing, and crusting, and lichenification (skin that has become thickened and leathery). Pruritus, a hallmark of the condition, is responsible for much of the disease burden for patients and their families.

AD is also called atopic eczema. Eczema is the common term for a variety of skin conditions, of which AD is the most severe. For many years, AD was thought to be the first manifestation of atopy (a familial propensity to become IgE-sensitised to environmental allergens) and the initial step to the so-called '*atopic march*' that ultimately leads to asthma and allergic rhinitis[1]. More recent research has suggested that the underlying pathogenesis is a complex interplay of genetic background, environmental influences, and immunological deviation that leads to an impaired epidermal barrier and a dominating type 2 immunity[20].

AD is now recognised as a lifelong condition with variable clinical manifestations and expressivity, in which defects of the epidermal barrier are central for the progress of the condition and the development of complications.

B 1.3.2 Epidemiology

Typically, AD develops during childhood and in approximately 60% of cases the disease occurs in the first year of life[7, 21]. Indeed, the onset of the disease for most adults with AD occurs during childhood[21-24]. The disease can be remitting/relapsing with repeated flares[21]. In about 70% of cases the disease greatly improves or resolves in childhood. However, early and severe onset, family history of AD, allergic rhinitis, pollen allergy, and oral allergy syndrome are risk factors for a disease course to continue beyond childhood[1, 25].

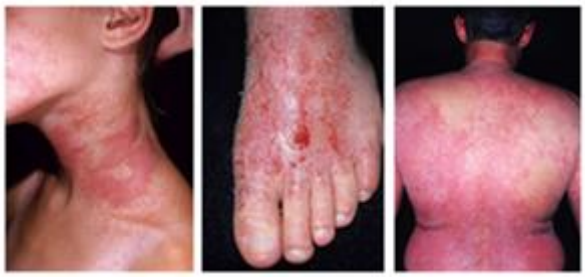
Worldwide, the lifetime prevalence of AD has increased over the last 30 years, and occurs in 10–20% of the population in developed countries. Prevalence is lower, but increasing, in developing countries[26]. In adults, the prevalence is estimated at about 2–3%[27], but some studies have suggested it may be as high as 10% [28]. The UK prevalence of AD is estimated at 2.5%[29], of which 69% are diagnosed and treated[30] , and of these, 7% have moderate-to-severe AD[31]. Moreover, patients who have 'outgrown' the disease may have hypersensitive skin and might have recurrences after long symptom-free periods[21].

B 1.3.3 Clinical features and diagnosis

AD is a highly heterogeneous disease with variations observed in age of onset (i.e. infant, adolescent and adult), course, presentation and comorbidities[32]. Diagnosis is made holistically based on a patient's medical history, characteristic clinical findings and exclusion of other skin conditions[33]. Signs and symptoms range from an occasional dry and scaly patch of skin in mild cases, to a chronic, debilitating disease with extensive skin lesions[2], see Figure 1.1. Essential features are pruritus and eczematous lesions, which can affect any

area of the body. Skin lesions in patients with severe AD are often persistent or relapsing and are characterised by redness of the skin (erythema), skin lesions (papules), and scaly plaques accompanied with the characteristic intense, protracted itching (pruritus)[20]. Pruritus, which can be persistent and consequently can disrupt sleep and/or cause anxiety or depression, is the most intrusive symptom reported by patients with moderate-to-severe AD[2, 4]. The disease course may be relapsing-remitting with acute flares on top of a background of persistent skin inflammation.

Figure 1.1 Examples of the visible signs of adults with moderate-to-severe AD: erythema, bleeding, oozing, cracking, flaking and dry/rough skin



In a survey by Allergy UK[34], patients were asked, 'What is the impact of AD on your quality of life?'.The burden of the disease comes through powerfully (see Appendix S for complete patient quotes):

'Its massive, constant itch and/or pain.'

'Blood and skin in my bed every morning, skin coming off in my clothing, having to cover myself in emollients etc all the time and getting criticised for leaving the car steering wheel etc greasy, my children not wanting to be near me when I'm "sticky".'

'My eczema is all over my body but mainly my face which flares often. I don't like going anywhere or being around people who doesn't know why my face is bright red and scabby. I have no self-esteem or confidence. It affects my relationship as I feel I'm not good enough even though we've been together 10 years.'

B 1.3.4 Measuring disease severity and clinical response

The current NICE guideline for AD for children is NICE GC57, which suggests that healthcare professionals should adopt a holistic approach when assessing a child's atopic dermatitis[35] (Table 1.3). There is no equivalent NICE guideline for adults. This should consider severity, quality of life (including everyday activities and sleep) and psychosocial wellbeing. Patients categorised as 'moderate' based on AD signs may be 'severe' based on patient-reported symptoms and vice-versa, while all might have significantly impaired QoL.

Table 1.3 Holistic assessment of severity, psychological and psychosocial wellbeing and quality of life

Skin/physical /severity		Impact on quality of life and psychosocial well being	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or without small areas of redness)	Mild	Little impact on everyday activities, sleep and psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact on everyday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep

Additional validated tools to measure impact on quality of life, such as Patient-Oriented Eczema Measure (POEM), and Children's Dermatology Life Quality Index (CDLQI) are also mentioned in CG57.

Tools exist to measure severity, including the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis index (SCORAD) and the Investigators' Global Assessment (IGA) Scale (see Appendix L for a full description of these assessment tools). Generally, these scales measure the degree and extent of erythema, skin papules, skin thickening, itch and may include other factors such as loss of sleep. Patients' response to treatment may also be included in the scoring system.

The EASI score assesses the extent of disease at four body sites and measures four clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of zero to three. The EASI score confers a maximum of 72 and evaluates two dimensions of AD: disease extent and clinical signs. The suggested severity strata for the EASI are as follows: 0 = clear; 0.1–1.0 = almost clear; 1.1–7.0 = mild; 7.1–21.0 = moderate; 21.1–50.0 = severe; 50.1–72.0 = very severe[36]. The EASI score does not assess symptoms like pruritus and sleep loss[37].

The psoriasis area and severity index (PASI) is used routinely in patients with psoriasis to describe signs and severity of the disease[38]. The principle of integrating disease extent and severity to describe disease led to the definition of the EASI[39]; however, these two scoring systems are not equivalent. Psoriasis is characterised by well-demarcated, dry, bright-red plaques with thick, non-adherent, silvery-white scales, usually on extensor surfaces and the scalp[23]. In contrast, AD lesions may present with acute (oozing, crusted, eroded vesicles or papules on erythematous plaques), subacute (thick and excoriated plaques), and chronic (lichenified, slightly pigmented, excoriated plaques) forms. Furthermore, xerosis (dry skin) and a lowered threshold for itching are usual hallmarks of AD[40]. These differences make EASI more difficult to implement than PASI and less appropriate as a standalone measure of disease burden or change in disease status.

The SCORAD index was also included in the clinical trials and has three elements: extent of disease, disease severity and subjective symptoms. These combine to give a maximum

possible score of 103[37]. The commonly used SCORAD strata to classify AD severity are mild = 0–25, moderate = 26–50 and severe = 51–103[41, 42]. This is not commonly used in the UK.

The IGA scale allows investigators to assess overall disease severity at one given time point, and it consists of a six-point severity scale from clear to very severe disease (0= clear, 1 =almost clear, 2 = mild disease, 3 = moderate disease, 4= severe disease and 5= very severe disease). The IGA scale uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment[37].

These clinical scales are widely used in clinical trials. However, clinical opinion obtained by us, during a recent advisory board suggests that in everyday UK practice physicians' judgement and response to treatment are more commonly used as an indicator of disease severity. There is no universal consensus on the most appropriate tool for the assessments of disease. No tool captures all the elements of AD important to patients and healthcare professionals such as the clinical signs, severity of itch and loss of sleep.

In the LIBERTY AD clinical trials, patients were considered to have moderate-to-severe disease if they had an IGA score ≥3 (SOLO 1 and 2, CHRONOS and CAFÉ), an EASI score ≥16 (CHRONOS) or EASI ≥20 (CAFÉ), at baseline and screening[43-45].

In addition to the clinical scales, there are several patient-reported scoring tools used to assess quality of life (QoL) in patients with AD, such as the Dermatology Life Quality Index (DLQI), POEM, or the Hospital Anxiety and Depression Scale (HADS). These are described in full in Appendix L and are summarised below.

The DLQI is a 10-question validated questionnaire used to measure the impact of skin disease on the QoL of an affected person[46]. The ten questions explore symptoms and feelings, the effect of AD on daily activities, leisure, work, school and personal relationships, as well as the response to treatment over the previous week. The patient scores each question from zero to three, giving a possible total score range from zero (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life). The following band descriptors are used to give clinical meaning to the DLQI score: 0-1 = no effect at all on patient's life; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect[47].

The POEM is a validated, reliable and simple patient-derived assessment measure of AD severity across aspects of the disease that are important to patients[48]. POEM incorporates seven questions that explore the presence of itch, sleep disturbance, bleeding, weeping/oozing, cracked skin, flaking skin and dry/rough skin. The patient answers the questions using a five-point scale, with a maximum total score of 28. The following severity bands are used to give clinical meaning to the POEM score: 0 to 2 = clear or almost clear; 3 to 7 = mild; 8 to 16; moderate; 17 to 24 = severe; 25 to 28 = very severe[49]. POEM is endorsed by the Harmonising Outcome Measures in Eczema (HOME) initiative[50].

The HADS is a well-established and validated tool that measures anxiety and depression, which commonly co-exist in patients with moderate-to-severe AD[51] (see Section B 1.3.6). The questionnaire comprises seven questions for anxiety and seven questions for

depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety (HADS-A) or depression (HADS-D). A cut-off of 8 or more for HADS-A or HADS-D is frequently used to determine the presence of overt anxiety or depression, respectively[52].

There is an ongoing debate about what the most appropriate tool for the assessment of disease is. Recently an expert panel of the International Eczema Council recommended that severity-based scoring systems alone cannot determine the need for systemic therapy and that holistic assessment is needed[12]. This includes consideration of signs and symptoms along with the impact on QoL, together with emotional and social functioning. Formal tools can be helpful, but the authors recognise the limitations of severity scoring with a single static point in time which can over- or underestimate the true AD severity due to the relapsing remitting nature of the disease. Similarly, QoL can be measured with instruments but clinicians can assess and document QoL by using simple, open-ended questions, such as *'How is your atopic dermatitis affecting you?'* or *'How does your atopic dermatitis affect your life at home or at school/work?'*

B 1.3.5 Pathophysiology

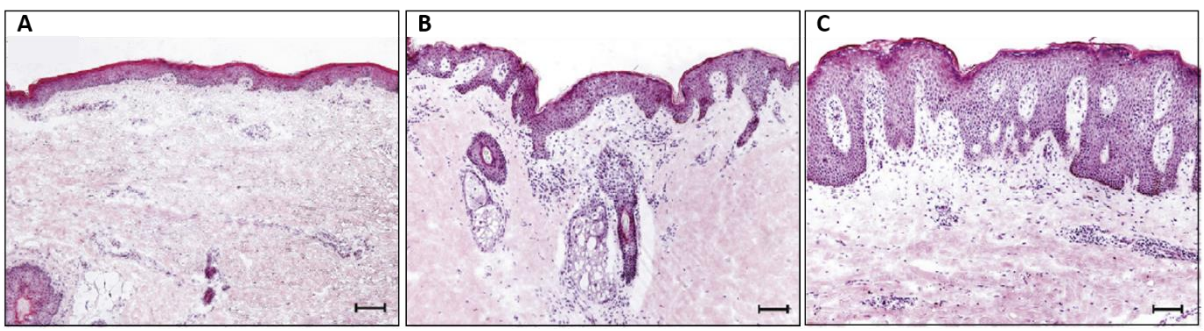
The pathophysiology of AD is complex and not yet fully understood. While the primary events and key drivers of AD are under debate, skin barrier dysfunction and immuno-inflammation are key factors.

Importantly, there is a growing understanding that the pathological changes associated with the AD are not restricted only to the affected skin, but can have systemic (whole-body) consequences[53, 54].

Skin is an efficient physicochemical, antimicrobial and immunological barrier. In patients with AD, well-established features are abnormalities of the epidermal barrier, such as decreased hydration and increased water loss, altered lipid composition, raised skin pH, and reduced skin microbiome diversity with an increased abundance of *S. aureus*. These features were regarded as secondary effects of immunological mechanisms, but genetic studies have shown that genetically determined epidermal defects confer susceptibility to AD[1].

In patients with AD, even non-lesional (apparently unaffected) skin is not healthy and is characterised by atypical immunological profiles, barrier dysfunction and persistent underlying inflammation (Figure 1.2)[55].

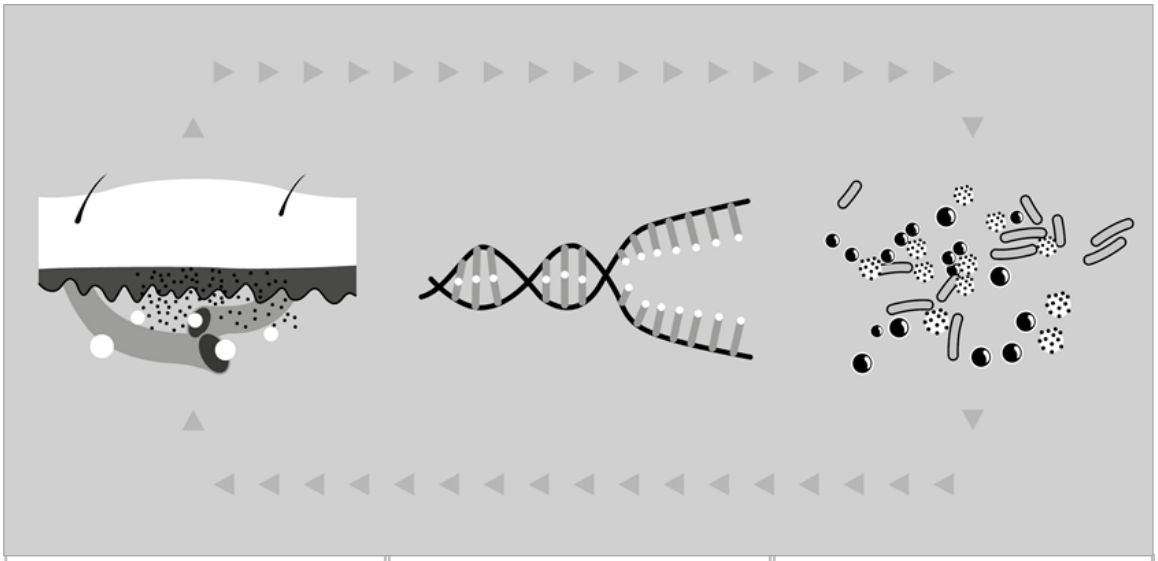
Figure 1.2 Immunohistochemistry staining of terminal differentiation proteins from healthy skin (A) and the skin without (B) and with (C) lesions from patients with AD[55]



Cutaneous inflammation is the other hallmark of AD and is characterised by successive and progressive patterns of inflammatory cell infiltration, particularly by $CD4^+$ lymphocytes. As seen above, non-lesional skin shows signs of subclinical inflammation and this is characterised by increased numbers of T-helper type 2 (Th2) cells[56]. The activation of this inflammatory pathway plays a central role in AD.

Two cytokines, interleukins IL-4 and IL-13, are critical in the initiation and maintenance of this Th2 inflammatory pathway. In AD, increased levels of IL-4 and IL-13 lead to amplified signalling of type 2 (including Th2) cytokines and chemokines, activation of subsequent proinflammatory signalling pathways, and further weakening of the epidermal barrier[16, 57]. The epidermal barrier disruptions and skin inflammation are mutually reinforcing processes[1]. Disruption of the epidermal barrier stimulates the inflammatory pathway, which in turn affects the epidermal structure and function, leading to a vicious cycle of promotion of Th2 responses, keratinocyte proliferation, and epidermal thickening[1] (Figure 1.3).

Figure 1.3 The complex pathophysiology underlying AD[27, 58, 59]

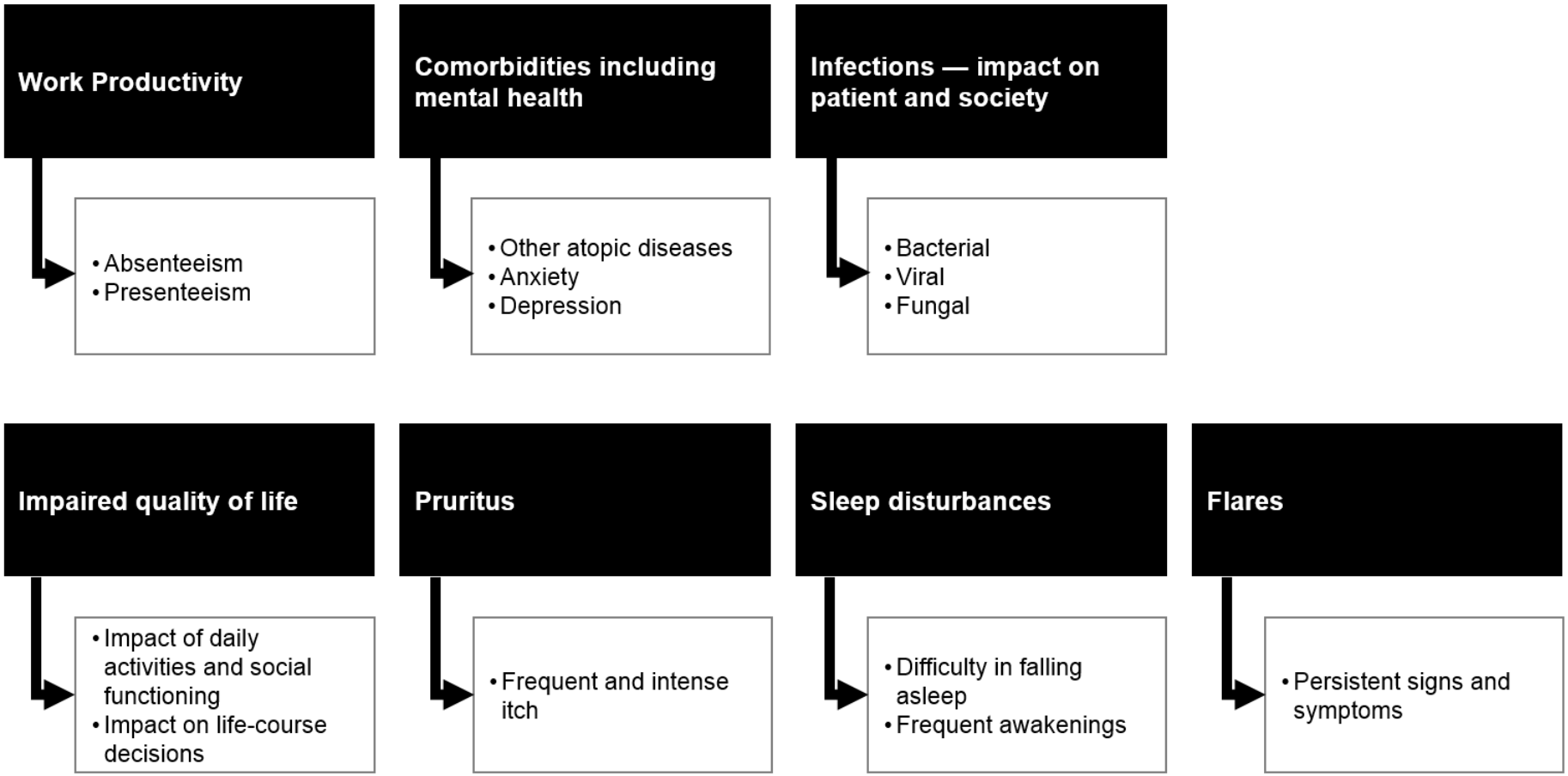


Immune-mediated inflammation	Genetic factors	Environmental triggers
Activation of Th2 cells along with other type 2 inflammatory cells plays a key role	Susceptibility genes: defects in structural proteins in the epidermal barrier	For example, allergens, microbes, diet, and stress

B 1.3.6 Disease burden of AD

A shown above AD is a disease with a complex pathophysiology and an equally complex set of wider consequences. It has an impact at the individual, familial, and, given its overall prevalence, at a societal/population level. (Figure 1.4).

Figure 1.4 Disease burden of AD[2, 60-63]



B 1.3.6.1 Societal burden of AD

The burden of AD has an important health impact at the population level and is ranked first among common skin diseases, with respect to disability-adjusted life years (DALYs) and years lived with a disease in the WHO 2013 Global Burden of Disease survey[1, 64] (see Figure 1.4). Importantly, the true burden of AD on society may be underestimated even by this comprehensive study, as the psychosocial effects and comorbidities are not considered in the analysis[1].

There is a significant economic burden associated with AD compared to people without AD resulting from loss of productivity[62, 65], high level of healthcare resource utilisation (e.g. during disease flares and presence of comorbidities)[1, 66]. The more severe the disease the higher the economic burden compared to milder disease[61, 67]. A recent, large-scale analysis of US healthcare claims data reported a significantly greater disease burden of comorbidities ($p<0.0001$), healthcare resource utilisation ($p<0.05$) and costs ($p<0.0001$) among adults with AD relative to matched non-AD controls[67]. Stratification of patients by disease severity revealed that comorbidity and economic burden were significantly greater ($p<0.0001$) in patients with higher disease severity than in those with lower disease severity. Flares (exacerbation of disease), in particular, has been reported to cost €2.3 billon/year in lost productivity across the European Union[62].

Patients with AD report lower work productivity compared to non-AD controls[61]. A recent real world study reported that compared to employed non-AD controls, patients with AD reported higher absenteeism (9.9% vs. 3.6%; $p <0.001$) and overall work impairment (25.6% vs. 18.1%, $p=0.004$)[5]. The magnitude of lost wages was significant in AD patients[5]. Similar results were seen in a large US study (n=75,000) workers with AD absenteeism and presenteeism for AD workers was 3- and 1.7-fold greater, respectively, compared with workers without AD[61]. UK specific data on economic impact of AD has not been widely studied and there is currently no robust UK data (see Section 3.5.2.1 and Appendix G), particularly for patients with moderate-to-severe disease. However, applying the average number of days lost to work through sickness (4.3) from the Office for National Statistics (ONS) 2016 data[68] to the US study above, would suggest there are 12.9 days per year lost productivity due to AD in the UK compared to 4.3 days in patients without AD.

B 1.3.6.2 Effect of AD on patients

The loss of the protective skin barrier and immune system dysregulation associated with AD contributes to the significant disease burden of AD. The intense, persistent pruritus, severity of skin lesions and flares experienced by patients with moderate-to-severe AD can significantly impact on daily functioning and lead to sleep deprivation, symptoms of anxiety or depression and poor health-related quality of life (HRQoL)[2, 62]. Compared with other dermatologic conditions, patients with moderate-to-severe AD report a more severe impact on HRQoL than patients with other skin conditions such as psoriasis, and chronic urticaria[2, 5, 6] (Figure 1.4). In addition, disruption of the epidermal barrier increases susceptibility to skin infections[1] and most patients with AD have at least one other allergic condition e.g. asthma[2] (Figure 1.4).

B 1.3.6.2.1 *Comorbidities*

Many patients with AD are living with comorbid asthma and other atopic allergic or atopic conditions, all of which have a similar aetiology driven by a common immune dysregulation (e.g. excess T-helper type 2 inflammation).

Up to 60% of adults with AD have one or more additional allergic condition[2, 27, 66, 69]. AD patients have a 33% greater risk of developing other atopic diseases, such as asthma (20% higher risk), allergic rhinitis (35%), allergic conjunctivitis (50%), and food allergies (135%) compared to patients without AD[66]. The presence of these conditions increases the disease burden, healthcare use and complexity of managing AD patients.

B 1.3.6.2.2 *Mental health*

Relative to the general population, adults with AD are at increased risk of anxiety and depression[5, 70-73]. A recent real world study showed that compared to non-AD controls, anxiety (29.8% vs. 16.1%; OR 2.2) and depression (31.2% vs 17.3% OR 2.2) was reported significantly ($p < 0.001$) more often in patients with AD[5]. Anxiety or depressive symptoms are present in almost half (43% to 46%) of patients with moderate-to-severe AD, and the prevalence of these psychological symptoms increases with disease severity[2, 5, 74, 75].

In addition to the 'atopic march' (See Section B 1.3.1) a 'psychiatric march' may exist in patients with AD[76]. The association between AD and suicide ideation has been reported in several studies, and most recently from the Danish Study of Functional Disorders (DanFunD)[77]. This study found significant associations between self-reported AD and clinician-diagnosed depression and anxiety, respectively. More patients with AD reported having suicidal ideation within the past week compared with non-AD subjects.

Similarly, in a German study a significantly higher level of suicidal ideation, anxiety and depression was shown among patients with atopic dermatitis[78]. Strong correlations between severity of symptoms and psychological burden were observed. Of patients with AD, 21.5% indicated recent suicidal ideation (control: 0%, $p=0.000$) and 6.6% attempted suicide (control: 0%, $p=0.035$)[78]. This is in line with earlier estimates in the literature which can be as high as 19.6%[79].

In a recent study by the University of Manchester which collected information on 922 suicides by people aged under 25 in England and Wales during 2014 and 2015, 9% of under twenty year olds with completed suicide had a medical history which included dermatological conditions (in particular acne and eczema)[80].

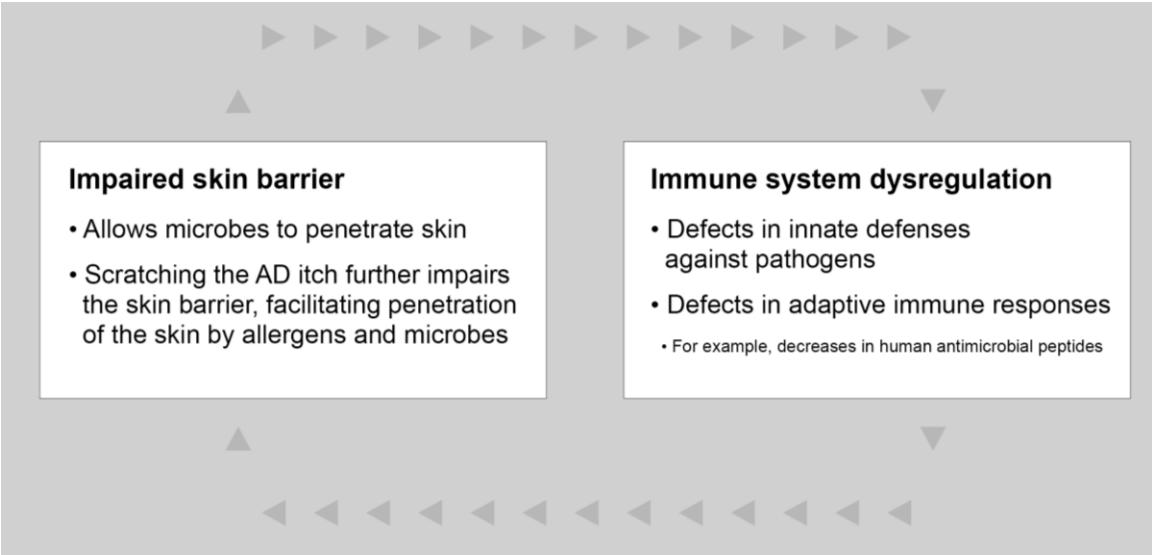
B 1.3.6.2.3 *Risk of infection*

The loss of the protective epidermal barrier associated with AD leads to water loss, and dry, cracked skin, that allows for the entry of microbes that can lead to fungal (e.g. *malassezia sympodialis*), viral (e.g. eczema molluscatum, eczema vaccinatum, or eczema herpeticum, which can be fatal in very rare cases)[81, 82], and bacterial skin infections (e.g. *staphylococcus aureus* or streptococci) (Figure 1.5). Patients may need to be admitted to hospital to treat severe infections.

Patients with AD exhibit defects in innate and acquired immune responses that result in further susceptibility to these infections, sometimes for periods of several weeks.

Staphylococcus aureus (*S. Aureus*) colonisation is present in 73% to 100% of patients with AD along with other secondary skin infections[58, 60, 83-89]. *S. aureus* skin colonisation, can exacerbate or contribute to persistent skin inflammation and increase the severity of AD[7, 83, 84, 86, 87, 90, 91]. Furthermore, the *S. aureus* carrier status of under-treated AD patients may represent a community risk for spreading methicillin resistant *S. aureus* infections[87].

Figure 1.5 Skin infection mechanisms[86, 87, 92, 93]



AD – atopic dermatitis

B 1.3.6.2.4 *Impact of disease on patient quality of life*

The visible and chronic nature of AD, including its comorbidities (e.g. skin infections, asthma, allergies) and its daily effects associated with the severe itching (pruritus), pain, and sleep disturbance, can be a source of emotional stress and has a profound negative impact on patients' mental and physical functioning, reducing their activity and HRQoL[2, 3]. Many adults with AD feel embarrassed and self-conscious, distressed and anxious, and often avoid home, work, and social activities[2, 3, 62, 75].

In the LIBERTY trial programme patients reported quality of life impairment at baseline comparable or lower than that reported for many late stage cancers[94] and DLQI scores which can be interpreted as ‘a very large effect on patient's life’ (DLQI 11-20)[47](Table 1.4).

Table 1.4. Baseline quality of life from the LIBERTY trial programme and the Early Access to Medicines Scheme (EAMS) for dupilumab*[43-45, 95-98]

	SOLO 1	SOLO 2	CHRONOS	CAFÉ	EAMS*
	N=671	N=708	N=740	N=235	N = 161
EQ-5D utility	0.631	0.595	0.638	0.698	NA
EQ-5D VAS	55.9	55.3	56.5	55.0	NA
DLQI	14.2	15.6	14.5	13.8	16.65

*See Section B 2.11.1.

DLQI, Dermatology Quality of Life Index; EQ-5D, European Quality of Life-5 Dimensions; VAS, visual analogue scale

A recent survey by Allergy UK, which included an open-ended question asking patients to describe the impact their condition has on their quality of life, has highlighted key aspects of the disease to patients[34]. Eighty per cent of respondents (n = 242) answered this question. Itch, sleep deprivation, depression, anxiety, pain, self-esteem, body image, relationships, the impact on clothing and usual activities, along with frustration at the lack of helpful therapies were all cited as important features of the disease. A full list of responses is provided in Appendix S**,** but the following are typical:

'Itching is maddening, scratching makes me sore and ruins the look of my skin. All of this is deeply depressing, because it will never leave me. Most people, including doctors, have no idea how awful eczema is to live with'

'Lack of sleep due to irritation and itching, I have to purchase specific clothing made of specific fabric, stress and anxiety, skin damage, family are upset, searching for cure or a solution or prevention of outbreak'.

'Having had to indure the ignorance and cruelty of teachers and other adults (including parents and GPs), and being hampered academically and in career terms by something so overwhelming but so misunderstood by most people. It's a living hell and the prospect of death is the only thing that really soothes me when it's really bad.'

B 1.3.6.2.5 *Impact of topical treatments on patient quality of life*

Not only does the disease impact on quality of life but the prolonged use of topical therapies in themselves can also be associated with anxiety and depression. For example during the development of the AD Control Tool (see Appendix R for more details) participants highlighted their frustrations in constantly dealing with their daily treatment routines (or "rituals") involving the application of prescription topical medicines and over-the-counter medicines and emollients. Patients often attempt to minimise the use of these products (see Appendix S for additional patient verbatim reports on this topic). To quantify the additional relationship between the use of topical therapies and QoL, we have carried out a time-trade-off (TTO) utility elicitation exercise.

It is very important to note that this study was *not* designed to measure quality of life associated with AD or any disease state. During the questionnaire no reference was made to any disease. The process of therapeutic management with different skincare regimens was the focus.

The exercise was performed on a sample of the public, selected to be broadly representative of the adult population in the UK and is described in detail Appendix R (Table 1.5)

Table 1.5 Average utility values for each skincare regimen

Skincare regimen	Mean Utility (SD)
Steroid twice daily and emollient four times daily	0.7968 (0.2159)
Steroid twice daily and emollient twice daily	0.8471 (0.1744)
Steroid once daily and emollient twice daily	0.8835 (0.1469)
Light emollient twice daily	0.9862 (0.0340)
Light emollient once daily	0.9906 (0.0267)
Light emollient once every other day	0.9997 (0.0021)
Light emollient on occasion, as needed	0.9999 (0.0012)

SD, standard deviation

There was very little difference in observed utility for skincare regimens associated with good response to treatment, all of which had utility values close to perfect health (0.986 to 0.999). However, values were much lower for skincare regimens followed by patients using combinations of steroid and emollient treatments (0.797 to 0.884). This study shows the significant QoL impact that burdensome skin care regimens may have. These elicited values are striking when compared to some chronic diseases, including arthritis (0.78), bronchitis (0.79), epilepsy (0.78), diabetes (0.79)[99].

The impact of the 'cosmetic characteristics' of treatments on patients is also important for adherence to treatment. For example, in a recent pan-European psoriasis study (n = 1281, UK cohort; n = 175) it was shown that compliance is strongly affected[100]. Seventy-three per cent of patients reported not complying with their treatment. The reasons cited included: texture, smell, difficulty in use, time taken to apply and stickiness[100].

B 1.3.6.2.6 *Pruritus (itch)*

Itch severity, frequency, duration and itch-related sleep disturbance significantly impact on patients' wellbeing. A multinational study of 380 adult patients with moderate-to-severe AD reported that despite treatment, they still had problems with itch frequency (85%), duration (41.5% reported itching for more than 18 hours a day) and the severity of itching. In addition, 55% of patients reported AD related sleep disturbances of more than five days a week[2]. More than half of adults with AD report at least five episodes of itch per day, and itch severity and frequency increases as the disease worsens[2, 74, 101-103]. Scratching in response to pruritus aggravates skin signs and symptoms such as abrasions, bleeding, oozing, crusting, and skin thickening (lichenification)[104] and perpetuates the 'itch scratch cycle'[2, 105, 106].

B 1.3.6.2.7 *Sleep disturbance*

Pruritus has a substantial impact on the sleep of AD patients. In the study by Simpson and colleagues, of the 380 AD patients 68.2% reported itch delaying falling asleep and itch occasionally or frequently waking them up[2]. More than a third of the patients in this study (36.1%) reported that their sleep was disturbed every night, with more than half reporting sleep disturbances 5-7 nights a week[2]. This study is supported by a recent real world survey which showed that patient-reported sleep-disorders were significantly more

frequently reported in subjects with AD compared to non-AD controls (33.2% vs. 19.2%, p<0.001)[5].

B 1.3.6.2.8 *Flares*

The 'escalation of treatment' and 'use of topical anti-inflammatory medications' have been suggested as good measures of flares in AD patients[107]. The authors in this study note that capturing disease flares in clinical trials through daily recording of medication use appears to be a good indicator of long-term control.

Periods of acute worsening (exacerbation of signs and symptoms, or flares with intense erythema with oozing, and crusting) occur frequently in patients with moderate-to-severe AD[62]. Patients with moderate-to-severe AD experience significantly more exacerbations than those with mild disease, reporting an average of 15.5 exacerbations compared with 2.8 exacerbations per year (P<0.0001)[63]. In a multinational study (ISOLATE) of 631 people with severe AD, flares were reported for up to 192 days per year, with patients spending more than half of each year in a state of exacerbated disease[62]. Flares disrupted the sleep for an average of 7.3 nights per flare (67 nights per year) and patients with severe AD had significantly more nights' sleep affected (14.6 nights per flare, equivalent to 162 nights per year)[62]. This can cause considerable distress to patients, with many feeling helpless, anxious and irritable and the majority worried about being seen in public during a flare[62, 108].

B 1.3.7 Current treatment options

Current treatment for AD in adults aims to control and prevent flares and relieve symptoms to enable patients to maintain daily functions and a favourable HRQoL[109]. The main principles of treatment are continuous epidermal barrier repair with emollients, avoidance of individual trigger factors, and anti-inflammatory therapy with topical corticosteroids (TCS) or calcineurin inhibitors (TCI). In patients with severe AD, phototherapy (UV therapy) or systemic immunosuppressants are used[7]. Ciclosporin is the only systemic immunosuppressant licenced for use in AD.

There is a NICE clinical guideline for the diagnosis and management of atopic eczema in children under 12 (CG57, published December 2007)[35] and a NICE Quality Standard for Atopic Eczema in under 12s (QS44, published September 2013)[81], but there are currently no NICE guidelines or quality standards on the diagnosis, treatment and management of moderate-to-severe AD in adults. Current European and other International guidelines for the treatment and management of AD in adults are listed in Appendix N. The European and US guidelines generally agree but there are notable differences regarding the recommendations for the use of diluted bleach baths, vitamin D, and environmental modifications[110].

Typically, AD is managed by a step-wise approach based on the level of disease severity and the lack of response to lower step treatments[7].

AD therapy routinely includes the use of emollients and topical agents for the protection/restoration of the skin barrier and to help relieve skin dryness and pruritus[109, 111]. If symptoms persist despite proper use of emollients, guidelines recommend the use of anti-inflammatory TCS and/or TCI to treat active lesions or as maintenance therapy to prevent

relapses[7, 33, 88, 109, 112, 113]. In some cases, these topical therapies have limited efficacy, and moderate-to-high potency TCS should not be used continuously on a long-term basis because of the risk of adverse effects such as thinning of the skin (skin atrophy), spider veins (telangiectasia) and secondary infections[7, 88, 109, 114].

Oral corticosteroids may be considered for short-term use but should be generally avoided because of the short- and long-term adverse effects which largely outweigh the benefits. Furthermore, disease rebound (worsening of skin lesions) may occur upon the discontinuation of therapy[7, 10].

Although phototherapy has been demonstrated to be efficacious for the management of active AD after the failure of topical therapies, it is generally positioned before systemic immunosuppressants and not widely used in the UK. This is due to cost, lack of clinical availability, lack of clinical experience and gaps in the evidence concerning its long-term efficacy and safety[115, 116].

Narrowband ultraviolet B (UVB) light is most commonly used, but there are many treatment protocols and parameters and no definitive recommendation or treatment guidelines [10]. Long-term, phototherapy increases the risk of developing skin cancer, and short-term application can have undesirable effects (e.g. itch, actinic damage, local erythema, tenderness, burning, and stinging)[10, 114]. Consequently, phototherapy has limited use in AD patients. Furthermore, it is not universally available.

Systemic immunosuppressants are used after non-responsiveness to topical treatments, but these do not specifically target the underlying mechanisms of the disease and their long-term use is limited by severe, and potentially life-threatening, adverse effects[7-10].

Ciclosporin is the only systemic immunosuppressant therapy licenced in the EU for the treatment of severe AD. However, due to dose-related adverse effects, its use is recommended for no more than 12 months with requirement for stringent safety monitoring and dose reduction as soon as a satisfactory response is achieved[9, 10, 112, 117-120]. Commonly recognised toxicities associated with ciclosporin include hypertension, impaired renal and hepatic function, and the potential for increased susceptibility to infections and cancer, particularly skin cancer[121]. This is because of the decreased ability of the immune system to recognise cancer cells (cancer immunosurveillance)[10, 117, 122]. In a prospective, five-year observational study of 1,252 psoriatic patients treated by ciclosporin, malignancies were diagnosed in 3.8% of patients, 49% being skin malignancies and the majority being squamous cell carcinomas (SCC). There was a six-fold higher incidence of skin malignancies than in the normal population with patients treated for more than two years having a higher risk of SCC development[123].

Other immunosuppressive drugs (methotrexate, azathioprine, mycophenolate mofetil) are not licenced, but are used off-label in some patients with severe AD if ciclosporin is not effective/contraindicated, or based on clinician preference[9, 10, 118]. These treatments are used temporarily to control disease flares, and long-term use is limited by their unfavourable risk/benefit profiles; guidelines generally suggest limiting their use to less than 12 months[7, 10, 124, 125].

B 1.3.8 Unmet need

For many patients with moderate-to-severe AD, the efficacy of current treatments is limited and carries the risk of side effects. Almost half of patients report that their disease is inadequately controlled (53%)[74, 126]. Hence, for patients for whom existing topical medications or systemic immunosuppressants have failed or are contraindicated, there are currently no treatment options beyond BSC. This is a significant unmet need characterised by high physical and psychological burden.

A recent patient survey by Allergy UK investigating patient views on AD and treatment included the following responses[34]:

"I'm constantly searching for a treatment that actually works"

"I have exhausted all treatment options"

"The textbook does not always work when it comes to treatment"

"I can't leave the house without a twice a day bathing and moisturising ritual which takes time and effort and costs a fortune in natural treatments because prescription does not work"

"When it's so sore and not responding to treatment this makes me depressed, and I have severe depression and anxiety due to my condition"

B 1.3.9 Anticipated place of dupilumab in therapy

Dupilumab is the first new treatment for AD in the UK in the last 15 years and the first biologic treatment for the disease.

Sanofi Genzyme has worked closely with the AD clinical community in the UK to understand where the greatest unmet need is, and, therefore, where the clinicians anticipate the value of dupilumab to be greatest in a routine clinical setting in an area where there are no other biologic treatments. It is expected that dupilumab will be used in moderate-to-severe patients previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. This is the base case population. This opinion was expressed by a panel of clinical experts during an advisory board held in September 2017[115].

Beyond best supportive care (BSC), no long-term safe and effective treatment options are available for these patients. BSC for this AD population in the UK is not well defined. Clinicians work hard to reduce the burden of AD, in doing so patients are treated with a range of systemic therapies. Data from EAMS indicate 96.4% enrolled had had previous exposure to a systemic immunosuppressant, 74% had had three or more previous systemic immunosuppressants (See Section B 2.11.1). In addition, clinicians in an advisory board (n=8) indicated short-term and frequent use of oral corticosteroids and extensive use of TCIs in this patient population on top of the systemic immunosuppressants. These patients would all also have TCS to use as required and are all advised to use emollients extensively.

In the economic model BSC is based on the trial treatment regimens and advice from clinicians in the advisory board: a combination of emollients, low-to-mid potency TCSs and rescue therapy (such as higher potency topical or oral corticosteroids and TCIs) due to data analysis timelines of the EAMS data.

A recent consensus statement by the International Eczema Council (IEC) on the use of systemic agents for the treatment of moderate-to-severe AD suggests that identification of patients should be by a holistic process[12].

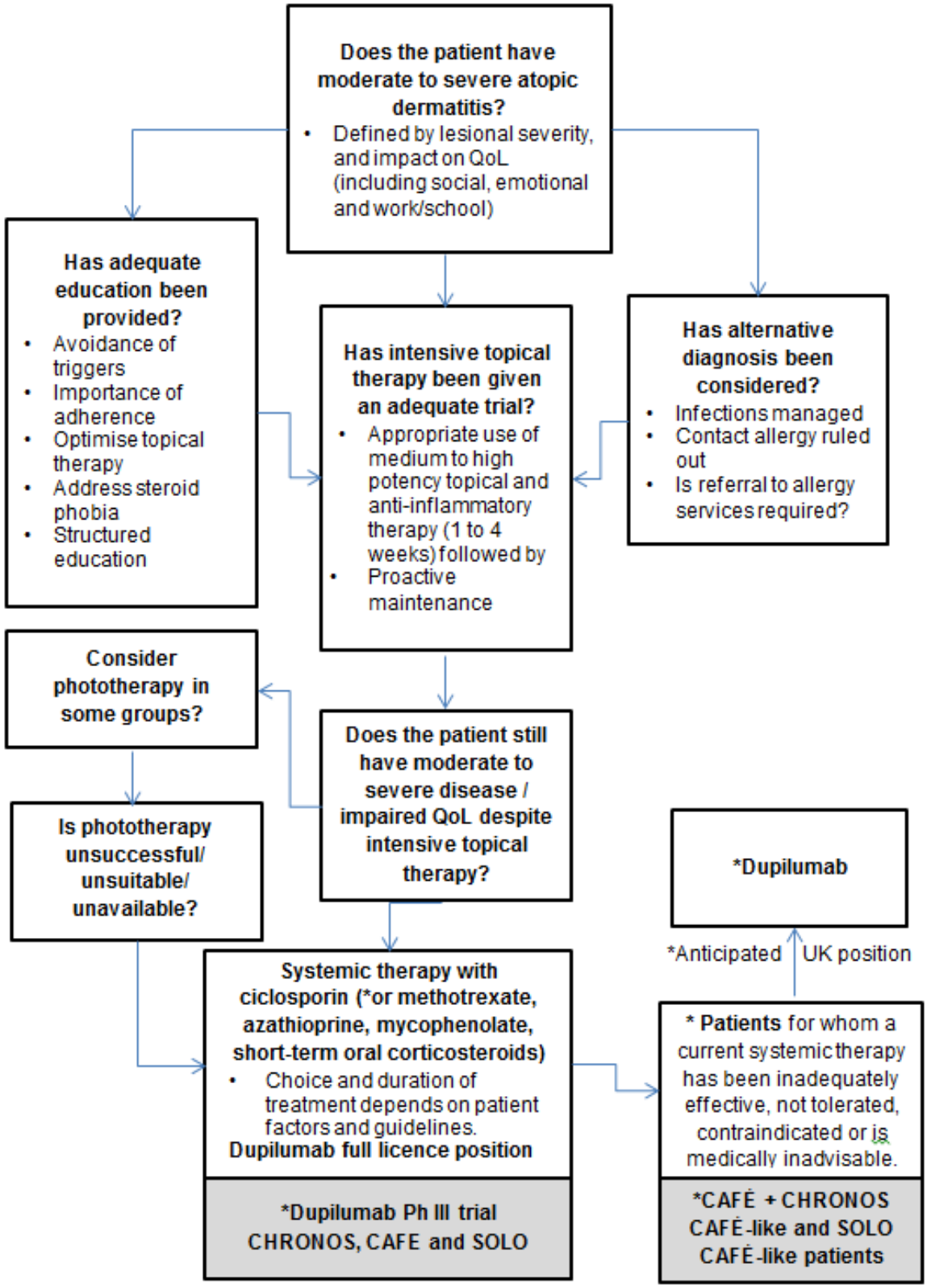
The consensus statement stresses the importance of optimising topical therapies and patient education ahead of consideration for systemic treatment.

Given the expected place in therapy for dupilumab, we believe that it should be used for moderate-to-severe patients previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. This treatment history serves in place of a formal scoring assessment and is in line with an holistic approach to AD care.

Dupilumab is not expected to change the current treatment pathway in the UK, but is expected to provide an additional step for those patients in whom all other lines of treatment were not successful.

The IEC treatment algorithm, which has been adapted to include dupilumab, is presented overleaf in Figure 1.6.

Figure 1.6 Adapted IEC algorithm for the treatment of atopic dermatitis with systemic agents and dupilumab [adapted from Simpson 2017][12]



*Sanofi adaptation

B 1.4 Innovation

Atopic dermatitis represents an area of high disease burden and unmet need

AD is becoming increasingly thought of as a systemic disorder[127]. A recent review of the literature by the International Eczema Council identified a strong pattern of immune activation in AD patients and tendency for skin and systemic infections. This review highlighted associations with cardiovascular, neuropsychiatric and malignant diseases[127]. The growing list of systemic and cutaneous comorbidities associated with AD points towards a high burden for patients and carers that is only recently becoming fully recognised. In the light of this expanding evidence base, the Councillors of the International Eczema Council emphasise the *'…urgent need for better interventions'*[127].

There are currently no effective treatments for patients who are intolerant, have an inadequate response, contraindicated to or for whom it is medically inadvisable to prescribe systemic immunosuppressant therapies.

We have discussed the treatment options available to people with AD in Section B 1.3.7. Although the oral immunosuppressive drugs provide broad-spectrum immunosuppression, they do not specifically target the underlying disease pathophysiology[7, 10, 88]. These agents are used on a temporary or short-term basis to control disease flares, but are not recommended for long-term use in patients, due to risk of toxicity. Ciclosporin is the only immunosuppressant licenced for the treatment of AD, but as a consequence of its adverse event profile, it should not be used for extended periods of time and therapy should be stopped after one (American Academy of Dermatology [AAD])[10] or two years (European Academy of Dermatology and Venerology [EADV])[9]. From a recent national survey among 61 UK dermatologists investigating treatment of moderate-to-severe AD in adults, the average duration for ciclosporin treatment was 5.8 months[116]. The short duration of treatment is in line with the NICE clinical guideline for psoriasis, which suggests a maximum of one year due to the risk of hypertension, renal impairment and cancer[38, 116].

There are currently no targeted biologic therapies for AD.

The targeted mechanism of action of dupilumab underpins the innovative nature of the medicine

A robust mechanistic understanding of the pathophysiology of AD has facilitated the development of dupilumab; this has led to a targeted approach to addressing the fundamental steps in the disease development. The dual IL-4/IL-13-targeted mechanism of action of dupilumab outlined in Section B 1.2 tackles the underlying inflammation associated with the T-helper type 2 (Th2) pathway. This pathway is also implicated in many of the atopic comorbidities, such as asthma and nasal polyposis accompanying AD. The translational nature of dupilumab is underscored by the promising Phase II data published in these areas[128-130] and the Phase III studies which are ongoing (e.g. LIBERTY ASTHMA QUEST, NCT02414854)[131].

The targeted nature of dupilumab also contributes to the favourable side effect profile observed in the AD study programme, in contrast to the known toxicity risk of the broad-spectrum immunosuppressant agents.

Dupilumab has been recognised by national and international regulators as an effective, innovative medicine in this area of high unmet need

The recently published Accelerated Access Review sets out recommendations to speed up access to innovative healthcare technologies to improve outcomes for NHS patients [https://www.gov.uk/government/organisations/accelerated-access-review]. As part of this emerging pathway for strategically-important innovations, the Early Access to Medicines Scheme (EAMS) was designed to provide accelerated access to life changing medicines that improve outcomes ahead of marketing authorisation[132]. Dupilumab was granted EAMS status in March 2017, and was the first medicine for a chronic condition to be recognised within the programme by the Medicines and Healthcare products Regulatory Agency (MHRA). This acknowledgement highlights both the innovative nature of dupilumab, and that the treatment of severe AD is an area of high unmet need.

The US Food and Drug Administration (FDA) has also acknowledged the importance of both the disease area and the innovative nature of dupilumab. In November 2014, dupilumab was granted Breakthrough Therapy Designation for the treatment of moderate-to severe AD in adults, recognising that dupilumab demonstrates substantial improvement over existing therapies on one or more clinically significant endpoints[133]. Priority Review was granted for the treatment of moderate-to severe AD in adults in September 2016. In October 2016, Breakthrough Therapy Designation was also granted by the FDA for dupilumab for the treatment of moderate-to-severe AD in patients 12 to 18 years of age, and for severe AD in patients six months to 12 years of age when topical medications are inadequate or inappropriate.

The benefits of dupilumab use may align with several of the Strategic Imperatives in the Five Year Forward View

The Five Year Forward View, published by the UK government in 2014, set out important goals for the NHS to work towards by 2020[134]. Long-term health conditions were a key feature of the report, and the Five Year Forward View document stated that '*Over the next five years the NHS must drive towards an equal response to mental and physical health and towards the two being treated together'.*

We have described the long-term burden of AD in Section B 1.3.6 and it is clear from our clinical trial programme, and the published literature and clinical opinion expressed to us that mental wellbeing is closely linked with physical health for patients with AD.

Another of the pillars of the Five Year Forward View is the call for the NHS to support people to get and stay in employment. It is known that people suffering from AD have more sick leave and work impairment than matched controls (See Section B 1.3.6.1).

During the LIBERTY programme, patients who were employed or enrolled in school were asked to report the numbers of sick leave/missed school days due to AD since the last study visit. For example, in the CAFÉ study at week 16, lost productivity was significantly greater in the placebo + TCS group (6.16 days) than in the dupilumab 300 mg Q2W + TCS (0.14 days) and dupilumab 300 mg QW + TCS (0.77 days) groups[98]. Similarly, at Week 16 a

significantly lower percentage of patients with no missed days was observed for the placebo + TCS (83.5%) group than the dupilumab 300 mg Q2W + TCS (91.6%) and dupilumab 300 mg QW + TCS (91.7%) groups.

Dupilumab is an innovative medicine

The Five Year Forward Plan recognises that *'…own life goals are what count; that services need to support families, carers and communities; that promoting wellbeing and independence need to be the key outcomes of care.'* and it goes on to state that: *'even people with long-term conditions, who tend to be heavy users of the health service, are likely to spend less than 1% of their time in contact with health professionals. The rest of the time they, their carers and their families manage on their own'*. This is especially true for patients with AD who report feelings of social isolation and depression[62].

The emphasis on the *'acceleration of useful innovation'* in the Five Year Forward Plan and the Accelerated Access review demonstrates the priority of the UK government to enable rapid access to innovative treatments in the UK. Set in this context, and considering the discussion above, we believe that dupilumab is an important innovation that will help patients and the NHS to meet their goals as they relate to AD.

Factors not captured in the Quality-Adjusted Life Year (QALY)

In line with the NICE template, we discuss the benefit of dupilumab treatment to society, carers and family, see Section B 3.9 for benefit beyond the QALY. In the economic section we present the impact of productivity losses and gains with dupilumab in a sensitivity analysis.

B 1.5 Equality considerations

The use of dupilumab is not anticipated to raise any equality issues however in recognition of the subgroup identified in the scope, we would like to highlight that assessing AD in patients with skin of colour is complicated. The challenges in assessing AD in these patients are not well recognised, addressed or documented[135]. AD tends to have more scattered papular lesions, lichen planus-like lesions, prurigo nodularis, lichenification, post-inflammatory changes and extensor involvement in patients with skin of colour, while white patients with AD tend to have more noticeable erythema and flexural involvement[136]. This issue is cited in Quality Standard QS44, which states that '*Healthcare practitioners should be aware of the potential difficulties of assessing eczema severity in children with darker skin tones*'[81].

AD outcome measures may have poor reliability and validity in highly pigmented patients, with variations in erythema perception being a contributor[137]. Therefore, eligibility and response criteria based solely on EASI or other such measures of severity may, in a small number of cases, be potentially discriminatory and a more holistic view should be taken.

B 2 Clinical effectiveness

- In adult patients with moderate-to-severe AD:
  - As a monotherapy, treatment with dupilumab significantly cleared or reduced the extent and severity of AD lesions and relieved pruritus, compared with placebo (44% (Q2W) to 53% (QW) of dupilumab patients vs. 12-15% of placebo patients achieved EASI-75 at 16 weeks, p<0.0001 for all comparisons with placebo).
  - When used concomitantly with topical corticosteroids (TCS), treatment with dupilumab was clinically and statistically superior to that of TCS + placebo, indicating a significant added benefit provided by dupilumab in patients treated with TCS (64% (Q2W) and 69% (QW) of dupilumab patients vs. 23% of placebo patients achieved EASI-75 at 16 weeks, p<0.0001 for both comparisons with placebo).
  - In patients with a history of intolerance, inadequate response or contraindication to oral ciclosporin, dupilumab + TCS therapy provided statistically significant and clinically meaningful improvements relative to placebo. (63% (Q2W) and 59% (QW) of dupilumab patients vs. 30% of placebo patients achieved EASI-75 at 16 weeks, p<0.0001 for both comparisons with placebo).
- The onset of the effect of dupilumab treatment on pruritus was rapid and apparent within 2 weeks of initiation. The effects were sustained with treatment up to 52 weeks.
- When tested across a range of prespecified variables (demographic, disease, drug) a consistent postitive treatment effect due to dupilumab was observed.
- In the popuation most relevant to UK clincal practice (patients who are contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant) the eficacy of duilumab is clincally and statistically significant vs. BSC (p<0.0001).
- Dupilumab was generally well tolerated with a safety profile largely comparable to placebo.
  - Adverse event rates were comparable between dupilumab and placebo with the exception of conjunctivitis which ocurred in up to 10% of patients treated with dupilumab
  - In the primary saftey pool there were four AE of special interest in the placebo group and two (Q2W) and one (QW) for dupilumab
- Adverse drug reactions were generally mild or moderate, transient, and manageable.
- There was no increased infection risk in patients treated with dupilumab, which is not the case with other systemic immune-modulatory treatments.
- Dupilumab-treated patients had a higher incidence of injection-site reactions, and conjunctivitis with unspecified cause and allergic conjunctivitis, reported in 5–10% of patients receiving dupilumab versus 1–2% receiving placebo.
- There are currently no important safety concerns for long-term treatment with dupilumab, unlike systemic immunosuppressants which are associated with toxicity and long-term side effects. This is also recognised in the first periodic saftey report from the MHRA for EAMS.

B 2.1 Identification and selection of relevant studies

A full systematic literature review (SLR) was carried out to identify evidence for the clinical efficacy, safety, and patient-reported outcomes of dupilumab and other conventional treatments for moderate-to-severe AD, including systemic immunosuppressants, phototherapy, or other systemic therapies in adult patients.

In line with the new template, full details of the search strategy and study selection methods used to identify the clinical evidence relevant to the technology being appraised are provided in Appendix D.

The SLR was consistent with the population, intervention, comparison, outcomes, study design, and time horizon (PICOS-T) framework described in

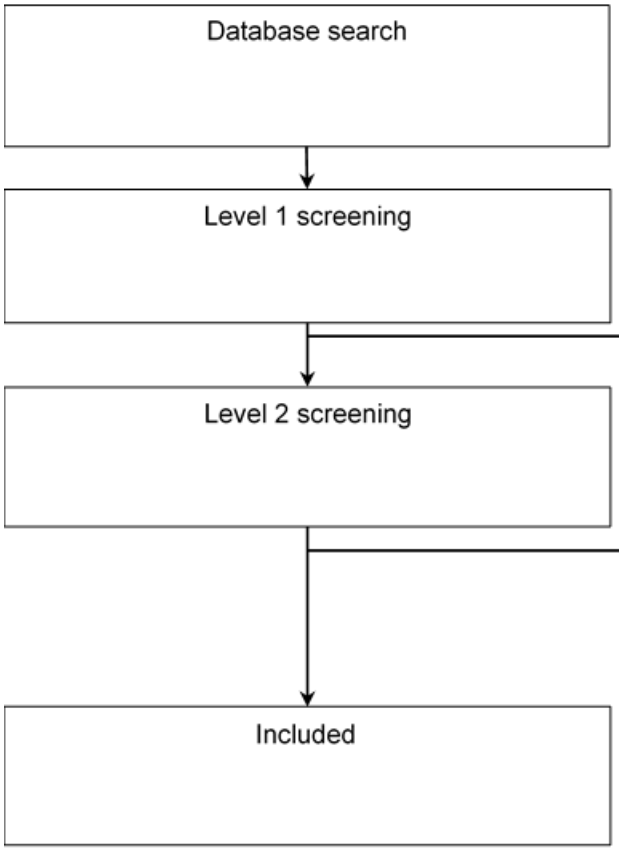
Table 2.1 below. The inclusion and exclusion processes are summarised in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 2.1 below.

Table 2.1 PICOS-T framework

	Efficacy, PROs, safety evidence
Population	• Adults or young adults (i.e., 15 years or older) with AD*
Interventions	• At least one of the following treatments for AD: 1. Dupilumab monotherapy 2. Dupilumab in combination with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) 3. Biologic drugs (with/without TCS or TCIs) 4. Systemic immunosuppressants (with or without TCS or TCIs) 5. Phototherapy (with/without TCS or TCIs) or extracorporeal photopheresis
Comparators	• Any
Outcomes	• At least one of the following outcomes (change from baseline): *Efficacy Outcomes* 1. EASI 2. IGA 3. SCORAD 4. BSA 5. GISS *PROs* 1. POEM 2. DLQI 3. Pruritus NRS 4. HADS 5. EQ-5D overall or any of the 5 domains or the EQ-5D VAS score (EQ-VAS) *Safety Outcomes* 1. AEs 2. SAEs 3. Treatment discontinuation (e.g. due to lack of efficacy or due to safety)
Study design	• Randomised controlled clinical study • Phase I, II, III, or IV clinical trials

*The decision to include patients aged 15 years or older was made after initial screening of the publications. Many publications included young adults (15-18 years old), therefore, to avoid discarding clinically meaningful information, publications that included results from patients aged at least 15 years were included, if they also included results from patients aged at least 18.
AD, atopic dermatitis; AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Sign Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; PRO, patient-reported outcome; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; TCI, topical calcineurin inhibitors TCS, topical corticosteroids; VAS, visual analogue scale

Figure 2.1 PRISMA diagram of selected publications



	Original	Update
Conference abstract or poster published before 2014	208 (6.0%)	0 (0.0%)

	Original	Update
Exclude	**3,177 (97.1%)**	**203 (81.5%)**
Design ineligible	1,574 (49.5%)	51 (25.1%)
Disease area ineligible	580 (18.3%)	57 (28.1%)
Exclusively/indistinguishable pediatric population	496 (15.6%)	28 (13.8%)
Treatment ineligible	359 (11.3%)	11 (5.4%)
Cell-based or non-human study	168 (5.3%)	45 (22.2%)
Duplicate publication	0 (0.0%)	11 (5.4%)

	Original	Update
Exclude	**50 (53.2%)**	**42 (91.3%)**
Design ineligible	18 (36.0%)	20 (43.5%)
Outcomes not of interest	9 (18.0%)	2 (4.3%)
Population mixed children/adults (<15 years old)	8 (16.0%)	2 (4.3%)
No treatment of interest	6 (12.0%)	2 (4.3%)
Duplicate publication	3 (6.0%)	8 (17.4%)
Disease area ineligible	2 (4.0%)	6 (13.0%)
Publication in German	2 (4.0%)	0 (0.0%)
Pediatric population	1 (2.0%)	1 (2.2%)
Publication in Japanese	1 (2.0%)	0 (0.0%)
Publication in French	0 (0.0%)	1 (2.2%)

	Original	Update
Include after hand search or recommendations	3	0

Studies related to UV therapy were considered not relevant to the decision problem as UV therapy (which is not universally available) is considered by clinicians for active symptom control directly after the failure of topical treatments and before the use of systemic agents. This is illustrated in the adapted treatment algorithm from the International Eczema Council (IEC) presented in Figure 1.6.

Several other therapies were identified in the SLR including mepolizumab, nemolizumab, omalizumab and intermediate immunoglobulin; all investigated in early stage trials and with no licence for the treatment of AD.

After exclusion of these studies there were 28 studies related to dupilumab and immunosuppressant therapy, which are listed in Table 2.2. A further four articles and conference proceedings were published after the searches were complete and identified through the Sanofi Genzyme internal processes (Table 2.2).

Table 2.2.Studies identified in the literature search or published subsequently

Study	Study design	Publication type	No. of patients	Treatment duration	Country
Articles related to dupilumab identified in the original and updated literature search					
Beck 2014[138]	RCT, Phase I/II	Full paper	31	4 weeks	Germany, Hungary, Poland
Beck 2014[138]	RCT, Phase I/II	Full paper	109	12 weeks	Czech Republic, France, Germany, Hungary, Poland
Bieber 2014[139]	RCT, NR	Conference abstract (as above)	109	12 weeks	NR
Hamilton 2014[140]	RCT, Phase II	Conference abstract (as above)	109	12 weeks	NR
Blauvelt 2016[141]	RCT, Phase II	Conference abstract	194	16 weeks	USA
Hamilton 2014[142]	RCT, Phase I	Conference abstract	18	4 weeks	USA
Hamilton 2014 (Combined parent trials)[142]	RCT, Phase II	Conference abstract	59	4 weeks	Australia, Germany, and New Zealand
Hamilton 2015[143]	RCT, Phase IIb	Full paper	379	16 weeks	Canada, Czech Republic, Germany, Hungary, Japan, Poland, and United States
Simpson 2015[144]	RCT, Phase II	Conference abstract	380	16 weeks	USA, Canada, Czech Republic, Germany, Hungary, Japan and Poland

Study	Study design	Publication type	No. of patients	Treatment duration	Country
Simpson 2016[75]	RCT, Phase IIb	Full paper	379	16 weeks	USA, Canada, Czech Republic, Germany, Hungary, Japan and Poland
Simpson 2016[45]	RCT, Phase III	Full paper	678 (SOLO1) 708 (SOLO2)	16 weeks	SOLO1:USA, Bulgaria, Canada, Denmark, Estonia, Finland, Germany, Japan, Singapore, Spain. SOLO2:France, Germany, Hong Kong, Italy, Korea, Republic of, Lithuania, Poland, United Kingdom
Thaci 2014[145]	RCT, Phase II	Conference abstract	31	4 weeks	
Thaci 2016[126]	RCT, Phase IIb	Full paper	379	16 weeks	Canada, Czech Republic, Germany, Hungary, Japan, Poland, and United States
Dupilumab articles published since the updated literature search					
Blauvelt 2017[43]	RCT, Phase III	Full paper	740	52 weeks	Australia, Canada, Czech Republic, Hungary, Italy, Japan, Netherlands, New Zealand, Poland, Romania, South Korea, Spain, UK, USA
Simpson 2017[146]	RCT, Phase III	Full paper	1,379	16 weeks	Populations form the SOLO studies
M. de Bruin-Weller, 2017[44]	RCT, Phase III	Full paper accepted for publication in the BJD	325	16 weeks	Germany and Poland
Deleuran 2017[147]	MAINTAIN OLE study	Poster	1492	Ongoing	International (patients were eligible from any dupilumab study)

Study	Study design	Publication type	No. of patients	Treatment duration	Country
Ciclosporin					
Czech 2000[148]	RCT NR	Full paper	106	8 weeks	Germany
Granlund 2001[149]	RCT, NR	Full paper	71	8 weeks	Finland, Norway
Haeck 2011[150]	RCT, NR	Full paper	50	36 weeks	Netherlands
Koppelhus 2014[151]	RCT, NR	Full paper	20	16 weeks	Denmark
Munro 1994[152]	RCT, NR	Full paper	24	8 weeks	UK
Ohtsuka 2015[153]	RCT, NR	Full paper	48	4 weeks	Japan
Salek 1993[154]	RCT, NR	Full paper	33	8 weeks	UK
Schmitt 2010[155]	RCT, Phase IV	Full paper	38	6 weeks	Germany
Sowden 1991[156]	RCT, NR	Full paper	33	8 weeks	UK
van Joost 1994[157]	RCT, NR	Full paper	46	6 weeks	Netherlands
Wahlgren 1990[158]	RCT, NR	Full paper	10	10 days	Sweden
Zurbriggen 1999[159]	RCT, NR	Full paper	14	8 weeks	Switzerland
Azathioprine and methotrexate					
Berth-Jones 2002[160]	RCT, NR	Full paper	37	12 weeks	UK
Meggitt 2006[161]	RCT, NR	Full paper	61	12 weeks	UK
Schram 2011[162]	RCT, NR	Full paper	42	12 weeks	Netherlands

NR, not reported; RCT, randomised controlled trial

As previously discussed, the likely position of dupilumab in the AD treatment pathway is for those patients with intolerance, inadequate response or contraindication to immunosuppressants. Hence, a comparison with many of the therapies listed in the PICOS-T for the SLR is not appropriate in this submission. However, as immunosuppressants are included in the scope, we have considered indirect comparisons with them in scenario analyses. A network meta-analysis was considered unfeasible as there is considerable heterogeneity in methodologies within the studies identified in the SLR (e.g. the same treatment administered in different doses or assessed at different time-to-endpoints, a small number of studies per treatment, and a lack of common comparators, see Appendix D). Furthermore, there is no active comparator within the dupilumab trials (see Section B 2.2). Guided by NICE DSU Technical Support Document 18[163], we have implemented a Matching-Adjusted Indirect Comparison (MAIC) to carry out scenario analysis for a comparison of dupilumab vs. ciclosporin — the only immunosuppressant with a licence for the treatment of AD) (see Section B 2.9 for further discussion).

B 2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness of dupilumab for the treatment of AD was examined in the comprehensive LIBERTY AD clinical trial programme consisting of 20 studies (see Appendix O). This programme includes seven pivotal studies which are summarised below in Table 2.3 to Table 2.8. Regarding comparators these trials are all versus placebo, with and without TCS and at different positions in the treatment pathway. An overview of clinical trial evidence reported in the clinical section is shown in Figure 2.2 overleaf.

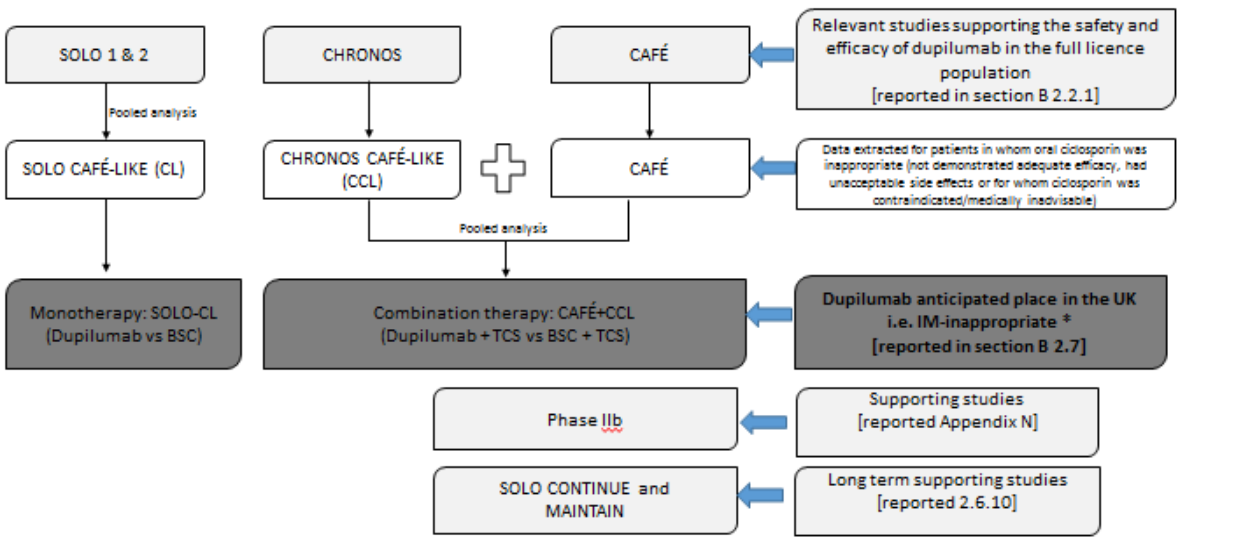
- Four main trials support the marketing authorisation of dupilumab CHRONOS (see Table 2.3)[43], CAFÉ (see Table 2.4)[44], SOLO1 and SOLO2 (see Table 2.5)[45]. These are reported in Sections B 2.3 to B 2.7 below and Appendix O.
- Two extension studies: One RCT (SOLO-CONTINUE) and one open-label extension (OLE) study (MAINTAIN) (see Table 2.7 and Table 2.8)[147]. One Phase IIb study (see Table 2.6)[126] is reported in Appendix P.

The schematic below provides an overview describing how the relevant clinical studies for dupilumab have been used to support its anticipated place in therapy. (Figure 2.2).

CHRONOS, CAFÉ and SOLO 1 &2 are the main studies so we report the methods and key efficacy results of each of these trials first. Of note in each of these studies the primary analysis excludes patients who had rescue treatment even if they had met the definition of response. As this is unlikely to reflect clinical practice we highlight analyses referred to as 'All observed' which does not exclude patients who received rescue treatment as this more closely reflects routine practice. This is also discussed in more detail in B 2.4.1.

In Section B 2.7 we present results from these studies as they have been used to reflect the decision problem and dupilumabs place in therapy (see section B 1.3.9) in patients for whom systemic immunosuppressant therapy is inappropriate.

Figure 2.2 Overview of clinical trials as reported in this submission



Best supportive care (BSC) is broadly defined as a combination of emollients, low to mid potency topical corticosteroids (TCS) and rescue therapy (such as higher potency topical or oral corticosteroids or topical calcineurin inhibitors (TCIs)).
*IM-inappropriate defined as adult patients with moderate-to-severe AD with a documented history of intolerance, inadequate response or contraindication to topical therapies (emollients, TCS, TCI) and for whom a current systemic immunosuppressant therapy has been inadequately effective, not tolerated or is medically inadvisable

B 2.2.1 Studies supporting clinical safety and efficacy of dupilumab

Table 2.3 Clinical effectiveness evidence: CHRONOS (R668-AD-1224)

Study	**CHRONOS, R668-AD-1224, NCT02260986[43]**				
Study design	Phase III, 64-week (52 weeks treatment + 12 weeks follow-up), multicentre, randomised, double-blind, placebo-controlled study				
Population	Adults patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS. N=740 (ITT)				
Intervention(s)	Dupilumab (300 mg Q2W or QW) + concomitant TCS				
Comparator(s)	Placebo + concomitant TCS				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓ *(see section B 2.7)*
	No			No	
Rationale for use/non-use in the model	The primary objective of the study was to demonstrate the efficacy and safety of dupilumab administered concomitantly with TCS through Week 16 in adult patients with moderate-to-severe AD compared to placebo administered concomitantly with TCS. CHRONOS also studied the long-term effects up to 52 weeks CHRONOS was used to populate the economic model. This is because: • Patients in CHRONOS received background TCS in line with usual clinical practice in the UK. • A subgroup of patients in CHRONOS had intolerance, inadequate response or contraindication to ciclosporin, thus matching expected use of dupilumab in the UK. This patient group is the CAFÉ-like population and was pooled with CAFÉ in the basecase. • CHRONOS is the only study with 52 Week data for the original randomised population.				
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • The proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16 and Week 52.or • IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 and Week 52. Outcomes are also reported as percentage changes in disease severity (EASI, SCORAD, IGA, POEM), impact on pruritus and sleep (Domains from SCORAD and POEM), and QoL measures (DLQI, HADS and EQ-5D). Adverse effects of treatment at Week 16 and Week 52. Time to rescue treatment. QoL benefit (e.g. DLQI, HADS and EQ-5D) at Week 16 and Week 52.				
All other outcomes	A list of the key primary and secondary outcomes is provided in Section B 2.6.1 below and a full list is presented in Appendix O				

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; ITT, intention-to-treat; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

Table 2.4 Clinical effectiveness evidence: CAFÉ (R668-AD-1424)

Study	**CAFÉ, R668-AD-1424, NCT02755649[44]**				
Study design	Phase III, 16 weeks treatment (plus 16 weeks follow-up) double-blind, randomised, placebo-controlled, parallel-group				
Population	Adult patients with moderate-to-severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable. N=325 ITT				
Intervention(s)	Dupilumab (300 mg Q2W or QW) + concomitant TCS				
Comparator(s)	Placebo + concomitant TCS				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓*(see section B 2.7)*
	No			No	
Rationale for use/non-use in the model	The primary objective of the study was to demonstrate the efficacy, safety, and tolerability of dupilumab administered to adult patients with moderate-to-severe AD treated concomitantly with TCS through week 16 who are not adequately controlled with or are intolerant to oral ciclosporin, or when this treatment is not medically advisable CAFÉ data was used in the economic model because: • Patients in CAFÉ received background TCS in line with usual clinical practice in the UK for patients with moderate-to-severe AD. • Patients in CAFÉ had a history of intolerance, inadequate response or contraindication to ciclosporin. This is in line with expected use of dupilumab in the NHS.				
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: The proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16. Outcomes are also reported as percentage changes in disease severity (EASI, SCORAD, IGA, POEM), impact on pruritus and sleep (Domains from SCORAD and POEM), and QoL measures (DLQI, HADS and EQ-5D). Adverse effects of treatment at Week 16. Time to rescue treatment. QoL benefit (e.g. DLQI, HADS and EQ-5D) at Week 16.				
All other reported outcomes	A list of the key primary and secondary outcomes is provided in Section B 2.6.2 below and a full list is presented in Appendix O				

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; ITT, intention-to-treat; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

Table 2.5 Clinical effectiveness evidence: SOLO1 and SOLO 2 (R668-AD-1334 and R668-AD-1416)

Study	**SOLO 1, R668-AD-1334, NCT02277743[45]** **SOLO 2 R668-AD-1416, NCT02277769[45]**				
Study design	Identical Phase III studies, 16-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies. Patients who achieved the primary endpoints (IGA 0/1 or EASI-75) were re-randomised to enter the 36-week SOLO-CONTINUE study. All other patients entered the 12-week follow-up period.				
Population	Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable. N=671 (ITT, SOLO 1). N=708 (ITT, SOLO 2).				
Intervention(s)	Dupilumab				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓ *(see section B 2.7)*
	No			No	
Rationale for use/non-use in the model	SOLO 1 and SOLO 2 were designed to demonstrate the efficacy and safety of dupilumab monotherapy. Patients were not permitted to receive concomitant TCS therapy in these studies. Both SOLO 1 & 2 included populations with prior immunosuppressant therapeutic history among which the most commonly used treatment was ciclosporin. (Placebo: 23.9% and 29.9%, Q2W: 26.6% and 28.4%, QW: 32.2% and 31.2% for SOLO1 & 2 respectively). These are the CAFÉ-like populations. The pooled placebo and Q2W patients were used in the modelling to investigate the ICER associated with monotherapy.				
Reported outcomes specified in the decision problem	Measures of disease severity and symptom control: • The proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16. • IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16. Outcomes are also reported as percentage changes in disease severity (EASI, SCORAD, IGA, POEM), impact on pruritus and sleep (Domains from SCORAD and POEM), and QoL measures (DLQI, HADS and EQ-5D). Adverse effects of treatment at Week 16 Time to rescue treatment QoL benefit (e.g. DLQI, HADS and EQ-5D) at Week 16				
All other reported outcomes	A list of the key primary and secondary outcomes is provided in Section B 2.6.3 below and a full list is presented in Appendix O				

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; ITT, intention-to-treat; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

B 2.2.2 Supporting studies

Table 2.6 Clinical effectiveness evidence: Phase IIb study (R668-AD-1021)

Study	**Phase IIb study, R668-AD-1021, NCT01859988[126]**				
Study design	Phase IIb randomised, double-blind, placebo-controlled, parallel-group, Phase IIb dose-ranging study, conducted in adult patients with moderate-to-severe AD consisting of 16 weeks of treatment and 16 weeks of follow-up.				
Population	Adult patients with moderate-to-severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable. N = 380 (ITT)				
Intervention(s)	Dupilumab				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	
	No			No	✓*(see Appendix N)*
Rationale for use/non-use in the model	This was a dose-ranging study with 1:1:1:1:1:1 randomisation to SC dupilumab at 300 mg once a week (QW), 300 mg every 2 weeks (Q2W), 200 mg Q2W, 300 mg every 4 weeks (Q4W), or 100 mg Q4W or placebo. Treatment was with dupilumab monotherapy. This study supports the efficacy and safety of dupilumab in patients treated with dupilumab versus topical emollients, rescue treatment and placebo but is not included in the economic model because patients were not permitted to receive concomitant TCS therapy. This is not reflective of typical UK clinical practice. Hence the results of the study are less relevant to the decision problem for UK clinical practice. For completeness the study methodology, adverse events and efficacy outcomes are summarised in Appendix N.				
Reported outcomes specified in the decision problem	Absolute and percentage changes to Week 16 in: Measures of disease severity: EASI, SCORAD, IGA, POEM. Symptom control: Pruritus NRS Incidence of TEAEs from baseline to week 32 QoL benefits were measured as exploratory outcomes (e.g. DLQI, HADS and EQ-5D). at Week 16				
All other reported outcomes	A full list of the primary and secondary outcomes is provided in Appendix N				

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; ITT, intention-to-treat; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; QW, once a week; Q2W, every two weeks; Q4W, every four weeks; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

Table 2.7 Clinical effectiveness evidence: SOLO-CONTINUE (R668-AD-1415)

Study	**SOLO-CONTINUE, R668-AD-1415, NCT02395133[147, 164]**				
Study design	Phase III randomised, double-blind, placebo-controlled study assessing efficacy and safety of 36-week maintenance treatment in patients achieving IGA 0/1 or EASI-75 with dupilumab in the studies SOLO 1 or SOLO 2.				
Population	All patients must have achieved an IGA 0 or 1 or EASI-75 at Week 16, in either initial SOLO study, after treatment with dupilumab SC 300 mg QW or 300 mg Q2W. N = 475 (ITT).				
Intervention(s)	Dupilumab				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	
	No			No	✓*(See Section B 2.6.4, Appendix F and Appendix P)*
Rationale for use/non-use in the model	Patients were randomised 2:1:1:1 to 1 of 4 regimens (Placebo, QW/Q2W, Q4W and Q8W), depending on the dupilumab dose regimen received in the initial-treatment study. This study supports the longer-term efficacy and safety of dupilumab in patients having responded to treatment (EASI-75) at week 16 versus topical emollients, rescue treatment and placebo but is not included in the economic model because patients were re-randomised at baseline. Note that patients were excluded from CONTINUE if they received rescue medication for AD in the initial-treatment study. Hence the results of the study are less relevant to the decision problem for UK clinical practice. For completeness the study methodology, adverse events and efficacy outcomes are summarised in Appendix F and Appendix P.				
Reported outcomes specified in the decision problem	Differences between baseline (Week 0 in CONTINUE) and Week 36 in EASI score and proportion of patients maintaining EASI-75 Absolute and percentage changes to Week 36 in: Measures of disease severity: EASI, SCORAD, IGA, POEM. Symptom control: Pruritus NRS, annualised event rate of flares, proportion of well controlled weeks. Incidence of TEAEs from baseline to Week 36. QoL benefits were measured as exploratory outcomes (e.g. DLQI, HADS and EQ-5D) at Week 16.				
All other reported outcomes	A full list of the primary and secondary outcomes is provided in Appendix F.				

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; ITT, intention-to-treat; POEM, Patient-Oriented Eczema Measure; QoL, quality of life; QW, once a week; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

Table 2.8 Clinical effectiveness evidence: MAINTAIN (R668-AD-1225)

Study	**MAINTAIN R668-AD-1225, NCT01949311**[147, 165]				
Study design	Phase III multicentre, OLE study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD who had previously participated in controlled studies of dupilumab or had been screened for a Phase III study (R668-AD-1334 or R668-AD-1416), but could not be randomised because of randomisation closure. N = 1492 (ITT)				
Population	Adult patients (≥18 years of age) with AD who participated in a prior dupilumab clinical study.				
Intervention(s)	Dupilumab				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	
	No			No	✓*(See Section B 2.10.6, Appendix F and Appendix P)*
Rationale for use/non-use in the model	Patients in the OLE study were characterised by their previous dupilumab exposure and were: dupilumab naïve patients (n= 606), retreated patients with a gap of >13 weeks between the last dupilumab injection in the parent study and the first injection in the OLE study (n = 381), interrupted treatment patients with gap of ≥6 weeks but ≤13 weeks (n = 409), continuous treatment patients (n=60) or patients whose treatment assignment is still blinded in the ongoing parent study (35). Only the interim analysis is available in which all treatment groups are aggregated. As an OLE study, patients were not randomised but were enrolled from several parent studies in which they had different treatments (dupilumab or placebo) and durations of treatment, as well as different intervals between the last treatment in the parent study and the first treatment in the OLE study. Due to the combination of these factors, the subsets of patients analysed are considered confounded and caution should be taken in drawing any meaningful efficacy conclusions from the data at this time. Hence it is not possible to determine the effect of continuous treatment of dupilumab. MAINTAIN is therefore not included in the economic model. For completeness the study methodology, adverse events and efficacy outcomes are summarised in Appendix F and Appendix P.				
Reported outcomes specified in the decision problem	The primary objective of this study was to assess the long-term safety of dupilumab administered in adult patients with AD. The secondary objective of the study was to assess the immunogenicity of dupilumab in adult patients with AD, in the context of re-treatment, and to monitor efficacy parameters associated with long-term treatment.				
All other reported outcomes	A full list of the primary and secondary outcomes is provided in Appendix F.				

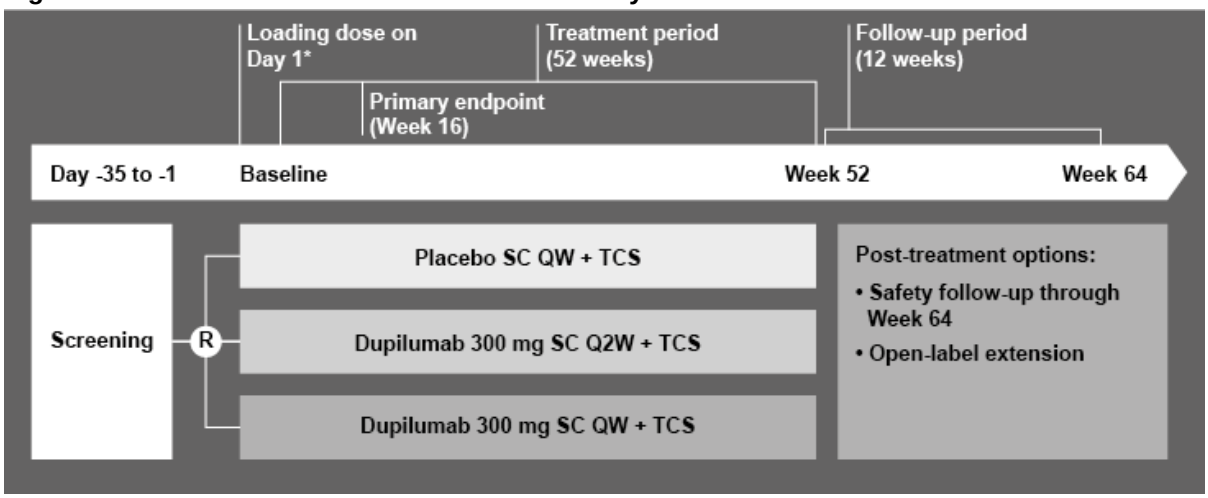
AD, atopic dermatitis; ITT, intention-to-treat; OLE, open-label extension

B 2.3 Summary of methodology of the relevant clinical effectiveness evidence

The trial designs for the studies relevant to the decision problem (CHRONOS, CAFÉ, SOLO 1 and SOLO 2) are summarised in Figure 2.3 to Figure 2.5. Full details of the methodology for each of these trials is contained in Table 2.9.

B 2.3.1 Study designs for CHRONOS, CAFÉ and SOLO 1 & 2

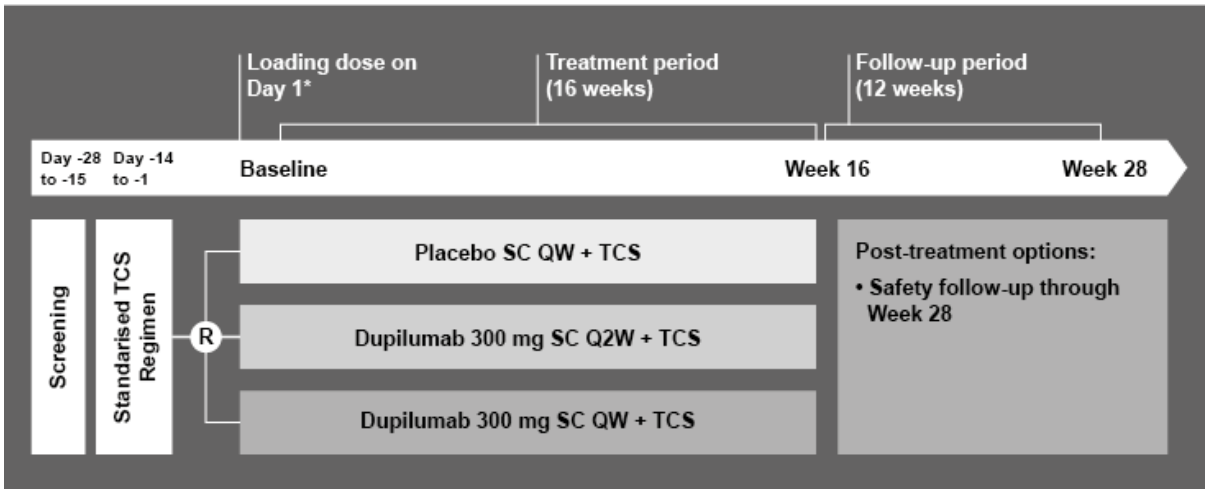
Figure 2.3 Trial schematic for the CHRONOS study[43, 95]



*Dupilumab 600 mg or matching placebo. Patients were required to use medium-potency TCS for the entire treatment period.

QW, once a week; Q2W, twice a week; R, randomisation; SC, subcutaneous; TCS, topical corticosteroid

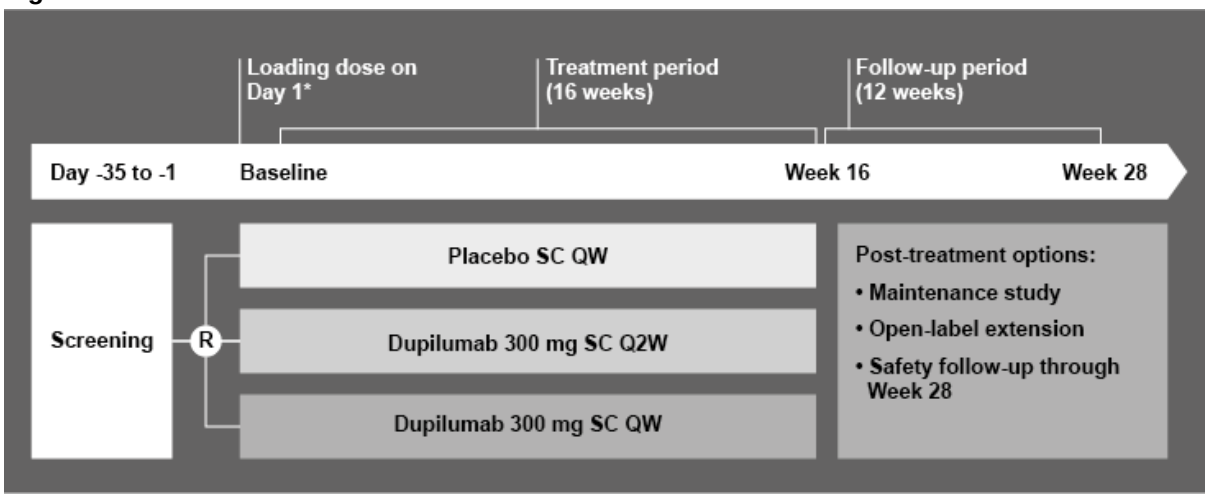
Figure 2.4 Trial schematic for the CAFÉ study[44, 98]



*Dupilumab 600 mg or matching placebo. Patients were required to use medium-potency TCS for the entire treatment period.

QW, once a week; Q2W, twice a week; R, randomisation; SC, subcutaneous; TCS, topical corticosteroid

Figure 2.5 Trial schematic for the SOLO 1 and SOLO 2 studies[45, 96, 97]



*Dupilumab 600 mg or matching placebo

QW, once a week; Q2W, twice a week; R, randomisation; SC, subcutaneous

B 2.3.2 Trial methodology

A comparative summary of the methodology for the four relevant RCTs is provided in Table 2.9 below.

Table 2.9 Comparative summary of trial methodology

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
Settings and locations where the data were collected	101 study locations in 10 countries (United States, Bulgaria, Canada, Denmark, Estonia, Finland, Germany Japan, Singapore, Spain).	93 study locations in 11 countries (United States, Canada, France, Germany, Hong Kong, Italy, Korea, Lithuania, Poland, Sweden, United Kingdom)	149 studies locations in 14 countries (United States, Australia, Canada, Czech Republic, Hungary, Italy, Japan, Republic of Korea, Netherlands, New Zealand, Poland, Romania, Spain, United Kingdom)	Approximately 115 study sites in countries where systemic CSA was approved for the treatment of AD including Austria, Belgium, Germany, Ireland, Netherlands, Poland, Russian Federation, Slovakia, Spain, and the United Kingdom.
Trial design	28-week (16-week treatment period plus 12-week follow-up) randomised, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab monotherapy in adults with **moderate-to-severe AD** whose disease was inadequately controlled with topical medications or for whom topical treatment was medically inadvisable.		64-week (52-week treatment period plus 12-week follow-up) randomised, double-blind, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab administered concomitantly with TCS in adults with **moderate-to-severe AD**.	32-week (4-week TCS run-in, 16-week treatment period plus 12-week follow-up) double-blind, randomised, placebo-controlled, parallel-group study to confirm the efficacy, safety, and tolerability of dupilumab administered to adults with **severe AD** with a documented history of intolerance, inadequate response or contraindication to CSA.
Eligibility criteria for participants	The target patient population is focused on patients for whom safe and effective therapies are not currently available and thereby have a high unmet medical need for new treatment options. The inclusion/exclusion criteria were identical in the two Phase III, replicate, confirmatory, monotherapy studies (SOLO 1 R668 AD 1334 and SOLO 2 R668-AD-1416), and were generally comparable across all other Phase III clinical studies in the trial programme. Eligible patients were adult (>18 years) males and females with chronic AD (present for at least 3 years and meeting the American Academy of Dermatology Consensus Criteria[27] and with a documented recent history (within 6 months before the screening visit) of an inadequate response to topical prescription medications, or in whom those therapies were not advisable. Active disease severity was gated to moderate-to-severe by baseline AD severity scores of IGA ≥3 (SOLO 1 and 2, CHRONOS, CAFÉ), EASI ≥16 (CHRONOS), EASI ≥ 20 (CAFÉ), and ≥10% BSA involvement with AD. In addition, an average maximum itch intensity of ≥3 on the pruritus NRS was required at baseline. The studies therefore represent a patient population with AD lesions affecting a large portion of their BSA and experienced high levels of AD symptoms, including pruritus, which are not adequately controlled by topical prescription therapies alone, and were candidates for systemic AD therapies.			

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
	A key feature of the CAFÉ study are the inclusion criteria concerning CSA, the definitions for which are provided below: A. No prior CSA exposure (patient was not a candidate for CSA treatment) due to: a. Medical contraindications, or b. Hypersensitivity to CSA active substance or excipients, or c. Use of concomitant medications prohibited with CSA, or d. Increased susceptibility to CSA induced renal damage, increased risk of serious infections, etc. B. Previously exposed to CSA and for whom CSA should not be continued or restarted due to: a. Previous intolerance and/or unacceptable toxicity, or b. Inadequate response — defined as flare of AD on CSA tapering after a maximum of 6 weeks of high-dose (5 mg/kg/day) to maintenance dose (2 to 3 mg/kg/day) or a flare after a minimum of 3 months on maintenance dose. Flare is defined as increase in signs and/or symptoms leading to escalation of therapy, which can be an increase in CSA dose, a switch to a higher potency class of TCS, or the start of another oral immunosuppressive drug, or c. Requirement for CSA at doses or duration beyond those specified in the prescribing information Exclusion criteria were used to prevent the enrolment of patients with concurrent conditions into the studies that could have jeopardised patient safety or could have confounded the study results. The complete list of inclusion and exclusion criteria for each trial are provided in Appendix O.			
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=) and comparator(s) (n=) Permitted and disallowed	617 patients were randomised in a 1:1:1 ratio to receive: 1. Dupilumab 300 mg SC QW for 16 weeks following a 600 mg loading dose on day 1 (N=223) 2. Placebo SC for dupilumab SC QW (N=224) 3. Dupilumab 300 mg SC Q2W following a	708 patients were randomised in a 1:1:1 ratio to receive: 1. Dupilumab 300 mg SC QW for 16 weeks following a 600 mg loading dose on day 1 (N=239) 2. Placebo SC for dupilumab SC QW (N=236) 3. Dupilumab 300mg SC Q2W following a	740 patients were randomised in a 3:1:3 ratio to receive: 1. Dupilumab 300 mg SC QW for 52 weeks following a 600 mg loading dose on day 1 (N=319) 2. Placebo SC for dupilumab SC QW (N=315) 3. Dupilumab 300mg SC Q2W following a 600 mg loading dose on day 1, alternating with placebo SC for 52 weeks (N=106) All patients also received medium-potency	325 patients were randomised in a 1:1:1 ratio to receive: 1. Dupilumab 300 mg SC QW for 16 weeks following a 600 mg loading dose on day 1 (N=110) 2. Placebo SC for dupilumab SC QW (N=108) 3. Dupilumab 300 mg SC Q2W following a 600 mg loading dose on day 1, alternating with placebo SC for 16 weeks (N=107) All patients also received medium-potency

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
concomitant medication	600 mg loading dose on day 1, alternating with placebo SC for 16 weeks. (N=224)	600 mg loading dose on day 1, alternating with placebo SC for 16 weeks. (N=233)	TCS Patients applied moisturisers at least twice daily for 7 days prior to randomisation and throughout the study. After the 35-day screening period dupilumab or placebo was given for 52 weeks.	TCS All patients were required to apply moisturisers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomisation and to continue throughout the study (all 64 weeks).
	Study drug could be self-administered by the patient or a caregiver after training by the clinic staff on preparation and administration of study drug on day 1. The patient/caregiver administered the study drug under the supervision of clinic staff at each clinic visit and administered it outside of the clinic during weeks in which no clinic visit was scheduled. Patients who preferred the clinic staff administer the study drug could choose to have injections administered in the clinic.			
	Randomisation was performed using a central randomisation scheme provided by an IVRS/IWRS, and stratified by disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) and by region (Japan vs. rest of world) for the SOLO and CHRONOS studies. For CAFÉ, additional stratification was by documented history of no prior CSA exposure and not currently a candidate for CSA treatment vs prior CSA exposure that should not have been continued or restarted.			
	Permitted medications and procedures included: • Basic skin care emollients, topical anaesthetics, topical and systemic antihistamines, and topical and systemic anti-infective medications for any duration. • Medications used to treat chronic disease such as diabetes, hypertension, and asthma were permitted. All patients were required to apply moisturisers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomisation and to continue throughout the study. However, to allow adequate assessment of skin dryness, moisturisers were not to be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. All types of moisturisers were permitted, but		Permitted medications and procedures included: • Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. • Use of TCS restricted to locally approved products and according local country guidelines. • Use of TCI was reserved for problem areas. Starting on day 1 [baseline], all patients were required to initiate treatment with TCS using a standardised regimen according to the following guidelines: • A medium-potency TCS was applied	Permitted medications and procedures included: • Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. • Low to medium dose TCS. Starting on day 1 [baseline], all patients were required to initiate treatment with TCS using a standardised regimen according to the following guidelines: • A medium-potency TCS was applied once daily to areas with active lesions. • A low potency TCS was used once daily on areas of thin skin (face, neck,

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
	patients could not initiate treatment Prohibited medications and procedures: • Treatment with a live (attenuated) vaccine • Treatment with immunomodulating biologics • Treatment with an investigational drug (other than dupilumab) • TCS or TCI could be administered during the study only if required for AD rescue • Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., CSA, MTX, MMF, AZA, etc.) • Major elective surgical procedures • Phototherapy • Tanning in a bed/booth		once daily to areas with active lesions. • A low potency TCS was used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium-potency TCS was considered unsafe. • After lesions were under control (clear or almost clear), treatment was switched from medium-potency to low potency TCS once daily for 7 days, then stopped. • If lesions returned, treatment with medium-potency TCS was reinstituted, with the step-down approach described above upon lesion resolution. • For lesions persisting or worsening under once daily treatment with medium-potency TCS, patients were treated (rescued) with high or super-high potency TCS, unless higher potency TCS were considered unsafe. The patient was monitored for signs of local or systemic TCS toxicity and treatment was stepped down or stopped, as necessary. Prohibited medications and procedures: • Treatment with a live (attenuated) vaccine • Treatment with immunomodulating biologics • Treatment with an investigational drug (other than dupilumab)	intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium-potency TCS was considered unsafe. • After lesions were under control (clear or almost clear), treatment was switched from medium-potency to low potency TCS once daily for 7 days, then stopped. • If lesions returned, treatment with medium-potency TCS was reinstituted, with the step-down approach described above upon lesion resolution. • For lesions persisting or worsening under once daily treatment with medium-potency TCS, patients were treated (rescued) with high or super-high potency TCS, unless higher potency TCS were considered unsafe. The patient was monitored for signs of local or systemic TCS toxicity and treatment was stepped down or stopped, as necessary. Prohibited medications and procedures: • Live (attenuated) vaccine Immunomodulating biologics • An investigational drug (other than dupilumab) • Treatment with a TCI, except when used for rescue • Treatment with high potency TCS, except when used for rescue • Treatment with TCS for patients who were

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
			• Treatment with wet wraps • Any other medications for AD that could have interfered with efficacy outcomes or affected the evaluation for AD severity. • Major elective surgical procedures • Tanning in a bed/booth • Live vaccines for approximately 3 months after stopping treatment with dupilumab	intolerant or hypersensitive to TCS • Systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g. CSA, AZA, MTX, MMF, JAK inhibitors, etc) • Tanning in a bed/booth • Phototherapy
	Rescue treatment Rescue treatment for AD if medically necessary (i.e., to control intolerable AD symptoms), was provided to study patients at the discretion of the investigator after week 2. Patients who received rescue treatment prior to week 2 were to permanently discontinue study treatment. Patients who received rescue treatment continued study treatment if rescue consisted of topical medications. TCI could be used for rescue, but were reserved for problem areas only, e.g. face, neck, intertriginous and genital areas, etc. Patients could be rescued directly with higher potency topical medications or with systemic treatments. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs (e.g. ciclosporin, MTX, MMF, AZA, JAK inhibitors, biologic agents, etc.) study treatment was immediately, temporarily discontinued. After the treatment with these medications was completed, study treatment could be resumed but not sooner than 5 half-lives after the last dose of systemic rescue medication. Dose modification for an individual patient was not allowed. Patients who were discontinued from study drug were to remain in the study and complete all study visits and assessments.			
Primary outcomes (including scoring methods and timings of assessments)	Co-primary efficacy endpoints: 1. Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16 2. Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16			Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16
Other outcomes used in the economic model/specified in the scope)	Key secondary endpoints at 16 weeks: (See Appendix O for a full list of secondary endpoints) • Percent change in EASI score from baseline • Proportion of patients who achieved EASI-50 • Percent change in weekly average of peak daily pruritus NRS from baseline • Proportion of patients achieving a reduction of ≥4		Key secondary endpoints at 16 weeks and 52 weeks: (See appendix O for a full list of secondary endpoints) • Percent change in EASI score from baseline • Proportion of patients who achieved EASI-50	Key secondary endpoints at 16 weeks: (See appendix O for a full list of secondary endpoints) • Percent change in EASI score from baseline • Proportion of patients who achieved EASI-50

Trial number (acronym)	SOLO 1 R668-AD-1334/ NCT02277743 [45, 96]	SOLO 2 R668-AD-1416/ NCT02277769 [45, 97]	CHRONOS R668-AD-1224/ NCT02260986 [43, 95]	CAFÉ R668-AD-1424/ NCT02755649 [44, 98]
	Points in weekly average of peak daily pruritus NRS from baseline • Change from baseline in weekly average of peak daily pruritus NRS • Change from baseline in DLQI • Change from baseline in POEM • Change from baseline in HADS Change from baseline in EQ-5D • Incidence of AEs • Sick leave/missed school days assessment		• Percent change in weekly average of peak daily pruritus NRS from baseline • Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline • Change from baseline in weekly average of peak daily pruritus NRS • Change from baseline in DLQI • Change from baseline in POEM • Change from baseline in HADS • Change from baseline in EQ-5D • Incidence of AEs • Sick leave/missed school days assessment	• Percent change in weekly average of peak daily pruritus NRS from baseline • Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline • Change from baseline in weekly average of peak daily pruritus NRS • Change from baseline in DLQI • Change from baseline in POEM • Change from baseline in HADS Change from baseline in EQ-5D • Incidence of AEs • Sick leave/missed school days assessment
Pre-planned sub-groups	See Section B 2.7 for subgroup analyses			

ACQ-5, Asthma Control Questionnaire, 5-item version; AD, atopic dermatitis; AE, adverse event; AZA, Azathioprine; BSA, body surface area; CSA, ciclosporin; CSR, Clinical Study report; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, EASI score ≥50% response; EASI-75, EASI score ≥75% response; EASI-90, EASI score ≥90% response; EOT, end of treatment; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IFN-γ, interferon gamma; IGA, Investigator's Global Assessment; IVRS/IWRS; Interactive Voice Response System/ Interactive Web Response System; MMF, mycophenolate mofetil; MTX, methotrexate; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse event; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; TCI, topical calcineurin inhibitors; TEAE, treatment-emergent adverse event; QW, once a week; Q2W, every two week

The assessment schedule for the EQ-5D, DLQI, POEM and HADS instruments is presented in Table 2.10 to Table 2.12 for the Phase III SOLO 1&2, CAFÉ and CHRONOS studies.

Table 2.10 Schedule of events – Treatment period - visits 1 to 14.

Study procedure	Screening	Baseline	Treatment period (SOLO 1&2, CAFÉ, CHRONOS)											
Visit (V)	V1	V2	V3	V4	V5[a]	V6	V7[a]	V8	V9[a]	V10	V11	V12	V13	V14
Week (W)	−35 to −1	D1	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Day (D)			D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit window			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
SOLO 1	X	X	X	X		X		X		X				X
SOLO 2	X	X	X	X		X		X		X				X
CAFÉ	X	X	X	X		X		X		X				X
CHRONOS	X	X	X	X		X		X		X				X

[a]The site contacted the patient by telephone to conduct these visits. The patient/caregiver may have administered study drug on these days. Patients who received study drug outside the study centre completed a dosing diary to document compliance with study drug administration and to document any related issues.

Table 2.11 Schedule of events – Treatment period cont. - visits 15 to 27.

Study procedure	Treatment period (SOLO 1&2, CAFÉ, CHRONOS)				FOLLOW UP (SOLO1&2, CAFÉ) EOS [b]					Treatment period (CHRONOS)		EOTP (CHRONOS)	
Visit (V)	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27
Week (W)	W13	W14	W15	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52
Day (D)	D92	D99	D106	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365
Visit window	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
SOLO 1				X	X	X	X						
SOLO 2				X	X	X	X						
CAFÉ				X	X	X	X						
CHRONOS				X	X	X	X	X	X	X	X	X	X

[a]The site contacted the patient by telephone to conduct these visits. The patient/caregiver may have administered study drug on these days. Patients who received study drug outside the study centre completed a dosing diary to document compliance with study drug administration and to document any related issues.

[b]In the SOLO and CAFÉ studies the follow-up period was for those patients who declined to enter the open-label extension or the maintenance study; for those patients, the end of treatment was week 16.

Table 2.12 Schedule of events – Follow up period, unscheduled visit and early termination.

Study procedure	**Follow up Period EOS (CHRONOS)**			**Unscheduled visit** (if applicable)	**Early termination** (if applicable)
Visit (V)	V28	V29	V30		
Week (W)	W56	W60	W64		
Day (D)	D393	D421	D449		
Visit window	±3d	±3d	±3d		
SOLO 1				X	X
SOLO 2				X	X
CAFÉ				X	X
CHRONOS	X	X	X	X	X

B 2.3.3 Baseline characteristics of study participants

Baseline patient characteristics, including disease severity and quality of life measures, were similar across the four Phase III studies as shown below in Table 2.13 to Table 2.15.

To enable interpretation of the following tables the published thresholds for each tool are provided below:

- EASI (0 to 72) severity strata for moderate-to-severe AD are as follows: moderate = 7.1–21.0; severe = 21.1–50.0; very severe = 50.1–72.0[36]

- IGA (0 to 4) severity strata for moderate-to-severe AD are as follows: moderate = 3; severe = 4; (Some iterations of the IGA score have 5 = very severe. The IGA scoring system used during the LIBERTY AD trial programme used the 0-4 scale)[37]

- SCORAD (0 to 103) severity strata for moderate-to-severe AD are as follows: moderate = 26–50; severe = 51–103[41, 42]

- Pruritus NRS (0 to 10) severity strata for moderate-to-severe pruritus are as follows: moderate = ≥4-<7; severe = ≥ 7–< 9; Very severe = ≥ 9[166]

- POEM: (0 to 28). The following severity bands are used to give clinical meaning to the POEM score: 0 to 2 = clear or almost clear; 3 to 7 = mild; 8 to 16; moderate; 17 to 24 = severe; 25 to 28 = very severe[49]

- DLQI: (0 to 30) The following band descriptors are used to give clinical meaning to the DLQI: 0-1 = no effect at all on patient's life; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect[47]

- HADS: (0 to 42 for total HADS) The HADS questionnaire comprises seven questions for anxiety (HADS-A) and seven questions for depression (HADS-D). Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety (HADS-A) or depression (HADS-D). A cut-off of 8 or more for HADS-A or HADS-D (or combined ≥11) is frequently used to determine the presence of overt anxiety or depression, respectively[52]

Baseline patient characteristics - CHRONOS

Demographic and baseline characteristics were similar among the treatment groups. Most patients were White (66.2%) or Asian (27.2%), with a mean age of 37.1±13.46 years. 60.3% of patients were men, and 39.7% were women. The mean (SD) duration of AD, the mean EASI score (severe at baseline) and the mean IGA score (moderate-to-severe at baseline) were similar between the treatment groups. 28.0% of patients had a history of prior cyclosporine treatment. 52.8% of patients had received systemic therapy for their AD, which included systemic corticosteroids (34.2%) and systemic nonsteroidal immunosuppressants (33.6%). Prior medication use was generally similar among all treatment groups.

Table 2.13 Baseline demographics and characteristics of participants in CHRONOS across treatment groups[95]

	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
N=740	**N=315**	**N=106**	**N=319**
Mean age – years (SD)	36.6 (13.01)	39.6 (13.98)	36.9 (13.67)
Gender (male) n (%)	193 (61.3%)	62 (58.5%)	191 (59.9%)
Weight (kg), mean (SD)	75.0 (18.61)	73.1 (17.73)	74.4 (17.63)
BMI, mean (SD)	25.8 (5.69)	25.5 (5.80)	25.6 (5.12)
Race, n (%) **White** **Black** **Asian** **Other or missing data**	 208 (66.0%) 19 (6.0%) 83 (26.3%) 5 (1.6%)	 74 (69.8%) 2 (1.9%) 29 (27.4%) 1 (0.9%)	 208 (65.2%) 13 (4.1%) 89 (27.9%) 9 (2.8%)
Duration of AD, mean years (SD)	27.5 (14.34)	30.1 (15.53)	27.9 (14.46)
Percent body surface area with AD, mean (SD)	56.9 (21.69)	59.5 (20.84)	54.1 (21.76)
EASI (0-72, >20=severe), mean (SD)	32.6 (12.93)	33.6 (13.30)	32.1 (12.76)
IGA score (0-4, 4=severe), mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)
Number of patients with IGA score 4, n (%)	147 (46.7%)	53 (50.0%)	147 (46.1%)
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	7.3 (1.84)	7.4 (1.66)	7.1 (1.90)
SCORAD score (0-103, >50=severe), mean (SD)	66.0 (13.53)	69.3 (15.24)	65.9 (13.63)
POEM score (0-28, >24=severe), mean (SD)	20.0 (5.99)	20.3 (5.68)	20.1 (6.05)
DLQI score (0-30, >10=very large effect), mean (SD)	14.7 (7.37)	14.5 (7.31)	14.4 (7.17)
Total HADS score (0-42, 11 clinically overt depression/anxiety), mean (SD)	12.6 (8.06)	12.9 (7.73)	12.8 (8.01)
GISS (0-12) score, mean (SD)	8.7 (1.84)	8.9 (2.04)	8.9 (1.80)
EQ-5D VAS (0-100), mean (SD)	56.5 (23.70)	57.9 (22.63)	56.0 (22.77)
EQ-5D (0-1) utility, mean (SD)	0.630 (0.3212)	0.648 (0.2768)	0.641 (0.2902)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QW, once a week; Q2W, every two weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale

Table 2.14 Baseline demographics and characteristics of participants in CAFÉ across treatment groups[98]

CAFÉ	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
N=325	**N=108**	**N=107**	**N=110**
Mean age – years (SD)	38.9 (13.35)	37.5 (12.89)	38.7 (13.21)
Gender (male) n (%)	68 (63.0%)	65 (60.7%)	66 (60.0%)
Weight (kg), mean (SD)	78.3 (18.45)	74.5 (15.41)	74.7 (16.78)
BMI, mean (SD)	26.1 (5.19)	24.7 (3.97)	25.2 (4.57)
Race, n (%) **White** **Black** **Asian** **Other or missing data**	 104 (96.3%) 0 2 (1.9%) 2 (1.9%)	 104 (97.2%) 0 2 (1.9%) 1 (0.9%)	 105 (95.5%) 2 (1.8%) 2 (1.8%) 1 (0.9%)
Duration of AD, mean years (SD)	29.2 (14.72)	29.6 (15.61)	32.3 (14.00)
Percent body surface area with AD, mean (SD)	55.0 (20.51)	56.1 (17.83)	56.0 (19.26)
EASI (0-72, >20=severe), mean (SD)	32.9 (10.80)	33.3 (9.93)	33.1 (11.02)
IGA score (0-4, 4=severe), mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)
Number of patients with IGA score 4, n (%)	52 (48.1%)	50 (46.7%)	52 (47.3%)
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	6.4 (2.23)	6.6 (2.10)	6.2 (2.01)
SCORAD score (0-103, >50=severe), mean (SD)	67.0 (12.20)	68.6 (11.91)	66.0 (12.70)
POEM score (0-28, >24=severe), mean (SD)	19.1 (5.99)	19.3 (6.21)	18.6 (6.97)
DLQI score (0-30, >10=very large effect), mean (SD)	13.2 (7.60)	14.5 (7.63)	13.8 (8.03)
Total HADS score (0-42, 11 clinically overt depression/anxiety), mean (SD)	13.0 (7.85)	12.8 (8.01)	13.3 (8.15)
GISS (0-12) score, mean (SD)	9.4 (1.63)	9.3 (1.64)	9.1 (1.63)
EQ-5D VAS (0-100), mean (SD)	53.4 (24.53)	55.5 (22.77)	55.9 (20.77)
EQ-5D (0-1) utility, mean (SD)	0.681 (0.2870)	0.717 (0.2590)	0.694 (0.2477)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QW, once a week; Q2W, every two weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale

Table 2.15 Baseline demographics and characteristics of participants in SOLO 1 and SOLO 2 across treatment groups[96, 97]

	SOLO 1 N=671			SOLO 2 N=708		
	Placebo	Dupilumab 300 mg Q2W	**Dupilumab 300 mg QW**	Placebo	Dupilumab 300 mg Q2W	**Dupilumab 300 mg QW**
	(N=224)	**(N=224)**	**(N=223)**	**(N=236)**	**(N=233)**	**(N=239)**
Mean age – years (SD)	39.5 (13.91)	39.8 (14.68)	39.3 (14.39)	37.4 (14.09)	36.9 (13.96)	37.1 (14.51)
Gender (male) n (%)	118 (52.7)	130 (58.0)	142 (63.7)	132 (55.9)	137 (58.8)	139 (58.2)
Weight (kg), mean (SD)	75.3 (18.36)	76.1 (17.06)	78.5 (18.45)	77.1 (18.14)	77.6 (19.51)	76.8 (19.25)
BMI, mean (SD)	26.4 (5.82)	26.3 (4.82)	26.7 (6.07)	26.6 (5.71)	26.4 (5.82)	26.4 (6.04)
Race, n (%) **White** **Black** **Asian** **Other or missing data**	 146 (65.2%) 16 (7.1%) 56 (25.0%) 6 (2.7%)	 155 (69.2%) 10 (4.5%) 54 (24.1%) 5 (2.2%)	 149 (66.8%) 20 (9.0%) 51 (22.9%) 3 (1.3%)	 156 (66.1%) 20 (8.5%) 50 (21.2%) 7 (3.0%)	 165 (70.8%) 13 (5.6%) 44 (18.9%) 6 (2.6%)	 168 (70.3%) 15 (6.3%) 45 (18.8%) 4 (1.7%)
Duration of AD, mean years (SD)	29.5 (14.46)	28.5 (16.12)	27.9 (15.79)	28.2 (14.41)	27.2 (14.24)	27.4 (15.01)
% body surface area with AD, mean (SD)	57.5 (23.38)	54.7 (23.19)	56.1 (22.96)	54.3 (23.06)	52.7 (21.23)	52.2 (21.51)
EASI (0-72, >20=severe), mean (SD)	34.5 (14.47)	33.0 (13.57)	33.2 (13.98)	33.6 (14.31)	31.8 (13.08)	31.9 (12.70)
IGA score (0-4, 4=severe), mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)
Number of patients with IGA score 4, n (%)	110 (49.1%)	108 (48.2%)	106 (47.5%)	115 (48.7%)	115 (49.4%)	112 (46.9%)
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	7.4 (1.77)	7.2 (1.89)	7.2 (2.06)	7.5 (1.85)	7.6 (1.60)	7.5 (1.81)
SCORAD score (0-103, >50=severe), mean (SD)	68.3 (13.96)	66.9 (13.97)	67.5 (13.61)	69.2 (14.91)	67.2 (13.48)	67.5 (13.10)
POEM score (0-28, >24=severe), mean (SD)	20.3 (5.90)	19.8 (6.37)	20.4 (6.25)	21.0 (5.94)	20.8 (5.49)	20.9 (5.59)
DLQI score (0-30, >10=very large effect), mean (SD)	14.8 (7.23)	13.9 (7.37)	14.1 (7.51)	15.4 (7.69)	15.4 (7.07)	16.0 (7.33)
Total HADS score (0-42, 11 overt depression/anxiety), mean (SD)	12.6 (8.33)	12.2 (7.26)	12.6 (7.95)	13.7 (8.32)	13.7 (7.52)	14.6 (8.24)
GISS (0-12) score, mean (SD)	9.0 (1.85)	8.9 (1.81)	8.9 (1.74)	9.2 (1.78)	9.0 (1.80)	9.0 (1.75)
EQ-5D VAS (0-100), mean (SD)	54.7 (24.83)	56.8 (23.34)	56.0 (24.83)	57.0 (24.38)	55.4 (22.96)	53.6 (23.82)
EQ-5D (0-1) utility, mean (SD)	0.603 (0.3413)	0.649 (0.3178)	0.640 (0.3205)	0.606 (0.3465)	0.607 (0.3212)	0.572 (0.3555)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QW, once a week; Q2W, every two weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale

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

Table 2.16 Summary of statistical analyses in the RCTs

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
SOLO 1 **R668-AD-1334/ NCT02277743** [45, 96]	The primary objective of the study is to demonstrate the efficacy of dupilumab monotherapy over 16 weeks compared to placebo treatment in adult patients with moderate-to-severe AD. Efficacy was measured by: • Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at week 16 The secondary objective of the study is to assess the safety of dupilumab monotherapy compared to placebo treatment in patients with moderate-to-severe AD. The following null and alternative hypotheses for each primary endpoint were tested for each dupilumab regimen group and the placebo group: H0: $p\ dupilumab = p\ placebo$, H1: $p\ dupilumab \neq p\ placebo$. where p stands for the percent of responders in a treatment group.	The full analysis set (FAS) includes all randomised patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomisation (as randomised). This is the primary analysis population for efficacy analyses. The per protocol set (PPS) includes all patient in the FAS except for those who are excluded because of major efficacy-related protocol violations. The safety analysis set (SAF) includes all randomised patients who received any study drug; it is based on the treatment received (as treated). The CMH test adjusted by randomisation strata (region, disease severity) was used for the proportion of patients with IGA 0 or 1 at week 16 or the proportion of patients with EASI-75 at week 16. The primary efficacy analyses were performed on FAS, as well as on PPS as a supporting analysis	In total the sample size of SOLO 1 was 600 randomised at a 1:1:1 ratio dupilumab 300 mg QW:300 mg Q2W:placebo. It was estimated that with 200 patients per group, the study would provide 99% power in power in both comparisons (between dupilumab 300 mg QW and placebo treatment, and between dupilumab 300 mg Q2W and placebo treatment). The same numbers of patients would also provide 99% power to detect a difference of 43% in the proportions of patients achieving EASI-75 response at week 16, assuming that the proportions were 58% and 15% for dupilumab and placebo, respectively. The sample size also ensured that sufficient safety information was collected, and to ensure that a sufficient number of responders would be available for inclusion in the maintenance study, The significance level was set to 2-sided, 0.025 in consideration of multiplicity of the 2 comparisons between each of the 2 dupilumab dose groups and placebo.	If a patient withdrew from the study, they were counted as a non-responder for the time points after withdrawal. If rescue treatment was used, the patient was counted as a non-responder from the time the rescue treatment was used. If a patient had a missing value at week 16, they were counted as a non-responder at week 16. Sensitivity analyses were conducted as follows: The LOCF approach, after censoring for rescue treatment use or study withdrawal to determine patient's status at week 16, was conducted to assess the robustness of the primary efficacy analysis with regard to handling of missing post-baseline data. All observed data, regardless if rescue treatment was used or data were collected after study withdrawal, were included for the primary endpoint. Patients with missing values were counted as non-responders. All observed data, regardless if rescue treatment was used or data were collected after study withdrawal, were included for the
SOLO 2 **R668-AD-1416/ NCT02277769** [45, 97]				

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				primary endpoint. Patients with missing values were not counted as non-responders.
CHRONOS **R668-AD-1224/ NCT02260986** [43, 95]	The primary objective was to demonstrate the efficacy of dupilumab administered concomitantly with TCS through week 16 in adult patients with moderate-to-severe AD compared to placebo administered concomitantly with TCS. The secondary objectives were to evaluate the long-term safety and efficacy at 52 weeks. The research objective was to assess the relationship between long-term exposure to dupilumab and potential biomarkers of AD in response to treatment. The following null and alternative hypotheses for each primary endpoint were tested for each dupilumab regimen group and the placebo group: H0: $p\ dupilumab = p\ placebo$, H1: $p\ dupilumab \neq p\ placebo$. Where *p* stands for the percent of responders in a treatment group.	The Full Analysis Set (FAS) included all randomised patients. Efficacy analyses were based on the treatment allocated by the IVRS/IWRS at randomisation (as randomised) and included the week 16 primary and secondary week 52 endpoints. The safety analyses were performed on the safety analysis set (SAF) which included all patients who received any study drug. For the safety analyses, the week 52 period was defined from day 1 to study completion date of the week 52 visit (365 days starting from the first dose of study drug if the date of the week 52 visit was unavailable), or the day of withdrawal from study before week 52, whichever was earlier. The CMH test adjusted for randomisation strata (region, disease severity) was used to analyse the percentage of patients with IGA 0 or 1 at week 16 or percentage of patients with EASI-75 at week 16. The primary efficacy analyses were performed on the FAS, as well as	The sample size was chosen to enable an adequate characterisation of the long-term safety profile, as well as efficacy of dupilumab in this patient population. It was estimated that with 300, 100, and 300 patients in the dupilumab 300 mg QW, dupilumab 300 mg Q2W, and placebo groups, respectively, the study could provide 99% power in both comparisons (between dupilumab 300 mg QW and placebo treatment, and between dupilumab 300 mg Q2W and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieved an IGA score 0 to 1 at week 16, assuming that the percentages were 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients could also provide 99% power in both comparisons assuming that the percentages of patients achieving EASI-75 responder at week 16 were 58% and 15% for dupilumab and placebo, respectively. The above assumptions were based on results from a Phase II study, R668-AD-	If a patient withdrew from the study, this patient was counted as a non-responder for the time points after withdrawal. To account for the impact of rescue treatment on the efficacy effect: For the binary efficacy endpoints (e.g. EASI-75), if rescue treatment was used the patient was specified as a non-responder from the time the rescue treatment was used. If the patient had a missing value at week 16, the patient was counted as a non-responder at week 16. Sensitivity Analyses Post-baseline LOCF approach after censoring for rescue medication use or study withdrawal to determine patient's status at week 16 was conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. All observed data, no matter if rescue medication was used or data was collected after study withdrawal, were included for the primary endpoint. Patients with missing values were counted as non-responders. All observed data, no matter if rescue treatment was used or data was collected after study

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		on the PPS as a supportive analysis.	1117. The power for each of the above calculations was based on a 2-sided 0.025 significance level, in consideration of the multiplicity between each of the 2 dupilumab dose groups with placebo. The sample size calculations were done using nQuery (7.0).	withdrawal, were included for the primary endpoint (regardless of rescue medication used) and missing data were not imputed as non-responders.
CAFÉ **R668-AD-1424/ NCT02755649** [44, 98]	The primary objective of the study is to evaluate the efficacy of 2 dose regimens of dupilumab (either QW or Q2W SC injections of 300 mg dupilumab following an SC loading dose of 600 mg on day 1) over 32 weeks compared to placebo, administered with concomitant TCS, in adult patients with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable. Efficacy was measured by the proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 The secondary objective of the study is to assess the safety and tolerability of the 2 dosing regimens of dupilumab compared to placebo, administered with concomitant TCS, in the same population. The following null and alternative	The full analysis set (FAS) includes all randomised patients. Efficacy analyses will be based on the treatment allocated (as randomised). This is the primary analysis population for efficacy analyses. The per protocol analysis set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. The Cochran-Mantel-Haenszel test adjusted by randomisation strata (disease severity [IGA 3 vs IGA 4] and prior CSA use [Yes, No]) will be used for the percentage of patients with EASI-75 at week 16. The primary efficacy analyses will be performed on FAS, as well as on PPS as a supporting analysis.	A total of 110 patients per arm, randomised in a 1:1:1 ratio to receive either QW or Q2W SC injections of 300 mg dupilumab or matching injectable placebo, will provide 99% power at the 2-sided 5% significance level for showing a difference in the primary efficacy endpoint of EASI-75 response rate at week 16 between the dupilumab and placebo treated groups. This assumes EASI-75 rates of 60.1% for the dupilumab arm and 26.4% for the placebo arm. There will be approximately 70 patients in the CSA prior exposure subgroup and approximately 40 patients in the CSA naïve subgroup.	If a patient withdraws from the study, this patient will be counted as a non-responder for the time points after withdrawal. If the patient has the missing value at week 16, then it will be counted as a non-responder at week 16. If rescue medication is used the patient will be specified as a non-responder from the time the rescue is used. Sensitivity analyses LOCF approach at week 16, with patient's status after rescue medication use or study withdrawal set to missing, will be conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. All observed data, no matter if rescue medication is used or data is collected after study withdrawal, will be included for the primary endpoint. Patients with missing values will be counted as non-

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	hypotheses for each primary endpoint were tested for each dupilumab regimen group and the placebo group: H0: $p\ dupilumab = p\ placebo$, H1: $p\ dupilumab \neq p\ placebo$. where *p* stands for the percent of responders in a treatment group.			responders. All observed data, no matter if rescue treatment is used or data is collected after study withdrawal, will be included for the primary endpoint (regardless of rescue medication used), missing data will not be imputed as non-responders.

AD, atopic dermatitis; CMH, Cochran-Mantel-Haenszel; CSA, ciclosporin; EASI, Eczema Area and Severity Index; EASI-75, EASI score ≥75% response; FAS, full analysis set; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; PPS, per protocol ansalysis set; RCT, randomised controlled trial; SC, subcutaneous; TCS, topical corticosteroid; QW, once a week; Q2W, every two weeks

B 2.4.1 Definitions of responder and non-responder for the analyses in the LIBERTY trial programme

A key feature of the LIBERTY trial programme is that all study designs allowed for rescue treatment (see Appendix O for a list of permitted rescue therapies). Flare was not an endpoint in the studies, but the receipt of rescue medication can be considered a proxy for flare. 'Escalation of treatment' or 'use of topical anti-inflammatory medications' have both been proposed in the literature as proxy indicators of AD flare[107].

For the primary analysis:

- If a patient withdrew from the study, they were counted as a non-responder for the time points after withdrawal.
- If a patient had a missing value at Week 16 (primary endpoint), they were also counted as a non-responder at Week 16.

For example, patients could be rescued with high potency TCS and continue study drug. However, if rescue with systemic agents occurred, dupilumab was discontinued but patients were eligible to re-start treatment after stopping the rescue treatment. For the primary analyses data were treated in the following way:

- For the binary efficacy endpoints (e.g. EASI-75), if rescue treatment was used the patient was specified as a non-responder from that point onwards even if they had responded according to objective measures such as EASI-75.
- The primary method of analysis for the continuous endpoints was by the multiple imputation (MI) with analysis of covariance (ANCOVA) model. Patients' efficacy data after rescue treatment usage were set to missing first, and then were imputed by the MI method.
    - The continuous endpoints were also tested using Last Observation Carried Forward (LOCF) and mixed-effect model repeated measures (MMRM) in sensitivity analyses to determine the impact of method of analysis.

Key sensitivity analyses were based on 'all observed' data no matter if rescue treatment was used or data was collected after withdrawal. This means that data collected after the use of rescue medication are retained in these analyses. The data analysed in this way are used in the base case for this submission because, in line with the marketing authorisation (see Section B 2.7.1), it is reasonable to expect that rescue medication (when required) will be used concomitantly with dupilumab. Hence, the 'all observed' results can be considered most closely generalisable to the real world setting. Both the primary and 'all observed' analyses are presented in Section B 2.6 below and Appendix O.

B 2.4.2 Participant flow in the relevant randomised controlled trials

For details of numbers of participants eligible to enter the trials, please refer to Appendix D.

B 2.5 Quality assessment of the relevant clinical effectiveness evidence

Risk of bias for each study was assessed using the Cochrane Risk of Bias tool [167]. All authors declared any conflict of interest within the primary manuscripts. A summary of the quality assessment for each of the relevant RCTs is provided in Table 2.17 and full details are provided in Appendix D.

The responses in the summary quality assessment results highlight the high-quality trial design. It is important to note that in the primary analyses patients were considered non-responders if they received rescue treatment. Sensitivity analysis included all the observed data (see Section B 2.4.1).

Table 2.17 Summary of the quality assessment results for parallel-group randomised controlled trials

	Studies not used in the economic model, but supportive of efficacy and safety		Studies used in the economic modelling	
Trial	**SOLO 1** [45, 96]	**SOLO 2** [45, 97]	**CHRONOS** [43, 95]	**CAFÉ** [44, 98][h]
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes measured were pre-defined within the study protocols.			
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	In the primary efficacy analysis patients that received rescue treatment were considered non-responders. Prespecified scenario analysis included all the observed data regardless of rescue treatment (see Section B 2.4.1)			

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[168]

B 2.6 Clinical effectiveness results of the relevant trials

B 2.6.1 CHRONOS efficacy evaluation

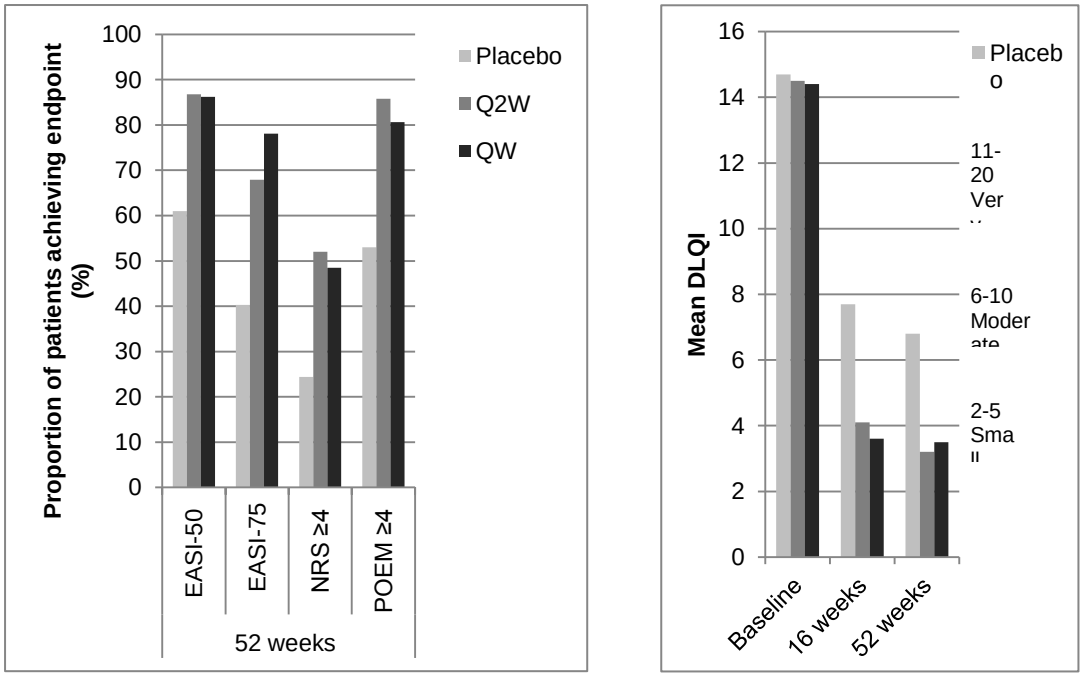
Efficacy of dupilumab, when used with as required TCS, was evaluated in the CHRONOS R668-AD-1224 study. As TCS represent the mainstay of pharmacological treatment of AD, many patients may use dupilumab in combination with them. This study was intended to inform 1-year treatment, with concomitant use of medium-potency TCS, for dupilumab on a background of emollients. It allowed for reduction in the volume of TCS used after clearing of AD skin lesions, which mirrors likely real world use of TCS. The 'All observed' sensitivity analyses can be considered most generalisable to the UK real world setting of dupilumab used concomitantly with TCS in UK clinical practice. Key results are discussed below and presented in Table 2.18 with further data provided in Appendix O.

Summary of the key results

Key measures of the clinical signs and symptoms of AD are exemplified by the EASI (0-72), pruritus NRS (0-10) and POEM (0-28) scores. The proportion of patients achieving EASI-50- and EASI-75 along with the proportion achieving the minimally clinically importance difference of four or more points for NRS and POEM are presented in Figure 2.6 overleaf at 52 weeks and in Table 2.18 to Table 2.20 below.

The improvement in these signs and symptoms has a profound effect on a patient's life, reducing the DLQI score for dupilumab treated patients by >10 from a level associated with 'Very large effect' to 'Small effect' [Figure 2.6][47].

Figure 2.6 CHRONOS improvement in the signs and symptoms of AD at 52 weeks and impact on quality of life as measured by DLQI at 16 and 52 weeks; all observed regardless of rescue treatment — FAS*[43, 95]

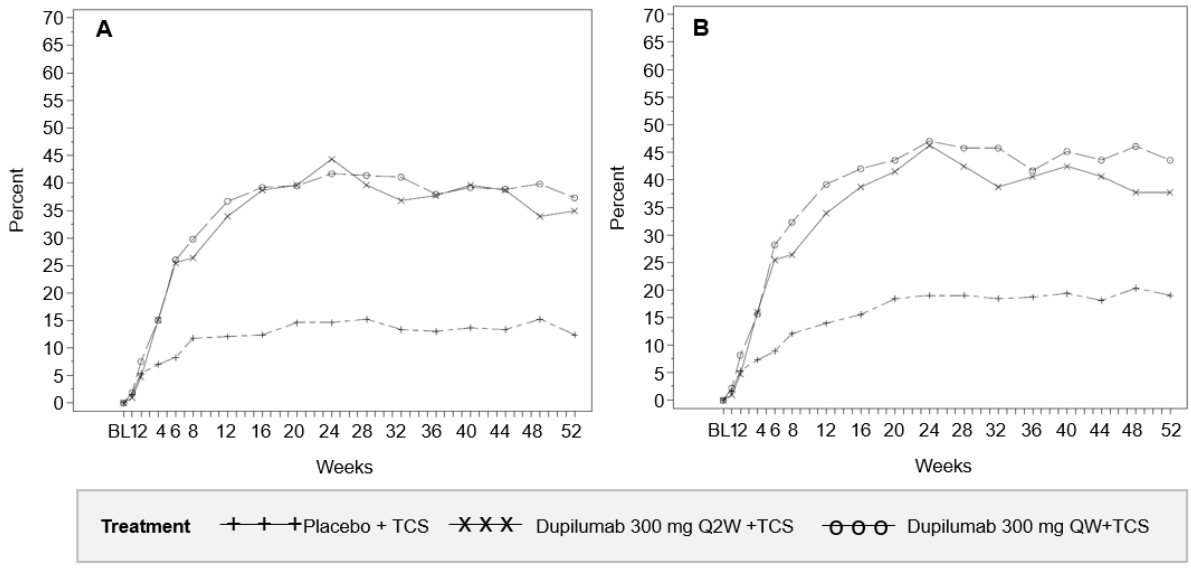


*p-values all <0.0001
AD, atopic dermatitis; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; POEM, Patient-Oriented Eczema Measure; FAS, full analysis set; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks. DLQI, Dermatology Quality of Life Index (2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect).

B 2.6.1.1 Primary endpoints

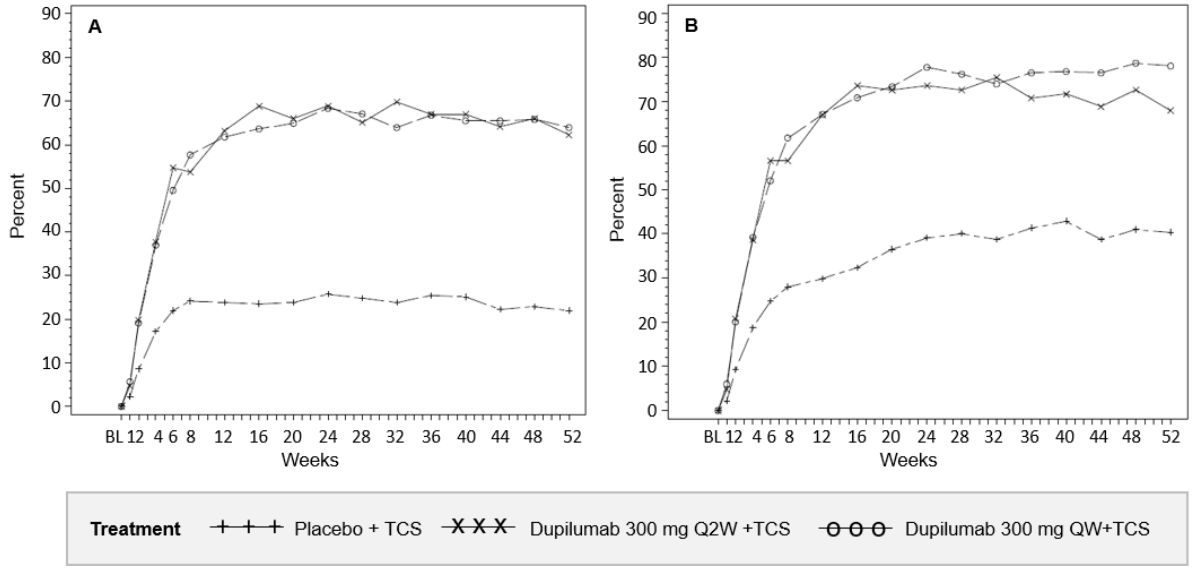
Both dupilumab dose regimens (300 mg QW and 300 mg Q2W) + TCS were superior to placebo + TCS in improving the extent and severity of AD skin lesions, with respect to the co-primary endpoints measured by the physician-reported IGA and EASI assessments (Table 2.18, Figure 2.7 and Figure 2.8). In the primary analysis, 39% of patients in each of the dupilumab + TCS treatment groups, compared with 12% of patients in the placebo + TCS group, achieved the co-primary endpoint of an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16, ($p<0.0001$ for each dose group vs. placebo + TCS) (Table 2.18 and Figure 2.7). Further, 64% and 69% of patients in the dupilumab 300 mg Q2W + TCS and 300 mg QW + TCS groups, respectively, achieved the EASI-75 co-primary endpoint at Week 16, compared with 22% of patients in the placebo + TCS group ($p<0.0001$ for each dose group vs. placebo + TCS) (Table 2.18 and Figure 2.8)

Figure 2.7 CHRONOS proportion of patients achieving IGA score of 0 or 1 and a reduction from baseline of ≥2 points through Week 52 with patients considered non-responders after rescue treatment (graph A) and all observed regardless of rescue treatment with missing considered non-responder (graph B) — FAS[95]



BL, baseline; EASI, Eczema Area Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid

Figure 2.8 CHRONOS proportion of patients achieving EASI-75 from baseline through Week 52 with patients considered non-responders after rescue treatment (graph A) and all observed regardless of rescue treatment with missing considered non-responder (graph B) — FAS[43, 95]



BL, baseline; EASI, Eczema Area Severity Index; EASI-75, EASI score ≥75% response; FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroids

Table 2.18 CHRONOS primary endpoints at Week 16 and 52 with patients considered non-responders after rescue treatment and all observed regardless of rescue treatment — FAS[43, 95]

Outcome *p-values all <0.0001	Week 16			Week 52		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=315)	(N=106)	(N=319)	(N=315)	(N=106)	(N=319)
Primary analysis (patients considered non-responder after rescue)						
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: N (%)*	39 (12.4)	41 (38.7)	125 (39.2)	39 (12.4)	37 (34.9)	119 (37.3)
Difference: % (95% CI)		26.3 (16.34, 36.26)	26.8 (20.33, 33.28)		22.5 (12.75, 32.30)	24.9 (18.49, 31.36)
Proportion of patients who achieved EASI−75: N (%)*	74 (23.5)	73 (68.9)	203 (63.6)	69 (21.9)	66 (62.3)	204 (63.9)
Difference: % (95% CI)		45.4(35.39, 55.36)	40.1(33.09, 47.20)		40.4 (30.06, 50.66)	42.0 (35.07, 49.02)
All observed regardless of rescue treatment						
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: N (%)*	49 (15.6)	41 (38.7)	134 (42.0)	60 (19.0)	40 (37.7)	139 (43.6)
Difference: % (95% CI)		23.1(13.03, 33.22)	26.5(19.72, 33.19)		18.7(8.49, 28.88)	24.5(17.57, 31.48)
Proportion of patients who achieved EASI−75: N (%)*	102 (32.4)	78 (73.6)	226 (70.8)	127 (40.3)	72 (67.9)	249 (78.1)
Difference: % (95% CI)		41.2(31.35, 51.06)	38.5(31.28, 45.65)		27.6(17.20, 38.01)	37.7(30.67, 44.81)

*p-values all <0.0001; CI, confidence interval; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; FAS, Full analysis set; IGA, Investigator's Global Assessment; QW, once a week; Q2W, every two weeks.

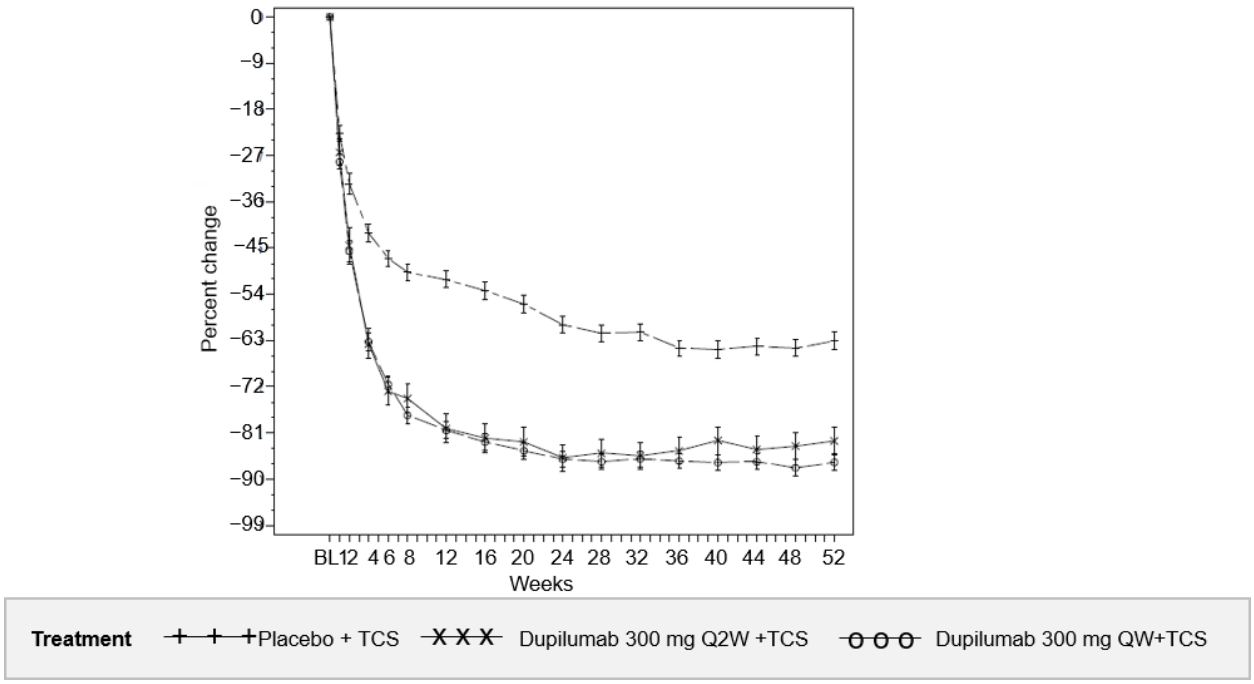
The methodology behind the 'All observed analysis' has been described in Section B 2.4.1. This is the most relevant analysis as it includes all the data from patients, irrespective of whether they have received rescue medication or not, as would be the case for patients in UK clinical practice. Hence, for the purposes of the economic model we include these data in the main analyses. All other data tabulated below is for the 'All observed' analysis. The equivalent dataset for the primary analysis is provided in Appendix O**.**

B 2.6.1.2 Secondary endpoints

Impact on clinical severity

Both dupilumab dose regimens (300 mg QW and 300 mg Q2W) + TCS were superior to placebo + TCS in improving the extent and severity of AD skin lesions, with respect to the secondary endpoints (Table 2.19) The improvements in the extent and severity of AD with dupilumab were sustained with continued long-term concomitant treatment for 52 weeks and similar efficacy results were seen to those observed for the co-primary endpoints at Week 16 (Table 2.18, Figure 2.7 and Figure 2.8). Consistent with the EASI-75 responder results, the percent reduction from baseline in EASI scores at Week 16 and 52 was significantly larger in the dupilumab + TCS groups than the placebo + TCS group (Table 2.19 and Figure 2.9).

Figure 2.9 CHRONOS LS mean (SE) in percentage change of EASI score from baseline to week 52 all observed regardless of rescue treatment with missing considered non-responder – FAS[95]



BL, baseline; EASI, Eczema Area Severity Index; FAS, full analysis set; LS, least squares; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

Table 2.19. CHRONOS key secondary efficacy outcomes at 16 and 52 weeks, all observed regardless of rescue treatment — FAS[95]

Outcome *p-values all <0.0001	Week 16			Week 52		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=315)	(N=106)	(N=319)	(N=315)	(N=106)	(N=319)
Percent change in EASI score from baseline: LS mean % change (SE)	-53.3 (1.68)	-82.0 (2.84)	-82.7 (1.64)	-63.1 (1.67)	-82.5 (2.70)	-86.7 (1.59)
Difference: LS mean (95% CI)		-28.7 (-35.06, -22.33)	-29.5 (-33.96, -24.97)		-19.4 (-25.60, -13.30)	-23.6 (-28.03, -19.17)
Proportion of patients who achieved EASI−50: n (%)	176 (55.9)	91 (85.8)	278 (87.1)	192 (61.0)	92 (86.8)	275 (86.2)
Difference: % (95%CI)		30.0(21.37, 38.58)	31.3(24.67, 37.87)		25.8(17.44, 34.24)	25.3(18.67, 31.84)
Percent change from baseline in SCORAD: LS mean % change (SE)	−39.4 (1.41)	−63.6 (2.41)	−66.6 (1.40)	−46.4 (1.47)	−65.7 (2.43)	−70.3 (1.43)
Difference: LS mean (95% CI)		−24.2 (−29.57, −18.76)	−27.2 (−30.95, −23.38)		−19.3 (−24.81, −13.77)	−23.9 (−27.87, −19.94)

CI, confidence interval; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-50, EASI score 50% response; FAS, Full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid; SCORAD, Severity Scoring of Atopic Dermatitis.

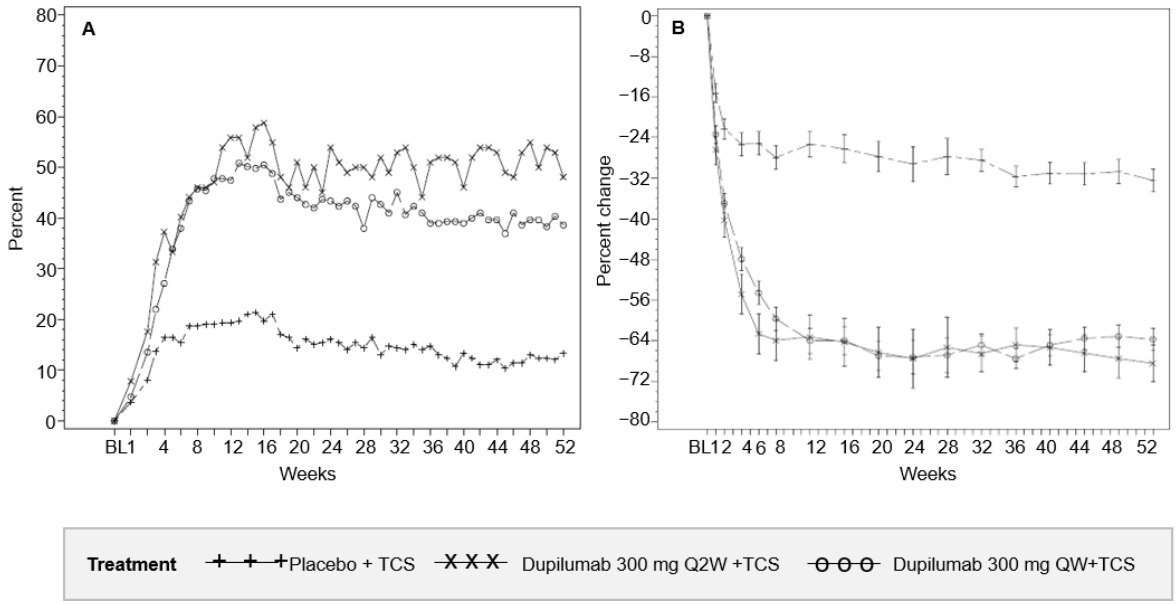
Impact on disease symptoms: Pruritus NRS and POEM

As discussed in Section B 1.3.6, the most burdensome aspect of AD to patients is the constant and unremitting itch. When used concomitantly with TCS, dupilumab was superior to placebo at improving pruritus, as measured by key secondary endpoints of patient-reported pruritus NRS. The proportions of patients who achieved ≥4-point or ≥3-point improvements in peak pruritus NRS were significantly greater with dupilumab + TCS than with placebo + TCS at all prespecified time points, except Week 2 for ≥4-point improvement for weekly dupilumab + TCS (Table 2.20 and Appendix O).

Significant improvements in peak pruritus NRS with dupilumab + TCS versus placebo + TCS were apparent as early as Week 2 and continued throughout the duration of the study up to Week 52, supporting the rapid and sustained action of dupilumab to reduce pruritus (Table 2.20 and Figure 2.10A).

During the study treatment period up to Week 52, there was a clear separation in the change in POEM between the dupilumab + TCS and placebo + TCS groups. The dupilumab + TCS groups showed a mean change (reduction or improvement) in POEM that was greater in magnitude than seen in the placebo + TCS group at every assessment during the study treatment period (Figure 2.10B)

Figure 2.10 CHRONOS proportion of patients achieving a reduction of ≥4 points in weekly average of peak daily pruritus NRS from baseline (graph A) and LS mean (SE) percentage change of POEM (graph B) through week 52; all observed regardless of rescue treatment with missing considered non-responder — FAS[95]



BL, baseline; FAS, full analysis set; LS, least squares; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

Table 2.20. CHRONOS key secondary patient-reported disease symptom outcomes in at 16 and 52 weeks; all observed regardless of rescue treatment — FAS[95]

Outcome *p-values all <0.0001	Week 16			Week 52		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=315)	(N=106)	(N=319)	(N=315)	(N=106)	(N=319)
Percent change in weekly average of peak daily pruritus NRS from baseline: LS mean % change (SE)	−33.1 (1.99)	−57.8 (3.86)	−57.6 (1.95)	−31.6 (2.54)	−58.6 (4.68)	−57.8 (2.42)
Difference: LS mean % (95% CI)		−24.7 (−32.94, −16.46)	−24.5 (−29.84, −19.19)		−27.0 (−36.79, −17.19)	−26.2 (−32.88, −19.50)
Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline: n/total N (%)	88/299 (29.4)	64/102 (62.7)	171/295 (58.0)	73/299 (24.4)	53/102 (52.0)	143/295 (48.5)
Difference: % (95%CI)		33.3(22.60, 44.02)	28.5(20.89, 36.18)		27.5(16.70, 38.40)	24.1(16.56, 31.56)
Change from baseline in weekly average of peak daily pruritus NRS: LS mean change (SE)	−2.55 (0.122)	−4.25 (0.208)	−4.33 (0.120)	−2.57 (0.144)	−4.44 (0.233)	−4.35 (0.137)
Difference: LS mean % (95% CI)		−1.70 (−2.167, −1.233)	−1.79 (−2.116, −1.459)		−1.88 (−2.400, −1.351)	−1.78 (−2.158, −1.400)
Change from baseline in POEM: LS mean change (SE)	-6.2 (0.36)	-12.9 (0.61)	-13.2 (0.36)	-6.7 (0.40)	-13.8 (0.66)	-13.2 (0.38)
Difference: LS mean (95% CI)		-6.7 (-8.09, -	-7.0 (-7.97, -		-7.0 (-8.51, -	-6.5 (-7.52, -5.40)

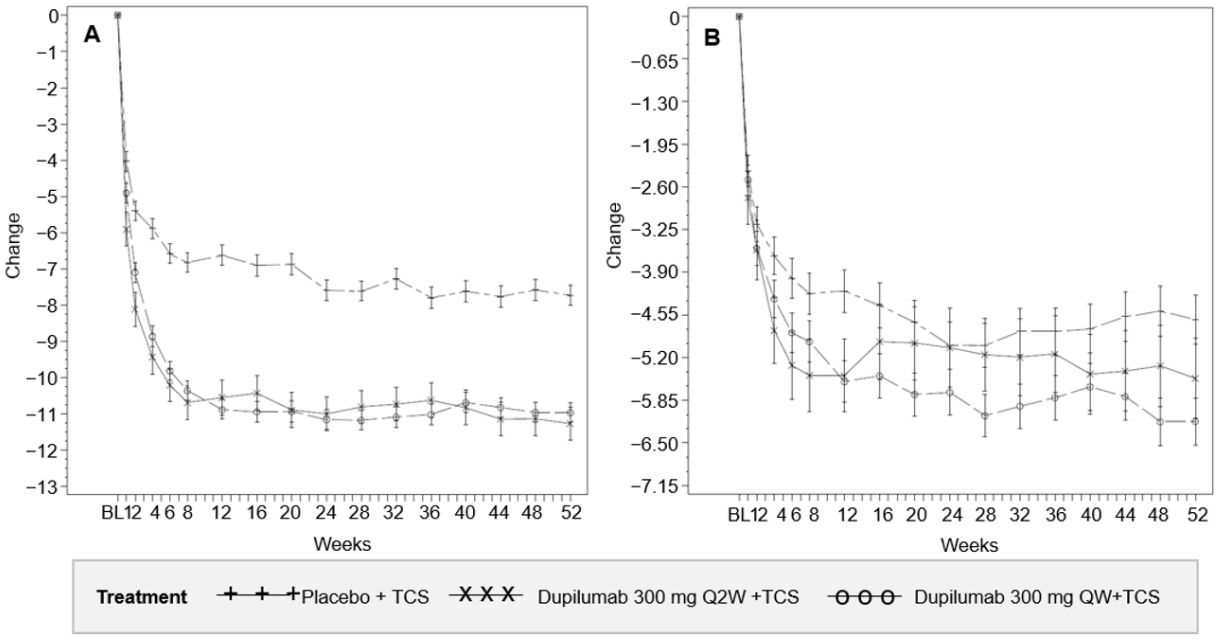
Outcome *p-values all <0.0001	Week 16			Week 52		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=315)	(N=106)	(N=319)	(N=315)	(N=106)	(N=319)
		5.34)	6.03)		5.57)	
Proportion of patients who achieved ≥4-point improvement (MCID) in POEM: n/total N (%)	176 (55.9)	89 (84.0)	275 (86.2)	167 (53.0)	91 (85.8)	257 (80.6)
Difference: % (95%CI)		28.1(19.21, 36.97)	30.3(23.67, 37.00)		32.8(24.21, 41.46)	27.5(20.53, 34.57)

*p-values all <0.0001. CI, confidence interval; POEM, Patient-Oriented Eczema Measure; FAS, Full analysis set; LS, least squares; MCID, Minimal clinically important difference; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroid.

Impact on quality of life and mental health

Dupilumab used concomitantly with TCS improved other patient-reported symptoms of AD, including impact on QoL, and anxiety and depression, versus TCS alone as assessed by greater reductions in DLQI, HADS and EQ-5D scores with results comparable between the primary and sensitivity analyses (Table 2.21, Figure 2.11 and Appendix O). In addition, higher proportions of patients on either dupilumab dose regime + TCS versus placebo + TCS achieved 4-point or higher improvement (minimal clinically important change [MCID] [Schram 2012, Basra 2015]) at Week 16 for DLQI (Q2W 81% and QW 74% vs 43%) and POEM (Q2W 77% and QW 77% vs 37%). This QoL response is in line with the magnitude of the EASI-50 response (Q2W 86% and QW 87% vs 56%) at Week 16 (Table 2.19) and was also observed at Week 52.

Figure 2.11. CHRONOS change (LS MEAN [SE] of DLQI (graph A) and total HADS (graph B) from baseline to Week 52, all observed regardless of rescue treatment — FAS[95]



BL, baseline; DLQI, Dermatology Quality of Life Index; FAS, full analysis set; LS, least squares; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

Table 2.21. CHRONOS quality of life and mental health outcomes at Week 16 and Week 52; all observed regardless of rescue treatment — FAS[95]

Outcome *p-values all <0.0001 unless otherwise stated	Week 16			Week 52		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=315)	(N=106)	(N=319)	(N=315)	(N=106)	(N=319)
Change from baseline in DLQI: LS mean change (SE)	−6.7 (0.29)	−10.2 (0.49)	−10.9 (0.28)	−7.5 (0.28)	−11.0 (0.46)	−11.0 (0.26)
Difference: LS mean (95% CI)		−3.5 (−4.62, −2.43)	−4.2 (−5.00, −3.46)		−3.6 (−4.61, −2.55)	−3.6 (−4.29, −2.83)
Proportion of patients who achieved ≥4-point improvement (MCID) in DLQI: n/total N (%)	193/315 (61.3)	86/106 (81.1)	259/319 (81.2)	187/315 (59.4)	91/106 (85.8)	246/319 (77.1)
Difference: % (95%CI)		19.9 (10.0, 29.7)	19.9 (12.7, 27.1)		26.5 (17.3, 35.7)	17.8 (10.3, 25.2)
Change from baseline in HADS total score: LS mean change (SE)	−4.3 (0.33)	−5.0 (0.57)	−5.4 (0.33)	−4.4 (0.36)	−5.5 (0.61)	−6.0 (0.36)
Difference: LS mean (95% CI)		−0.7 (−1.95, 0.59)	−1.1 (−1.96, −0.16)		−1.1 (−2.43, 0.32)	−1.6 (−2.58, −0.62)
p−value		0.2955	0.0207		0.1315	0.0013
Change from baseline in EQ-5D Index Utility Score: LS mean change (SE)	0.18 (0.01)	0.22 (0.02)	0.26 (0.01)	0.18 (0.01)	0.24 (0.02)	0,27 (0.01)
Difference: LS mean (95% CI)		0.05 (0.00, 0.09)	0.08 (0.05, 0.11)		0.06 (0.02, 0.10)	0.09 (0.06, 0.12)
p-value		0.0336			0.0023	
Change from baseline in EQ-5D VAS: LS mean change (SE)	11.1 1.00)	20.0 (1.70)	21.8 (0.98)	15.3 (1.03)	21.8 (1.66)	23.0 (0.98)
Difference: LS mean (95% CI)		9.0 (5.21, 12.83)	10.7 (7.98, 13.34)		6.4 (2.64, 10.20)	7.7 (4.94, 10.38)
p-value					0.0009	

DLQI, Dermatology Quality of Life Index; EQ-5D, European Quality of Life-5 Dimensions; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; LS, least squares; MCID, Minimal clinically important difference; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

B 2.6.1.3 Use of rescue medication

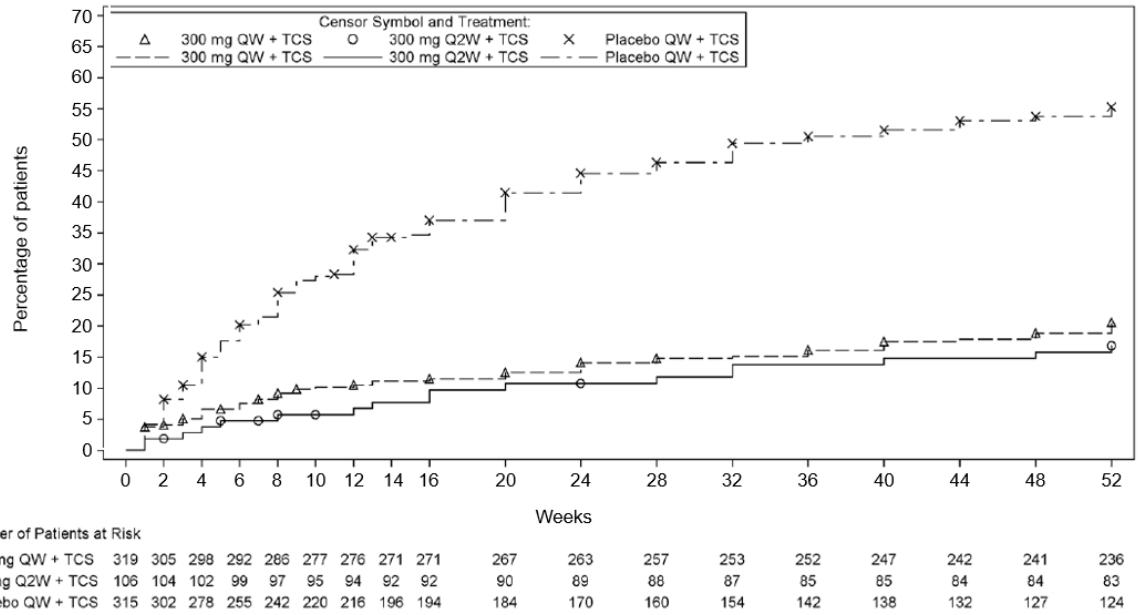
Dupilumab + TCS reduced use of rescue treatments, including TCI, oral corticosteroids, and systemic immunosuppressants (Table 2.22) compared to the placebo group. About 16% of patients treated with dupilumab + TCS received rescue treatment, 53% of patients treated with placebo plus topical corticosteroids required rescue treatment; all prespecified sensitivity analyses that included all observed data (regardless of rescue medication use) also remained significant and were consistent with the primary analyses fewer dupilumab treatment patients needed rescue treatment. Kaplan Meier curves of time to first rescue treatment use (topical or systemic are shown in Figure 2.12).

Table 2.22 CHRONOS rescue medication or procedures during the 52-week treatment period – FAS[43, 95]

	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
	(N=315)	(N=106)	(N=319)
Rescue therapy n(%)			
Any rescue therapy	167 (53.0%)	17 (16.0%)	64 (20.1%)
Topical corticosteroids	151 (47.9%)	16 (15.1%)	59 (18.5%)
Systemic corticosteroids	32 (10.2%)	7 (6.6%)	10 (3.1%)
Immunosuppressants	25 (7.9%)	1 (0.9%)	4 (1.3%)
Oral calcineurin inhibitors	14 (4.4%)	0	3 (0.9%)
Selective immunosuppressants	7 (2.2%)	0	7 (2.2%) 0 1 (0.3%)
Other immunosuppressants	7 (2.2%)	1 (0.9%)	1 (0.3%)

FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroids

Figure 2.12 CHRONOS Kaplan Meier curves of time to first rescue treatment use (topical or systemic) –FAS[95]



FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid

B 2.6.2 CAFÉ efficacy evaluation

Efficacy of dupilumab used concomitantly with TCS in adults with severe AD with intolerance, inadequate response, or contraindication to ciclosporin, was demonstrated in the CAFÉ study. This 16-week treatment study was designed to examine concomitant use of TCS with dupilumab compared to concomitant TCS use with placebo, and a potential dupilumab corticosteroid sparing effect in this population. The choice of TCS as required is consistent with BSC for moderate-to-severe AD patients considered eligible for treatment with systemic ciclosporin. The results from the 'All observed' sensitivity analyses can be

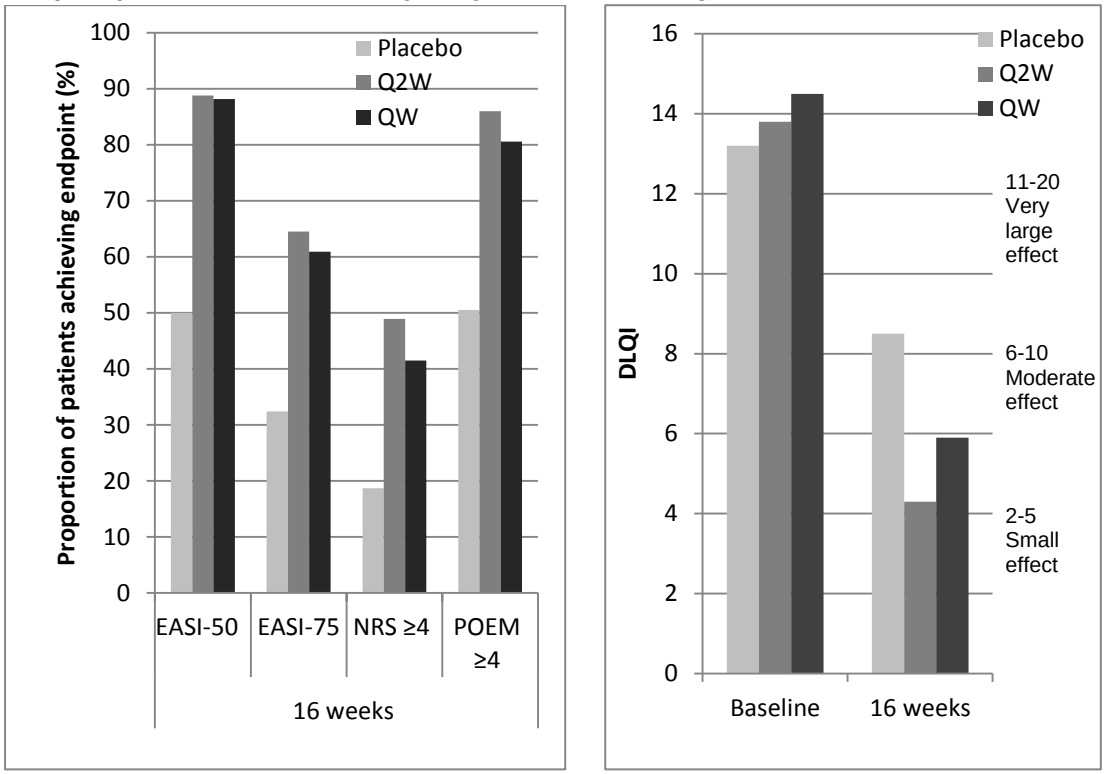
considered most generalisable to the real world setting as previously discussed. Key results are discussed below with further data provided in Appendix O.

Summary of the key results

The proportion of patients achieving EASI-50 and EASI-75 along with the proportion achieving the minimally clinically importance difference of four or more points for NRS and POEM at 16 weeks are presented in Figure 2.13 overleaf and in Table 2.23 to

Table 2.25 below. From baseline to week 16 the DLQI score for patients in the dupilumab arm changed from 'very large effect' to 'small effect'on a patient's life[47].

Figure 2.13. Improvement in the signs and symptoms of AD in CAFÉ at 16 weeks and impact on quality of life as measured by DLQI; all observed regardless of rescue treatment — FAS*[98]



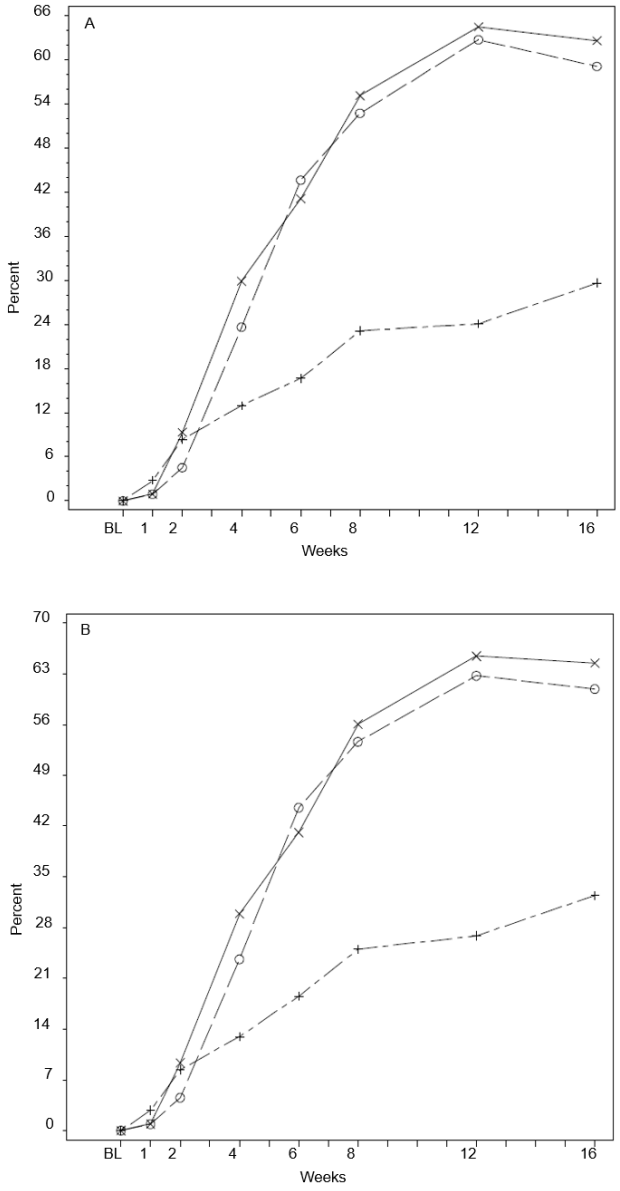
*p-values all <0.0001

AD, atopic dermatitis; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; POEM, Patient-Oriented Eczema Measure; FAS, full analysis set; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks. DLQI, Dermatology Quality of Life Index (2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect).

B 2.6.2.1 Primary endpoints

The primary endpoint in CAFÉ was the proportion of patients with ≥75% improvement from baseline in EASI score (EASI-75) at Week 16. Statistically and clinically significant results for dupilumab + TCS were achieved for the primary endpoint (62.6% dupilumab 300 mg Q2W + TCS, 59.1% dupilumab 300 mg QW + TCS, and 29.6% placebo + TCS, p<0.0001 for both comparisons) (Table 2.23). There was a clear separation in the proportion of patients achieving EASI-75 between the dupilumab and placebo groups, evident at Week 4 (Figure 2.14). There was little difference between the primary and all observed data.

Figure 2.14. CAFÉ proportion of patients achieving EASI-75 from baseline through Week 16 with patients considered non-responders after rescue treatment (A) and all observed regardless of rescue treatment with missing considered non-responder (B) — FAS[44, 98]



BL, baseline; EASI-75, Eczema Area Severity Index; EASI score ≥75% response; FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroids

Table 2.23 CAFÉ primary endpoint at Week 16 with patients considered non-responders after rescue treatment and all observed regardless of rescue treatment — FAS[44, 98]

Outcome *p-Values all <0.0001	Primary analysis: (MI method for continuous variables) Patients considered non-responders after rescue treatment			All observed regardless of rescue treatment		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS
	(N=108)	(N=107)	(N=110)	(N=108)	(N=107)	(N=110)
Proportion of patients who achieved EASI-75: N (%)*	32 (29.6)	67 (62.6)	65 (59.1)	35 (32.4)	69 (64.5)	67 (60.9)
Difference: % (95% CI)*		33.0(20.41, 45.57)	29.5(16.87, 42.05)		32.1(19.42, 44.73)	28.5(15.81, 41.19)

*p-Values all <0.0001; CI, confidence interval; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; FAS, Full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid

The 'All observed' analyses are presented for all other outcomes described below and the primary analyses can be found in Appendix O.

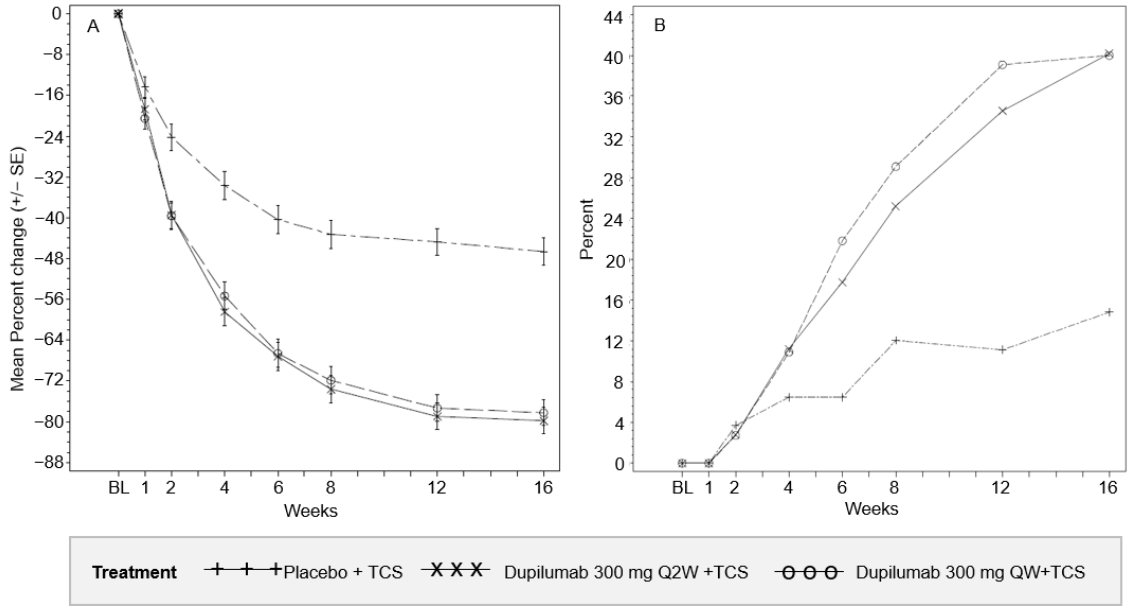
B 2.6.2.2 Secondary endpoints

Impact on clinical severity

Statistically and clinically significant results for dupilumab + TCS were achieved for all secondary endpoints of disease severity and extent of involvement such as EASI, IGA, SCORAD, GISS and percent BSA (Table 2.24, Figure 2.15 and Appendix O).

The proportion of patients achieving IGA 0 or 1 and a reduction from baseline of ≥2 points at week 16 was significantly higher in the dupilumab 300 mg Q2W + TCS group (40.2%) and dupilumab 300 mg QW + TCS group (40.0%) than the placebo + TCS group (14.8%) ($p<0.0001$ for both dose comparison with placebo) (Table 2.24). Consistent with the EASI-75 responder results, the percent reduction from baseline in EASI score at Week 16 was significantly larger in the dupilumab + TCS groups than the placebo + TCS group, (Q2W: -79.8%; QW: 77.7%, placebo: 47.0%) and was apparent from Week 1 onwards (Table 2.24 and Figure 2.15).

Figure 2.15. CAFÉ LS mean (SE) in percentage change of EASI score from baseline to Week 16 (graph A) and percentage of patients achieving IGA 0 or 1 and a reduction of >=2 points from baseline to week 16 (graph B); all observed regardless of rescue treatment (B) — FAS[98]



BL, baseline; EASI, Eczema Area Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

Table 2.24. CAFÉ key secondary efficacy outcomes at Week 16; all observed regardless of rescue treatment — FAS[98]

Outcome *p-Values all <0.0001	All observed regardless of rescue treatment		
	Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS
	(N=108)	(N=107)	(N=110)
Percent change in EASI score from baseline: LS mean % change (SE)	-47.0 (2.63)	-79.8 (2.64)	-77.7 (2.61)
Difference: LS mean (95% CI)*		-32.8 (-39.94, -25.59)	-30.7 (-37.80, -23.50)
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: N (%)*	16 (14.8)	43 (40.2)	44 (40.0)
Difference: % (95% CI)*		25.4 (13.92, 36.83)	25.2 (13.84, 36.53)
Proportion of patients who achieved EASI-50: n (%)	54 (50.0)	95 (88.8)	97 (88.2)
Difference: % (95%CI)*		38.8(27.62, 49.95)	38.2(26.99, 49.38)
Percent change from baseline in SCORAD: LS mean % change (SE) (MI method)	-30.2 (2.48)	-62.1 (2.50)	-57.9 (2.46)
Difference: LS mean (95% CI)*		-31.9 (-38.68, -25.13)	-27.7 (-34.43, -20.96)

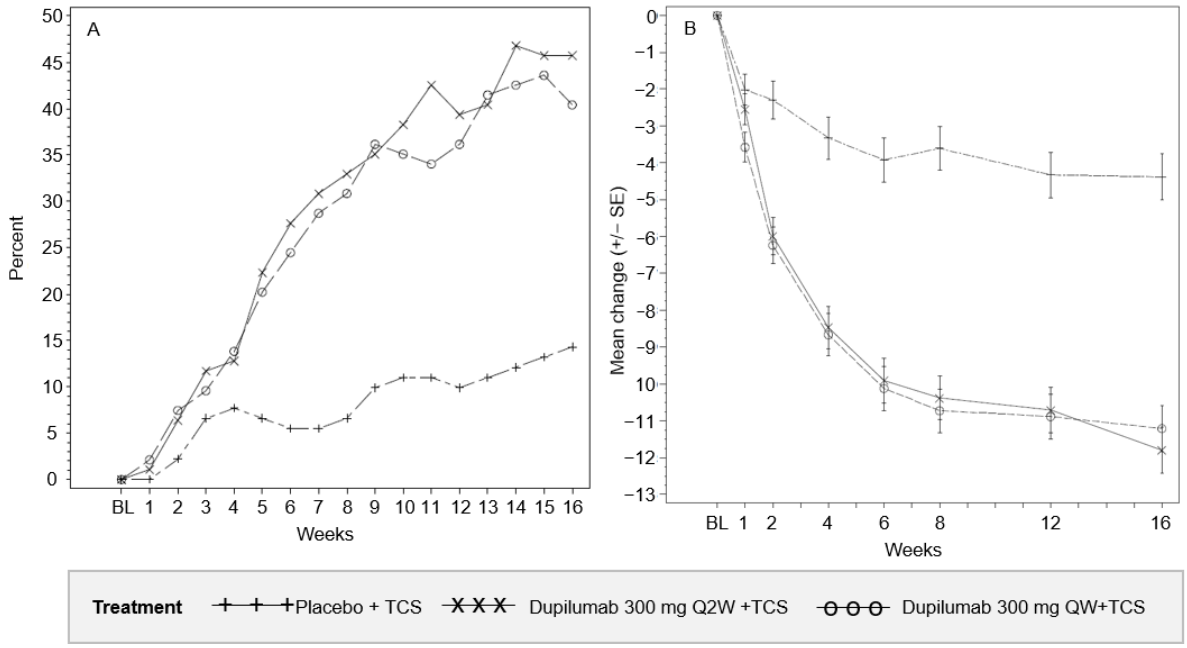
*p-Values all <0.0001; CI, confidence interval; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-50, EASI score 50% response; FAS, Full analysis set; IGA, Investigators' Global Assessment; QW, once a week; Q2W, every two weeks; SCORAD, Severity Scoring of Atopic Dermatitis.

Impact on disease symptoms: Pruritus NRS and POEM

When used concomitantly with TCS, dupilumab was superior to placebo at improving the patient-reported pruritus NRS in this patient population with a history of intolerance or inadequate response to previous treatment with ciclosporin, or for whom treatment with ciclosporin is medically inadvisable. Significant improvements in peak pruritus NRS with dupilumab + TCS versus placebo + TCS were apparent as early as Week 2 and continued throughout the duration of the study up to Week 16 (Table 2.25 and Figure 2.16A). The proportions of patients who achieved ≥4-point improvement in peak pruritus NRS were significantly greater with dupilumab + TCS than with placebo + TCS (Table 2.25 and Figure 2.16A).

The dupilumab +TCS groups showed a mean change (reduction or improvement) in POEM that was greater in magnitude than seen in placebo + TCS at every assessment during the study treatment period (Table 2.25 and Figure 2.16B). A statistically significant decrease in POEM from baseline to week 16 was observed in the dupilumab groups vs. placebo (LS mean [SE] vs baseline, Q2W: -11.8 (0.63), QW: -11.2 (0.62); placebo, -4.4 (0.62) (Table 2.25 and Figure 2.16B).

Figure 2.16. CAFÉ proportion of patients achieving a reduction of ≥4 points in weekly average of peak daily pruritus NRS from baseline(Graph A) and percent change (LS mean [SE]) of POEM from baseline to week 16; all observed regardless of rescue treatment with missing considered non-responder (Graph B) — FAS[98]



FAS, full analysis set; LS, least squares; NRS, numerical rating scale; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids

Table 2.25. CAFÉ key secondary patient-reported disease symptom outcomes at Week 16; all observed regardless of rescue treatment — FAS[98]

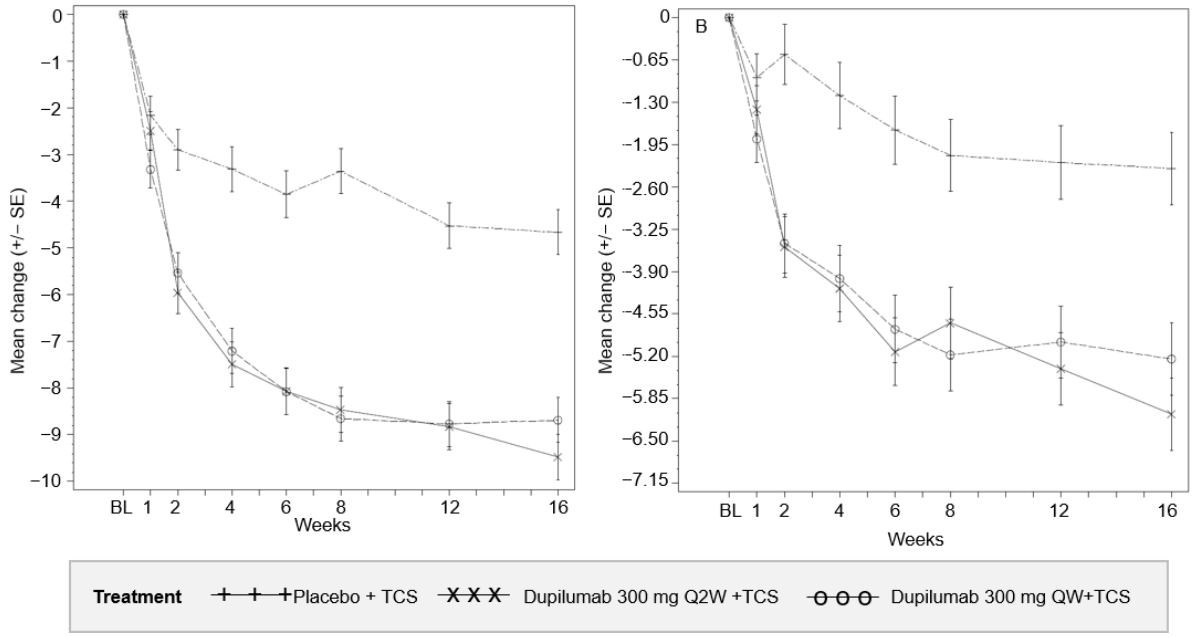
Outcome *p-Values all <0.0001	All observed regardless of rescue treatment		
	Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS
	(N=108)	(N=107)	(N=110)
Percent change in weekly average of peak daily pruritus NRS from baseline: LS mean % change (SE)	-25.1 (3.44)	-53.7 (3.44)	-51.6 (3.41)
Difference: LS mean % (95% CI)*		-28.6 (-37.98, -19.22)	-26.5 (-35.87, -17.18)
Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline: n/total N (%)	17/91 (18.7)	46/94 (48.9)	39/94 (41.5)
Difference: % (95%CI)*		30.3 (17.36, 43.15)	22.8 (10.03, 35.59)
Change from baseline in weekly average of peak daily pruritus NRS: LS mean change (SE)	-1.74 (0.195)	-3.50 (0.196)	-3.33 (0.194)
Difference: LS mean % (95% CI)*		-1.76 (-2.298, -1.231)	-1.59 (-2.120, -1.057)
Change from baseline in POEM: LS mean change (SE)	-4.4 (0.62)	-11.8 (0.63)	-11.2 (0.62)
Difference: LS mean (95% CI)*		-7.4 (-9.15, -5.74)	-6.8 (-8.49, -5.10)
Proportion of patients who achieved ≥4-point improvement (MCID) in POEM: n/total N (%)	54 (50.0)	92 (86.0)	87 (79.1)
Difference: % (95%CI)		36.0(24.48, 47.48)	29.1(16.98, 41.20)

*p-values all <0.0001. CI, confidence interval; POEM, Patient-Oriented Eczema Measure; FAS, Full analysis set; LS, least squares; MCID, Minimal clinically important difference; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroid.

Impact on quality of life and mental health

Dupilumab used concomitantly with TCS improved other patient-reported symptoms of AD, including impact on sleep, QoL, and anxiety and depression, versus TCS alone as assessed by greater reductions in DLQI, HADS and EQ-5D scores (Table 2.26 and Figure 2.17). In addition, higher proportions of patients on either dupilumab dose regime + TCS versus placebo + TCS achieved 4-point or higher improvement (MCID) at Week 16 for DLQI (Q2W 88% and QW 78% vs 44%) and POEM (Q2W 77% and QW 84% vs 42%). This QoL response is in line with the magnitude of the EASI-50 response (Q2W 85% and QW 86% vs 43%) at Week 16 (Table 2.24).

Figure 2.17. CAFÉ change (LS MEAN [SE] of A: DLQI and B: Total HADS from baseline to Week 16, all observed regardless of rescue treatment — FAS[98]



BL, baseline; DLQI, Dermatology Quality of Life Index; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; LS, Least squares; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroid

Table 2.26. CAFÉ quality of life and mental health outcomes at Week 16; all observed regardless of rescue treatment — FAS[98]

Outcome *p-Values all <0.0001 unless otherwise stated	All observed regardless of rescue treatment		
	Placebo QW+TCS	Dupilumab	
		Q2W + TCS	QW + TCS
	(N=108)	(N=107)	(N=110)
Change from baseline in DLQI: LS mean change (SE) (MI method)	-4.7 (0.48)	-9.5 (0.49)	-8.6 (0.48)
Difference: LS mean (95% CI)*		-4.8 (-6.14, -3.49)	-4.0 (-5.27, -2.64)
Proportion of patients who achieved ≥4-point improvement (MCID) in DLQI: n/total N (%)	51/108 (47.2)	88/107 (82.2)	79/110 (71.8)
Difference: % (95%CI)		35.0 (22.2, 47.8)	24.6 (11.1, 38.1)
			p 0.0002
Change from baseline in HADS: LS mean change (SE) (MI method)	-2.3 (0.55)	-6.1 (0.56)	-5.2 (0.55)
Difference: LS mean (95% CI)*		-3.8 (-5.29, -2.25)	-2.9 (-4.43, -1.41)
Change from baseline in EQ-5D Index Utility Score: LS mean change (SE)	0.10 (0.02)	0.19 (0.02)	0.16 (0.02)
Difference: LS mean (95% CI)		0.09 (0.04, 0.13)	0.06 (0.01, 0.11)
p-value		0.0005	0.0138
Change from baseline in EQ-5D VAS: LS mean change (SE)	6.1 (1.88)	21.2 (1.89)	18.0 (1.88)
Difference: LS mean (95% CI)		15.0 (9.89, 20.21)	11.9 (6.75, 17.05)

*p-Values all <0.0001; DLQI, Dermatology Quality of Life Index; EQ-5D, European Quality of Life-5 Dimensions; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; LS, least squares; MCID, Minimal clinically important difference; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroids.

B 2.6.2.3 Use of rescue medication

Multiple sensitivity analyses using all observed data confirmed the results of the primary analysis, demonstrating that these outcomes were not driven by the analytic method of categorising patients who used rescue treatment as non-responders, even though rescue was more common in the placebo group.

By Week 16, a higher proportion of patients in the placebo + TCS group than the dupilumab + TCS treatment groups received systemic (4.6% placebo, 0% dupilumab Q2W, and 0.9% dupilumab QW) or topical (14.8% placebo + TCS, 3.7% dupilumab 300 mg Q2W, and 3.6% dupilumab QW) rescue medications. Kaplan Meier curves of time to first rescue treatment use (topical or systemic) are shown in Figure 2.18.

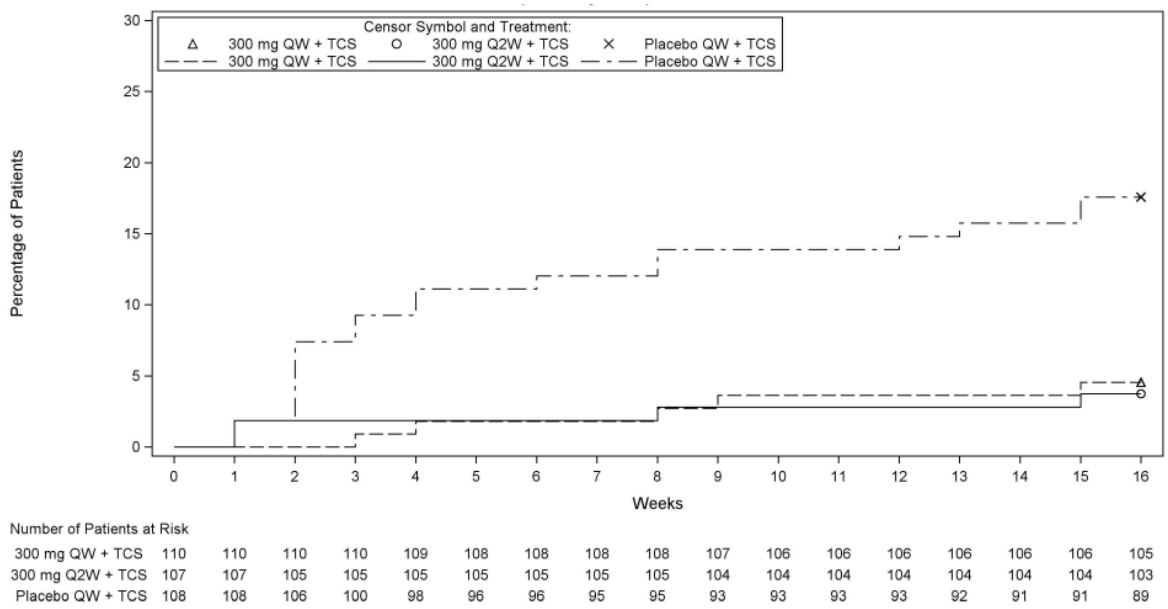
Not only was use of rescue treatment, in the form of high and very high potency TCS and systemic immunosuppressants, reduced in dupilumab treated patients, the mean weekly dose of background medium-potency TCS was also significantly reduced. The baseline mean (standard deviation [SD]) weekly dose (mg) of TCS use was 34.8 (35.319) for patients in the dupilumab Q2W group, 26.51 (28.756) for patients in the dupilumab QW group, and 31.99 (31.947) for patients in the placebo group. Weekly dose of TCS use during the treatment period for the dupilumab groups was significantly smaller than for the placebo group (least squares [LS] mean [standard error, SE],15.0 [1.51]) in the dupilumab Q2W group and in the dupilumab QW group (LS mean [SE], 17.5 [1.49]) compared with the placebo group (LS mean [SE], 25.1 [1.48]). The LS mean difference in weekly TCS dose vs placebo was -10.1 ($p<0.0001$) for dupilumab Q2W and -7.6 ($p=0.0003$) for dupilumab QW.

Table 2.27. CAFÉ rescue medication or procedures during the 16-week treatment period — FAS[44, 98]

Rescue therapy N (%)	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
	(N=108)	(N=107)	(N=110)
Any rescue therapy	19 (17.6%)	4 (3.7%)	5 (4.5%)
Topical corticosteroids	16 (14.8%)	3 (2.8%)	4 (3.6%)
Systemic corticosteroids	2 (1.9%)	0	0
Immunosuppressants	3 (2.8%)	0	1 (0.9%)
Oral calcineurin inhibitors	3 (2.8%)	0	0
Systemic immunosuppressants	0	0	1 (0.9%)

FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid

Figure 2.18 CAFÉ Kaplan Meier curves of time to first rescue treatment use (topical or systemic) –FAS[98]



FAS, full analysis set; QW, once a week; Q2W, every two weeks; TCS, topical corticosteroid

B 2.6.3 SOLO 1 and SOLO 2 efficacy evaluations

Efficacy of dupilumab as a monotherapy in patients with moderate-to-severe AD was demonstrated in two Phase III, replicate, confirmatory, placebo-controlled, 16-week monotherapy studies (SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416).

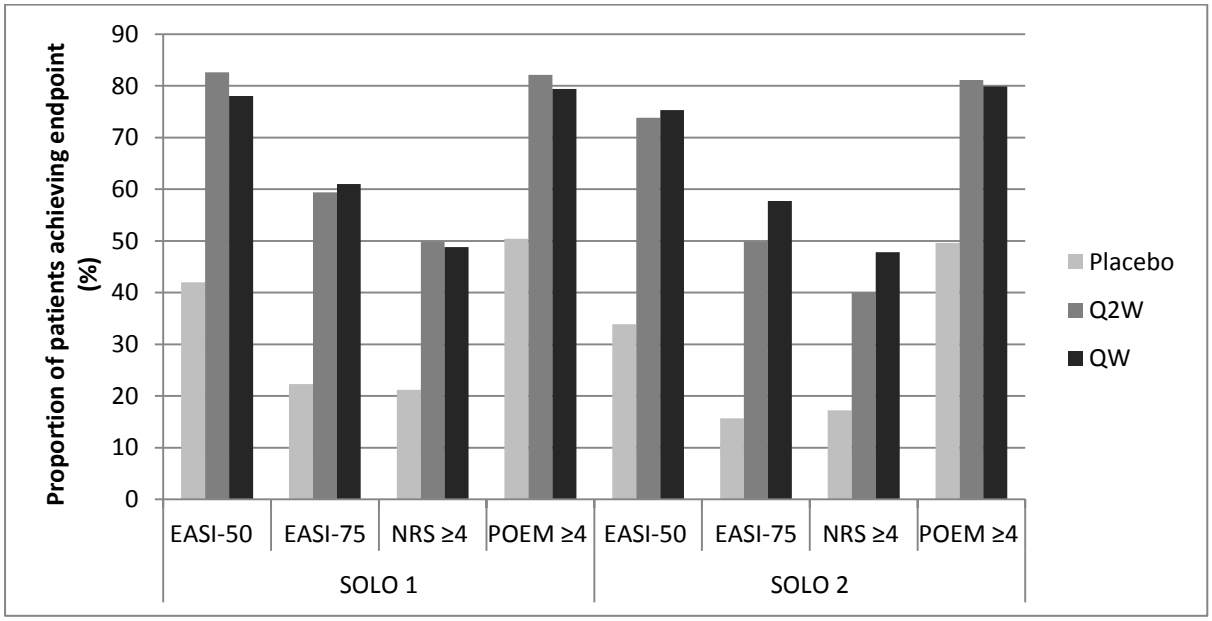
Summary of the key results

In the SOLO studies dupilumab demonstrated superiority over placebo for all co-primary and secondary endpoints measuring the extent and severity of AD, and its impact on QoL and anxiety and depression.

The proportion of patients achieving EASI-50 and EASI-75 along with the proportion achieving the minimally clinically importance difference of four or more points for NRS and POEM at Week 16 are presented in Figure 2.19 and Table 2.28 to Table 2.30 below. This illustrates the benefit of dupilumab monotherapy in the key signs and symptoms of AD.

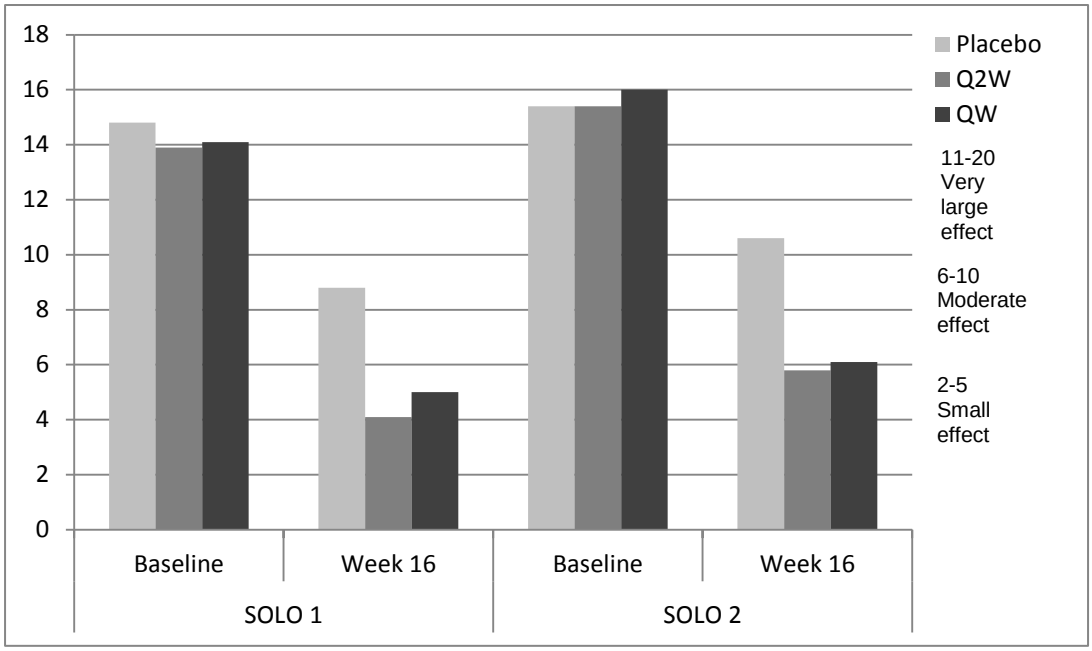
The impact on QoL of dupilumab monotherapy in the SOLO studies is shown in Figure 2.20. Results are comparable between SOLO 1 and SOLO 2 and show significant improvement in QoL as measured by the DLQI to the extent that patients treated with dupilumab report values equivalent to a ‘small effect’ on patient’s life at week 16.

Figure 2.19. SOLO 1 and 2 improvement in the signs and symptoms of AD at Week 16; all observed regardless of rescue treatment — FAS*[96, 97]



*p-values all <0.0001. AD, atopic dermatitis; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; FAS, full analysis set; QW, once a week; Q2W, every two weeks

Figure 2.20. SOLO 1 and 2 improvement in DLQI at Week 16; all observed regardless of rescue treatment — FAS*[96, 97]

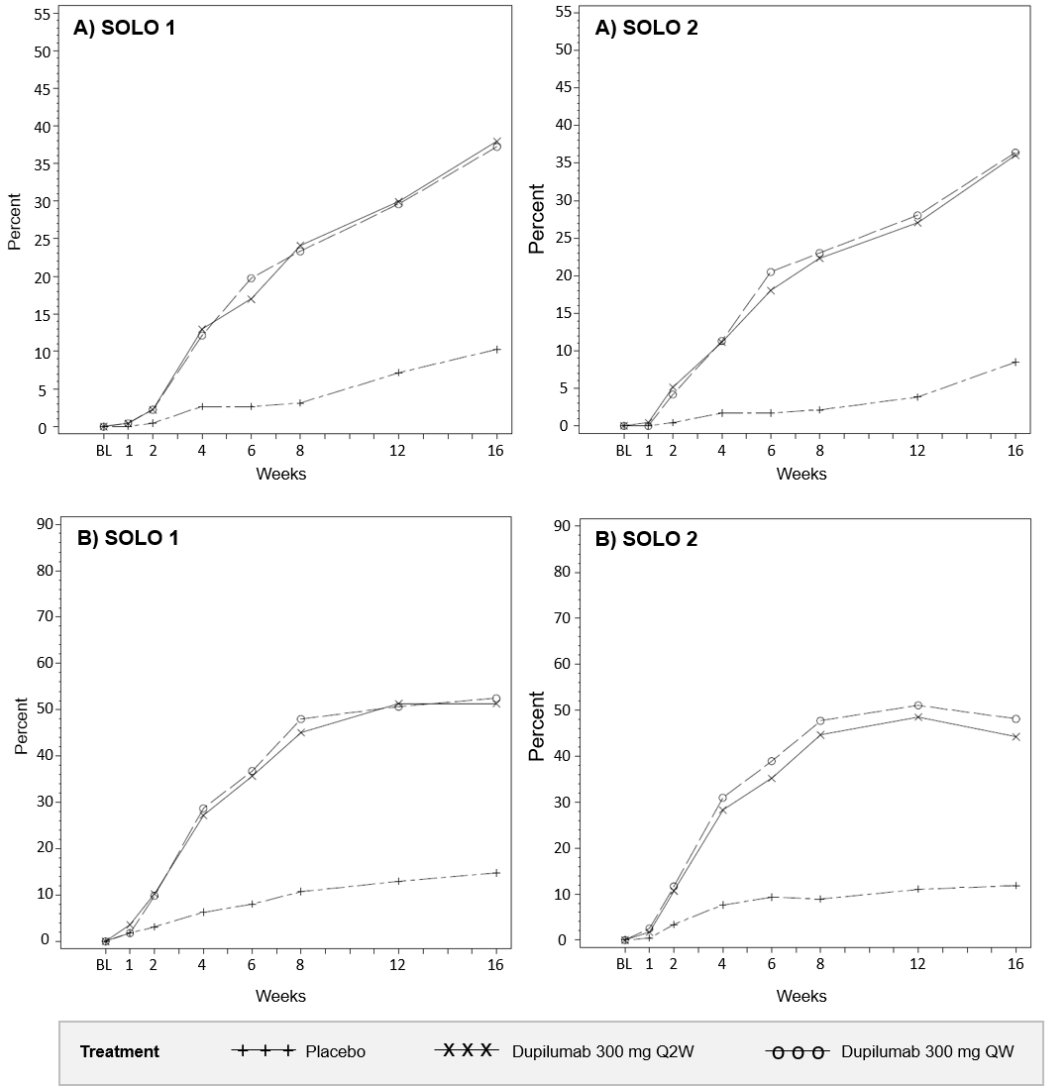


*p-values all <0.0001; FAS, full analysis set; QW, once a week; Q2W, every two weeks. DLQI, Dermatology Quality of Life Index (2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect).

B 2.6.3.1 Primary endpoints

The SOLO1 and SOLO2 trials met both co-primary endpoints measuring the extent and severity of AD skin lesions (proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at Week 16; proportion of patients with EASI-75 at Week 16 (Table 2.28 and Figure 2.21 [only primary analysis shown for brevity]). At Week 16 significantly more patients receiving dupilumab, than those receiving placebo, had an IGA score of 0 or 1 and an improvement of ≥2 points from baseline (~36%–38% patients in the dupilumab arms vs. ~8.5-10% in the placebo arm, p<0.0001 for all comparisons with placebo), and had an improvement of at least 75% on the EASI scale (EASI-75) (~44% to 53% patients in the dupilumab arm vs. ~12% to 15% in the placebo arm, p<0.0001 for all comparisons with placebo) (Table 2.28).

Figure 2.21. SOLO 1 and SOLO 2 co-primary outcomes from baseline through Week 16: A) Proportion of patients achieving IGA 0 to 1 and a reduction of ≥2 points; B) Proportion of patients achieving EASI-75) — FAS[45, 96, 97]



A) Proportion of patients achieving IGA 0 to 1 and a reduction of ≥2 points from baseline to Week 16
B) Proportion of patients achieving EASI-75 from baseline to Week 16
Analyses were performed on FAS, patients considered non-responders after rescue treatment use
BL, baseline; Eczema Area Severity Index; EASI-75, EASI score ≥75% response; FAS, full analysis set; IGA, Investigator's Global Assessment; QW, once a week; Q2W, every two weeks

Table 2.28. SOLO 1 & 2 primary endpoints at Week 16 with patients considered non-responders after rescue treatment and all observed regardless of rescue treatment — FAS[45, 96, 97]

Outcome *p-values all <0.0001	SOLO 1			SOLO 2		
	Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W	QW		Q2W	QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Patients considered non−responders after rescue treatment						
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: N (%)=	23 (10.3)	85 (37.9)	83 (37.2)	20 (8.5)	84 (36.1)	87 (36.4)
Difference: % (95% CI)*		27.7 (20.18, 35.17)	27.0 (19.47, 34.44)		27.6 (20.46, 34.69)	27.9 (20.87, 34.99)
Proportion of patients who achieved EASI−75: N (%)	33 (14.7)	115 (51.3)	117 (52.5)	28 (11.9)	103 (44.2)	115 (48.1)
Difference: % (95% CI)*		36.6 (28.58, 44.63)	37.7 (29.70, 45.77)		32.3 (24.75, 39.94)	36.3 (28.69, 43.81)
All observed regardless of rescue treatment						
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: N (%)	29 (12.9)	91 (40.6)	85 (38.1)	25 (10.6)	87 (37.3)	91 (38.1)
Difference: % (95% CI)*		27.7 (19.89, 35.47)	25.2 (17.43, 32.91)		26.7 (19.40, 34.09)	27.5 (20.18, 34.78)
Proportion of patients who achieved EASI−75: N (%)	50 (22.3)	133 (59.4)	136 (61.0)	37 (15.7)	116 (49.8)	138 (57.7)
Difference: % (95% CI)*		37.1 (28.62, 45.49)	38.7 (30.26, 47.07)		34.1 (26.19, 42.03)	42.1 (34.27, 49.86)

*p-values all <0.0001; CI, confidence interval; EASI, Eczema Area Severity Index; EASI-75, EASI score 75% response; FAS, Full analysis set; IGA, Investigators' Global Assessment; QW, once a week; Q2W, every two weeks.

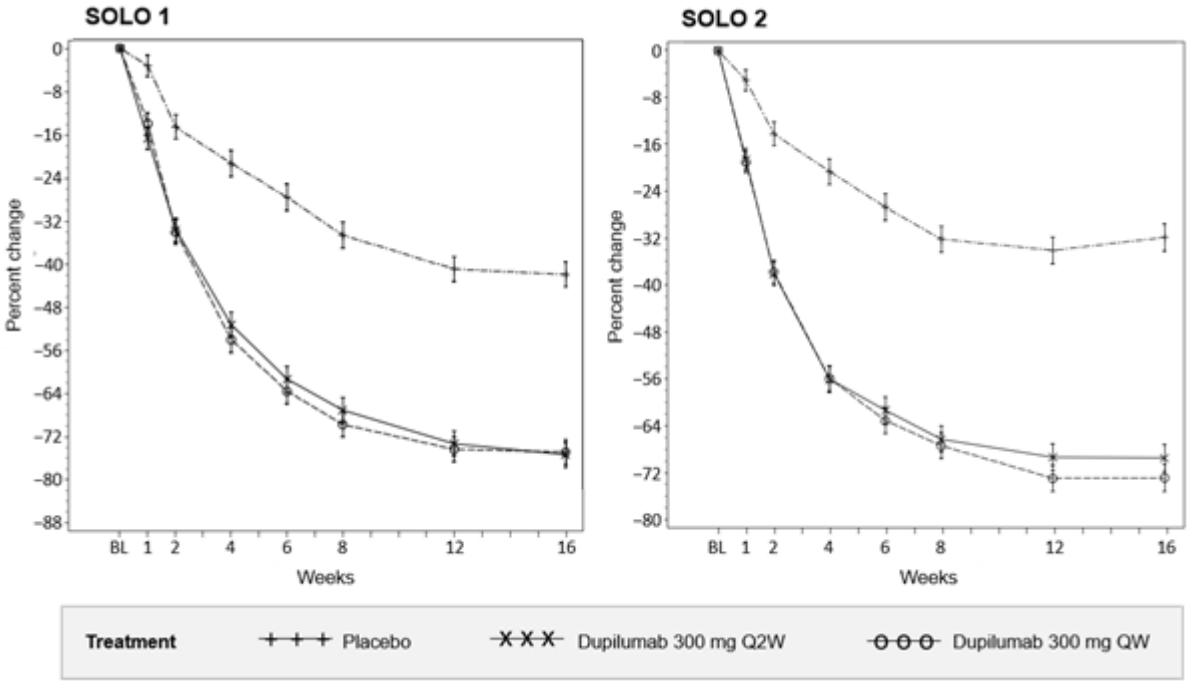
The 'All observed' analyses are shown for all other outcomes below and the primary analyses can be found in Appendix O.

B 2.6.3.2 Secondary endpoints

Impact on clinical severity

All secondary endpoints measuring the extent and severity of AD were met in the two SOLO trials. Dupilumab monotherapy was associated with significant and rapid improvements in disease activity when compared with placebo (p<0.0001 for all comparisons between dupilumab and placebo) (Table 2.29, Figure 2.22 and Appendix O).

Figure 2.22. SOLO 1 and SOLO 2 LS mean (SE) percent change of EASI score from baseline through to Week 16 all observed regardless of rescue treatment — FAS[96, 97]



Analyses were performed on FAS, patients considered non-responders after rescue treatment use.

BL, baseline; EASI, Eczema Area Severity Index; FAS, full analysis set; QW, once a week; Q2W, every two weeks; SE, standard error; TCS, topical corticosteroid

Table 2.29. SOLO 1 & 2 key secondary efficacy outcomes at Week 16; all observed regardless of rescue treatment — FAS[96, 97]

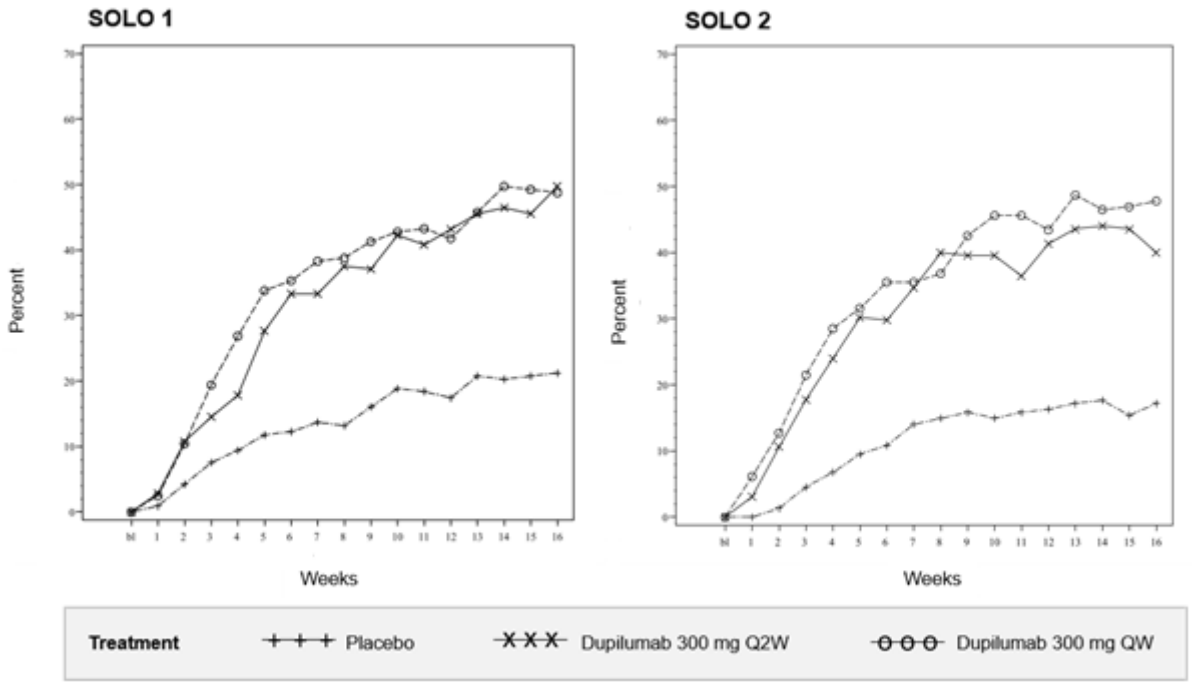
Outcome *p-values all <0.0001 unless otherwise stated	SOLO 1			SOLO 2		
	Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W	QW		Q2W	QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Percent change in EASI score from baseline: LS mean % change (SE) (MI method)	−41.5 (2.30)	−74.6 (2.27)	−74.1 (2.28)	−31.1 (2.28)	−67.7 (2.25)	−71.0 (2.23)
Difference: LS mean (95% CI)*		−33.1 (−39.12, −27.08)	−32.6 (−38.67, −26.50)		−36.7 (−42.67, −30.67)	−40.0 (−45.97, −33.97)
Proportion of patients who achieved EASI−50: n (%)	94 (42.0)	185 (82.6)	174 (78.0)	80 (33.9)	172 (73.8)	180 (75.3)
Difference: % (95%CI)*		40.6 (32.47, 48.78)	36.1 (27.62, 44.51)		39.9 (31.65, 48.19)	41.4 (33.27, 49.56)
Percent change from baseline in SCORAD: LS mean % change (SE) (MI method)*	−31.9 (1.92)	−59.6 (1.92)	−57.2 (1.89)	−20.9 (1.90)	−52.2 (1.87)	−54.6 (1.88)
Difference: LS mean (95% CI)*		−27.6 (−32.67, −22.60)	−25.3 (−30.35, −20.29)		−31.2 (−36.23, −26.23)	−33.6 (−38.64, −28.58)

*p-Values all <0.0001; CI, confidence interval; EASI, Eczema Area Severity Index; EASI-50, EASI score 50% response; FAS, Full analysis set; IGA, Investigators' Global Assessment; LS, least squares; QW, once a week; Q2W, every two weeks; SCORAD, Severity Scoring of Atopic Dermatitis.

Impact on disease symptoms: Pruritus NRS and POEM

A significantly greater proportion of patients randomised to dupilumab achieved a rapid improvement on the patient-reported pruritus NRS (defined as a ≥4-point) compared with placebo as early as Week 2, and the proportion of patients responding on the pruritus NRS continued to increase throughout the treatment period (Figure 2.23). Percent reductions and magnitudes of change in pruritus NRS scores from baseline to Week 16 were also statistically significantly greater for patients in the dupilumab groups than for patients in the placebo groups (p<0.0001 for all comparisons between dupilumab and placebo) (Table 2.30).

Figure 2.23 SOLO 1 and 2 proportion of patients achieving a reduction of ≥4 points in weekly average of peak daily pruritus NRS from baseline; all observed regardless of rescue treatment with missing considered non-responder — FAS[96, 97]

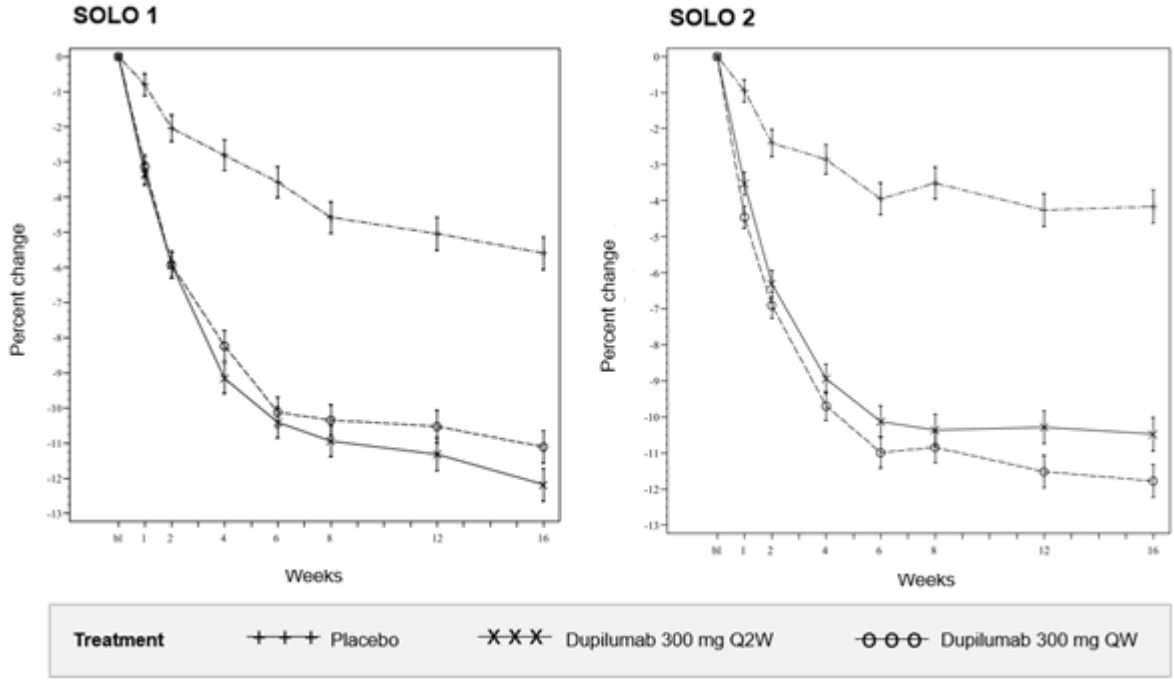


Analyses were performed on FAS, patients considered non-responders after rescue treatment use.

BL, baseline; FAS, full analysis set; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks

During the study treatment period up to week 16, there was a clear separation in the change in POEM between the dupilumab and placebo groups. The dupilumab groups showed a mean change (reduction or improvement) in POEM that was greater in magnitude than seen in placebo at every weekly assessment during the study treatment period (Table 2.30). The separation in the percentage change in POEM between dupilumab and placebo groups was evident from Week 1 in both studies (Figure 2.24). Significantly more patients achieved a reduction in POEM of 4 or more points than placebo (Q2W 81-82% and QW 79-80% vs 50%: all p-values <0.0001) (Table 2.30).

Figure 2.24. SOLO 1 and 2 percent change (LS mean [SE]) in POEM from baseline to Week 16 in; all observed regardless of rescue treatment with missing considered non-responder — FAS[96, 97]



BL, baseline; POEM, Patient-Oriented Eczema Measure; FAS, Full analysis set; LS, least squares; QW, once a week; Q2W, every two weeks; SE, standard error

Table 2.30. SOLO 1 & 2 key secondary patient-reported disease symptom outcomes at Week 16; all observed regardless of rescue treatment — FAS[96, 97]

Outcome *p-values all <0.0001 unless otherwise stated	SOLO 1			SOLO 2		
	Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W	QW		Q2W	QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Percent change in weekly average of peak daily pruritus NRS from baseline: LS mean % change (SE)	−28.7 (2.32)	−53.3 (2.31)	−49.8 (2.32)	−19.2 (2.18)	−45.2 (2.17)	−49.5 (2.21)
Difference: LS mean % (95% CI)*		−24.5 (−30.61, −18.45)	−21.0 (−27.15, −14.89)		−26.0 (−31.72, −20.21)	−30.3 (−36.17, −24.40)
Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline: n/total N (%)	45/212 (21.2)	106/213 (49.8)	98/201 (48.8)	38/221 (17.2)	90/225 (40.0)	109/228 (47.8)
Difference: % (95%CI)*		28.5 (19.86, 37.22)	27.5 (18.70, 36.36)		22.8 (14.70, 30.91)	30.6 (22.44, 38.78)
Change from baseline in weekly average of peak daily pruritus NRS: LS mean change (SE)	−2.15 (0.150)	−3.94 (0.150)	−3.79 (0.149)	−1.49 (0.156)	−3.37 (0.156)	3.77 (0.154)
Difference: LS mean % (95% CI)*		−1.78 (−2.178, −1.389)	−1.64 (−2.036, −1.246)		−1.88 (−2.294, −1.472)	−2.28 (−2.690, −1.872)

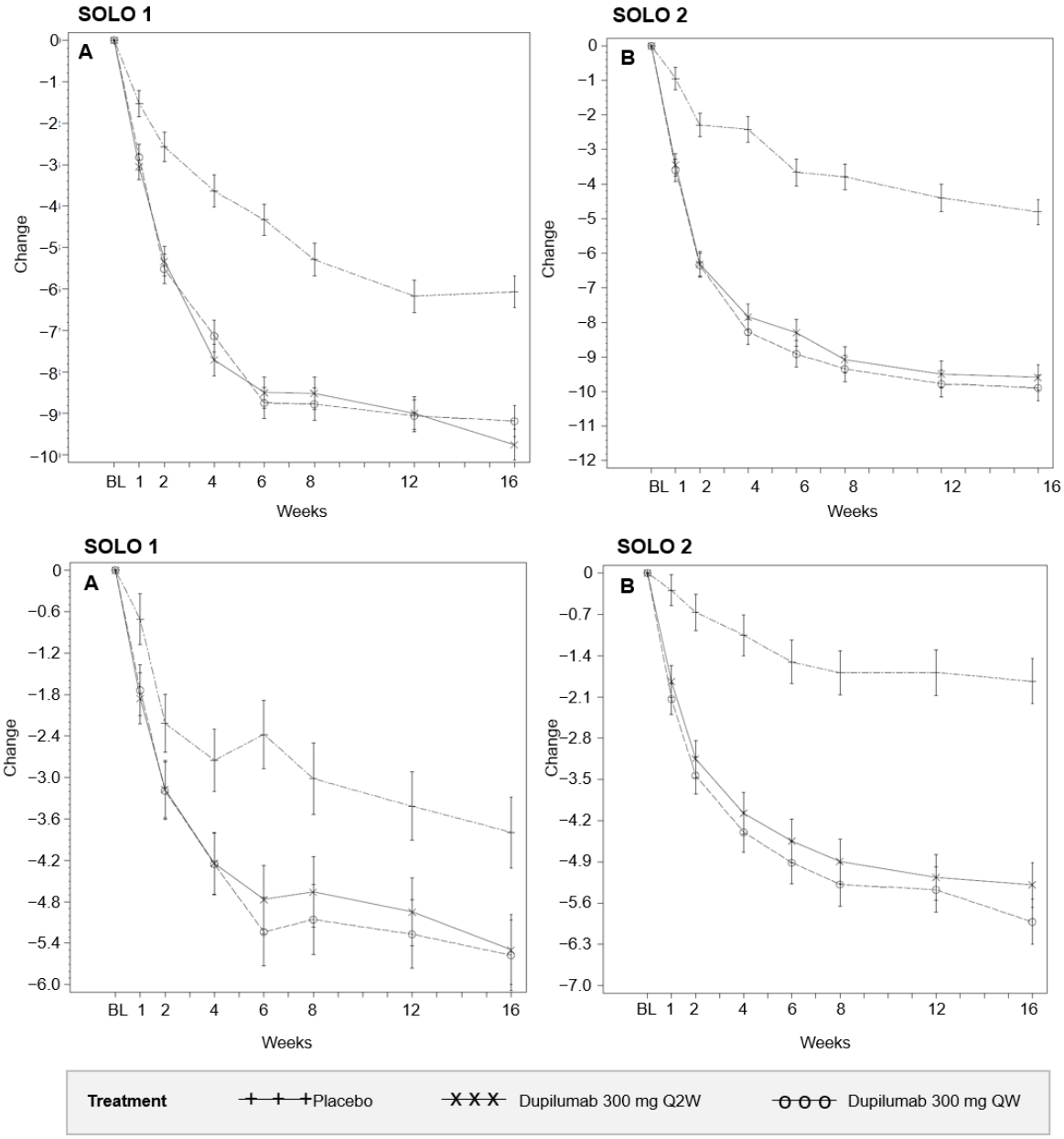
Outcome *p-values all <0.0001 unless otherwise stated	SOLO 1			SOLO 2		
	Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W	QW		Q2W	QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Change from baseline in POEM: LS mean change (SE) (MI method)	−5.6 (0.46)	−12.2 (0.46)	−11.0 (0.45)	−4.2 (0.45)	−10.5 (0.46)	−11.7 (0.45)
Difference: LS mean (95% CI)*		−6.7 (−7.87, −5.43)	−5.4 (−6.66, −4.23)		−6.3 (−7.50, −5.10)	−7.6 (−8.77, −6.36)
Proportion of patients who achieved ≥4-point improvement (MCID) in POEM: n/total N (%)	113 (50.4)	184 (82.1)	177 (79.4)	117 (49.6)	189 (81.1)	191 (79.9)
Difference: % (95%CI)		31.7(23.45, 39.94)	28.9(20.50, 37.36)		31.5(23.42, 39.66)	30.3(22.19 , 38.49)

*p-values all <0.0001. CI, confidence interval; POEM, Patient-Oriented Eczema Measure; FAS, Full analysis set; LS, least squares; NRS, Numeric Rating Scale; QW, once a week; Q2W, every two weeks; SE, standard error

Impact on quality of life and mental health

In the two SOLO trials, dupilumab monotherapy significantly reduced other patient-reported symptoms, including impact on sleep, symptoms of anxiety or depression, and QoL compared with placebo QoL, as assessed by greater reductions in DLQI, HADS and EQ-5D scores (Table 2.31 and Figure 2.25). Higher proportions of patients on either dupilumab dose regime + TCS versus placebo + TCS achieved 4-point or higher improvement (MCID)[169, 170] at Week 16 for DLQI (Q2W 64-73% and QW 58-62% vs 28-31%). This QoL response is in line with the magnitude of the EASI-50 response (Q2W 74-83% and QW 75-78% vs 34-42%) at Week 16 (Table 2.29).

Figure 2.25. SOLO 1 and 2 change (LS mean [SE]) of DLQI (graph A SOLO 1; graph B: SOLO 2) and total HADS (graph C SOLO 1; graph D: SOLO2) from baseline to Week 16, all observed regardless of rescue treatment — FAS[96, 97]



BL, baseline; DLQI, Dermatology Quality of Life Index; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; LS, Least squares; QW, once a week; Q2W, every two weeks; SE, standard error

Table 2.31. SOLO 1 & 2 quality of life and mental health outcomes at Week 16; all observed regardless of rescue treatment — FAS[96, 97]

Outcome *p-values all <0.0001 unless otherwise stated	SOLO 1			SOLO 2		
	Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W	QW		Q2W	QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Change from baseline in DLQI: LS mean change (SE)	−6.0 (0.38)	−9.8 (0.38)	−9.1 (0.38)	−4.8 (0.37)	−9.6 (0.37)	−9.9 (0.37)
Difference: LS mean (95% CI)*		−3.8 (−4.82, −2.83)	−3.1 (−4.13, −2.14)		−4.8 (−5.78, −3.85)	−5.2 (−6.13, −4.18)
Proportion of patients who achieved ≥4-point improvement (MCID) in DLQI: n/total N (%)	132/224 (58.9)	170/224 (75.9%)	157/223 (70.4%)	125/236 (53.0)	184/233 (79.0)	184/239 (77.0)
Difference: % (95%CI)		17.0 (8.0, 25.9)	11.5 (2.2, 20.7)		26.0 (17.3, 34.7)	24.0 (15.3, 32.8)
p-value			0.0111			
Change from baseline in HADS: LS mean change (SE)	−3.7 (0.55)	−5.4 (0.56)	−5.4 (0.53)	−1.9 (0.38)	−5.4 (0.38)	−6.0 (0.37)
Difference: LS mean (95% CI)*		−1.7 (−2.81, −0.63)	−1.7 (−2.78, −0.63)		−3.5 (−4.46, −2.47)	−4.1 (−5.08, −3.12)
P−value		0.0019	0.0018		<0.0001	<0.0001
Change from baseline in EQ-5D Index Utility Score: LS mean change (SE)	0.15 (0.01)	0.26 (0.01)	0.24 (0.01)	0.11 (0.1)	0.23 (0.01)	0.26 (0.01)
Difference: LS mean (95% CI)		0.11 (0.07, 0.14)	0.09 (0.05, 0.12)		0.12 (0.08, 0.15)	0.14 (0.11, 0.18)
Change from baseline in EQ-5D VAS: LS mean change (SE)	10.1 (1.32)	20.7 (1.30)	16.8 (1.31)	6.7 (1.29)	15.6 (1.28)	19.5 (1.28)
Difference: LS mean (95% CI)		10.7 (7.22, 14.13)	6.7 (3.21, 10.19)		8.9 (5.54, 12.33)	12.8 (9.43, 16.25)

*p-Values all <0.0001 unless otherwise stated based on CMH test stratified by Region strata and baseline IGA strata; CI, confidence interval; DLQI, Dermatology Quality of Life Index; EQ-5D, European Quality of Life-5 Dimensions; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; LS, least squares; QW, once a week; Q2W, every two weeks; SE, standard error

B 2.6.3.3 Use of rescue medication

In the two trials, more patients in the placebo group than in either dupilumab group received rescue treatment. In SOLO 1, rates of rescue treatment were 21% in the Q2W group, 23% among QW group, and 51% in placebo; in SOLO 2, the rates were 15%, 21%, and 52%, respectively (Table 2.32). Patients in the placebo groups were more likely to receive systemic rescue therapies (glucocorticoids or immunosuppressant agents) (Table 2.32).

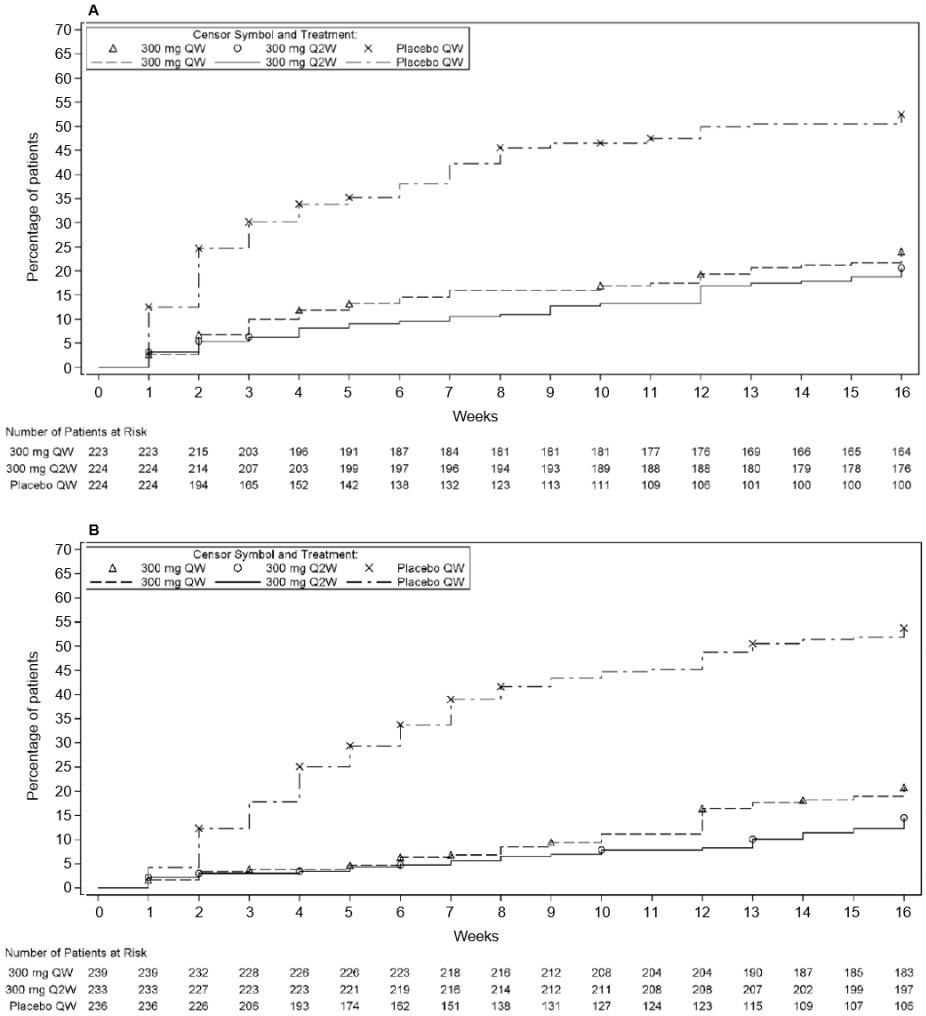
The effect of rescue therapy was not included in the primary efficacy analyses — patients that received rescue therapy were censored as non-responders. Sensitivity analyses of all observed values, including those that were observed after rescue with systemic therapies, corroborate that dupilumab treatment is superior despite that more rescue therapy was used in the placebo group. Kaplan Meier curves of time to first rescue treatment use (topical or systemic are shown in Table 2.29.

Table 2.32 SOLO 1 & SOLO 2 proportion of patients receiving rescue therapy at Week 16[45, 96, 97]

	SOLO 1			SOLO 2		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW
	(N=224)	(N=224)	(N=223)	(N=236)	(N=233)	(N=239)
Rescue therapy n (%)						
Any rescue therapy	115 (51.3%)	47 (21.0%)	52 (23.3%)	123 (52.1%)	35 (15.0%)	49 (20.5%)
Systemic corticosteroids	17 (7.6%)	2 (0.9%)	5 (2.2%)	30 (12.7%)	3 (1.3%)	6 (2.5%)
Immunosuppressants	5 (2.2%)	3 (1.3%)	2 (0.9%)	16 (6.8%)	1 (0.4%)	2 (0.8%)
Oral calcineurin inhibitors	4 (1.8%)	2 (0.9%)	1 (0.4%)	13 (5.5%)	1 (0.4%)	2 (0.8%)
Systemic immunosuppressants	0	1 (0.4%)	1 (0.4%)	0	0	0
Other immunosuppressants	1 (0.4%)	0	0	4 (1.7%)	0	0

QW, once a week; Q2W, every two weeks

Figure 2.26 SOLO 1 (A) and SOLO 2 (B) Kaplan Meier Curves of time to first rescue treatment use (topical or systemic) – FAS[45, 96, 97]



FAS, full analysis set; QW, once a week; Q2W, every two weeks

B 2.6.4 SOLO-CONTINUE

LIBERTY AD SOLO-CONTINUE was a double-blind, placebo-controlled, randomised maintenance study assessing continuation of the dose regimens administered in the initial-treatment study compared with dose frequency reductions and dose withdrawal. The study was conducted in a subset of patients who had participated in one of the two initial-treatment (parent) studies (SOLO 1 or SOLO 2) and achieved a high-threshold clinical response IGA 0 or 1 or 75% reduction in EASI (EASI-75), after 16 weeks of treatment with dupilumab 300 mg QW or Q2W as monotherapy. Thus SOLO-CONTINUE was a study conducted in patients who achieved high-level clinical response (IGA 0 or 1, with 2 or more points improvement, or EASI-75) after 16-week treatment in SOLO 1 and SOLO.

The treatment duration in this study was 36 weeks, which was considered sufficient for assessing the ability of different dupilumab dose and frequency regimens to maintain the treatment response achieved in the initial 16-week study. The 36-week duration of treatment in this study was also selected for practical reasons, so that the full clinical investigation (SOLO +SOLO-CONTINUE) would amount to a 52-week treatment study.

B 2.6.4.1 Results

Patients were re-randomised to receive QW, Q2W, Q4W or Q8W doses. The Q2W or QW doses showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner (

Table 2.33).

- Maintenance of clinical response in patients who had achieved IGA 0 or 1 or EASI-75 after an initial 16-week treatment with dupilumab 300 mg QW or Q2W was investigated in this 36-week treatment study, in which patients were randomised to continue the same dupilumab dose regimens from the parent study, decrease dosing frequency to 300 mg Q4W or Q8W, or discontinue dupilumab altogether and receive placebo during the current study.

- Maintenance of response was assessed using continuous endpoints (percent change in EASI and percent change in NRS) and categorical endpoints (e.g., EASI-75, IGA 0 or 1, NRS≥3 worsening). Based on all efficacy endpoints, the best maintenance of response was achieved by the group of patients who continued the same dose regimen from the parent study (300 mg QW or Q2W).

Table 2.33 CONTINUE overview of co-primary and key secondary efficacy results – FAS[164]

Outcome	Placebo	Dupilumab 300 mg		
		Q8W	Q4W	Q2W/QW
	N=83	N=84	N=86	N=169
Co-primary endpoints				
LS mean change (SE) between baseline and Week 36 in percent change in EASI score from parent study baseline*	21.67 (3.134)	6.84[§] (2.434)	3.84[§] (2.283)	0.06[§] (1.736)
Percent of patients with EASI-75 at Week 36 for patients with EASI-75 at baseline, n(%)[†]	24/79 (30.4)	45/82[‡] (54.9)	49/84[‖] (58.3)	116/162[§] (71.6)
Key secondary endpoints				
Percent of patients whose IGA response at Week 36 was maintained within 1 point of baseline in the subset of patients with IGA (0,1) at baseline, n(%)[†]	18/63 (28.6)	32/64[¶] (50.0)	41/66[‖] (62.1)	89/126[§] (70.6)
Percent of patients with IGA (0,1) at Week 36 in the subset of patients with IGA (0,1) at baseline, n(%)[†]	9/63 (14.3)	21/64[¶] (32.8)	29/66[‖] (43.9)	68/126[§] (54.0)
Percent of patients whose peak pruritus NRS increased by ≥3 points from baseline to Week 35 in the subset of patients with peak pruritus NRS ≤7 at baseline, n (%)[†]	56/80 (70.0)	45/81 (55.6)	41/83[¶] (49.4)	57/168[§] (33.9)

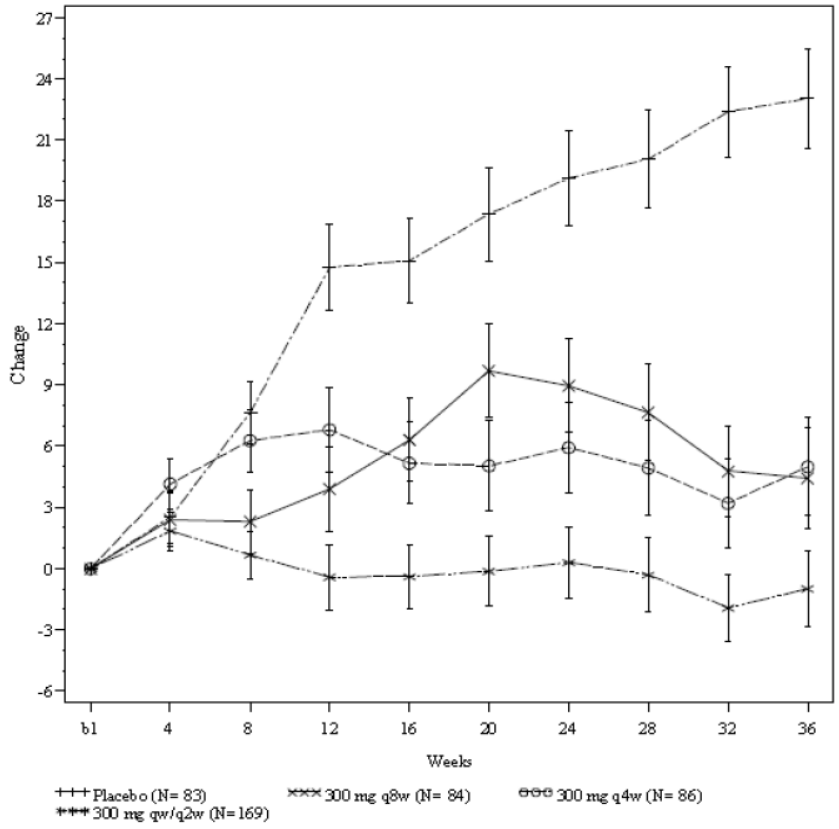
*MI method with data treated as missing after rescue treatment use. [§]P≤0.0001 based on treatment difference (dupilumab group vs. placebo) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment, region, baseline IGA strata (0,1,>1) and dupilumab regimen received in parent studies as fixed factors

[†]Patients considered non-responder after rescue treatment use. P-values based on difference versus placebo and derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA=0 vs. 1 vs. >1), region (Americas, Europe, and Asia-Pacific including Japan), and dupilumab regimen received in parent. [¶]P<0.05, [‡]P<0.01, [‖]P<0.001, [§]P≤0.0001

ANCOVA; analysis of covariance EASI, Eczema Area and Severity Index; EASI-75, ≥75% reduction in EASI scores; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; MI, multiple imputation; NRS, Numerical Rating Scale; QW, once a week; Q2W, once every two weeks, Q4W, once every four weeks; Q8W, once every 8 weeks; SE, standard error

Results over time for all observed values (regardless of whether rescue treatment was used) are shown in Figure 2.27. This figure clearly shows that there were minimal changes in EASI score in the dupilumab 300 mg Q2W/QW group over the 36-week maintenance period. In contrast, EASI scores increased progressively over the 36-week maintenance period in the placebo group, despite more patients in the placebo group receiving rescue treatment than dupilumab patients. Even when including data from patients who received rescue treatment, the dupilumab 300 mg Q4W and Q8W groups did not achieve the level of response maintenance observed in the dupilumab 300 mg Q2W/QW group (see also Appendix P).

Figure 2.27 LS mean (±SE) of difference between current study baseline and each visit through Week 36 in percent change in EASI score from parent study baseline - All observed data regardless of rescue treatment use (FAS)[164]

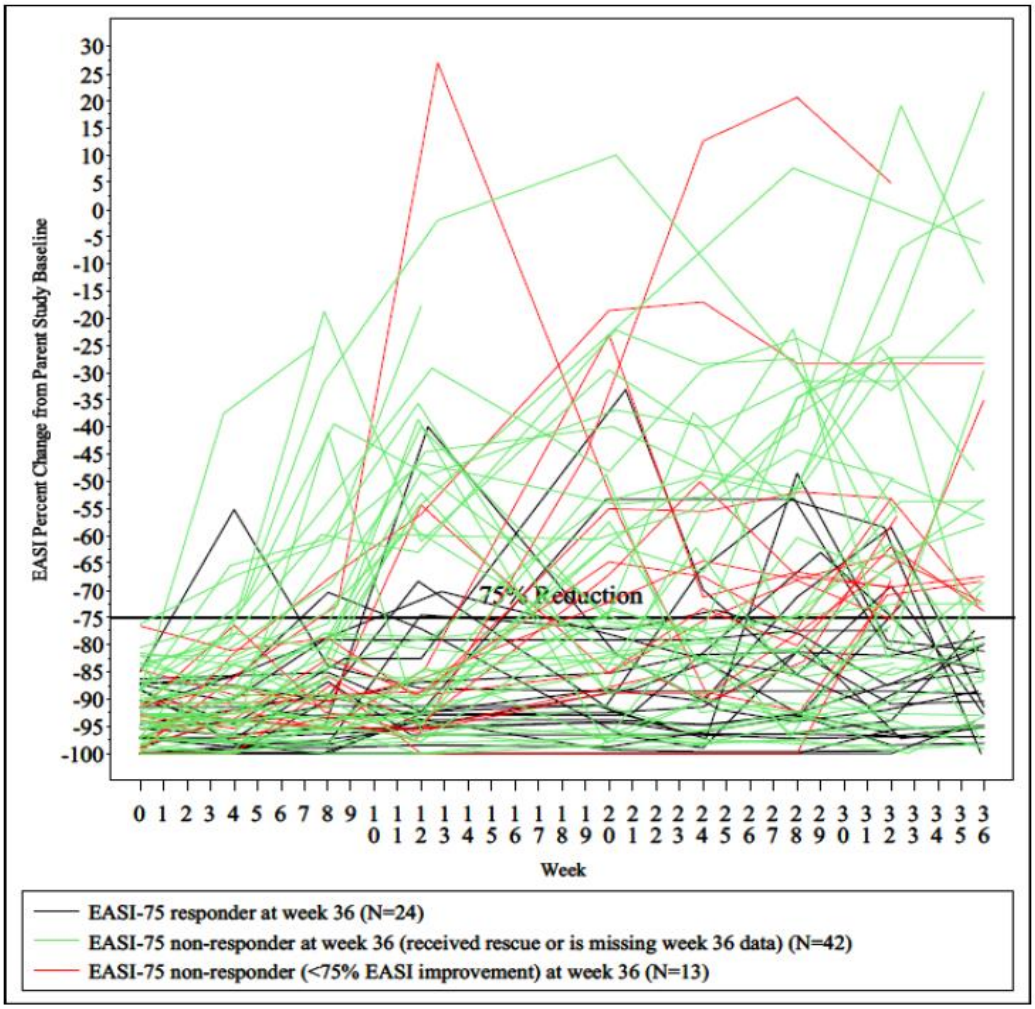


# in each visit										
300 mg QW/Q2W(N=169)	169	168	166	163	162	160	161	161	161	160
300 mg Q4W (N= 86)	86	86	85	82	82	82	82	80	79	80
300 mg Q8W (N= 84)	84	82	82	81	82	80	80	79	76	77
Placebo (N= 83)	83	80	81	79	78	78	76	78	78	78

BL, baseline; EASI, Eczema Area and Severity Index; FAS, full analysis set; QW, once a week; Q2W, once every two weeks, Q4W, once every four weeks; Q8W, once every 8 weeks

Individual patient data collected in this study reflect the variability of the outcome measures, particularly for the IGA. A considerable number of responders and non-responders (particularly near-responders) trade places at various time points. This is especially applicable to dupilumab treated patients, a higher proportion of whom achieve significant clinical responses (eg IGA 0 or 1), compared to placebo patients. For these patients, a very small change in disease severity can reverse their “responder” or “non- responder” status.

Figure 2.28 Spaghetti plot of percent change of EASI total score from parent study baseline during 36-week treatment period for patients with EASI-75 at current study baseline, All observed values regardless of rescue treatment use (FAS – patients with EASI-75 at baseline)



EASI, Eczema Area and Severity Index; EASI-75, EASI socre ≥75% response; FAS, full analysis set

Therefore, a limitation of this study is that it includes a subset of patients attaining high-threshold clinical response (IGA 0 or 1 or EASI-75) after an initial 16-week dupilumab monotherapy treatment. This subset represented approximately half of the dupilumab treated population in the initial 16-week studies. Other patients, who had achieved clinically meaningful improvements during the initial-treatment studies, but below the IGA 0 or 1 or EASI-75 thresholds, were not included in this maintenance study.

In summary, for all endpoints, including percent change in EASI, EASI-75, IGA 0 or 1, Pruritus NRS ≥3, and percent change in pruritus NRS, maintenance of clinical response was most consistently achieved in the group of patients who continued the dupilumab dose regimen (dupilumab 300 mg QW or 300 mg Q2W) from the initial 16-week treatment study. The 300 mg Q4W and Q8W regimens were suboptimal with respect to efficacy, and showed no safety advantages.

B 2.7 Clinical evidence used in the economic model

In this section the clinical evidence from LIBERTY AD trials used to inform the economic analysis and model in section B 3.2 is reported. The baseline patient characteristics of the relevant patient population are summarised. This is followed by a discussion of the approach taken for measurement of response in the economic model (which is intended to reflect UK clinical practice) versus the approach to response in the clinical trials supporting the marketing authorisation.

B 2.7.1 Patient population relevant to the UK

The base case population is adult patients with moderate-to-severe AD not adequately controlled by topical therapies and who are contra-indicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. The base case population is a subgroup of the full licence population. According to UK clinical opinion this is the most likely place in the therapy pathway for dupilumab as it reflects the highest unmet need in UK clinical practice. Without dupilumab as a treatment option, these patients would typically be treated with BSC.

Evidence informing the base case population was taken from subgroups in the SOLO 1, SOLO 2 and CHRONOS studies who met the base case population definition. The CAFÉ study included adults with severe AD and for whom oral ciclosporin was medically inadvisable (not demonstrated adequate efficacy, had unacceptable side effects or for whom ciclosporin was contraindicated). Therefore, in this study, **all** included patients reflect the UK clinical practice described above. In CHRONOS the study population consisted of patients with moderate-to-severe AD who were not adequately controlled with medium to high potency TCS (±TCI, as appropriate). A the prespecified subset of patients from CHRONOS reflects the CAFÉ study. This subset includes all patients who showed an inadequate efficacy response to oral ciclosporin, patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or because treatment with oral ciclosporin was otherwise medically inadvisable.

This subset we refer to in the submission as CHRONOS-CAFÉ-like (CCL) population. As both CAFÉ and CHRONOS-CAFÉ-like subgroups evaluated dupilumab when used concomitantly with TCS these two subgroups were pooled and are referred to as the CAFÉ+CCL population in this submission. The characteristics of the participants in this pooled analysis are provided in Table 2.34.

The base case analysis also considers monotherapy use with dupilumab. SOLO 1 and SOLO 2 were designed to demonstrate the efficacy and safety of dupilumab monotherapy. Patients were not permitted to receive concomitant TCS therapy in these studies. For the economic evaluation we have used the prespecified subgroup of patients who showed an inadequate efficacy response to oral ciclosporin, inadequate efficacy response or were intolerant to oral ciclosporin or patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or otherwise medically inadvisable. In this submission we refer to this population as the SOLO CAFÉ-like populations. Aside from the monotherapy dupilumab, this pooled subgroup is similar to the CAFÉ+CCL population. The characteristics of the participants in this pooled analysis are provided in Table 2.34.

The dupilumab licence does not specify a prior history of treatment with ciclosporin and since there is no evidence to suggest otherwise, we have assumed that ciclosporin, azathioprine or methotrexate may be considered broadly comparable for the purposes of the modelling. While they are not exactly interchangeable with each other and clinicians have different preferences for their use, they are considered at the same point in the clinical treatment pathway and clinicians have informed us that an alternative to these therapies is required due to the poor risk-benefit profile that these therapies offer. Evidence from the LIBERTY programme suggests that previous exposure or no previous exposure to an immunosuppressant does not alter the efficacy of dupilumab (see forest plots in Appendix E).

Table 2.34 Baseline demographics and characteristics of patients used in the economic modelling

	CAFÉ + CHRONOS-CAFÉ-like			SOLO CAFÉ-like		
	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
	N=169	N=130	N=163	N = 88	N = 104	N = 96
Mean age – years (SD)	38.1 (13.0)	37.8 (12.9)	38.4 (12.9)	38.8 (12.9)	38.0 (13.5)	37.6 (12.5)
Gender (male) n (%)	102(60.4%)	77(59.2%)	98(60.1%)	55 (62.5%)	75 (72.1%)	56 (58.3%)
Weight (kg), mean (SD)	76.0 (18.4)	73.9 (15.2)	74.3 (17.3)	73.8 (15.9)	74.1 (17.1)	77.1 (17.7)
BMI, mean (SD)	25.6 (5.0)	24.7 (4.1)	25.2 (4.7)	25.5 (4.6)	25.1 (4.6)	26.2 (5.3)
Race, n (%) **White** **Black** **Asian** **Other**	 152(89.9%) 3 (1.8%) 12 (7.1%) 2(1.2%)	 121(93.1%) 1 (0.8%) 7 (5.4%) 0	 145(89.0%) 2 (1.2%) 14 (8.6%) 2 (1.2%)	 52 (59.1%) 0 30 (34.1%) 6 (6.8%)	 75 (72.1%) 1 (1.0%) 23 (22.1%) 5 (4.8%)	 69 (71.9%) 2 (2.1%) 23 (24.0%) 2 (2.0%)
Duration of AD (years), mean (SD)	28.9 (15.1)	29.9 (15.4)	31.6 (14.5)	29.9 (14.7)	29.0 (14.4)	28.3 (15.3)
Percent BSA with AD, mean (SD)	58.9 (21.7)	57.3 (18.5)	57.3 (20.5)	59.9 (23.7)	58.8 (21.9)	59.0 (22.7)
EASI (0-72, >20=severe), mean (SD)	34.8 (12.0)	33.6 (10.5)	34.2 (11.7)	35.6 (14.3)	36.9 (14.6)	35.7 (14.7)
IGA score (0-4, 4=severe), mean (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.6 (0.5)	3.7 (0.5)	3.6 (0.5)
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	6.9 (2.1)	6.9 (2.1)	6.6 (2.0)	7.8 (1.5)	7.6 (1.6)	7.4 (1.8)
SCORAD score (0-103, >50=severe), mean (SD)	68.7 (12.8)	69.3 (12.9)	67.6 (13.4)	72.8 (13.4)	72.2 (13.9)	70.9 (13.4)
POEM score (0-28, >24=severe), mean (SD)	19.9 (6.0)	19.8 (6.1)	19.4 (7.0)	21.9 (5.6)	22.0 (5.4)	21.6 (6.1)
DLQI score (0-30, >10=very large effect), mean (SD)	14.8 (7.7)	14.6 (7.5)	15.0 (8.0)	16.6 (7.9)	15.7 (6.8)	16.8 (7.8)
Total HADS score (0-42, 11 overt depression/anxiety), mean (SD)	13.2 (8.1)	12.8 (7.9)	14.4 (8.8)	14.8 (8.8)	13.3 (7.7)	15.6 (8.0)
EQ-5D VAS, mean (SD)	51.3 (25.2)	56.2 (22.7)	53.0 (21.9)	47.1 (23.1)	50.2 (23.2)	47.6 (22.5)
EQ-5D utility, mean (SD)	0.632 (0.324)	0.719 (0.249)	0.646 (0.282)	0.520 (0.377)	0.575 (0.315)	0.540 (0.382)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; DUP, dupilumab; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; PBO, placebo; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale; QW weekly dosing; Q2W dosing every other week.

B 2.7.1.1 Definition of response used in the economic model

To determine response to AD treatment clinicians review a wide range of signs and symptoms along with improvement in quality of life and social functioning. This is highlighted in the children's guideline issued by NICE for AD which indicates a holistic approach should be taken when assessing atopic dermatitis[35]. Therefore, it is important to understand what factors associated with successful treatment for AD are key to both patients and clinicians.

A new instrument called the AD Control Tool (ADCT) is being developed by Sanofi Genzyme to help patients with moderate-to-severe AD measure their level of control, as well as to improve communications with their physicians. To develop this tool, information and concepts were obtained from a literature review and expert clinician interviews followed by patient interviews. The development of the ADCT is described in more detail in Appendix R2 and the six items included are listed below:

1. Overall severity of symptoms
2. Frequency of intense episodes of itching
3. Intensity of bother
4. Frequency of impact on sleep
5. Intensity of impact on daily activities
6. Intensity of impact on mood or emotions

The LIBERTY trial programme collected a large and comprehensive group of outcome measures to quantify the impact of treatment with dupilumab on the extent of disease severity, quality of life and psychosocial aspects of the disease. Depending on the instrument, these were clinician or patient assessed. The outcomes measured by these instruments are aligned with the six items in the ADCT which means that the full impact of treatment with dupilumab was assessed within the trial programme. The range of measures is illustrated in Table 2.26 below.

Table 2.35 Items of fundamental importance to patients and alignment to clinical trial measures

Key factors important to patients (6 ADCT items)	Measure included in the clinical trial programme	Outcome measured
Overall severity of symptoms	**EASI, SCORAD, IGA, GISS** Clinician assessment	Disease signs: Absolute and relative changes
Overall severity of symptoms	**POEM** Patient assessment	Disease signs: Absolute and relative changes
Frequency of intense episodes of itching	**Peak Pruritus NRS** Clinician assessment	Itch. Absolute and relative changes measured. Proportion of patients with clinically significant change
Intensity of bother	**DLQI, EQ-5D** Patient assessment	Quality of life. Absolute and relative changes measured. Also, proportion of patients with clinically significant change
Frequency of sleep impact	**POEM sleep item, SCORAD VAS: Sleep loss** Patient assessment	Sleep disturbance

Key factors important to patients (6 ADCT items)	Measure included in the clinical trial programme	Outcome measured
Intensity of mood or emotions impact	**HADS, EQ-5D** Patient assessment	Anxiety and depression

ADCT, atopic dermatitis control tool; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigators' Global Assessment; GISS Global Individual Sign Score; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Severity Scoring of Atopic Dermatitis; VAS, Visual Analogue Scale.

We have considered the best way to implement the outcomes measured in the study programme while capturing the factors most important to patients and clinicians described by the ADCT. There is undoubtedly a continuum of benefit for patients treated with dupilumab as shown by all the measures listed in Table 2.26, and so the imposition of a binary rule at the 16 Week endpoint specified in the studies to determine efficacy response is not ideal.

In addition to response being an a continuum rather than a binary outcome (for example for some people EASI-49 would be a profound improvement to their disease but they would not be classified in this model as a responder), AD is also a fluctuating disease. This is exemplified in SOLO-CONTINUE where the bulk of EASI scores were below the EASI 75 and EASI 50 thresholds however inspection of the EASI scores at each visit shows some patients to have a fluctuating response that would require clinician interpretation to understand if their disease is moving towards a state of being in control (see Figure 2.28). A snapshot at a single point using a single measure such as EASI is not adequate to describe progress towards control and clinicians will need to take a holistic approach in their decision making. This is emphasised in the SmPC which states that '*some patients with partial response at 16 weeks may subsequently improve with continued treatment beyond 16 weeks*[11]. However, within the confines of the economic model a pragmatic approach was required. We have discussed options with clinicians. The consensus from these discussions is that; 1) a measure of response which captures clinical signs alongside quality of life improvement is required — improvement in clinical signs (such as skin clearance) alone is not comprehensive enough, and 2) a decision point beyond 16 weeks would be preferable.

The co-primary outcomes in the study programme were based on a 75% reduction in EASI score and attainment of IGA 0-1 (with at least a 2-point improvement) which were requested by the regulators (EU and US respectively). Change in EASI score was identified by the clinicians consulted at an advisory board (n=8) as the most robust way to measure improvement in the signs of AD. EASI-50 represents a distinct clinical benefit particularly for patients with moderate-to-severe AD for whom topical therapy is failing. In the anticipated patient population in the UK, both topical and systemic immunosuppressants have failed. Therefore EASI-50 is the appropriate efficacy outcome for real world clinical practice.

Most of the clinicians consulted had used dupilumab and they advised that in their experience almost all patients will respond and that an EASI-50 response is life changing for many patients. However patients starting from a high absolute EASI score it may take longer than 16 weeks to reach this point and clinicians suggest that 24 weeks is a better timeframe. In addition, clinicians reported anecdotally that they had observed AD of the head and face to take longer to clear that AD affecting other areas of the body, but given the burden on

patients of AD affecting the face they again considered in this situation a patient may need a longer time-period before assessment.

The DLQI instrument is well known to dermatologists and covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. This is in routine use in dermatology clinics for psoriasis. The minimally clinically important difference in DLQI is a change of 4 or more points and this response was considered to be adequate by the clinical experts to capture significant quality of life benefit for patients with AD.

Our advisory board attendees considered that the application of a response criterion based on EASI-50 and DLQI 4 or more points change in the economic model would be an effective proxy method to capture sufficient clinical benefit to justify continuing treatment.

In the model base case, as in the clinical trials response as defined above, is assessed at week 16. However in the 52-week CHRONOS study all patients continued on treatment regardless of clinical assessment at Week 16 and a proportion of patients who did not achieve EASI-50 and DLQI ≥4 at Week 16 went on to achieve this at Week 24. These data are shown below (Table 2.36) and have been tested in a sensitivity analysis reported in section B 3.7.2.

Table 2.36 EASI50 and DLQI ≥4 response status at 24 weeks conditional on response at week 16. (All observed regardless of rescue treatment).

	EASI50+DLQI4 Non-Resp. at Week 16 (N=24)	EASI50+DLQI4 Resp. at Week 16 (N=82)
EASI50+DLQI4 Response status at Week 24 [n (%)]		
Number	24	82
Non-Responder	17 (70.8%)	1 (1.2%)
Responder	7 (29.2%)	81 (98.8%)

DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; EASI-50, EASI score ≥50% response

As can be seen nearly 30% of non-responders at week 16 in this patient population were responders at week 24 (it should be noted that 1% of responders at week 16 measured as non-responders at week 24). Of the responders at week 16, 98.8% maintained response at week 24.

B 2.7.1.2 Efficacy outcomes used in the economic model

Regulatory decisions about the efficacy of a novel therapy, compared with a control treatment should be made, as far as is possible, in the absence of confounding factors. In the LIBERTY AD programme the primary clinical endpoints were assessed only for patients that had not required escalation of treatment (defined as rescue therapy due to exacerbation of AD symptoms). This is the primary analysis. In the language of the LIBERTY AD trial programme, patients that needed rescue therapy were 'censored' from the primary analysis. However, data collection for these patients continued. In contrast to a regulatory decision HTA agencies need to consider the impact of a new drug within a health system in terms of

both total costs and full health outcomes, and therefore the impact of rescue treatment in both arms is important evidence. As such the economic model reported here uses the 'all observed' dataset, which includes those patients that required a rescue intervention. The data for the 'all observed' methodology are presented below as these mirror clinical practice (Table 2.37).

The data show that patients experienced clinically meaningful improvements in signs, symptoms and quality of life impact of AD at week 16.The proportion of patients who achieved EASI−50 AND DLQI ≥ 4 was significantly higher in the dupilumab arms compared to placebo arms ($p<0.0001$ for both the 'primary' and 'all observed' analyses supporting the UK place in therapy) (Table 2.37).

The proportion of patients who achieved EASI−75 (co-primary endpoint) was also statistically significantly higher in the dupilumab arms compared to placebo arms ($p<0.0001$) in both CAFÉ+CHRONOS-CAFÉ-like pooled analyses and the SOLO-CAFÉ-like subgroup (Table 2.37).

Scenario analysis including the full licence population is also included in the economic analysis. Evidence informing this analysis is derived from the ITT population from pooled analysis for SOLO 1 & 2, CHRONOS and CAFÉ. These results have been reported in section B 2.6.

A comparison to ciclosporin has also been performed as specified in the NICE scope. This analysis is based on the MAIC reported in section B 2.9.

Table 2.37 Efficacy outcomes for patients included in the pooled CAFÉ / CHRONOS CAFÉ-like data and used in the economic modelling — All observed values regardless of rescue treatment use.

	CAFÉ / CHRONOS CAFÉ-like pool			SOLO-CAFÉ-like subgroup		
	Placebo QW + TCS	Dupilumab 300mg Q2W + TCS	Dupilumab 300mg QW + TCS	Placebo QW + TCS	Dupilumab 300mg Q2W + TCS	Dupilumab 300mg QW + TCS
All patients	**N=169**	**N=130**	**N=163**	**N = 88**	**N = 104**	**N = 96**
Proportion of patients who achieved EASI−50 AND DLQI ≥ 4: n (%)	47/169 (27.8%)	95/130 (73.1%)	117/163 (71.8%)	21/88 (23.9%)	61/104 (58.7%)	58/95 (61.1%)
Difference: % (95%CI)*		45.3% (34.4% to 56.1%)	44.0% (33.7% to 54.2%)		34.8% (20.7% to 48.8%)	37.2% (22.8% to 51.5%)
P-value†		<0.0001	<0.0001			<0.0001
EASI total score change from baseline to week 16	-14.56 (0.978)	-26.48 (1.109)	-26.02 (0.963)	-11.70 (1.259)	-23.54 (1.192)	-25.59 (1.186)
Difference: LS mean (SE)*		-11.93 (1.203)	-11.46 (1.118)	-	-11.84 (1.621)	-13.89 (1.656)
P-value†		<0.0001	<0.0001		<.0001	<.0001
Weekly average of pruritus NRS change from baseline to week 16	-2.17 (0.187)	-3.89 (0.213)	-3.91 (0.185)	-2.00 (0.256)	-3.30 (0.244)	-3.54 (0.240)
Difference: LS mean (SE)*		-1.72 (0.231)	-1.73 (0.215)		-1.30 (0.332)	-1.54 (0.338)
P-value†		<0.0001	<0.0001		0.0001	<.0001
EASI-75 at week 16: N (%)	51/169 (30.2%)	87/130 (66.9%)	103/163 (63.2%)	15/88 (17.0%)	47/104 (45.2%)	49/95 (51.6%)
Difference: % (95% CI)*		36.7%(25.4% - 48.1%)	33.0%(22.3% - 43.7%)		28.1% (14.7% - 41.6%)	34.5% (20.7% - 48.4%)
P-value†		<0.0001	<0.0001		<0.0001	<0.0001

Change from baseline in EQ-5D LS mean change (SE)	0.119 (0.0187)	0.194 (0.0212)	0.195 (0.0185)	0.161 (0.0205)	0.281 (0.0238)	0.318 (0.0236)
Difference: LS mean (SE)*		0.075 (0.0231)	0.076 (0.0214)		0.121 (0.324)	0.157 (0.0330)
p-value†		0.0012	0.0004		0.0002	<0.0001
Patients achieving EASI50 and DLIQ≥4	**N=47**	**N=95**	**N=117**	**N=21**	**N=61**	**N=58**
EASI total score change from baseline to week 16	-27.96 (0.823)	-29.11 (0.662)	-28.97 (0.572)	-28.24 (1.198)	-29.88 (0.789)	-30.53 (0.761)
Difference: LS mean (SE)*	-	-1.15 (0.892)	-1.01 (0.851)	-	-1.64 (1.409)	-2.29 (1.399)
P-value†		0.1999	0.2376		0.2463	0.1037
Peak pruritus NRS change from baseline to week 16	-3.63 (0.308)	-4.27 (0.248)	-4.38 (0.214)	-3.16 (0.435)	-3.83 (0.293)	-4.25 (0.278)
Difference: LS mean (SE)*	-	-0.65 (0.333)	-0.75 (0.319)	-	-0.67 (0.519)	-1.10 (0.509)
P-value†		0.0525	0.0195		0.1987	0.0331
EQ-5D Utility change from baseline to week 16	0.259 (0.0259)	0.257 (0.0209)	0.246 (0.0180)	0.291 (0.0422)	0.313 (0.0281)	0.353 (0.0271)
Difference: LS mean (SE)*	-	-0.002 (0.0281)	-0.013 (0.0268)	-	0.022 (0.0500)	0.061 (0.0494)
P-value†		0.9330	0.6345		0.6612	0.2155

*Difference is dupilumab minus placebo. CI calculated using normal approximation. † P-values were derived by the Cochran-Mantel-Haenszel test CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; TCS, topical corticosteroid; QW weekly dosing; Q2W dosing every other week.

B 2.7.1.3 Safety outcomes used in the economic model

The number of key adverse events per 100-patient years is presented in Table 2.38 below. In line with best practice we have used the full SAF in the economic model.

Table 2.38 Adverse event rates (number of events per 100 patient years) from the CHRONOS, CAFÉ and pooled SOLO studies (SAF)

Preferred Term	nE (nE/100PY)	nE (nE/100PY)	nE (nE/100PY)
CHRONOS nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	280.4	100.4	291.9
Injection site reaction	0	35 (34.870)	228 (78.112)
Allergic conjunctivitis	21 (7.488)	20 (19.926)	70 (23.982)
Infectious conjunctivitis	2 (0.713)	0	4 (1.370)
Oral herpes	13 (4.636)	7 (6.974)	28 (9.593)
CAFÉ nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	33.6	33.2	34
Injection site reaction	0	1 (3.010)	5 (14.723)
Allergic conjunctivitis	9 (26.771)	18 (54.178)	11 (32.391)
Infectious conjunctivitis	3 (8.924)	14 (42.138)	8 (23.557)
Oral herpes	0	3 (9.030)	5 (14.723)
SOLO nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	135.5	140.8	135.9
Injection site reaction	0	124 (88.098)	196 (144.187)
Allergic conjunctivitis	4 (2.952)	16 (11.367)	13 (9.563)
Infectious conjunctivitis	3 (2.214)	23 (16.341)	16 (11.770)
Oral herpes	8 (5.905)	19 (13.499)	16 (11.770)

BSC, best supportive care; FAS, full analysis set; QW, once every week; Q2W, once every two weeks; nE/110PY, number of events per 100 patient years

B 2.7.2 Homogeneity of treatment effect in the studies.

To assess the homogeneity of the treatment effect across subgroups, treatment-by-factor interactions were tested and descriptive p-values were provided. Baseline characteristics were analysed by subgroups of sex, age group, race, ethnicity, baseline weight group, duration of AD, BMI, region, baseline disease severity, baseline severe EASI, baseline peak NRS, BSA, SCORAD score, previous use of ciclosporin, methotrexate or azathioprine, previous systemic use of systemic immunosuppressants for AD, history of asthma, history of nasal polyps, history of allergic rhinitis and history of food allergies.

The following subgroup analyses were performed for all the studies:

- The proportion of patients with IGA 0 or 1 and reduction from baseline of ≥2 points at week 16 (and week 52 for CHRONOS)
- The proportion of patients with co-primary efficacy endpoint of EASI-75 at week 16

- The proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily Pruritus NRS score at week 16 (and week 52 for CHRONOS)
- The proportion of patients achieving a reduction of ≥3 points from baseline in weekly average of peak daily Pruritus NRS score at week 16 (and week 52 for CHRONOS)
- The percent change from baseline to week 16 (and week 52 for CHRONOS) in weekly average of peak daily Pruritus NRS score
- The proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily Pruritus NRS score at week 4
- The proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily Pruritus NRS score at week 2

Representative forest plots for pre-planned key subgroups and endpoints for the CHRONOS and CAFÉ studies are presented in Appendix E for:

- Co-primary efficacy endpoint of EASI-75.
- First secondary efficacy endpoint of proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily Pruritus NRS score.

Consistent dupilumab treatment effect in all the trials was observed among the majority of subgroups examined. Importantly, there was no difference by previous immunosuppressant use, disease severity, weight, or race across the primary and key secondary endpoints. Tests for interactions were carried out based on Logistical Regression Models or ANCOVA as described in Appendix E and no significant ($p<0.05$) interactions were identified.

B 2.8 Meta-analysis

Given the expectation for the use of dupilumab in adults who have a history of intolerance, inadequate response or contraindication to approved systemic therapies, the most relevant comparator is BSC. Therefore, we do not expect dupilumab to displace other therapeutic options.

A network meta-analysis was considered unfeasible to compare against the systemic immunosuppressants listed in the scope as there is considerable heterogeneity in methodologies within the studies identified by the SLR (e.g. the same treatment administered in different doses or assessed at different time-to-endpoints, a small number of studies per treatment, a lack of common comparators and few common endpoints, see Appendix D). However, to address the decision problem as fully as possible we have considered an indirect comparison with ciclosporin in scenario analysis using a MAIC methodology in line with recommendations in the DSU Technical Support Document 18[163]. Ciclosporin is the only immunosuppressant licenced for the treatment of AD and while the evidence base is limited for ciclosporin, we could map to outcomes to the CHRONOS study. The MAIC is described below and results are reported in Section B 3.7.3.

B 2.9 Indirect and mixed treatment comparisons

Ciclosporin is the only licenced immunosuppressant therapy available for people with AD but there is no head-to-head trial that directly compares dupilumab to ciclosporin. The SLR reported in Section B 2.1 and Appendix D identified trials for dupilumab, ciclosporin, and other therapies (i.e., other systemic treatments and phototherapy), but identified no common comparators to enable a network meta-analyses or a Bucher indirect comparison for

dupilumab versus ciclosporin and the outcomes of interest. To address this for use in scenario analysis, an indirect comparison of efficacy and safety was made using the MAIC approach. The MAIC analysis is described in summary below and full description is provided in Appendix D.

Brief description of the approach

MAIC provides an alternative when standard indirect comparisons (network meta-analyses or Bucher comparisons) are infeasible due to no common comparators or common endpoints, as is the case here. The MAIC method differs from other indirect comparison approaches in that it utilises patient-level data for the treatment of interest along with published aggregate trial level data for the comparator. The method matches patient baseline characteristics (e.g. demographic and clinical) between the two treatments by re-weighting individual patients in the patient-level dataset by their odds of having been enrolled in the competitor trial based on their baseline characteristics. After matching, the baseline characteristics between the two treatment groups are balanced on measured characteristics, and outcomes are compared across the balanced trial populations in a hypothetical head-to-head trial.

For the comparison of dupilumab vs. ciclosporin two series of analyses were undertaken to target the key efficacy outcome of EASI:

- A MAIC of dupilumab versus ciclosporin

Estimation of the efficacy and safety of dupilumab compared to ciclosporin was carried out using patient-level clinical trial data for dupilumab along with published, aggregate-level data for ciclosporin. EASI was not available in the MAIC and so SCORAD was assessed.

- Estimation of treatment responders for dupilumab versus ciclosporin

The correlation between SCORAD and EASI was explored. This enabled the proportion of EASI responders to be estimated for each treatment from their available SCORAD data.

Further responder analysis utilised patient-level data for both dupilumab and ciclosporin. These data were pooled, and regression models were used to estimate the proportion of EASI responders for each treatment, adjusting for baseline characteristics.

Data sources

Dupilumab: Patient-level data for dupilumab were obtained from CHRONOS to assess outcomes in the MAIC out to 52 weeks where possible, and to provide evidence for comparison vs. patients naïve to or previously treated with ciclosporin. The population in CHRONOS represents the full licenced population in the UK, which includes patients who are eligible for systemic treatments. Therefore, CHRONOS is the appropriate study to use for a comparison with ciclosporin.

Ciclosporin: The ciclosporin trials were obtained from several sources, including the SLR for efficacy and safety described in Appendix D which identified 12 ciclosporin studies published between 1980 and April 2017. Two other sources for candidate trials were considered. The

first was a systematic review and meta-analysis published by Schmitt in 2007 that included single-arm and controlled randomised trials of ciclosporin until August 2005[171]. This review identified 15 ciclosporin studies. The second source was a targeted literature review that focused on the time-period after Schmitt (i.e., studies published between 2005 and April 2017) and targeted prospective studies that would have been excluded in the SLR of AD treatments. This included trials with a single-arm study design or a mixed-age patient population. Only studies published in English that included adults in the study population were considered. In total, two relevant ciclosporin trials were identified from the targeted literature review — Haeck (2011)[150] and Jin (2015)[172].

Candidate trials were assessed for relevance that included the following features:

- Evaluation of an efficacy measure that was reported in the LIBERTY trial programme and captured extent and severity of disease (e.g. EASI, SCORAD) or relevant symptoms (e.g. pruritus NRS)
- Analysis time points of 8 weeks or later (priority was given to trials with timepoints of 16 weeks or later)
- A minimum of 15 patients in the ciclosporin treatment arm
- Populations including adults (trials focused exclusively on children were rejected)
- A relevant ciclosporin dosing schedule for an MAIC with dupilumab (ciclosporin cycling studies and treat-to-cure studies were rejected)

A summary of studies organised by potential outcome is provided in Appendix D

Two ciclosporin trials were identified from among the candidate trials for potential MAIC analysis. The first was Haeck (2011), a single-centre randomised controlled trial conducted in the Netherlands[150]. The trial recruited adult AD patients with insufficient response to potent TCS treatment and included 26 patients in its ciclosporin treatment arm. These patients were administered high-dose ciclosporin (5 mg/kg daily) for 6 weeks (divided into two daily doses) followed by low-dose ciclosporin (3 mg/kg daily) for a maintenance period of 30 weeks. The second study was Jin (2015), a single-centre randomised controlled trial conducted in South Korea[172]. The trial recruited patients ages 7 years and older with moderate-to-severe AD and included 17 patients in its monotherapy ciclosporin arm. These patients were administered low-dose ciclosporin (2 mg/kg daily divided into two daily doses) for a period of 8 weeks. A feasibility assessment was conducted to evaluate key points of similarity and heterogeneity between the CHRONOS trial and the Haeck (2011) and Jin (2015) studies. This included trial design, treatment arms, patient population, inclusion and exclusion criteria, sample size, outcome assessments, and analysis timepoints. Appendix D includes a side-by-side comparison of these trials.

Data extraction and variable generation

Individual patient-level data were obtained for the CHRONOS trial, and relevant characteristics and outcomes were abstracted for the analysis dataset. These included the baseline characteristics that were also available in the Haeck (2011) or Jin (2015) studies[150, 172]. It also included characteristics used in Haeck's or Jin's patient selection criteria. A full list of the abstracted variables is provided in Appendix D. One dupilumab patient was excluded

due to missing objective SCORAD at baseline. In total, 105 dupilumab Q2W + TCS were included.

Matching Average Baseline Characteristics between Dupilumab Q2W + TCS and Ciclosporin

The MAIC approach was applied separately for the comparisons of dupilumab Q2W + TCS versus ciclosporin from Haeck (2011) and ciclosporin from Jin (2015)[150, 172]. Average baseline characteristics were matched between the dupilumab patients and the ciclosporin trial populations. Specifically, individual patients in the dupilumab Q2W + TCS treatment arm were assigned weights such that: 1) their weighted mean baseline characteristics exactly matched those reported for patients in the given ciclosporin trial, and 2) each individual patient's weight was equal to his or her estimated odds of being in the given ciclosporin trial versus the dupilumab Q2W + TCS treatment arm of the CHRONOS trial. Weights meeting these conditions were obtained from a logistic regression model of the propensity of enrolment in the given ciclosporin trial versus the CHRONOS trial's dupilumab Q2W treatment arm, with baseline characteristics used for matching included as predictors in the model. For each MAIC analysis, outcomes were compared post-matching for the dupilumab Q2W + TCS treatment arm and the given ciclosporin trial. Categorical outcomes were compared using the weighted Chi-square test, while continuous outcomes were compared using weighted T-test. A full description is provided in Appendix D.

Results from the MAIC

For the comparison with Haeck, 2011, after matching from the total 105 patients from the dupilumab Q2W + TCS treatment arm included in the MAIC procedure, the effective sample size of dupilumab patients was 21, reflecting an approximate number of dupilumab patients with overlap of baseline characteristics with the ciclosporin patients in Haeck (2011). In total, 26 patients were included in the ciclosporin treatment arm of Haeck (2011). For the comparison with Jin, 2015, the number of dupilumab patients was 61, reflecting an approximate number of dupilumab patients with overlap of baseline characteristics with the ciclosporin patients in Jin (2015). In total, 17 patients were included in the ciclosporin treatment arm of Jin (2015).

The distribution of the weights for the analyses are provided in Appendix D. The comparison of efficacy and safety outcomes between the dupilumab Q2W + TCS patients and ciclosporin patients before and after matching is shown in Table 2.39 and Table 2.40.

Table 2.39 Matching-adjusted indirect comparison of dupilumab (CHRONOS) and ciclosporin (Haeck), matching on all baseline characteristics[†][95, 150]

	Before weighting			After weighting		
	dupilumab[‡] (N=105)	ciclosporin[§] (N=26)	P-value	dupilumab (ESS=21)	ciclosporin (N=26)	P-value
Baseline characteristics[‖]						
Age (years), mean±SD	39.4 ± 13.8	36.9 ± 15.1	0.447	36.9 ± 12.5	36.9 ± 15.1	1.00
Male, %	59.0%	65.4%	0.554	65.4%	65.4%	1.00
Female, %	41.0%	34.6%	0.554	34.6%	34.6%	1.00
Objective SCORAD, mean ± SD[¶]	56.2 ± 12.9	42.2 ± 10.6	<0.001	42.2 ± 10.6	42.2 ± 10.6	1.00
TARC (log10 pg/mL), mean ± SD[¶,**]	3.6 ± 0.6	3.3	<0.001	3.3 ± 0.6	3.3	1.00
IgE (log10 kU/L), mean ± SD[¶,**]	3.3 ± 0.9	3.6	0.001	3.6 ± 0.6	3.6	1.00
High QoL, %[¶,††]	1.0%	0.0%	0.617	0.0%	0.0%	1.00
Moderate QoL, %[¶,††]	37.1%	42.3%	0.627	42.3%	42.3%	1.00
Low QoL, %[¶, ††]	61.9%	57.7%	0.693	57.7%	57.7%	1.00
Outcomes at Week 16[‡‡]						
Objective SCORAD, mean ± SD[¶]	20.7 ± 12.7	28.3 ± 7.5	<0.001	19.6 ± 10.2	38.3 ± 7.5	<0.001
High QoL, %[¶,††]	40.0%	26.9%	0.217	37.2%	57.7%	0.431
Moderate QoL, %[¶,††]	43.8%	57.7%	0.204	40.6%	57.7%	0.246
Low QoL, %[¶,††]	9.5%	7.7%	0.772	18.9%	7.7%	0.288
Missing QoL, %[¶,††]	6.7%	7.7%	0.853	3.3%	7.7%	0.440
Outcomes at Week 36[§§]						
Objective SCORAD, mean ± SD[¶]	18.9 ± 13.3	24.1 ± 9.1	0.018	16.1 ± 11.7	24.1 ± 9.1	0.003
All-cause treatment discontinuation, %	11.4%	15.4%	0.581	6.8%	15.4%	0.269
High QoL, %[¶,††]	39.0%	26.9%	0.251	36.4%	26.9%	0.470
Moderate QoL, %[¶,††]	44.8%	46.2%	0.898	51.9%	46.2%	0.691
Low QoL, %[¶,††]	7.6%	11.5%	0.519	7.8%	11.5%	0.602
Missing QoL, %[¶,††]	8.6%	15.4%	0.298	3.9%	15.4%	0.123

ESS, effective sample size; IgE, immunoglobulin E; Q2W, every two weeks; QoL, quality of life; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation; TARC, thymus and activation-regulated kinase

† Dupilumab baseline age, sex, objective SCORAD, TARC, IgE, and categories of QoL were matched to ciclosporin baseline characteristics.

‡ Patient-level data from patients enrolled in LIBERTY AD CHRONOS trial randomised to the 300 mg dupilumab Q2W arm were used to generate baseline characteristics; one patient was excluded due to missing baseline objective SCORAD.

§ Summarised baseline characteristics were extracted from the ciclosporin arm of a trial described by Haeck 2011. Ciclosporin was given at 5 mg/kg daily for 6 weeks, followed by 3 mg.kg daily for 30 weeks.

ǁ Ciclosporin baseline characteristics (except for age) were assessed prior to the 6-week run-in period (i.e., Week-6 according to Haeck 2011.

¶ For ciclosporin, objective SCORAD, TARC, IgE and QoL were extracted from figures using ENGAUGE digitization software[173]

** Standard deviations for baseline TARC and baseline IgE were not extracted due to time constraints.

†† QoL was assessed using the Dermatology Life Quality Index and was categorised into 3 groups: scores 0 to 1 (High QoL), 2 to 10 (Moderate QoL), and 11 to 30 (Low QoL).

‡‡ For ciclosporin, outcomes at Week 16 were assessed 16 weeks following the first dose of ciclosporin and were classified as "Week 10" according to Haeck 2011.

§§ For ciclosporin, outcomes at Week 36 were assessed 36 weeks following the first dose of ciclosporin and were classified as "Week 30" according to Haeck 2011

Table 2.40 Matching-adjusted indirect comparison of dupilumab (CHRONOS) and ciclosporin (Jin), matching on select baseline characteristics†[95, 172]

	Before weighting			After weighting		
	dupilumab‡ (N=105)	ciclosporin§ (N=17)	P-value	dupilumab (ESS=61)	ciclosporin (N=17)	P-value
Baseline characteristics						
Age (years), mean±SD	39.4 ± 13.8	36.9 ± 15.1	<0.001	40.1 ± 15.7	19.5 ± 9.8	<0.001
Male, %	59.0%	65.4%	0.636	52.9%	52.9%	1.00
Female, %	41.0%	34.6%	0.636	47.1%	47.1%	1.00
Objective SCORAD, mean ± SD	56.2 ± 12.9	42.2 ± 10.6	0.980	56.1 ± 9.0	56.1 ± 9.0	1.00
History of asthma, %	48.6%	3.3	0.017	17.6%	17.6%	1.00
History of allergic rhinitis, %	51.4%	3.6	0.908	52.9%	52.9%	1.00
Outcomes at Week 8						
Objective SCORAD, mean ± SD	24.3 ± 13.0	47.9 ± 14.9	<0.001	23.2 ± 12.7	47.9 ± 14.9	<0.001
Percent decrease in objective SCORAD from baseline, mean ± SD	55.6 ± 22.1	14.5 ± 23.9	<0.001	58.3 ± 20.9	14.5 ± 23.9	<0.001
SCORAD50, %ǁ	68.4%	5.9%	<0.001	73.9%	5.9%	<0.001
Treatment discontinuation due to safety, %¶	1.0%	5.9%	0.138	0.3%	5.9%	0.329
Outcomes at Week 16 (dupilumab) vs. Week 8 (ciclosporin)						
Objective SCORAD, mean ± SD	20.7 ± 12.7	47.9 ± 14.9	<0.001	20.8 ± 12.1	47.9 ± 14.9	<0.001

Percent decrease in objective SCORAD from baseline, mean ± SD	62.1 ± 21.8	14.5 ± 23.9	<0.001	62.3 ± 21.8	14.5 ± 23.9	<0.001
SCORAD50, %‖	72.4%	5.9%	<0.001	73.1%	5.9%	<0.001
Treatment discontinuation due to safety, %¶	1.0%	5.9%	0.138	0.3%	5.9%	0.329

ESS, effective sample size; E; Q2W, every two weeks; SCORAD, Scoring Atopic Dermatitis; SD, standard deviation;
† Dupilumab sex, baseline, objective SCORAD, history of asthma and history of allergic rhinitis were matched to ciclosporin baseline characteristics.
‡ Patient-level data from patients enrolled in LIBERTY AD CHRONOS trial randomised to the 300 mg dupilumab Q2W arm were used to generate baseline characteristics; one patient was excluded due to missing baseline objective SCORAD.
§ Summarised baseline characteristics were extracted from the ciclosporin + placebo arm of a trial described Jin et al. 2015. Ciclosporin was given at 2 mg/kg daily for 8 weeks. Baseline and outcome measurements of SCORAD described in Jin et al. are assumed objective SCORAD, however this is not explicitly stated.
‖ SCORAD50 is defined as a >50% reduction in objective SCORAD from baseline.
¶ In the Jin et al. publication, 21 patients were originally enrolled in the ciclosporin + placebo arm, 17 of whom completed the study and were analysed. Treatment discontinuation due to safety was only reported among these 17 patients.

Key findings of the study are:

- The various MAIC comparisons were hampered by small sample sizes and small effective sample sizes, although the findings were largely consistent across the comparisons.

- MAIC adjustment did not result in large changes to the absolute SCORAD improvement for dupilumab. For instance, at week 16 the mean objective SCORAD changed only slightly from 20.7 to 19.6 (Haeck) or from 20.7 to 20.8 (Jin). At week 36 in Haeck, this decrease was slightly greater from 18.9 to 16.1[150, 172].

- After weighting, improvements in absolute SCORAD values were significantly higher for dupilumab in comparisons to Haeck (2011) (22.6 dupilumab vs. 3.9 ciclosporin at 16 weeks) and Jin (2015) (32.9 vs. 8.2). In the comparison to Jin (2015), where percentage changes in SCORAD (62.3% vs. 14.5%; p<0.001) or SCORAD50 (73.1% vs. 5.9%; p<0.001) responder rates could be compared, these were significant as well[150, 172].

- After weighting comparisons of QoL based on DLQI in the Haeck (2011) comparison were inconclusive. At 16 weeks, the proportion with a high QoL (37.2% vs. 57.7%) favoured ciclosporin and the proportion with a low QoL (18.9% vs. 7.7%) were higher for dupilumab than for

- ciclosporin. At week 36, the proportion with a high QoL was higher for dupilumab (36.4% vs. 26.9%), while the proportion with a low QoL (7.8% vs. 11.5%) was lower for dupilumab[150]. None of the QoL comparisons was significant.

- All-cause discontinuation was lower for dupilumab at 36 weeks (6.8% vs. 15.4%; p=0.269 in the Haeck study), though not significant. AE-related discontinuation could be assessed only in the Jin (2015) comparison, in which AE-related discontinuation was lower for dupilumab than for ciclosporin, although not significant (0.3% vs. 5.9%; p=0.329)[150, 172].

A discussion of the strengths and weaknesses of the study is provided in Appendix D.

Conclusions from the MAIC

Using methods for indirect comparisons across the separate trial populations, the evidence suggests that dupilumab Q2W + TCS is associated with superior efficacy compared to low-dose ciclosporin as well as high-dose ciclosporin initiation followed by low-dose maintenance therapy with ciclosporin.

The second part of the analysis was designed to provide an estimate of response for dupilumab vs. ciclosporin using EASI thresholds to facilitate scenario analysis in the economic model. This is discussed below and in full detail in Appendix D

Overview of the analyses to estimate response using EASI thresholds.

The responder analyses were structured in two steps. In step 1, a mapping was established between objective SCORAD and the responder thresholds for EASI, using the patient-level data for dupilumab that contained both EASI and SCORAD measurements. The objective of this process was to identify SCORAD cut-offs that corresponded (i.e., were "mapped") to the EASI outcomes of interest—EASI-50 and EASI-75—for each analysis timepoint. Similar methods to extrapolate one outcome from a related outcome have been applied in previous studies[174, 175]. In step 2, the SCORAD cut-offs from step 1 were used to estimate EASI-50 and EASI-75 responders for dupilumab and ciclosporin, using available SCORAD data. Each step is summarised below and described in more detail in Appendix D.

Step 1: Mapping objective SCORAD to the EASI responder thresholds

The mapping of objective SCORAD to EASI-50 and EASI-75 was conducted separately for the analyses involving data from Haeck (2011) and Jin (2015)[150, 172]. For each analysis, the mapping used the dupilumab Q2W + TCS data with weights applied from the MAIC with the given ciclosporin study. Application of these weights helped to address cross-trial heterogeneity of patient characteristics and ensure greater comparability of the dupilumab and ciclosporin populations.

The mapping procedure for the responder analyses using data from Haeck (2011) versus data from Jin (2015) followed the same general approach but with key differences. These differences reflected variation in the ciclosporin trials' reporting of SCORAD[150, 172]. In Haeck (2011), SCORAD results consisted of the mean and standard error of the SCORAD level at

baseline and follow-up; the study did not report the percentage change from baseline. While the change from baseline could have been calculated from the reported quantities, the standard deviation of this quantity, which the analysis is sensitive to, could not[150]. By contrast, the results in Jin (2015) consisted of the mean and standard deviation of the SCORAD percentage change from baseline as well as the level at baseline and follow-up[172].

For each endpoint, EASI-50 or EASI-75, a set of potential SCORAD cut-offs were identified. SCORAD levels below the cut-off represented greater improvement relative to the cut-off's benchmark (i.e., "responders"), while SCORAD levels above the cut-off denoted insufficient improvement relative to the cut-off benchmark (i.e., "non-responders"). For each endpoint, the potential cut-offs were evaluated in terms of sensitivity, specificity, and prediction accuracy in the MAIC-weighted dupilumab data.

Validation analyses were performed to assess the SCORAD cut-offs selected for the EASI thresholds. The analyses were conducted using the other dupilumab treatment arm from CHRONOS—QW + TCS—with weights applied from MAICs of the QW + TCS arm with Haeck (2011) and Jin (2015). Validity of the SCORAD cut-offs for EASI-50 and EASI-75 was assessed by using the cut-offs to predict the MAIC-weighted proportion of responders among the dupilumab QW +TCS patients. These predicted proportions were then compared to the actual MAIC-weighted proportion of responders among these patients.

Results for SCORAD to the EASI responder thresholds

The full results for the mapping exercise are presented in Appendix D and a summary of the results and validation exercises are tabulated below (Table 2.41 and Table 2.42).

For the comparison from Haeck (Table 2.41), the SCORAD cut-off that best predicted the actual proportion of responders corresponded to SCORAD levels of 36 and 25 for EASI-50 and EASI-75, respectively. For Week 36, this corresponded to SCORAD levels of 46 and 24 for EASI-50 and EASI-75, respectively. Overall, the SCORAD cut-offs for EASI-75 performed better than those for SCORAD50. The SCORAD cut-offs for EASI-75 predicted the actual MAIC-weighted proportion of responders within 0.02 or less. By contrast, the SCORAD cut-offs for EASI-50 predicted the actual MAIC-weighted proportion of responders within 0.08 and 0.07.

Table 2.41. Results and validation analyses for the selected SCORAD cut-offs based on the MAIC-weighted QW + TCS dupilumab data (with data from Haeck, 2011[150])

Week	EASI threshold	Selected SCORAD cut-off (level at endpoint)	Predicted proportion of responders for the EASI threshold	Actual proportion of responders for the EASI threshold
16	50	36	0.96	0.88
16	75	25	0.79	0.77
36	50	46	0.99	0.92
36	75	24	0.8	0.8

EASI, Eczema Area Severity Index; MAIC, Matching-Adjusted Indirect Comparison; QW, once a week; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

For the results from Jin, EASI-50 and EASI-75 corresponded to SCORAD percent decreases of 29% and 55% respectively. (Table 2.42). Results from the validation analyses for the SCORAD cut-offs showed strong ability of the cut-offs to predict the actual MAIC-weighted proportion of responders among the dupilumab QW + TCS patients. In contrast to the results above, the SCORAD cut-off for EASI-50 performed slightly better than that for SCORAD75. The SCORAD cut-off for EASI-50 predicted the actual MAIC-weighted proportion of responders within 0.01, while the cut-off for EASI-75 predicted the actual MAIC-weighted proportion of responders within 0.05.

Table 2.42 Results and validation analyses for the selected SCORAD cut-offs based on the MAIC-weighted QW + TCS dupilumab data (with data from Jin, 2015[172])

Week	EASI threshold	Selected SCORAD cut-off (percentage decrease)	Predicted proportion of responders for the EASI threshold	Actual proportion of responders for the EASI threshold
8	50	29	0.88	0.87
8	75	55	0.58	0.63

EASI, Eczema Area Severity Index; MAIC, Matching-Adjusted Indirect Comparison; QW, once a week; SCORAD, Severity Scoring of Atopic Dermatitis; TCS, topical corticosteroid

Step 2 Estimated proportions of treatment responders for the EASI thresholds

Results for the responder analyses, involving CHRONOS and Haeck (2011) are shown in Table 2.43). For the Week 16 endpoint, dupilumab had a numerically higher proportion of responders than ciclosporin for both EASI-50 and EASI-75. This trend was considerably more pronounced for EASI-75 than EASI-50. For EASI-75, 33% of ciclosporin patients were estimated to be responders by Week 16 compared to 70% to 78% of dupilumab patients (depending on the estimation approach). By contrast for EASI-50, 84% of ciclosporin patients were estimated to be responders by Week 16 compared to 89% to 95% of dupilumab patients (depending on the estimation approach).

Results for week 36 followed similar trends to those for Week 16 with greater differences observed between dupilumab and ciclosporin for EASI-75 than EASI-50. For EASI-75, 49% of ciclosporin patients were estimated to be responders compared to 75% to 78% of dupilumab patients (depending on the estimation approach). For EASI-50, the proportion of responders was similar for ciclosporin and dupilumab. Nearly all ciclosporin patients (99%) were estimated to be responders, while 96% to 99% of dupilumab patients were estimated to be responders.

For both treatments, the proportion of responders was estimated to increase from the Week-16 endpoint to the Week-36 endpoint for each EASI threshold.

Table 2.43. Estimated proportion of treatment responders for the EASI thresholds and endpoints (with Haeck[150])

Study	Intervention	Week	SCORAD cut-off (level at endpoint)	SCORAD Mean (level at endpoint)	SCORAD SD (level at endpoint)	Est. EASI proportion	SE† (Est. EASI proportion)
EASI-50 by Week 16*							
Haeck	Ciclosporin	16	36	28.35	7.55	0.84	0.06
CHRONOS	Dupilumab	16	36	-	-	0.89	0.07
CHRONOS	Dupilumab	16	36	19.64	10.24	0.95	0.04
EASI-75 by Week 16*							
Haeck	Ciclosporin	16	25	28.35	7.55	0.33	0.07
CHRONOS	Dupilumab	16	25	-	-	0.78	0.08
CHRONOS	Dupilumab	16	25	19.64	10.24	0.70	0.08
EASI-50 by Week 36*							
Haeck	Ciclosporin	36	46	24.12	9.06	0.99	0.01
CHRONOS	Dupilumab	36	46	-	-	0.96	0.03
CHRONOS	Dupilumab	36	46	16.09	11.7	0.99	0.01
EASI-75 by Week 36*							
Haeck	Ciclosporin	36	24	24.12	9.06	0.49	0.08
CHRONOS	Dupilumab	36	24	-	-	0.78	0.08
CHRONOS	Dupilumab	36	24	16.09	11.7	0.75	0.08

*Each sub-table contains two rows for CHRONOS. The first row estimates EASI responders among dupilumab Q2W + TCS patients, using a "direct approach." For the Haeck analysis, this involved computing the MAIC-weighted proportion of dupilumab patients with a SCORAD level below the identified cut-off at the given endpoint (i.e., week 16 or week 36). The second row estimates EASI responders among dupilumab Q2W + TCS patients, using a distributional assumption approach. (This is like how EASI responders were estimated for the ciclosporin patients.) More specifically, the SCORAD level was assumed to follow a normal distribution for the given endpoint. (The mean and SD for this are included in the table.) The distribution and SCORAD cut-off were then used to estimate the proportion of EASI responders.

†Standard errors were computed using a parametric bootstrap approach.

EASI, Eczema Area and Severity Index; EASI-50; EASI score ≥50% response; EASI-75, EASI score ≥75% response; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation

Results for the responder analyses, involving CHRONOS and Jin (2015) are shown in Table 2.44. For both EASI thresholds, dupilumab had a considerably higher proportion of responders than ciclosporin by week 8. This was more pronounced for EASI-75 than for EASI-50. For EASI-75, only 5% of ciclosporin patients were estimated to be responders compared to 56% to 67% of dupilumab patients (depending on the estimation approach). For EASI-50, 27% of ciclosporin patients were estimated to be responders compared to 89% to 92% of dupilumab patients (depending on the estimation approach).

Table 2.44. Estimated proportion of treatment responders for the EASI thresholds and endpoints (with Jin[172])

Study	Intervention	Week	SCORAD cut-off (Percent decrease)	SCORAD Mean (Percent decrease)	SCORAD SD (Percent decrease)	Est. EASI proportion	SE† (Est. EASI proportion)
EASI-50 by Week 8*							
Jin	Ciclosporin	8	29	14.5	23.9	0.27	0.09
CHRONOS	Dupilumab	8	29	-	-	0.89	0.04
CHRONOS	Dupilumab	8	29	58.34	20.92	0.92	0.03
EASI-75 by Week 8*							
Jin	Ciclosporin	8	55	28.35	7.55	0.05	0.04
CHRONOS	Dupilumab	8	55	-	-	0.67	0.04
CHRONOS	Dupilumab	8	55	19.64	10.24	0.56	0.06

*Each sub-table contains two rows for CHRONOS. The first row estimates EASI responders among dupilumab Q2W + TCS patients, using a "direct approach." For the Haeck analysis, this involved computing the MAIC-weighted proportion of dupilumab patients with a SCORAD level below the identified cut-off at the given endpoint (i.e., week 16 or week 36). The second row estimates EASI responders among dupilumab Q2W + TCS patients, using a distributional assumption approach. (This is like how EASI responders were estimated for the ciclosporin patients.) More specifically, the SCORAD level was assumed to follow a normal distribution for the given endpoint. (The mean and SD for this are included in the table.) The distribution and SCORAD cut-off were then used to estimate the proportion of EASI responders.

†Standard errors were computed using a parametric bootstrap approach.

EASI, Eczema Area and Severity Index; EASI-50; EASI score ≥50% response; EASI-75, EASI score ≥75% response; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation

Conclusions for the responder analyses

- Overall, the results suggest stronger efficacy benefits for dupilumab than ciclosporin, as captured by EASI responder thresholds extrapolated from SCORAD data. These results were most evident for the EASI-75 threshold.
- Differences in treatment responders for dupilumab versus ciclosporin were more pronounced for the comparison involving CHRONOS and Jin (2015) than the comparison involving CHRONOS and Haeck (2011). This may, in part, reflect the lower ciclosporin dosage used in Jin (2015) than Haeck (2011).
- Results from the analysis involving CHRONOS and Haeck (2011) suggest that treatment responders for dupilumab and ciclosporin increase over time.

A discussion of the strengths and weaknesses of the analysis is provided in Appendix D.

B 2.9.1 Uncertainties in the indirect and mixed treatment comparisons

The above analyses are associated with uncertainty due to small sample sizes, trial heterogeneity and the low number of prognostic factors available to us. Therefore, the results should be interpreted with caution. In the absence of more robust comparative

studies this these data provide a directional indication of the relative benefit of dupilumab with respect to ciclosporin.

This technique circumvented existing data limitations for the two treatments (dupilumab and ciclosporin) that prevented construction of network meta-analyses for the outcomes of interest.

The MAIC approach does not introduce bias for outcomes that are not linearly related to patient characteristics, such as event risks. Additionally, the validity of standard errors and confidence intervals generated by MAIC has been demonstrated in a simulation study[176]. MAIC has been applied in multiple disease areas to support reimbursement submissions and publications and has been recognised in guidance from The National Institute for Health and Care Excellence[163].

B 2.10 Adverse events

B 2.10.1 Overview of the safety of the technology in relation to the decision problem

Overall, the dupilumab safety database supporting this submission includes safety data from a total of 3,200 subjects (2,728 patients with AD and 472 healthy subjects) in 17 Phase I to III studies. Of these, 2,526 patients with AD were exposed to dupilumab in 11 studies (10 placebo-controlled studies and one OLE study, excluding healthy volunteers) with a treatment period of ≥4 weeks.

The duration of dupilumab exposure for adult patients with AD is as follows:

- At least 1 year (364 days) for 645 patients with 300 mg weekly (QW), 58 patients with 300 mg every 2 weeks (Q2W) (739 patients, total duration any dupilumab dose)
- At least 1.5 years (546 days) for 91 patients with 300 mg QW (309 patients, total duration any dupilumab dose)
- At least 2 years (728 days) for 160 patients (total duration any dupilumab dose)

The objective of the clinical safety analysis was to detect safety signals and understand the safety profiles of dupilumab when used as a monotherapy, concomitantly with TCS, and as a long-term therapy. Safety analyses were performed for individual studies and combined (pooled) data.

Pooled safety data and the data from the individual studies are presented below in Section B 2.10.2 to B 2.10.5 (full details of the pooled safety data can be found in the EPAR in Appendix C).

Adverse event data from the extension studies, LIBERTY AD SOLO-CONTINUE and LIBERTY AD MAINTAIN, are provided in Appendix F. The long-term safety profiles for dupilumab reported from these two studies support those observed in SOLO 1, SOLO 2, CHRONOS and CAFÉ, with no new safety signals identified.

B 2.10.2 Analysis of pooled data

Safety data from the 2,526 AD patients exposed to dupilumab in the 11 studies with a treatment period of ≥4 weeks have been integrated into three pools; the Primary Safety Pool, the Supportive Safety Pool, and the Exposure Pool (data cut-off date 31 May 2016) (Table 2.45).

A summary of the Primary Safety Pool is provided below, and full details of the pooled safety data are provided in the EPAR in Appendix C.

The first two pools provide a comprehensive evaluation of dupilumab as monotherapy. The treatment-emergent AE (TEAE), serious AE (SAE), drug-related TEAE, drug-related TE SAE, treatment discontinuation due to TEAE, and AE of special interest profiles for dupilumab monotherapy were similar within the Primary Safety Pool and the Supportive Safety Pool.

The Exposure Pool provides a comprehensive evaluation of the overall extent of exposure to dupilumab in patients with AD. Analysis of safety parameters was not performed on the Exposure Pool because of differences in exposure, observation duration, and study design (e.g. monotherapy vs concomitant treatment with TCS) across the studies.

Table 2.45. Pooled safety data (data cut-off date of 31 May 2016 for the EPAR): patient numbers[177]

	Total	Exposed to dupilumab
Overall • 17 Phase I to III studies in healthy subjects and patients with AD	3,200	2,728
Primary Safety Pool (Pool 1) • Three Phase IIb/III studies of 16-week monotherapy in patients with AD: 1. SOLO1 2. SOLO2 3. R668 AD-1021	1,564	1,047
Supportive Safety Pool (Pool 2) • Six monotherapy studies in patients with AD with a treatment period 12–16 weeks: 1. R668 AD-1117 2. R668-AD-1021 (Phase IIb) 3. R668-AD-1307 4. R668-AD-1314 5. R668-AD-1334 (SOLO 1) 6. R668-AD-1416 (SOLO 2)	2,047*	1,352*
Exposure Pool (Pool 3)† • Eleven studies in patients with AD with a treatment period 12–16 weeks: 1. R668 AD-0914 2. R668-AD-1026 3. R668-AD-1121 4. R668-AD-1117 5. R668-AD-1021 6. R668-AD-1307 7. R668-AD-1314 8. SOLO1 9. SOLO2 10. CHRONOS 11. R668-AD-1225	2,978†	2,526†

*includes patients exposed to ≥300 mg monthly dose; †includes all patients who received at least 1 dose

†Pool 3 does not include CAFÉ as this study closed in December 2016[98]. Safety data from CAFÉ are presented in Section B 2.10.4

AD, atopic dermatitis

B 2.10.2.1 Primary Safety Pool (SOLO1, SOLO2, and the pivotal Phase IIb study)

B 2.10.2.1.1 *Treatment-emergent adverse events (Primary Safety Pool)*

In the Primary Safety Pool, approximately 69% of patients experienced a treatment-emergent adverse event (TEAE). The percentage of patients who experienced at least one TEAE during the 16-week treatment period and/or who had at least one TEAE leading to permanent study drug discontinuation was similar across all treatment groups (Table 2.46).

A higher percentage of placebo than dupilumab patients had at least one treatment-emergent serious adverse event (TE SAE) (5.0% placebo, 2.5% dupilumab Q2W and 2.1% dupilumab QW) and a slightly higher percentage of placebo patients discontinued due to TE SAE (1.4% placebo, 0.8% dupilumab Q2W and 0.4% dupilumab Q2W).

TE SAE (determined by the study investigators) reported for ≥2 patients in any treatment group in the monotherapy studies either occurred only in the placebo group (sepsis, suicidal ideation, and acute kidney injury), or occurred at a higher frequency in the placebo group than in the dupilumab groups (dermatitis atopic). All other TE SAEs occurred in one patient.

Table 2.46. Primary Safety Pool (data cut-off date of 31 May 2016 for the EPAR) – Summary of TEAE in any treatment group during the 16-Week monotherapy treatment period[177]

N, (%)	Placebo (N=517)	Dupilumab		
		300 mg Q2W (N=529)	300 mg QW (N=518)	Combined (N=1047)
Any TEAE	359 (69.4)	366 (69.2)	357 (68.9)	723 (69.1)
Any drug-related TEAE	104 (20.1)	146 (27.6)	158 (30.5)	304(29.0)
Any TEAE causing permanent discontinuation	10 (1.9)	10 (1.9)	8 (1.5)	18 (1.7)
Maximum intensity for any TEAE				
Mild	143 (27.7)	197 (37.2)	191 (36.9)	388 (37.1)
Moderate	173 (33.5)	149 (28.2)	145 (28.0)	294 (28.1)
Severe	43 (8.3)	20 (3.8)	21 (4.1)	41 (3.9)
Death	0	0	1 (0.2)	1 (<0.1)
Any TE SAE	26 (5.0)	13 (2.5)	11 (2.1)	24 (2.3)
Any drug-related TE SAE	3 (0.6)	2 (0.4)	2 (0.4)	4 (0.4)
Any TE SAE causing permanent discontinuation	7 (1.4)	4 (0.8)	2 (0.4)	6 (0.6)

EPAR, European Public Assessment Report; QW, one a week; Q2W, every two weeks; TEAE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse event

The profiles of the most common drug-related TEAEs of the two dupilumab groups were similar with respect to the types of TEAEs by primary system organ class and preferred term (

Table 2.47).

In patients treated with dupilumab as monotherapy for 16 weeks, 69% patients reported >1% event; infections and infestations (>30%), skin and subcutaneous tissue disorders (>19%), general disorders and administration site conditions (>16%), and nervous system disorders (>11%) (

Table 2.47).

In patients treated with dupilumab as monotherapy for 16 weeks, the following TEAEs were the most commonly reported: injection site reaction, nasopharyngitis, headache, upper respiratory tract infection, conjunctivitis, oral herpes, herpes simplex, diarrhoea, conjunctivitis allergic, conjunctivitis bacterial, blepharitis, dry eye, fatigue, nausea, arthralgia, myalgia, alopecia, rash, injection site erythema, cough, oropharyngeal pain, raised blood creatine phosphokinase increased, eosinophilia, hypertension and pain in extremity (Table 2.47). Most cases were mild to moderate in severity.

For infections and infestations, the percentage of patients who experienced at least 1 TEAE was similar across all treatment groups; 33.1% in the dupilumab Q2W group, 34.2% in the dupilumab 300 mg QW group, and 32.3% in the placebo group (Table 2.47). However, within this system organ class patient group there was some difference in reporting rates; higher rates of sinusitis, oral herpes, conjunctivitis bacterial, herpes simplex, URTI and nasopharyngitis in the dupilumab group compared with placebo (Table 2.47

Table 2.47). Most of these events were mild to moderate in severity, resolved during the treatment period and did not lead to study medication discontinuation.

For infections and infestations, the proportion of patients with a TE SAE was 0.2% in the dupilumab Q2W treated group, 0.8% in the dupilumab QW group and 1% in the placebo group. There were no discernible trends at the system organ class or preferred term levels for the remaining SAEs in the dupilumab treated and placebo populations. Three cases of myocardial infarction (two reported as acute) were reported in the dupilumab treatment groups in the monotherapy studies.

For eye disorders, although there was an increased incidence of allergic conjunctivitis, blepharitis and dry eye in the dupilumab patients, this was against a high incidence of pre-existing background history of eye disorders (23% patients had a past medical history of allergic conjunctivitis). The majority were mild to moderate in severity and resolved with treatment. However, 20% of cases had not resolved during the study period. There were no serious cases.

No clinically meaningful difference in the TEAE profile was observed in any of the subgroups studied including age (≥18 to <40 years, ≥40 to <65 years, ≥65 years), sex (male, female), ethnicity (Hispanic or Latino, not Hispanic or Latino), race (White, Black or African American, Asian, or other), duration of AD (<26 years, ≥26 years), baseline weight (<70kg, ≥70kg to <100 kg, ≥100 kg), body mass index at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2), region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe), region for Japan submission (Japan, rest of world) and the results elicited no safety concerns for any subgroup.

The TEAE profile in patients for whom oral ciclosporin treatment was medically inadvisable was similar to that in the remaining patients with respect to all types of TEAEs, and there is no new safety signal in this subset compared to the rest of the study patients.

Table 2.47. Primary Safety Pool (data cut-off date of 31 May 2016 for the EPAR) – Summary of TEAE ≥1% in any treatment group by primary system organ class and preferred term during the 16-Week monotherapy treatment period[177]

N (%)	Placebo (N=517)	Dupilumab		
		300 mg Q2W (N=529)	300 mg QW (N=518)	Combined (N=1047)
≥1 TEAE	359 (69.4)	366 (69.2)	357 (68.9)	723 (69.1)
Infections and infestations	167 (32.3)	175 (33.1)	177 (34.2)	352 (33.6)
Nasopharyngitis	52(10.1)	55 (10.4)	58 (11.2)	113 (10.8)
Upper respiratory tract infection	15 (2.9)	18(3.4)	24 (4.6)	42 (4.0)
Conjunctivitis	3 (0.6)	21 (4.0)	20 (3.9)	41 (3.9)
Oral herpes	8 (1.5)	20 (3.8)	13 (2.5)	33 (3.2)
Conjunctivitis bacterial	2 (0.4)	7 (1.3)	8 (1.5)	15 (1.4)
Herpes simplex	4 (0.8)	9 (1.7)	4 (0.8)	13 (1.2)
Folliculitis	10 (1.9)	4 (0.8)	8 (1.5)	12 (1.1)
Bronchitis	6 (1.2)	5 (0.9)	4 (0.8)	9 (0.9)
Urinary tract infection	9 (1.7)	7 (1.3)	2 (0.4)	9 (0.9)
Impetigo	8 (1.5)	5 (0.9)	3 (0.6)	8 (0.8)
Skin infection	7 (1.4)	5 (0.9)	2 (0.4)	7 (0.7)
Sinusitis	6 (1.2)	2 (0.4)	2 (0.4)	4 (0.4)
Skin and subcutaneous tissue disorders	187 (36.2)	109 (20.6)	102 (19.7)	211 (20.2)
Dermatitis atopic	158 (30.6)	70 (13.2)	62 (12.0)	132 (12.6)
Alopecia	4 (0.8)	3 (0.6)	9 (1.7)	12 (1.1)
Rash	2 (0.4)	6 (1.1)	2 (0.4)	8 (0.8)
Pruritus	10 (1.9)	1 (0.2)	6 (1.2)	7 (0.7)
Pruritus generalised	6 (1.2)	1 (0.2)	3 (0.6)	4 (0.4)
General disorders and administration site conditions	59 (11.4)	85(16.1)	100 (19.3)	185 (17.7)
Injection site reaction	28 (5.4)	51 (9.6)	72 (13.9)	123 (11.7)
Fatigue	7 (1.4)	12 (2.3)	9 (1.7)	21 (2.0)
Injection site erythema	2 (0.4)	6 (1.1)	7 (1.4)	13 (1.2)
Pyrexia	6 (1.2)	6 (1.1)	5 (1.0)	11 (1.1)
Nervous system disorders	49 (9.5)	67 (12.7)	58 (11.2)	125 (11.9)
Headache	26 (5.0)	45 (8.5)	41 (7.9)	86 (8.2)
Dizziness	12 (2.3)	6 (1.1)	5 (1.10)	11 (1.1)
Musculoskeletal and connective tissue disorders	32 (6.2)	52 (9.8)	41 (7.9)	93 (8.9)
Back pain	12 (2.3)	9 (1.7)	12 (2.3)	21 (2.0)
Arthralgia	9 (1.7)	15 (2.8)	4 (0.8)	19 (1.8)
Pain in extremity	5 (1.0)	7(1.3)	4 (0.8)	11 (1.1)
Myalgia	2 (0.4)	6 (1.1)	3 (0.6)	9 (0.9)
Gastrointestinal disorders	34 (6.6)	46 (8.7)	44 (8.5)	90 (8.6)
Diarrhoea	9 (1.7)	18 (3.4)	10 (1.9)	28 (2.7)
Nausea	5 (1.0)	10 (1.9)	11 (2.1)	21 (2.0)
Eye disorders	15 (2.9)	33 (6.2)	42 (8.1)	75 (7.2)

N (%)	Placebo (N=517)	Dupilumab		
		300 mg Q2W (N=529)	300 mg QW (N=518)	Combined (N=1047)
Conjunctivitis allergic	5 (1.0)	16 (3.0)	12 (2.3)	28 (2.7)
Blepharitis	1 (0.2)	2 (0.4)	6 (1.2)	8 (0.8)
Dry eye	0	1 (0.2)	6 (1.2)	7 (0.7)
Respiratory, thoracic and mediastinal disorders	31 (6.0)	37 (7.0)	33 (6.4)	70 (6.7)
Cough	4 (0.8)	10 (1.9)	7 (1.4)	17 (1.6)
Oropharyngeal pain	5 (1.0)	8 (1.5)	9 (1.7)	17 (1.6)
Asthma	8 (1.5)	7 (1.3)	1 (0.2)	8 (0.8)
Investigations	21 (4.1)	28 (5.3)	23 (4.4)	51 (4.9)
Blood creatine phosphokinase disorders	9.7 (1.7)	10 (1.9)	5(1.0)	15 (1.4)
Blood and lymphatic system disorders	21 (4.1)	19 (3.6)	9 (1.7)	28 (2.7)
Lymphadenopathy	8 (1.5)	7 (1.3)	5 (1.0)	12 (1.1)
Eosinophilia	2 (0.4)	9 (1.7)	1 (0.2)	10 (1.0)
Vascular disorders	10 (1.9)	14 (2.6)	10 (1.9)	24 (2.3)
Hypertension	6 (1.2)	9 (1.7)	5 (1.0)	14 (1.3)
Psychiatric disorders	24 (4.6)	11 (2.1)	10 (1.9)	21 (2.0)

EPAR, European Public Assessment Report; QW, one a week; Q2W, every two weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event

B 2.10.2.1.2 *AE of special interest (Primary Safety Pool)*

The AE of special interest assessed in the dupilumab Phase III clinical programme are summarised in Table 2.48. AE of special interest were prospectively identified by the study investigators in the dupilumab clinical programme; except for conjunctivitis, which was identified following the analysis of the SOLO studies. The AE of special interest prospectively identified were based on the pharmacologic properties of dupilumab and its mechanism of action, conditions associated with or diagnosed in patients with AD, or the fact that dupilumab is a protein biologic that is administered SC. In addition, immunogenicity to dupilumab was monitored by measuring anti-drug antibody (ADA) responses and their potential effects on safety and efficacy were evaluated.

Table 2.48. Adverse events of special interest assessed in the dupilumab clinical trial programme[177]

Events included and analysed as adverse events of special interest in the dupilumab clinical trial programme
• Anaphylactic reactions • Acute allergic reactions requiring treatment • Mycosis fungoides or cutaneous T-cell dyscrasias • Any severe infection • Any infection requiring treatment with parenteral antibiotics • Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks • Any clinical endoparasitosis • Any opportunistic infection • Severe ISRs lasting longer than 24 hours • Suicidal behaviour (suicidal ideation, suicidal behaviour, depression suicidal, suicide attempt and completed suicide) • Conjunctivitis (post-hoc analysis)

The proportion of patients who had at least one AE of special interest during the 16-week treatment period in the monotherapy safety pool was low across treatment groups (approximately 4.0%), and was lower for dupilumab 300 mg Q2W and 300 mg QW patients (approximately 2% and 1%) than placebo patients (approximately 4%) (Table 2.49). The proportion of patients who had at least one serious AE of special interest during the 16-week treatment period was low overall (approximately 1%), and was lower for dupilumab 300 mg Q2W (0.2%) and dupilumab 300 mg QW (0.4%) patients than placebo patients (1.2%) (Table 2.49).

AE of special interest were reported within the Primary Safety Pool as follows:

- Acute allergic reactions requiring treatment occurred in 0.6% of dupilumab 300mg Q2W, 0.2% of dupilumab QW and 0.6% of placebo patients (Table 2.49) with an average time to onset of 107–110 days across the treatment groups and most acute allergic reactions requiring treatment had clear precipitating agents responsible for the reactions. A review of urticarial events indicated that incidence of these events was not increased with dupilumab treatment, there were no cases of anaphylactic reactions, and no severe injection site reactions lasting longer than 24 hours.

- Opportunistic infections occurred in 0.8% of dupilumab 300mg Q2W, 0.4% of dupilumab QW and 1.0% of placebo patients (Table 2.49) and were identified as herpes viral infections eczema herpeticum and herpes zoster. The incidence of these opportunistic infections during the treatment period was either higher in the placebo group (herpes zoster) or similar between the dupilumab and the placebo groups (eczema herpeticum) and all opportunistic herpes viral infections resolved by study end.

- Severe infections were reported in 0.9% of dupilumab 300mg Q2W, 0.2% of dupilumab QW and 1.7 % of placebo patients (Table 2.49), and infections requiring treatment with parenteral antibiotics were reported in 1.0% of dupilumab 300mg Q2W, 1.9% of dupilumab QW and 0.7% of placebo patients. No infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks or cases of clinical endoparasitosis were reported.

- Suicidal behaviour was reported in 0% of dupilumab 300mg Q2W, 0.2% of dupilumab QW and 0.6 % of placebo patients (Table 2.49). One case of completed suicide (from the SOLO 2 study) was reported in the dupilumab 300 mg QW arm reported for the Primary Safety Pool. The death was not considered to be drug-related. See below.

- Conjunctivitis was reported in 9.3% of dupilumab 300mg Q2W, 7.9% of dupilumab QW and 2.1 % of placebo patients (Table 2.49). Although conjunctivitis and eye disorders (dry eye, eye pruritus, and blepharitis) were observed more commonly in dupilumab than placebo patients, most cases were mild to moderate in severity and resolved with local treatment.

- Malignancy-related TEAEs were reported in 1.3% of dupilumab 300mg Q2W, 1.4% of dupilumab QW and 1.2 % of placebo patients (Table 2.49) and the most commonly reported were benign lesions. Although two serious malignancy-related TEAEs were

reported in patients treated with dupilumab QW (Hodgkin Lymphoma) and Q2W (Lipoma) both were considered not related to study drug by the study investigators.

The proportion of patients with at least one AE of special interest or serious AE of special interest, and the profile of AE of special interest and serious AE of special interest during the entire study period was like that observed for the 16-week treatment period and for the follow-up period and the exposure-adjusted patient and event incidence of AE of special interest showed similar trends as to the crude patient incidence of AE of special interest.

Although the mean time to first occurrence of any AE of special interest during the 16-week treatment period was similar between all treatment groups (range: 104.6 [±25.57] days for placebo to 108.5 [±19.34] days for dupilumab 300 mg Q2W), the cumulative incidence of any AE of special interest during the 16-week treatment period was lower over time for dupilumab compared to the placebo.

Of the patients who reported any event, only one patient (dupilumab 300 mg QW) discontinued study treatment due to the event (conjunctivitis). However, of the 103 conjunctivitis TEAEs reported during the treatment period in dupilumab treated patients in the Primary Safety Pool, 78.6% of the events resolved or were resolving during the treatment period.

Suicide must also be considered as a discontinuation. A 31-year-old man with a history of depression, including hospitalisation for depression, and suicidal ideation completed suicide. This event that occurred 8 days after the most recent dose of dupilumab[45].

Table 2.49. Primary Safety Pool – Treatment-emergent AE of special interest[177]

	Placebo, % (N=517)	Dupilumab	
		300 mg Q2W, % (N=529)	300 mg QW, % (N=518)
≥1 AE of special interest	~4.0	~2.0	~1.0
≥1 serious AE of special interest	1.2	0.2	0.4
Acute allergic reaction	0.6	0.6	0.2
Opportunistic infection	1.0	0.8	0.4
Severe infection	1.7	0.9	0.2
Suicidal behaviour	0.6	0	0.2
Conjunctivitis	2.1	9.3	7.0
Malignancy	1.2	1.3	1.4

AE, adverse event; QW, once a week; Q2W, every two weeks

B 2.10.3 Summary of adverse events in CHRONOS

Table 2.50 summarises the AE reported in CHRONOS during the 16- and 52-week treatment periods. Overall, dupilumab was well tolerated in this study and the incidence of TEAEs was similar across all treatment groups during both the 16-week and 52-week periods. The safety profile of dupilumab + TCS during the 52-week treatment period was consistent with the 16-week period with no new safety signals observed with long-term treatment. This was also consistent with the monotherapy studies SIOLO 1 and 2.

Importantly, compared to placebo there was no increase in infections with dupilumab overall or for specific infection AE of special interest. There were no reports of anaphylactic reactions associated with dupilumab. The incidence of hypersensitivity was similar in all treatment groups. The dupilumab + TCS groups had higher rates of injection site reactions than the placebo + TCS group; with higher rates reported for QW versus Q2W dupilumab. Injection site reactions were mild or moderate, and rates declined over time.

Due to a higher frequency of reports of conjunctivitis and selected eye-related disorders with dupilumab + TCS treatment, an ad-hoc analysis of these reports with additional preferred terms (PTs) that could indicate a conjunctivitis-like event was performed using narrow and broad Customised MedDRA queries (CMQs). Overall, the rate of conjunctivitis of any cause was higher in the dupilumab + TCS groups than in the placebo + TCS group at week 16 and week 52, using both broad and narrow CMQs. None of these events were serious and only one event led to permanent study drug discontinuation. Most of the events had resolved by the end of the study.

Higher proportions of patients in the placebo + TCS group than in the dupilumab + TCS groups had TE SAEs at 52 weeks (5.1% placebo + TCS versus 3.3% combined dupilumab + TCS) and TEAEs leading to permanent study drug discontinuation (7.9% placebo + TCS versus 2.6% combined dupilumab + TCS).

There was one death during the study of a 27-year-old female patient in the dupilumab QW group who died in a car accident.

Dupilumab treatment was associated with a low incidence of immunogenicity. Treatment-emergent, persistently positive ADA responses were observed in a higher proportion of patients in the placebo + TCS group (3.02.9% [9/306]) than in either dupilumab + TCS group (dupilumab Q2W + TCS, 1.9% [2/105]; dupilumab QW + TCS, 1.3% [4/308]). Treatment-boosted ADA (Patients with positive ADA response at baseline and at least 4-fold increase in titre in the post-baseline period) assay responses were observed in a single patient in each treatment group. No patients had a high-titre response in the ADA assay (Titre > 10000) and only two dupilumab patients had a moderate titre (1000 =< titre =< 10000) at weeks 16 and 36.

Table 2.50. CHRONOS summary of TEAE with incidence ≥2% in any treatment group during the 52-Week treatment period — SAF[95]

Event n (%)	16 weeks			52 weeks		
	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N = 315)	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N =315)
TEAE or TE SAE						
At least 1 TEAE	215 (68.3)	81 (73.6)	228 (72.4)	268 (85.1)	97 (88.2)	263 (83.5)
At least 1 TE SAE	6 (1.9)	3 (2.7)	4 (1.3)	16 (5.1)	4 (3.6)	10 (3.2)
Death†	0	0	0	0	0	1 (0.3)
TEAE leading to treatment discontinuation	15 (4.8)	1 (0.9)	8 (2.5)	25 (7.9)	2 (1.8)	9 (2.9)
Non-infectious TEAE						

Event n (%)	16 weeks			52 weeks		
	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N = 315)	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N =315)
Injection site reaction	18 (5.7)	11 (10.0)	51 (16.2)	25 (7.9)	16 (14.5)	61 (19.4)
Fatigue	7 (2.2)	1 (0.9)	6 (1.9)	10 (3.2)	1 (0.9)	11 (3.5)
Pyrexia	4 (1.3)	2 (1.8)	1 (0.3)	7 (2.2)	4 (3.6)	7 (2.2)
Exacerbation of atopic dermatitis	86 (27.3)	12 (10.9)	25 (7.9)	147 (46.7)	22 (20.0)	55 (17.5)
Erythema	1 (0.3)	1 (0.9)	6 (1.9)	2 (0.6)	1 (0.9)	10 (3.2)
Acne	6 (1.9)	0	6 (1.9)	8 (2.5)	1 (0.9)	7 (2.2)
Pruritus	1 5 (0.31.6)	1 (0.9)	3 1 (0.3)	9 (2.9)	1 (0.9)	4 (1.3)
Urticaria	8 (2.5)	1 (0.9)	3 (1.0)	10 (3.2)	1 (0.9)	3 (1.0)
Headache	15 (4.8)	4 (3.6)	20 (6.3)	19 (6.0)	5 (4.5)	25 (7.9)
Arthralgia	8 (2.5)	2 (1.8)	4 (1.3)	15 (4.8)	5 (4.5)	10 (3.2)
Back pain	6 (1.9)	1 (0.9)	2 (0.6)	11 (3.5)	2 (1.8)	8 (2.5)
Pain in extremity	0	0	5 (1.6)	2 (0.6)	0	8 (2.5)
Osteoarthritis	0	1 (0.9)	1 (0.3)	3 (1.0)	3 (2.7)	2 (0.6)
Muscle spasms	4 (1.3)	0	0	7 (2.2)	0	1 (0.3)
Cough	5 (1.6)	2 (1.8)	6 (1.9)	8 (2.5)	3 (2.7)	10 (3.2)
Oropharyngeal pain	7 (2.2)	1 (0.9)	4 (1.3)	12 (3.8)	3 (2.7)	10 (3.2)
Asthma	11 (3.5)	3 (2.7)	0	19 (6.0)	5 (4.5)	2 (0.6)
Allergic conjunctivitis	9 (2.9)	7 (6.4)	19 (6.0)	15 (4.8)	12 (10.9)	47 (14.9)
Blepharitis	2 (0.6)	5 (4.5)	8 (2.5)	3 (1.0)	6 (5.5)	11 (3.5)
Eye pruritus	2 (0.6)	2 (1.8)	9 (2.9)	4 (1.3)	4 (3.6)	14 (4.4)
Dry eye	1 (0.3)	2 (1.8)	3 (1.0)	4 (1.3)	3 (2.7)	6 (1.9)
Diarrhoea	7 (2.2)	0	5 (1.6)	13 (4.1)	1 (0.9)	12 (3.8)
Nausea	7 (2.2)	2 (1.8)	6 (1.9)	12 (3.8)	2 (1.8)	9 (2.9)
Abdominal pain	7 2 (20.6)	2 (1.8)0	6 3 (1.90)	4 (1.3)	0	7 (2.2)
Toothache	2 (0.6)	0	0	8 (2.5)	1 (0.9)	4 (1.3)
Blood creatine phosphokinase increased	6 (1.9)	1 (0.9)	8 (2.5)	9 (2.9)	3 (2.7)	11 (3.5)
Blood lactate dehydrogenase increased	4 (1.3)	4 (3.6)	1 (0.3)	5 (1.6)	4 (3.6)	1 (0.3)
Seasonal allergy	4 (1.3)	2 (1.8)	5 (1.6)	6 (1.9)	2 (1.8)	9 (2.9)
Psychiatric disorders	7 (2.2)	5 (4.5)	4 (1.3)	18 (5.7)	9 (8.2)	11 (3.5)
Infectious TEAE						
Infections and infestations	111 (35.2)	39 (35.5)	109 (34.6)	182 (57.8)	64 (58.2)	167 (53.0)
Nasopharyngitis	33 (10.5)	15 (13.6)	37 (11.7)	62 (19.7)	25 (22.7)	62 (19.7)
Upper respiratory tract infection	20 (6.3)	7 (6.4)	21 (6.7)	32 (10.2)	11 (10.0)	43 (13.7)

Event n (%)	16 weeks			52 weeks		
	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N = 315)	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N =315)
Sinusitis	3 (1.0)	0	10 (3.2)	9 (2.9)	2 (1.8)	18 (5.7)
Urinary tract infection	2 (0.6)	0	2 (0.6)	13 (4.1)	2 (1.8)	13 (4.1)
Influenza	6 (1.9)	1 (0.9)	2 (0.6)	16 (5.1)	4 (3.6)	9 (2.9)
Viral upper respiratory tract infection	4 (1.3)	2 (1.8)	7 (2.2)	9 (2.9)	3 (2.7)	9 (2.9%)
Conjunctivitis bacterial	2 (0.6)	1 (0.9)	6 (1.9)	5 (1.6)	2 (1.8)	9 (2.9)
Conjunctivitis	2 (0.6)	0	3 (1.40)	5 (1.6)	1 (0.9)	8 (2.5)
Gastroenteritis	05 (1.6)	1 (0.9)	1 (0.3)	9 (2.9%)	5 (4.5%)	4 (1.3%)
Oral herpes	5 (1.6)	3 (2.7)	8 (2.5)	9 (2.9)	4 (3.6)	15 (4.8)
Herpes simplex	1 (0.3)	1 (0.9)0	2 (0.64 (1.3))	2 (0.6)	3 (2.7)	5 (1.6)
Pharyngitis	2 (0.6)	0	3 (1.0)	8 (2.5)	3 (2.7)	5 (1.6)
Rhinitis	2 (0.6)	1 (0.9)	5 (1.6)	4 (1.3)	1 (0.9)	7 (2.2)
Folliculitis	2 5 (0.61.6)	1 (0.9)	3 2 (1.00.6)	7 (2.2)	2 (1.8)	4 (1.3)
Impetigo	3 (1.0)	0	1 (0.3)	10 (3.2)	1 (0.9)	4 (1.3)
Skin infection	7 (2.2)	0	1 (0.3)	7 (2.2)	0	1 (0.3)

AE, Adverse event; TEAE, Treatment-emergent adverse event; TE SAE, Treatment-emergent serious adverse event; SAF, safety analysis set; Q2W, every other week; QW, every week

B 2.10.4 Summary of adverse events in CAFÉ

Dupilumab was generally safe and well tolerated in the CAFÉ study, with an acceptable safety profile compared to placebo. TEAEs at 16 weeks reported by ≥2% of patients in any treatment group are summarised in Table 2.51. The proportion of patients with at least one TEAE or TE SAE during the 16-week treatment period was similar across all treatment groups (Table 2.51). The proportion of patients with TEAEs leading to permanent discontinuation of study drug was low and comparable across treatment groups.

'Infections and Infestations' as a group had the highest incidence of TEAEs which was reported for similar proportion of patients in the dupilumab Q2W (45.8%), dupilumab QW (42.7%) and placebo (40.7%) groups.

The incidence of non-herpetic skin infections was 8.3% in the placebo + TCS group compared to 3.6% in the dupilumab 300 mg QW + TCS group (p=0.15) and 1.9% in the dupilumab 300 mg Q2W group (p=0.032). The reduced incidence of non-herpetic skin infections in dupilumab + TCS-treated patients is consistent with previous studies and may be related to restoration of skin barrier function, reduced scratching, or improved antimicrobial or innate immune response.

The proportion of patients who had at least one severe TE SAE during the 16-week treatment period was similar and low overall for the Q2W (1.9% [2/107]), QW (1.9% [2/110]), and placebo (1.9% [2/108]), groups.

AD was the only TEAE that occurred at a severe intensity in more than one patient in any treatment group. Severe AD was reported for a lower proportion of patients in the dupilumab treatment groups (Q2W,1.9% [2/107]; QW, 1.8% [2/110]) than the placebo group (5.6% [6/108]).

In the group of PTs included in the "Narrow Conjunctivitis" cluster a higher incidence of conjunctivitis was observed for both doses of dupilumab compared with placebo (dupilumab Q2W 28.0%; dupilumab QW 16.4%; placebo 11.1%). One event in the Q2W group was considered severe. No patients discontinued the trial due an adverse event of conjunctivitis and all, but two, patients continued into the OLE trial. Patients in this trial who experienced a TEAE in the Narrow Conjunctivitis cluster in comparison to those who did not were slightly older (40.7 years vs. 37.8 years); male (78.3% vs. 57.4%) with greater disease severity at baseline by several measures: duration of AD (34.8 years vs. 29.4 years); EASI score (34.4 vs. 32.8) and percent BSA (61.2% vs. 54.4%). While the underlying mechanistic reasons have not yet been elucidated, these data suggest that greater disease severity may be a predisposing factor for developing conjunctivitis.

Laboratory values, vital signs, and electrocardiographic assessments did not indicate noteworthy differences among treatment groups. All treatment groups had shifts from normal eosinophils at baseline to high values during the study. However, a higher proportion of patients in the dupilumab treatment groups compared with patients in the placebo groups had this shift. No patient had relevant laboratory test abnormalities that led to treatment discontinuation or met seriousness criteria.

Table 2.51. CAFÉ summary of TEAE with incidence ≥2% in any treatment group during the 16 Week treatment period — SAF[98]

Event n (%)	Placebo + TCS (N = 108)	Dupilumab Q2W +TCS (N = 107)	Dupilumab QW + TCS (N = 110)
TEAE and TE SAE			
At least 1 TEAE	75 (69.4)	77 (72.0)	76 (69.1)
At least 1 TE SAE	2 (1.9)	2 (1.9)	2 (1.8)
Death	0	0	0
TEAE leading to treatment discontinuation	1 (0.9)	0	2 (1.8)
Non-infectious TEAE			
Injection site reaction	0	1 (0.9)	4 (3.6)
Injection site erythema	1 (0.9)	1 (0.9)	3 (2.7)
Injection site swelling	1 (0.9)	0	3 (2.7)
Oedema peripheral	3 (2.8)	0	2 (1.8)
Fatigue	1 (0.9)	4 (3.7)	3 (2.7)
Exacerbation of atopic dermatitis	16 (14.8)	8 (7.5)	9 (8.2)
Headache	9 (8.3)	10 (9.3)	10 (9.1)
Allergic conjunctivitis	7 (6.5)	16 (15.0)	10 (9.1)
Lacrimation increased	1 (0.9)	1 (0.9)	3 (2.7)
Eye pruritus	0	0	3 (2.7)
Rhinitis allergic	1 (0.9)	7 (6.5)	4 (3.6)
Cough	1 (0.9)	4 (3.7)	3 (2.7)

Event n (%)	Placebo + TCS (N = 108)	Dupilumab Q2W +TCS (N = 107)	Dupilumab QW + TCS (N = 110)
Oropharyngeal pain	2 (1.9)	3 (2.8)	1 (0.9)
Rhinorrhoea	3 (2.8)	0	3 (2.7)
Asthma	3 (2.8)	1 (0.9)	1 (0.9)
Myalgia	0	0	4 (3.6)
Back pain	3 (2.8)	1 (0.9)	2 (1.8)
Blood and lymphatic disorders	4 (3.7)	4 (3.7)	1 (0.9)
Hypertension	1 (0.9)	1 (0.9)	3 (2.7)
Diarrhoea	2 (1.9)	3 (2.8)	2 (1.8)
Abdominal pain	4 (3.7)	0	4 (3.6)
Infectious TEAE			
Infections and infestations	44 (40.7)	49 (45.8)	47 (42.7)
Nasopharyngitis	18 (16.7)	22 (20.6)	17 (15.5)
Conjunctivitis	3 (2.8)	12 (11.2)	8 (7.3)
Gastroenteritis	1 (0.9)	2 (1.9)	3 (2.7)
Respiratory tract infection viral	1 (0.9)	0	4 (3.6)
Upper respiratory tract infection	1 (0.9)	1 (0.9)	3 (2.7)
Pharyngitis	3 (2.8)	1 (0.9)	2 (1.8)
Oral herpes	0	3 (2.8)	5 (4.5)
Herpes simplex	3 (2.8)	1 (0.9)	1 (0.9)

AE, Adverse event; TEAE, Treatment-emergent adverse event; TE SAE, Treatment-emergent serious adverse event; SAF, safety analysis set; Q2W, every other week; QW, every week

B 2.10.5 Summary of adverse events in SOLO 1 and SOLO 2

Table 2.52 shows the observed AEs in SOLO 1 and SOLO 2 as reported at study end[45]. The incidence of AEs was similar in the dupilumab and placebo groups. Exacerbations of AD were more common in the placebo groups. Dupilumab treated patients had a higher incidence of injection site reactions, and conjunctivitis with unspecified cause and allergic conjunctivitis, which were reported in 5–10% of patients receiving dupilumab versus 1–2% receiving placebo. Bacterial or viral conjunctivitis was reported in <2% of the patients in any group[45]. In the dupilumab groups, 8–19% patients experienced injection site reactions, versus 6% in the placebo groups. Most injection site reactions were mild to moderate and did not result in treatment discontinuation.

The incidence of SAEs was low during the 16-week treatment period and lower for patients treated with dupilumab than for patients receiving placebo. The only SAE reported in more than two patients in any treatment group was a serious exacerbation of AD, which was reported in two patients receiving dupilumab every other week, and three patients receiving placebo in SOLO 1, and in one patient receiving weekly dupilumab and in five patients receiving placebo in SOLO 2[45]. SAE and AE leading to treatment discontinuation were uncommon in both trials.

Two deaths were reported in SOLO 2: a 31-year-old man with a history of depression, including hospitalisation for depression, and suicidal ideation completed suicide, an event

that occurred 8 days after the most recent dose of dupilumab (see Table 2.52); and a 49-year old asthmatic woman who was not receiving an asthma-control medication died of an asthma attack, 84 days after the last dose of dupilumab and after study completion[45].

Dupilumab treatment was associated with a low incidence of immunogenicity, and development of ADA did not significantly impact exposure, efficacy, or safety in most patients[96, 97]. The proportion of patients who developed treatment-emergent responses in ADA assay was slightly higher in the dupilumab 300 mg Q2W group (6.8–8.0%) than in the dupilumab 300 mg QW (2.7–2.9%) and placebo groups (1.0–1.8%)[96, 97].

Table 2.52. SOLO1 and SOLO 2 Summary of TEAE with incidence ≥2% in any treatment group during the 16-Week treatment period — SAF[96, 97]

Event n (%)	SOLO 1			SOLO 2		
	Placebo (N=222)	Dupilumab Q2W (N=229)	Dupilumab QW (N=218)	Placebo (N=234)	Dupilumab Q2W (N=236)	Dupilumab QW (N=237)
AE or SAE						
At least 1 AE	145 (65.3)	167 (72.9)	150 (68.8)	168 (71.8)	154 (65.3)	157 (66.2)
At least 1 SAE	11 (5.0)	7 (3.1)	2 (0.9)	13 (5.6)	4 (1.7)	8 (3.4)
Death	0	0	0	0	1 (0.4)*	1 (0.4)
AE leading to treatment discontinuation	2 (0.9)	4 (1.7)	4 (1.8)	5 (2.1)	2 (10.8)	3 (1.3)
Non-infectious AE						
Injection site reaction	13 (5.9)	19 (8.3)	41 (18.8)	15 (6.4)	32 (13.6)	31 (13.1)
Fatigue	1 (0.5)	5 (2.2)	2 (0.9)	3 (1.3)	6 (2.5)	5 (2.1)
Exacerbation of atopic dermatitis	67 (30.2)	30 (13.1)	21 (9.6)	81 (3534.6)	32 (1413.6)	38 (16.0)
Pruritus	5 (2.3)	0	1 (0.5)	5 (2.1)	1 (0.4)	3 (1.3)
Alopecia	1 (0.5)	2 (0.9)	0	3 (1.3)	1 (0.4)	7 (3.0)
Headache	13 (5.9)	21 (9.2)	11 (5.0)	11 (54.7)	19 (8.1)	22 (9.3)
Dizziness	3 (1.4)	3 (1.3)	0	6 (2.6)	3 (1.3)	4 (1.7)
Allergic conjunctivitis	2 (0.9)	12 (5.2)	7 (3.2)	2 (10.9)	2 (10.8)	3 (1.3)
Diarrhoea	4 (1.8)	7 (3.1)	7 (3.2)	3 (1.3)	9 (3.8)	3 (1.3)
Nausea	1 (0.5)	5 (2.2)	2 (0.9)	3 (1.3)	5 (2.1)	7 (3.0)
Arthralgia	3 (1.4)	6 (2.6)	1 (0.5)	6 (2.6)	6 (2.5)	2 (0.8)
Back pain	4 (1.8)	2 (0.9)	5 (2.3)	5 (2.1)	7 (3.0)	5 (2.1)
Blood creatine phosphokinase increased	4 (1.8)	5 (2.2)	2 (0.9)	3 (1.3)	4 (1.7)	1 (0.4)
Oropharyngeal pain	1 (0.5)	2 (0.9)	1 3 (1.5)	4 (1.7)	5 (2.1)	4 (1.7)
Depression	2 (0.9)	1 (0.4)	1 (0.5)	5 (2.1)	0	0
Hypertension	2 (0.9)	3 (1.3)	3 (1.4)	4 (1.7)	5 (2.1)	2 (0.8)
Infectious AE						
Infections and infestations	63 (28.4)	80 (34.9)	74 (33.9)	76 (32.5)	65 (27.5)	68 (28.7)
Nasopharyngitis	17 (7.7)	22 (9.6)	25 (11.5)	22 (9.4)	20 (8.5)	20 (8.4)
Upper respiratory tract infection	5 (2.3)	6 (2.6)	11 (5.0)	5 (2.1)	7 (3.0)	9 (43.8)

Event n (%)	SOLO 1			SOLO 2		
	Placebo (N=222)	Dupilumab Q2W (N=229)	Dupilumab QW (N=218)	Placebo (N=234)	Dupilumab Q2W (N=236)	Dupilumab QW (N=237)
Conjunctivitis	2 (0.9)	11 (4.8)	7 (3.2)	1 (0.4)	9 (3.8)	9 (3.8)
Oral herpes	4 (1.8)	9 (3.9)	4 (1.8)	4 (1.7)	8 (3.4)	9 (3.8)
Herpes simplex	3 (1.4)	7 (3.1)	2 (0.9)	1 (0.4)	0	1 (0.4)
Skin infection	2 (0.9)	2 (0.9)	1 (0.5)	5 (2.1)	1 (0.4)	1 (0.4)

*Patient died during the follow-up period after completing treatment with the study drug

AE, Adverse event; TEAE, Treatment-emergent adverse event; TE SAE, Treatment-emergent serious adverse event; SAF, safety analysis set; Q2W, every other week; QW, every week

B 2.10.6 Long-term safety of dupilumab MAINTAIN and CONTINUE

The long-term safety profiles of dupilumab reported from extension studies, LIBERTY AD SOLO-CONTINUE and LIBERTY AD MAINTAIN, support those reported from SOLO 1, SOLO 2, CHRONOS and CAFÉ, with no new safety signals identified[147, 164, 165]. Adverse event data from -CONTINUE and MAINTAIN are provided in Appendix F.

B 2.10.7 Conclusion of the safety analysis

Within the clinical trial programme, up to the EPAR cut-off (31st May 2016) 2,728 healthy subjects and patients with moderate-to-severe AD have received at least one dose of dupilumab either as part of a randomised placebo-controlled or OLE study and the absolute numbers and percentages of the AEs have been reported.

The results of the pooled safety analyses and safety analyses from individual studies presented above demonstrate that dupilumab QW or Q2W is generally well tolerated with an acceptable safety profile largely comparable to placebo. There were no important differences between the safety profiles of patients treated with dupilumab monotherapy or in combination with TCS. The adverse drug reactions identified identified to date for dupilumab are commonly seen in the AD patient population; they occurred with relatively low frequency with dupilumab treatment, and were generally mild or moderate, transient, and manageable. More significant serious allergic reactions were very rare. With exception of injection site reactions, there were no adverse reactions related to dose frequency and the safety database confirms the safety of long-term treatment with dupilumab 300 mg QW or Q2W.

An important difference in the safety profile of dupilumab compared to all other available systemic immune-modulatory treatments is the absence of an infection safety signal; no increased overall risk of infection was observed in patients treated with dupilumab. Furthermore, there are currently no important significant safety concerns for long-term treatment with dupilumab unlike compared to those experienced following long-term use of systemic immunosuppressants. which are associated with toxicity and long-term side effects, thus limiting their use to short courses and/or intermittent therapy.

B 2.11 Ongoing studies

In addition to the studies cited below, a number of disease registries in other countries are planned which will include patients treated with dupilumab. These are unlikely to report within the timeframe of the submission or within the next 12 months.

Table 2.53 Dupilumab studies for the adult AD indication listed on clinicaltrials.gov (19/01/2017)

Trial name NCT Number (other No.)	Phase	Title	N	Outcome	Completion date	Brief summary
LIBERTY AD MAINTAIN NCT01949311 (R668-AD-1225)[178]	III	An open-label study of dupilumab in patients With AD who participated in previous dupilumab clinical trials	Est. 2000	**Primary outcome:** the incidence and rate (events per patient-year) of TEAEs through the last study visit. **Secondary outcomes:** IGA scores, NRS Pruritus score, SCORAD score, PEOM, BSA involvement, HADS, DLQI, Safety.	Estimated December 2018	This is an OLE study for patients who participated in placebo-controlled AD trials. The study primarily evaluates long-term safety (adverse events) and immunogenicity. Efficacy parameters are based on IGA, EASI and the pruritus NRS.

AD, atopic dermatitis; DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index; HADS, Hospital Anxiety and Depression Scale IGA, Investigators' Global Assessment; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Severity Scoring of Atopic Dermatitis; TEAE, Treatment-Emergent Adverse Event

B 2.11.1 LIBERTY AD MAINTAIN

LIBERTY AD MAINTAIN is a Phase III, multicentre, open-label, extension study designed to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD. The target population is adult patients with AD who had participated in a prior dupilumab clinical study and who were not eligible to participate in the Phase III maintenance study. This study also includes patients who had met the inclusion criteria for SOLO 1 or SOLO 2 but these studies had closed.

The primary objective of this study is to assess the long-term safety of dupilumab administered to adult patients with AD. However, as one of the secondary objectives of this study is to assess the efficacy of dupilumab in AD patients in the context of re-treatment, key efficacy results are presented for the entire study population, along with two relevant subsets: patients who were dupilumab naïve coming into the OLE and patients who were retreated with dupilumab (>13 weeks between the last treatment in the parent study and the first injection in the OLE).

The study consists of a treatment period up to 148-weeks (approximately 3 years), during which patients are treated weekly with dupilumab (200 mg QW SC [per the original protocol] or 300 mg QW SC [after protocol amendment 2]), and a 16-week follow-up period.

In this study, patients are allowed concomitant use of TCI, TCS, and additionally, patients can receive rescue treatments for intolerable AD symptoms or to manage serious concurrent conditions during the study. Rescue treatments include systemic corticosteroids, nonsteroidal systemic immunosuppressive medications, and phototherapy. Systemic rescue treatments are considered prohibited medications, and as such, patients are to be discontinued from study drug for the duration of treatment with these prohibited medications, plus 5 half-lives.

This study is currently ongoing. In the first interim analysis all data up to the data cut-off of 11 April 2016 was analysed. At this time, 399/1491 (26.8%) patients had completed the study up to the week 52 visit and 60/1491 (4.0%) had completed up to the week 100 visit. Overall, 1415/1491 (94.9%) patients were ongoing in the study and 76/1491 (5.1%) were withdrawn from the study. The three most frequently cited reasons for withdrawal from the study were withdrawal by patient, AEs, and lack of efficacy.

Key efficacy outcomes from MAINTAIN are reported below and in Appendix P. Primary safety endpoints are provided in section B 2.10.6 and Appendix F.

B 2.11.1.1 Efficacy results

Patients in MAINTAIN all receive dupilumab QW which is not the licenced dose. However, it should be noted that in the Phase III studies efficacy and safety associated with the Q2W and QW doses were comparable.

At baseline, 18.2% (266/1460) of patients had EASI-75. At week 16 and week 52, 75.0% (875/1166) and 87.1% (350/402) of patients achieved EASI-75 relative to baseline of the parent study, respectively. Results of the key secondary endpoints were further supported by additional secondary efficacy endpoints in the total patient population, which showed improvements with long-term dupilumab treatment for continuous variable analyses (change and/or percent change from baseline in both the parent and current studies in pruritus NRS, EASI, DLQI, and POEM scores) as well as responder analyses (proportion of patients with prespecified reductions in IGA, pruritus NRS, and EASI) over time (see Appendix P)

Efficacy results from retreated and dupilumab naïve patients

An evaluation of efficacy parameters in the subset of patients who had a treatment interruption period of >13 weeks showed no meaningful differences compared to the subset of patients who were dupilumab naïve. These results are discussed further in Section 5.3.

This study demonstrated that long-term dupilumab treatment provided substantial and sustained clinical benefits to patients with moderate-to-severe AD who had previously participated in placebo-controlled dupilumab clinical trials. Substantial and sustained clinical benefits were observed in patients regardless of their baseline disease activity and the length of time since their prior dupilumab treatment

MAINTAIN is not a placebo-controlled study which recruited patients from dupilumab naïve and experienced cohorts who had with differing times between last dupilumab treatment in their previous studies and entering MAINTAIN. Therefore, the results from MAINTAIN are

not directly applicable to the economic modelling. However, the results to date demonstrate the continuing efficacy and safety of dupilumab in patients with moderate-to-severe AD.

B 2.11.2 Early Access to Medicines Scheme (EAMS)

Dupilumab was granted Promising Innovative Medicine (PIM) designation by the MHRA on the 23rd December 2015 and application for the EAMS was made on 5th Dec 2016. Positive Scientific Opinion was received on the 13th March 2017. EAMS enrolment ended at Marketing authorisation. For the purpose of EAMS, the indication was as follows:

Dupilumab is being made available to adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all other approved therapies. Dupilumab can be used with or without topical corticosteroids.

Following the granting of positive scientific opinion, dupilumab is the first biologic therapy to be available to patients with moderate-to-severe AD. The first patient was enrolled on the 25th of April 2017 and the first patient was initiated on the 3rd of May 2017. Twelve hospitals have taken part in the scheme.

B 2.11.2.1 Collection and analysis of EAMS baseline data

Patients were independently selected for entry in EAMS by their treating clinician. It was made clear to clinicians that in this pre-licence period treatment should be initiated for the most burdened patients.

At the point of application patient baseline data was collected including; disease severity (IGA, EASI, DLQI scores), previous medical history, current and past medication use, as well as demographic information (gender, age, weight and height). Consent for the company to hold baseline data for the purpose of assessing eligibilty to enter the scheme was obtained from all patients. By the time EAMS had closed to new entrants at granting of marketing authorisation, 244 patients had enrolled in the scheme. Consent to analyse the baseline data provided on application to the scheme was obtained from 165/244 (68%) patients.

These data (n=165) were retrospectively analysed by an external agency according to a pre-specified Statistical Analysis Plan (SAP) (Appendix Q).

B 2.11.2.2 EAMS baseline characteristics

Demographics and baseline scores

The EAMS cohort for whom baseline data were available comprised 165 patients (98 male; 66 female and one adult gender not reported) with a mean age of 40.32 years (95% CI 38.12 to 42.52; SD 14.25; median 38; IQR 24). Overall, 44% of the sample were young adults, 41% middle-aged and 15% older adults. Patient distribution by age and gender is shown in Table 2.54.

Table 2.54 Age and gender of patients enrolled in the dupilumab EAMS

Age group	Gender		
	Female	Male	Not reported
Young adults (18-35)	29	43	0
Middle-aged adults (36-55)	33	35	0
Older adults (56 and over)	4	20	1
Total	66	98	1

EAMS, Early Access to Medicines Scheme

Data for the EASI, IGA and DLQI scores were available for 160, 156 and 161 patients, respectively (varies due to inconsistency in reporting). IGA data were re-categorised for nine patients as reported in the SAP (Appendix Q). Baseline patient severity and DLQI scores for the analysed cohort are shown in Table 2.55.

Table 2.55 Baseline severity/DLQI scores for patients enrolled in the dupilumab EAMS

Measure	N	Median	Mean (SD)	95% CI	Range	IQR
EASI	160	21	23.5 (13.1)	21.5 – 25.5	0.6 -72.0	17
IGA	156	4	3.5 (0.7)	3.4 – 3.6	1 - 4	1
DLQI	161	16	16.65 (7.54)	15.47 – 17.82	1 - 30	12

DLQI, Dermatology Quality of Life Index; EAMS, Early Access to Medicines Scheme; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment

Across the full cohort, the median EASI score was 21, which would be categorised as 'severe'[36]. The median IGA score was 3.5 and the mean DLQI score was 16 which would be categorised as a 'very large' impact on a pateint's life[47].

Treatment history

Previous immunosuppressant treatment history: Overall, the majority of patients (96.4%; see Table 2.56) had been prescribed at least one immunosuppressant, with ciclosporin being most commonly prescribed in all patient groups (prescribed to 92.1% of the cohort overall). Over one third of the sample (37.6%) had been prescribed three different immunosuppressants, and a further 36.4% had been prescribed four different immunosuppressants.

Table 2.56 Previous immunosuppressant treatment history

	Young Adults (*n*=72)	Middle-Aged Adults (*n*=68)	Older Adults (*n*=25)	Total (*n*=165)
Immunosuppressant type*				
Azathioprine	48 (66.7%)	55 (80.9%)	19 (76.0%)	**122 (73.9%)**
Ciclosporin	69 (95.8%)	63 (92.6%)	20 (80.0%)	**152 (92.1%)**
Mycophenolate mofetil	30 (41.7%)	44 (64.7%)	16 (64.0%)	**90 (54.5%)**
Methotrexate	55 (76.4%)	58 (85.3%)	18 (72.0%)	**131 (79.4%)**
Other†	0	2 (2.9%)	0	**2 (1.2%)**

	Young Adults (*n*=72)	Middle-Aged Adults (*n*=68)	Older Adults (*n*=25)	Total (*n*=165)
One or more	**69 (95.8%)**	**67 (98.5)**	**23 (92.0%)**	**159 (96.4%)**
Total number of immunosuppressants prescribed				
None reported	3 (4.2%)	1 (1.5%)	2 (8.0%)	**6 (3.6%)**
One	5 (6.9%)	4 (5.9%)	0	**9 (5.5%)**
Two	16 (22.2%)	7 (10.3%)	3 (12.0%)	**26 (15.8%)**
Three	27 (37.5%)	22 (32.4%)	13 (52.0%)	**62 (37.6%)**
Four	21 (29.2%)	32 (47.1%)	7 (28.0%)	**60 (36.4%)**
Five	0	2 (2.9%)	0	**2 (1.2%)**

*Categories are not mutually exclusive. †"Other" = Leflunomide.

***Current immunosuppressant treatment**:* Table 2.57 shows that 41.6% the sample were currently prescribed at least one immunosuppressant at the time of EAMS enrolment, with methotrexate and ciclosporin being the most common**.**

Table 2.57 Current immunosuppressant prescriptions

	Young Adults (*n*=72)	Middle-Aged Adults (*n*=68)	Older Adults (*n*=25)	Total (*n*=165)
Immunosuppressant type*				
Azathioprine	5 (6.9%)	2 (2.9%)	0	**7 (4.2%)**
Ciclosporin	11 (15.3%)	8 (11.8%)	4 (16.0%)	**23 (13.9%)**
Mycophenolate mofetil	6 (8.3%)	5 (7.4%)	3 (12.0%)	**14 (8.5%)**
Methotrexate	8 (11.1%)	16 (23.5%)	1 (4.0%)	**25 (15.2%)**
Other†	0	1 (1.5%)	0	**1 (0.6%)**
Total number of immunosuppressants prescribed				
None reported	43 (59.7%)	37 (54.4%)	18 (72.0%)	**98 (59.4%)**
One	28 (38.9%)	30 (44.1%)	6 (24.0%)	**64 (38.8%)**
Two	1 (1.4%)	1 (1.5%)	1 (4.0%)	**3 (1.8%)**

*Categories are not mutually exclusive. †"Other" = Leflunomide

B 2.11.2.3 Interpretation of the EAMS baseline characteristics

Overall, the demographics analysed for patients enrolled in EAMS (EAMS cohort) were broadly similar to those of patients in the Phase III trial cohort (patients treated with dupilumab Q2W in the Phase III clinical trials (SOLO 1, SOLO 2, CHRONOS, CAFÉ). Both cohorts had a higher proportion of male patients and had a median age in the 'middle-aged adult' group (Table 2.58)[43-45].

Table 2.58 Patient Demographics EAMS vs. Phase III trial population[95-98]

	Phase III trial (dupilumab Q2W treatment group)				EAMS
Baseline Demographic	**SOLO 1 (N=224)**	**SOLO 2 (N=233)**	**CHRONOS (N=106)**	**CAFÉ (N=107)**	**EAMS (N=165)**
Male sex (%)	58	59	58	61	59
Median age (years)	38	34	41	38	40

EAMS, Early Access to Medicines Scheme

Patients enrolled into EAMS were heavily pre-treated. The use of one or more immunosuppressant was reported in 96.4% of patients and the use of three or more immunosuppressants in 75.2% of patients. This is likely a reflection of the instruction to reserve EAMS dupilumab treatment to clinician's most severe treatment. 92.1% of patients had received prior treatment with ciclosporin, one of the subgroups entered into the CAFE trial.

Mean baseline IGA scores were consistent across cohorts (Table 2.59). However, patients enrolled in EAMS had a numerically a numerically greater DLQI score than those in the Phase III trial cohort, indicating a higher burden of disease (Table 2.59). Patients in the EAMS cohort also had a numerically lower mean EASI score (Table 2.59).

Table 2.59 Baseline severity/DLQI scores EAMS vs. dupilumab Q2W Phase III trial populations[95-98]

	Phase III trial (Dupilumab Q2W treatment group)						
Severity score	**SOLO 1 (n=224)**	**SOLO 2 (N=233)**	**CHRONOS (N=106)**	**CAFÉ (N=107)**	**CAFÉ + CCL**	**SOLO CL**	**EAMS***
Mean IGA	3.5	3.5	3.5	3.5	3.5	3.6	3.5
Mean EASI	33.0	31.8	33.6	33.3	34.2	36.1	23.5
Mean DLQI	13.9	15.4	14.5	14.5	14.8	16.4	16.7

*Number of patients varies by score due to inconsistency in reporting; IGA N=156, EASI N=160, DLQI N=161

DLQI, Dermatology Quality of Life Index; EAMS, Early Access to Medicines Scheme; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment

A comparison with the UK patients enrolled in EAMS shows that the pooled population CAFÉ + CHRONOS CAFÉ-like used in the base case exhibits similar demographics, DLQI (14.8 vs. 16.7) and IGA (3.5 vs. 3.5) scores. However, the mean EASI score in EAMS is 23.5 which while still severe according to literature is lower than baseline in the trial programme (EASI 31.8 (SOLO 2) to 33.6 (CHRONOS)). In real-world clinical practice (exemplified by EAMS patients) it is not unreasonable to expect that EASI scores, which measure the signs of AD, will be lower than those recorded in the trials. The difference in EASI score could be attributed to current treatments received by patients at entry into EAMS. The analysis of EAMS data shows that a proportion of patients were receiving treatment at the time of entry with systemic immunosuppressants (41%). This treatment may have made led to some improvement in their scores, despite this; patients remained uncontrolled and were considered suitable candidates for treatment with dupilumab through the EAMS by clinicians.

B 2.11.2.4 Safety reporting in EAMS

The first safety periodic report was submitted to the MHRA in September 2017 and covered the period 03 May 2017 – 03 August 2017. The summary of the Assessment by the MHRA dated the 19th of September 2017 is presented below and the full report is provided in Appendix Q. (At the time of writing dupilumab had not received marketing authorisation from the EMA).

'Dupilumab is indicated through the EAMS scheme for the treatment of adult patients with severe atopic dermatitis who have failed to respond or who are intolerant of or ineligible for all approved therapies. The SO was granted on 13 March 2017 and remains active. The CHMP adopted a positive opinion for the EU MAA on 20 July 2017; the EC decision is pending.'

This is the first periodic report, covering the period 03 May 2017 – 03 August 2017

During the reporting period forty-four [44] patients had received dupilumab. Twenty-four adverse event reports referring to 77 adverse events were received and recorded in the Sanofi Pharmacovigilance database. No new safety concerns were identified. No changes to the treatment protocol or RMP are required.

The benefit-risk for dupilumab remains positive and the EAMS criteria continue to be met.'

B 2.11.2.5 Summary

The MHRA made dupilumab available through EAMS, in the pre-licence stage, because of the high level of unmet need in patients suffering with AD, and lack of existing licenced therapies. Clinicians were advised that treatment was to be reserved for their most severe patients, due to product availability.

The EAMS baseline data demonstrates that despite clinicians being certain of the severity of patients, even their most "severe" patients demonstrate a wide range of EASI scores. Using the ranges given by Leshem et al.[36], an EASI score of 21 is classified as severe, however, with a median of 21 in EAMS, 50% of patients scored lower than this. Therefore in real world practice, clinicians take a number of factors into account when classifying AD severity, including previous and current immunosuppressant use and inadequate response.

B 2.12 Interpretation of clinical effectiveness and safety evidence

The burden AD imposes on patients is described in Section B 1.3.6. The lives of patients with moderate-to severe disease are blighted by the breadth of the impact that AD has. Its signs: sore, red, dry, crusty, oozing leathery skin; its symptoms: itch, sleeplessness, chronic skin infections; and its impact on health-related quality of life: activities of daily living, social engagement, personal relationships, anxiety, depression and suicidal thoughts are substantial and in many patients unrelenting. To understand what dupilumab means for patients, clinicians and the treatment pathway in the UK, it is important to understand the magnitude of the benefit it has across the breadth of AD.

The baseline characteristics of patients in the LIBERTY trial programme reveal a population of patients have a high disease burden with moderate-to-severe AD lesions affecting a large

portion of their body surface area (BSA) (greater than 50% BSA involvement CHRONOS and CAFÉ). They experienced high levels of AD symptoms, including pruritus (baseline NRS was 7.3 and 6.4, indicating severe itch, CHRONOS and CAFÉ respectively). Their disease could not be adequately controlled with topical prescription medications, or otherwise topical mediations were not advised due to important side effects or safety risks. Their baseline EQ5D was 0.64 and 0.70 with DLQI baseline scores greater than greater than 14.5 and 13.8 (CHRONOS and CAFÉ respectively) indicating 'very large effect' [on quality of life].

In the patients who reflect the anticipated UK population in clincial practice, the baseline characteristics from the LIBERTY programme describe a 'sicker' population. These patients are those in whom systemic immunosuppresant therapy has failed—average EASI scores at baseline where higher (34.2 in CAFÉ+CHRONOS-CAFÉ-like patients and 36.1 in SOLO-CAFÉ-like patients, NRS average 7-8) and reduced quality of life. (EQ-5D QoL was 0.67 CAFÉ+CHRONOS-CAFÉ-like patients and 0.55 SOLO-CAFÉ-like patients; anxiety or depression (HADS) baseline scores were 13.5 and 14.6 n CAFÉ+CHRONOS-CAFÉ-like patients and SOLO-CAFÉ-like patients respectively).

In the real world previous treatment history (encompassing inadequately effective, not tolerated or contraindicated therapies i.e. medically inadvisable) coupled with physician opinion, serves as holistic assessment of eligibility for treatment with dupilumab.

Dupilumab has demonstrated improvement in all populations against the range of clinically relevant measures, improving signs, symptoms and therefore quality of life.

Dupilumab improves the signs of AD: skin dryness, erythema (redness), oozing and crusting, and thickened skin (lichenification)

In SOLO1 and 2 high numbers of patients responded to treatment with dupilumab monotherapy 300 mg Q2W and consistent and significant reduction in the extent and severity of AD lesions was observed. Statistically significant, clinically meaningful treatment benefit compared with placebo was demonstrated across an array of endpoints. Response, measured against IGA 0-1 with 2 or more points reduction, EASI-75, EASI-90, EASI-50 all reported a statistically significant benefit with dupilumab compared to placebo, $p<0.0001$ (for the all observed patients, (See Section B 2.6.3). In addition to responder rate, the size of benefit with dupilumab compared with placebo was demonstrated against thresholds defined as clinically meaningful.

- At week 16, 49% to 61 % of dupilumab patients and 15% to 22% of placebo patients achieved EASI-75 in SOLO 1&2 (All observed analysis, $p<0.0001$).

- The improvements in disease activity were rapid, with an increase in responder rates apparent within 2 weeks of dupilumab treatment, and these improvements continued for the duration of treatment as shown by percentage change in EASI score from baseline ($p< 0.0001$).

In trials that allowed TCS, dupilumab was statistically superior with clinically meaningful benefit compared with TCS alone at improving the extent and severity of AD skin lesions, measured by IGA and EASI-75, EASI-90 and EASI-50.

- In CHRONOS 69% and 64% of patients, dupilumab 300 mg Q2W + TCS and 300 mg QW + TCS respectively, achieved IGA 0 or 1 and reduction of ≥2 points from baseline. In placebo patients 24% met this threshold (all observed analysis, p<0.0001). This effect was maintained to 52 weeks.

- 74% and 71% of dupilumab patients, Q2W + TCS and QW + TCS respectively, achieved EASI-75 at week 16 compared with 32% of placebo + TCS patients (CHRONOS, All observed analysis, p<0.0001). Again, this was maintained to 52 weeks.

Dupilumab provides rapid, sustained and significant improvement in the pruritus symptom of AD

Moderate-to-severe AD is characterised by intense, persistent debilitating itch (pruritus), which is responsible for much of the patients' and their families' disease burden and is a major diagnostic criteria[2, 179]. Itch can be a constant presence in patients' lives, in terms of duration and intensity. Its impact on sleep contributes to daytime fatigue, reducing daily productivity[180], adversely affecting mood and increasing stress therefore risk of mental health problems[181].

In the placebo-controlled Phase III studies, eligible patients were required to have a baseline weekly average of daily peak pruritus NRS score ≥3 points (0 being 'no itch' and 10 being the 'worst itch imaginable'). In SOLO 1&2 baseline NRS was 7.6 (Q2W) and 7.8 (placebo). Clinically meaningful improvement in itch is a 3 to 4 point reduction inpeak pruritus NRS.

Dupilumab monotherapy was statistically superior to placebo: 40% to 50% dupilumab patients achieved a reduction of ≥4 NRS points, baseline to week 16, compared with 17% to 21% of placebo patients (all observed analysis, p<0.0001).

Strikingly, this improvement in itch was rapid and observed at Week 2: the percentage change from baseline was 15% to 17% (p<0.0001) in these early weeks (the same trend is seen at week 4). This ≥4 point NRS reduction was statistically different between treatment arms: week 2 (p=0.0097/SOLO1 and p<0.0001/SOLO2), week 4 (p=0.0002/SOLO1 and p<0.0001/SOLO2). When used concomitantly with TCS in the long-term CHRONOS study, dupilumab was superior to TCS alone at improving peak pruritus. Baseline NRS was 7.3 (placebo) and 7.4 (dupilumab Q2W) indicating a high disease burden.

- 62% and 58% of dupilumab patients (Q2W + TCS and QW + TCS, respectively) achieved a reduction of ≥4 NRS points from baseline at week 16, compared with 29% of placebo + TCS patients (all observed analysis, p<0.0001).

At every assessment point in the CHRONOS trial dupilumab + TCS reported statistically superior NRS reduction (improvement in itch compared with placebo). From week 3 p-values <0.0001.

To summarise, the unrelenting, persistent,sleep disrupting itch that patients find so distressing is rapidly, substantially and sustainably improved with dupilumab treatment.

Dupilumab has a positive impact on QoL and other patient-reported outcomes

Dupilumab as monotherapy and with TCS resulted in statistically significantly greater reductions from baseline compared to placebo or TCS therapy alone across a range of HRQ-L measures: DLQI, EQ-5D, POEM and HADS. These scales indicate there was an improvement in patient-reported symptoms, anxiety and depression , ($p<0.0001$ except total HADS where $p<0.002$: All observed analysis).

In SOLO 1&2 patients had baseline DLQI scores of 14.0 to 15.0, this is indicative of a 'very large effect' on quality of life. Their baseline EQ5D scores 0./631 and 0.595. A rapid and sustained improvement in DLQI and EQ5D scores: A reduction (improvement) of DLQI 9.0 to 9.5 points was observed at week 16 for dupilumab vs. 4.8 to 6.0 for placebo patients (all observed analysis, $p<0.0001$; LS mean change). An increase (improvement) of EQ5D 0.23 to 0.26 for dupilumab patients vs. 0.11 to 0.15 for placebo patients was observed at week 16 (All observed analysis, $p<0.0001$; LS mean change).

The same treatment effect is seen when dupilumab is used concomitantly with TCS, in the long-term CHRONOS study, at 16 and 52 weeks.

- LS mean change in DLQI of 11.0 points was observed for dupilumab vs. 7.5 for placebo treated patients at 52 weeks. (All observed analysis, $p<0.0001$).

- Similarly LS mean changes in EQ-5D were between 0.24 and 0.27 for dupilumab treated patients vs. 0.11 to 0.18 for placebo. (All observed analysis, $p<0.0001$: QW and $p=0.002$: QW).

Results from the CAFÉ study in patients for whom ciclosporin was medically inadvisable at 16 weeks confirmed the observations from CHRONOS.

These results support those of the primary and key secondary endpoints, and show that dupilumab monotherapy and combination with TCS results in clinically significant improvements in both the extent and clinical severity of AD, and in patients' experience of their symptomsIn addition to the improvements in signs, symptoms and HRQoL reported above, dupilumab treatment also has a beneficial impact on flares (exacerbation of disease needing treatment escalation). Emerging evidence is also suggesting it reduces bacterial skin infection and the rare but serious eczema herpeticum.

Dupilumab reduces the need for rescue therapy

The use of rescue medication was significantly reduced with dupilumab treatment compared to placebo (Table 2-29)[45, 96, 97]. Patients in the placebo groups were more likely to receive systemic rescue therapies (glucocorticoids or immunosuppressant agents) and received rescue treatments earlier than dupilumab treated patients (Section B 2.6.3.3,Figure 2.26) [45, 96, 97]. Dupilumab when used concomitantly with TCS reduced the use of rescue treatments, including high potency topical corticosteroids, oral corticosteroids, and systemic immunosuppressants (Section B 2.6.1.3, Table 2.22)[43, 95].

In the CAFÉ study, the TCS sparing effect of dupilumab was recorded. The baseline mean weekly dose (mg) of TCS use was 34.81, 26.51 and 31.99, dupilumab Q2W + TCS, dupilumab QW + TCS and placebo + TCS group respectivley. Weekly dose of TCS reduced by 49% in the dupilumab group and by ~20% in the placebo group (p=0.0003) indicating dupilumab has a steroid sparing effect. Clinical opinion provided to us at an advisory board suggested that patients would likely cease the use of TCS altogether or drastically reduce it if they respond to dupilumab.

Dupilumab may reduce the incidence of skin infection

Low rates of skin infections in the individual LIBERTY studies did not reveal a benefit of dupilumab on this outcome. However, a recently published metanalysis of eight LIBERTY studies established a 46% reduction in skin infections compared with placebo ((RR=0.54, 95% CI: 0.42-0.70)[182]. This finding was robust to sensitivity analyses, examining results by different doses, treatment duration and dupilumab monotherapy. While there was no significant association between dupilumab and herpes infections (RR=1.16 95% CI: 0.78-1.74) dupilumab was associated with decreased odds of eczema herpeticum (OR=0.34, 95% CI: 0.14-0.84).

The reason for the decrease in skin infections and eczema herpeticum with dupilumab is unknown, but is likely related to improvement in AD severity, improvement in the skin barrier and reduced itch leading to reduced re-infection and treatment of the aberrant immune response.

The benefit/risk ratio of any novel therapy needs to be considered to understand what it means for patients, clinicians and usual care. Current treatment options for this patient population have serious side effects which limit their usefulness in the long-term management of this lifelong disease. Patients with moderate-to-severe disease that cannot achieve control with safe doses of TCS TCIs become candidates for systemic therapies.

Non-selective immunosuppressants are used off-label in AD. These drugs have well-established toxicity profiles (e.g., myelosuppression and hepatotoxicity for methotrexate, leucopenia for azathioprine) which limits their long-term use. Ciclosporin, a potent, non-selective immunosuppressant is currently approved to treat moderate-to-severe AD, refractory to topical treatment[183]. Its use is limited due to high toxicity with a maximum treatment duration of up to one year. Ciclosporin also interacts with other commonly used medicines, which can potentially affect their metabolism and efficacy. In contrast the side effect profile of dupilumab is comparable to placebo.

Dupilumab side effect profile

Dupilumab was well tolerated. There were no important differences between the safety profiles of patients treated with dupilumab monotherapy or in combination with TCS or with placebo.

The most common adverse reactions were injection site reactions, conjunctivitis, blepharitis, and oral herpes. Conjunctivitis and eye disorders (dry eye, eye pruritus, and blepharitis) were observed more commonly in the dupilumab groups than the placebo group in all safety pools and long-term combination and open-label studies.

Conjunctivitis was not a prespecified adverse event of special interest (AESI) but was included as an AESI after evaluation of the Phase III results and ad-hoc analyses were performed on a grouped MedDRA preferred terms consistent with conjunctivitis: 2.1% (11/517) for placebo, 9.3% (49/529) for dupilumab 300 mg Q2W, and 7.9% (41/518) for dupilumab 300 mg QW. The majority of events were mild to moderate and responded with topical preparations. Of the patients who reported any event of this conjunctivitis category, only one patient in the dupilumab 300 mg QW group discontinued study treatment due to the event.

It is noted in the EPAR that the higher incidence of conjunctivitis and oral herpes with dupilumab treatment in the AD programme was not observed in data from the asthma and nasal polyposis programmes and that moderate-severe AD may be a risk factor[177]. EAMS clinicians have informed us that they are recommending over-the-counter artifical tears as prophyaxis against conjunctivitis.

B 2.12.1 The strengths and limitations of the clinical evidence base for the technology

LIBERTY AD was a large and inclusive RCT programme which evaluated the safety and efficacy of dupilumab in a number of important populations. All studies included moderate-to-severe patients who were inadequately controlled after optimisation on topical therapies. In addition, the CAFÉ study examined patients who were inadequate responders, intolerant, or contraindicated to ciclosporin therapy. The programme included a comprehensive set of measures which were both clinician and patient assessed.

There is consensus among clinicians that the novel therapies for AD should be trialled as monotherapy to help interpret effect size separately from concomitant TCS, hence the trial design of SOLO, however it is anticipated that dupilumab will be used in conjunction with TCS, for which CHRONOS and CAFÉ were designed. The CAFÉ study also demonstrated reduced use of concomitant TCS and rescue medication in the treatment arms, further supplementing the positive clinical score and patient-reported outcome measure improvements with dupilumab therapy. “CAFÉ-like” subpopulations were enrolled into the monotherapy study SOLO and the TCS background study CHRONOS.

The longest RCT data available for the licenced dose (300mg Q2W) come from CHRONOS which was 52 weeks. However, MAINTAIN (R668-AD-1225) was a Phase 3, multicentre, open-label, extension study conducted in Europe, Japan, Asia-Pacific, and North America to assess the longer-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD (see Appendix F and P). The study consisted of a treatment period up to 148-weeks (approximately 3 years), during which patients were treated weekly with dupilumab (200 mg QW SC [per the original protocol] or 300 mg QW SC [after protocol amendment 2]), and a 16-week follow-up period.

This is study is ongoing. At the time of this first-step analysis, 399/1491 (26.8%) patients had completed the study up to the week 52 visit and 60/1491 (4.0%) had completed up to the week 100 visit. Overall, 1415/1491 (94.9%) patients were ongoing in the study and 76/1491 (5.1%) were withdrawn from the study.

An evaluation of efficacy parameters in the subset of patients who had a treatment interruption period of >13 weeks showed no meaningful differences compared to the subset of patients who were dupilumab naïve. This study demonstrated that long-term dupilumab treatment provided substantial and sustained clinical benefits to patients with moderate-to-severe AD who had previously participated in placebo-controlled dupilumab clinical trials. Substantial and sustained clinical benefits were observed in patients regardless of their baseline disease activity and the length of time since their prior dupilumab treatment.

Although this study does not include the licenced dose (Q2W), no meaningful differences have been observed in the response rate of the 300 mg QW regimen over the 300 mg Q2W regimen in completed or ongoing dupilumab trials.

Insufficient data are available to compare dupilumab to the immunosuppressants methotrexate and azathioprine and so no formal comparison could be made with these treatments. Instead we have conducted a MAIC with ciclosporin in order to address the decision problem and full licence population. While the results of this analysis are uncertain due to sample size the findings were largely consistent across the comparisons. EASI scores were not available in the evidence base for ciclosporin but comparison with SCORAD and DLQI could be made. Improvements in absolute SCORAD values were significantly higher for dupilumab but none of the improvements in DLQI were statistically significant.

Conclusion

In summary, the data indicate that dupilumab was well tolerated and had a favourable safety profile in the treatment of patients with moderate-to-severe AD, when used as monotherapy and when used concomitantly with TCS in the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. This includes subgroup of patients for whom treatment with systemic treatments (such as ciclosporin) would be medically inappropriate. Long-term treatment in CHRONOS and MAINTAIN did not reveal additional safety concerns associated with dupilumab, and indeed that substantial and sustained clinical benefits can be achieved with continuous treatment of dupilumab.

B 2.12.2 External validity of the trial evidence

The clinical evidence for dupilumab reflects UK practice and the clinical benefit in the most difficult to treat patients (moderate-to-severe patients previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable). The patient population included in the dupilumab studies comprised adults with AD with moderate-to-severe AD lesions affecting a large portion of their BSA. Their disease could not be adequately controlled with topical prescription medications, or otherwise topical mediations were not advised due to important side effects or safety risks. These patients experienced high levels disease burden, including pruritus. This population included patients who had been, or would typically be, candidates for systemic treatment in UK clinical practice. Thus previous treatment history is sufficient to define the cohort of patients eligible for dupilumab.

The trial evidence base includes the monotherapy studies SOLO 1 and 2 and the studies in which topical medications (TCS with or without TCI, as applicable) are used concomitantly; CHRONOS and CAFÉ. Furthermore CAFÉ reflects the post- or contraindicated immunosuppressant position. All the studies allowed for rescue therapy at the discretion of the investigator which mirrors real world clinical practice.

According to UK clinicians we spoke with dupilumab is mostly likely to be used after systemic treatment and in combination with concomitant TCS as required. This group of patients is described by the CAFÉ+CHRONOS CAFÉ-like patients. To reflect those patients who are suitable for dupilumab monotherapy (i.e not suitable for TCS) and require systemic treatment, the SOLO-CAFÉ-LIKE cohort has also been analysed. In both these cohorts the improvement in the key signs and symptoms important to patients in their day-to-day lives were demonstrated in the studies by improvements in signs (IGA 0 (clear) or 1 (mild) plus ≥2 points reduction from baseline, $p<0.0001$), EASI-75 (and EASI-50), $p<0.0001$), itching (peak pruritus, $p<0.0001$), quality of life (DLQI, $p<0.0001$ and EQ-5D, $p=0.0002$) and anxiety and depression (total HADS, $p<0.002$).

Clinical consensus and prior NICE guidelines suggest that a measure of response which captures clinical signs alongside quality of life improvement is required to assess effiacy. Change in EASI score was identified by the clinicians we spoke to as the most robust way to measure improvement in the signs of AD. The regulatory defined end point of EASI-75 used in the studies is not relevant to clincal practice (and HTA) and the clinical advisory board suggested that EASI50 is a more realistic efficacy outceome to measure the signs of AD. However this does not include broader symptoms or QoL impact. A DLQI improvement of 4 or more points to capture significant quality of life benefit for patients with AD is regarded as an appropriate measure by clinicians and so the combination of EASI50 *and* DLQI 4 or more points is used as the efficacy response criterion in the modelling. Results for this group of patients remained statistically significant and consistent with the result of the full trial population, justifying it use in the economic case. This is also consistent with the rule stated in the SmPC which does not explicitly state the outcome measures to be used but allows provision for clinical opinion.

Therefore, since a clinically relevant reduction in DLQI (≥4 points) to reflect QoL benefit and therefore EASI-50 AND DLQI ≥4 is considered in this submission.

Recognition of the clinical value of dupilumab for treatment of AD in the UK

Dupilumab is the first new treatment for AD to be licenced for use in the UK in the last 15 years and the first biologic treatment for the disease. It represents an effective option for those patients who have failed all other lines of treatment and yet still experience the burden of severe AD.

The clinical evidence presented in this submission demonstrates the safety and efficacy of dupilumab in patients with moderate-to-severe AD with or without TCS, including patients in whom systemic immunosuppressants are not medically advisable (intolerance/contraindications or inadequate response to immunosuppressants).

Dupilumab is expected to be used for patients with moderate-to-severe AD with concomitant TCS as required and for whom current systemic therapies have been inadequately effective, not tolerated or contraindicated. Hence dupilumab will provide an additional step to the current treatment pathway in the UK. This treatment position is based upon UK clinical opinion from a clinical advisory board and is in line with use within the EAMS programme. It correlates with the IEC's recent comprehensive treatment algorithm[12].

B 2.12.3 Life expectancy of people with the disease or condition in England

There is very little evidence in the literature which examining the impact of AD on mortality, either directly or because of suicide.

To our knowledge the only long-term study that has been published examining the direct influence of AD on mortality employed used data taken from the Danish nationwide registers. Between 1996 and 2002 all Danes aged 18 years or older with a first-time hospitalisation due to AD or psoriasis and AD-matched healthy control subjects were observed. This study showed that 10-year mortality was increased after hospitalisation for AD compared with the general population, but significantly reduced compared with psoriasis. (HR 0.75; 95% CI 0.57-1.00), but increased when compared with the general population (HR 1.71; 95% CI 1.20-2.44)[184]. However, the authors note that they could not establish causation due to the observational nature of the study and that differences in 10-year survival between patients hospitalised for AD and psoriasis may, at least in part, be a result of modifiable risk factors including obesity, smoking, and physical inactivity.

The association between AD and suicide and suicidal ideation has been reported in several studies[77-79](see Section B 1.3.6.2.2).

A direct link between AD and increased mortality has not been established and there is insufficient evidence to directly link suicidal ideation with completed suicides. There is published evidence to suggest an association but insufficient data to attribute a direct causal effect on life expectancy of patients with AD. We have taken a conservative approach not implemented a mortality increase in the model for patients with dupilumab.

B 2.12.4 Regulatory endpoints versus real world endpoints

In the LIBERTY AD RCT programme—designed for regulatory purposes—co-primary endpoints included high-threshold dichotomous endpoints EASI-75 or IGA 0 or 1 (clear or almost clear) and patients were conservatively deemed 'non-responders' because they received rescue treatments or because their data were missing at the assessment point. This was irrespective of their EASI scores this time or at the time of rescue treatment. This approach—where rescued patients and patients with missing data were automatically counted as "non-responders", whether or not there was evidence of loss of response at the time of rescue or before the data was missing — is conservative and consequently, these analyses underestimate maintenance of response.

Responder analyses using dichotomous endpoints like IGA 0 or 1 or EASI-75 suffer from an inherent loss of information rooted in the process of dichotomization. For example, a patient with 74% reduction in the EASI score would be counted as EASI-75 non-responder, despite having achieved highly meaningful clinical improvement. The dichotomous analysis places high responders like this in the same category with patients who did not improve or even

worsened during the study. Treatment effect remains uncharacterised in patients who find themselves below the response threshold at the specific analysis time point.

In a disease like AD which has a chronic relapsing/remitting (wax/wane) nature, dichotomous endpoints can be particularly problematic because the true treatment effect is further compounded by the fact that responder rates are based on a single post-baseline measurement, disregarding treatment responses at prior or subsequent time points.

In routine practise it is likely that patients commonly fluctuate above and below these regulator-defined responder thresholds over time. In this patient population, "responder" and "non-responder" categories are not necessarily definitive and irreversible. Evidence that this approach taken in LIBERTY AD studies is conservative can be seen in the SOLO-CONTINUE study and CHRONOS study.

This is an important aspect that sets AD apart from other less fluctuating skin diseases, and requires a comprehensive approach to adequately characterise maintenance of response to treatment. Continuous endpoints, in contrast, do not suffer from these limitations. Therefore, while responder rates like IGA 0 or 1 and EASI-75 could be useful from a regulatory perspective, particularly for discerning differences among treatment groups, and for understanding responsiveness at a patient-level, they tend to underestimate maintenance of response, and used alone they are misleading for characterising the ability of the study drug to sustain its effect over time.

This continuum of benefit for patients treated with dupilumab has been recognised by the regulators and is reflected in the dupilumab SmPC[11]. The SmPC states that some patients with partial response at 16 weeks may subsequently improve with continued treatment beyond 16 weeks as some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks'.

B 2.13 Number of eligible patients for dupilumab

The eligible population for treatment with dupilumab is 17 per 100,000 adults with moderate-to-severe AD (Table 2.60).

Table 2.60. Calculation of eligible population per 100,000 for dupilumab.

	2018	Source
England Adult Population	43,991,000	To estimate population 18yrs and older the 15-19yr age band was divided by 40% to give assuming linear distribution of population across each age year. Projections were taken from the ONS data set for each future year[185]
Adult prevalence of AD	2.5%	Barbarot 2017[29]
Diagnosed and treated	69.0%	DRG report 2015[30]
Diagnosed population, n	758,845	Calculation
Proportion of moderate AD	4.9%	Adelphi DSP Data on file[31]
Proportion of severe AD	2.1%	Adelphi DSP Data on file[31]
Moderate/Severe Population, n	53,119	Calculation
Eligible for IM (label	27.0%	Adelphi DSP Data on file[31] (Assumed increase by 2%

	2018	Source
population)		each year)
IM Treated Mod/Sev AD patients	14342	Calculation
Uncontrolled on IMs	53%	Wei 2016[186]
Uncontrolled eligible population	7659	Calculation

AD, atopic dermatits; DRG, Decision Resources Group; DSP, Disease Specific Programme; EADV, European Acadmeny of Dermatology and Venereology; IM, immunosuppresants; ONS, Office for National Statistics

The estimated number of patients likely to be treated with dupilumab in years 1 to 5 are tabulated below (Table 2.61)

Table 2.61 Uptake and market share

	2018	2019	2020	2021	2022
Eligible Patient Population	7659	8277	8900	9527	10158
Estimated uptake	5.0%	13.0%	19.0%	28.0%	38.0%
Prevalent (existing) dupilumab patients	0	383	1076	1691	2668
Incident (new) dupilumab patients	383	693	615	977	1193
Include EAMS patients in Year 1	244	244	244	244	244
Total Patients	**627**	**1320**	**1935**	**2912**	**4104**

B 2.14 End of life criteria

Dupilumab does not meet the criteria for an end of life medicine.

B 3 Cost effectiveness

A cost-effectiveness analysis was undertaken to evaluate dupilumab compared with best supportive care (BSC) from the perspective of the NHS in England in the treatment of the expected UK atopic dermatitis (AD). Each population is assessed with topical corticosteroids (TCS, the more likely UK situation) and without TCS (monotherapy).

Populations:

- **Base case**: patients with moderate-to-severe AD who were contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. This is a subgroup of the licenced population.
- In **Scenario Analyses** the full licenced population - patients eligible for systemic therapy - was compared with i) BSC, based on LIBERTY trial data ii) ciclosporin, based on a matched indirect treatment comparison (see Section B 2.9).

- A cost utility model is presented consisting of a one-year decision tree followed by a 3-state Markov model (health states are annual cycles).
- Model inputs: **Clinical efficacy** data for the base case are from the LIBERTY trial programme. **Quality of Life (QoL)** data are based on directly observed LIBERTY trial data. **Resource utilisation** data and **units costs** are based on UK-specific real world studies and published UK costs.
- Assessment of benefit
  - A proxy for the **holistic assessment of treatment benefit** in AD used in the model is the composite measure EASI-50 and DLQI ≥4, capturing both the signs of AD and QoL impact. [Section B 2.7.1.1] Assessment of benefit occurs at wk 16 or wk 24.
  - The extensive **health related quality of life** data (EQ5D) from the trial are adjusted in a mixed regression model for baseline characteristics. Assumptions are tested in the sensitivity analysis.
  - Resource use from UK-specific observational studies, UK KOL input and market research provide robust estimates of resource use in absence of published data. A limitation is the true cost of BSC in the base case population.
- This submission used the **DH approved Patient Access Scheme**. Sensitivity analyses were performed across various parameters.

Results

Dupilumab vs. BSC in the **base case population: estimate ICER range £28,874/QALY to £24,703/QALY** (with and without TCS respectively). The DSA indicates the ICER estimates are stable against a range of assumptions. Baseline utility score and maintenance of persistence of QoL are the biggest drivers of the ICERs. The probabilistic sensitivity analysis (PSA) indicates dupilumab is cost-effective 70% and 0% of the time (dupilumab vs BSC, with TCS) and 100% and 0% of the time (dupilumab vs VSC, monotherapy) at £30,000 and £20,000 willingness to pay thresholds respectively.

Scenario Analysis: estimated ICER range for the full licence population is £25,188/QALY (vs BSC with TCS) to £28,092/QALY (vs ciclosporin without TCS).

The **incremental QALY gain** in the base case population is **1.4 to 1.8** (>1.0 in all non-structural sensitivity analyses) with a treatment that doesn't affect mortality is a remarkable gain.

While these ICERs are above £20,000 dupilumab is an innovative medicine, which meets the large unmet need, with ICERs that are stable under a range of assumptions and provides significant societal benefit.

B 3.1 Published cost-effectiveness studies

A systematic literature (SLR) review was conducted to identify economic evaluations of dupilumab or other AD therapies. A full description of the SLR is provided in Appendix G (including search strategy, included and excluded records with reasons and data extraction tables). Key features of the review are summarised in Table 3.1.

Table 3.1.Summary of the eligibility criteria for the systematic review of economic evaluations of atopic dermatitis treatment

	Inclusion Criteria	Exclusion Criteria
Population	Studies that report on adults (aged 18 and over) AD of any severity including eczema and atopic eczema. Studies reporting mixed populations of adults and children will only be eligible if they report data separately for the adults.	Studies of participants aged under 18. Studies of patients described as having hand eczema [protocol amendment].
Intervention	Any intervention	
Comparators	Any comparator	
Outcomes	Total costs; Summary health outcomes (Quality-adjusted Life Years (QALYs)); Incremental cost-effectiveness ratios (ICER).	
Study design	Economic evaluations Published economic models Health technology assessment (HTA) reports investigating the cost-effectiveness of treatments. Studies published as abstracts or conference presentations with sufficiently disaggregated data. SLRs for reference checking for eligible studies only.	Case reports; Case studies. News Comments Editorials Letters
Limits	English language studies. Conference abstracts published from 2015 onwards.	Non- English language studies. Conference papers published before 2015.

AD, atopic dermatitis; HTA, health technology assessment; ICER, incremental cost effectivenss ratio; QALY, quality-adjusted life year; SLR, systematic literature review

B 3.1.1 Searches

Nine bibliographic databases and eight conferences were searched between 22nd and 23rd May 2017 to identify relevant studies. Two reviewers independently assessed the eligibility of records based on title and abstract and then the full text. One reviewer extracted data from each eligible study, with a second reviewer checking the extracted data.

B 3.1.2 Results

The search identified 3093 records. Following deduplication, 2418 records were assessed for relevance. Screening by abstract removed a further 2383 records. Thirty-five full papers

were retrieved and a further 21 studies excluded at that point (see Figure 3.1 PRISMA diagram for review process). Fourteen studies were included in the final review.

One study reported dupilumab, 13 studies reported other interventions: pimecrolimus (5 studies); tacrolimus (7 studies), emollient cream (4 studies), corticosteroids (7 studies), phototherapy (1 study) and barrier strengthening cream (2 studies). The 13 non-dupilumab studies are summarised in Appendix G. One study examinign the cost effectiveness of ciclosporing vs. UV therapy was also identified[187] This is reoprted is also reported in Appendix G.

B 3.1.2.1 Published dupilumab cost-effectiveness study

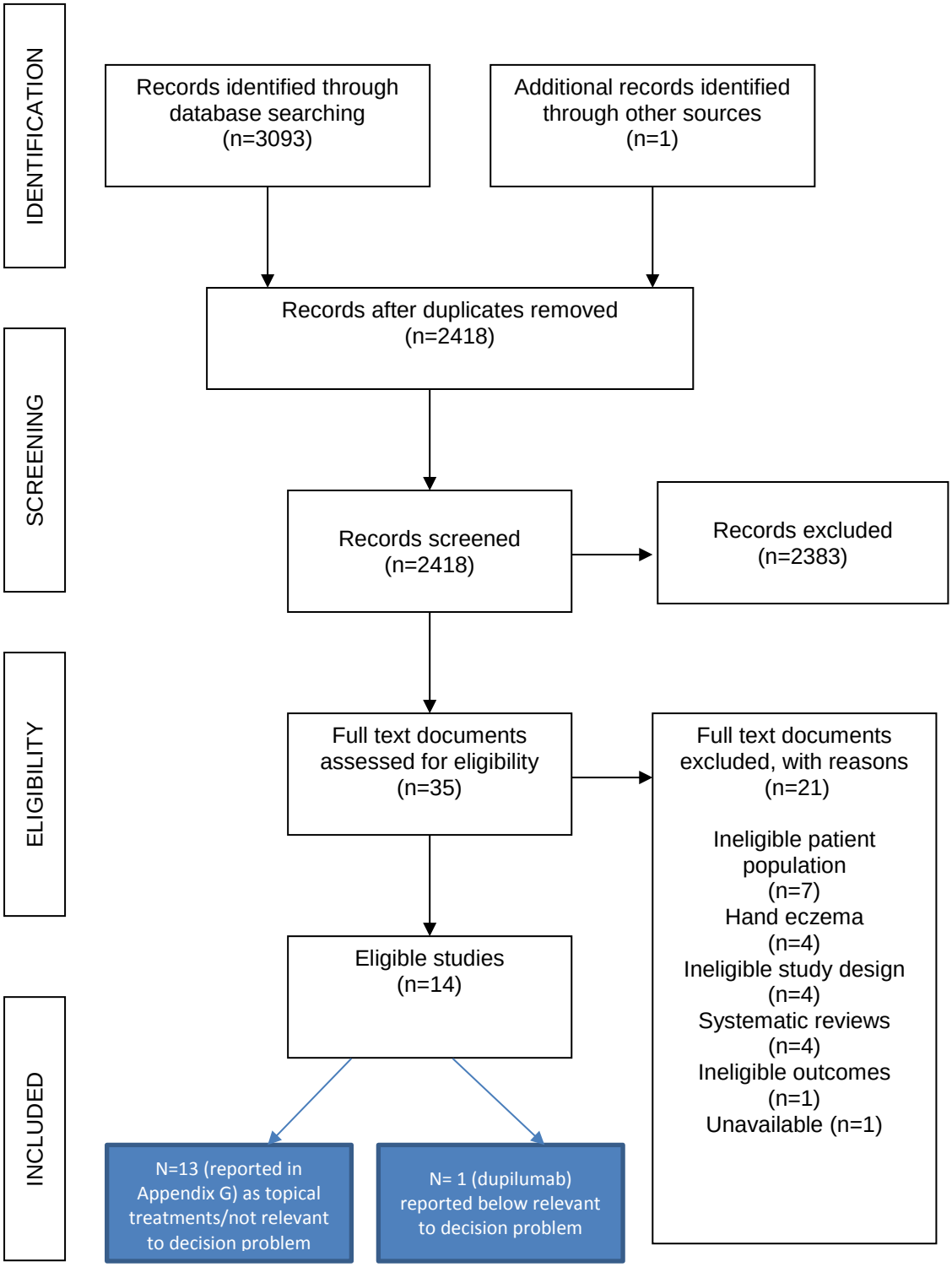
The dupilumab cost-effectiveness study was published by the Institute for Clinical and Economic Review (ICER) in June 2017[188] and subsequently published as a peer reviewed manuscript [189]. A summary of the analysis is provided in Table 3.2.

Table 3.2. Summary of the published cost-effectiveness study for dupilumab.

Study	ICER 2017[188], Kurznik, 2017[189]
Year	2017
Summary of model	Cost utility analysis conducted to estimate the cost-effectiveness of dupilumab for moderate-to-severe AD compared to usual care (emollients) in the US over a lifetime horizon. A Markov model was developed in Microsoft Excel with health states based on treatment response.
Patient population average age in years	38
QALYs (intervention, comparator)	Total lifetime per patient QALYs: Dupilumab:16.28. Emollients: 14.37
Costs (currency) (intervention, comparator)	Total lifetime per patient cost: Dupilumab: $509,593. Emollients: $271,461
ICER (per QALY gained)	The incremental cost per QALY for dupilumab compared to emollients was $124,541 in the base case. It was reduced to $101,830 if net price instead than list price for dupilumab was used.

AD, atopic dermatidis; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 3.1 Study selection process for the SLR of UK economic evaluation data in adults with AD



The models identified in the SLR were, with the exception of the dupilumab study, for topical treatments that examined short-term or episodic therapy, rather than long-term treatment. They were not used to inform the development of the dupilumab economic model as they i) did not assess chronic treatment well, ii) did not reflect the same treatment pathway/place in the treatment pathway as required for this analysis iii) had a high reliance on assumptions due to evidence gaps.

We were aware however, of the economic models used for the assessment of biologic psoriasis treatments and this informed the development of the *de novo* model presented here. The most cited psoriasis model is the York model[190] used in a range of technology assessments[191-193]. The York model is a simple 12-week decision tree reflecting the duration of the psoriasis trials. Thereafter, patients are categorised as responders or non-responders, with responders continuing on active therapy while non-responders move to BSC. Long-term treatment is handled via a Markov model with treatment being a proxy for a health state (there is an 'on active treatment' state and an 'on BSC' state). Patients remain in the health state in which they entered the Markov model, (ie on active treatment or on BSC).

Both psoriasis and AD are chronic diseases in which assessment for response to biologic therapy is expected 3 to 6 months following treatment initiation. These consistent themes allowed the York psoriasis model to be adapted for the economic model for this appraisal. The ICER assessment for dupilumab is based on this same *de novo* Sanofi Genzyme model submitted here.

B 3.2 Economic analysis

The economic analysis presented here is a cost-effectiveness analysis comparing dupilumab with BSC for the treatment of moderate-to-severe AD in patients who were contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. This is the base case population for this economic analysis in line with anticipated position for dupilumab in UK clinical practice based on clinician feedback. In real world clinical practice, it is the patients' prior history regarding systemic immunosuppressants that is likely to determine eligibility for treatment with dupilumab, specifically the base case population of patients who were contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.

These patients have the highest unmet need for an effective treatment, as the only option for these patients is BSC. The base case is a subgroup of the full licenced population, the full population is presented in scenario analysis.

The perspective adopted is that of NHS England. Personal social service costs are not included as they are not expected to be a sigificant cost element in this disease area. Discounting is applied at 3.5% for both costs and benefits.

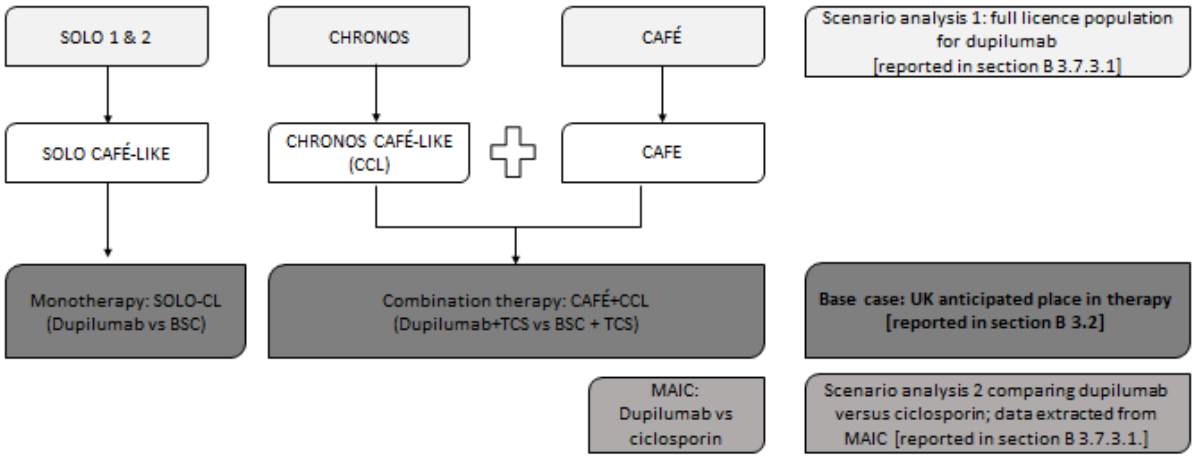
In the following sections we describe the model structure and how the economic model links trial data to real world clinical practice. The model inputs presented are: baseline patient characteristics, clinical efficacy data including adverse events; valuation of the clinical data in utilities; resource utilisation rates and unit costs, a summary of the critical inputs and

assumptions required for the model and discussion of what is tested in the sensitivity and scenario analyses.

B 3.2.1 Linking the trial data to real world clinical practice in the model

The evidence for the base case is derived from two pooled analyses: CAFÉ pooled with the CHRONOS CAFÉ-like (CCL) population (referred to as CAFÉ+CCL) and SOLO 1 pooled with SOLO 2 (SOLO CAFÉ-like, SOLO-CL); see Figure 3.2.

Figure 3.2. Schematic showing evidence supporting the economic analyses



Best supportive care (BSC) is broadly defined as a combination of emollients, low-to-mid potency topical corticosteroids (TCS) and rescue therapy (such as higher potency topical or oral corticosteroids or topical calcineurin inhibitors (TCIs)).

These pooled analyses, (CAFÉ-CCL and SOLO CAFÉ-LIKE) include patients that meet the base case population definition: patients who were contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. CAFÉ+CCL patients also received concomitant TCS as required reflecting the UK treatment approach for patients with moderate-to-severe disease. Although less common in the UK, there may be patients who cannot take TCS and would be best described by SOLO-CL monotherapy data.

Scenario analyses have been performed based on different patient populations treated with dupilumab to evaluate the full licence:

- Scenario 1: Dupilumab with TCS compared with BSC with TCS in the population of patients eligible for systemic therapy. This scenario analysis uses patient data from the CHRONOS-full analysis set (FAS), CAFÉ FAS and SOLO pooled FAS analyses, in line with the full licence population.
- Scenario 2: Dupilumab monotherapy and dupilumab with TCS compared with ciclosporin in the population of patients eligible for systemic therapy. This scenario is based on data from the matched adjusted indirect comparison (MAIC) described in Section B 2.9. This scenario is provided for completeness against the Final Appraisal Scope as it is anticipated that dupilumab would be used routinely for the base case patient population.

B 3.2.2 Response definitions used in the model

The primary endpoint in all the pivotal studies was efficacy, measured as a percentage reduction in EASI score at 16 weeks. We discuss in the clinical section B 2.7, the different requirements of regulators and HTA agencies with regard to trial endpoints. In line with the holistic approach to AD care advocated in the NICE Child Atopic Eczema Guidelines[81] we use a composite measure of response that incorporates improvement in signs (EASI 50) and QoL (DLQI). Therefore, in the base case we use EASI-50 plus a DLQI ≥4 as the definition of response (See Section B 1.3.4 for discussion). This approach is endorsed by UK clinicians.

Analysis of the EASI-50 and DLQI response criteria is done based on the 'all observed' dataset, which aligns with clinical practice. In the clinical trials, the primary analysis 'censored' patients at the point they received any rescue treatment and classified them as a non-responder. In the real world patients receive rescue treatments from time to time and therefore we use the 'all observed' data in the model.

In line with the SmPC, while consider should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks and 24 weeks is a more appropriate assessment point [11] according to UK clinicians. This is tested in sensitivity analysis (See B 3.7.2).

B 3.2.3 Model overview

A *de novo* model was developed to estimate the long-term cost-effectiveness of dupilumab compared to BSC for the base case population defined above. The model estimates costs and outcomes and is a combined decision tree and Markov model, in Microsoft Excel®.

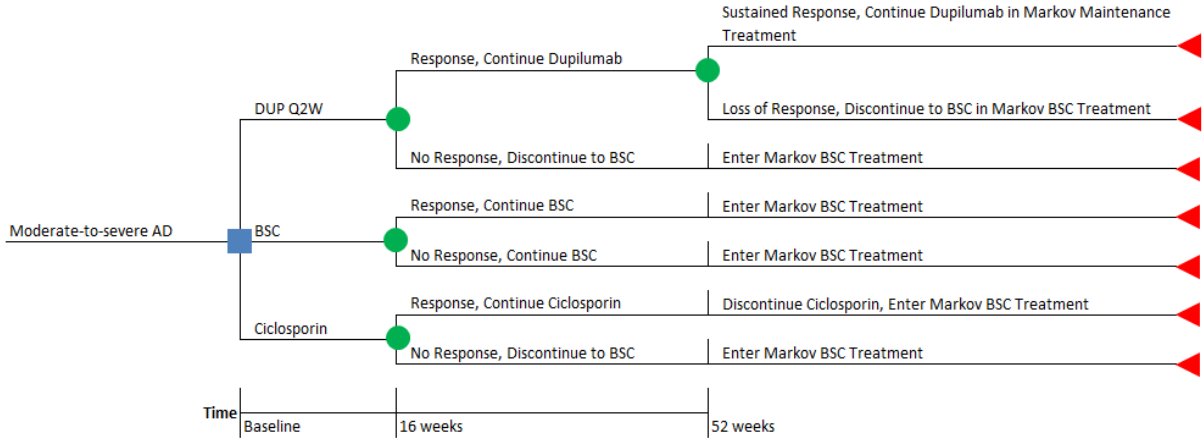
The model considers an NHS England perspective, in which direct medical costs incurred by the NHS for AD treatment are compared, health benefits are compared and incremental cost-effectiveness ratios (ICERs) are estimated. It also includes an option to include productivity costs to give a societal perspective. The analysis is conducted over a lifetime time horizon in line with the NICE reference case.

The model structure is designed to reflect UK clinical practice for AD. It consists of a one-year decision tree which reflects short-term treatment decisions and initial response to treatment. This is followed by a three-state Markov model, which reflects the long-term course of AD, using treatment states (as opposed to health states). The Markov cycles are one year long, continuing in the model for a lifetime (100 years, lifetime time horizon). As shown in the decision tree below (Figure 3.3), patients with moderate-to-severe AD enter the model at which point they can either be treated with dupilumab or BSC or an immunosuppressant (ciclosporin). At week 16 a clinical assessment is undertaken to determine response to treatment (See Section B 2.7.1.1 for definition and justification of response used in the model).

Patients responding to dupilumab at week 16 continue on the same treatment for the remainder of the year. Non-responding patients at week 16 move to the BSC arm of the decision tree accruing the costs and utilities associated with the 'Non Response, Discontinue to BSC' branch for the remainder of the year. BSC patients remain on BSC regardless of response status.

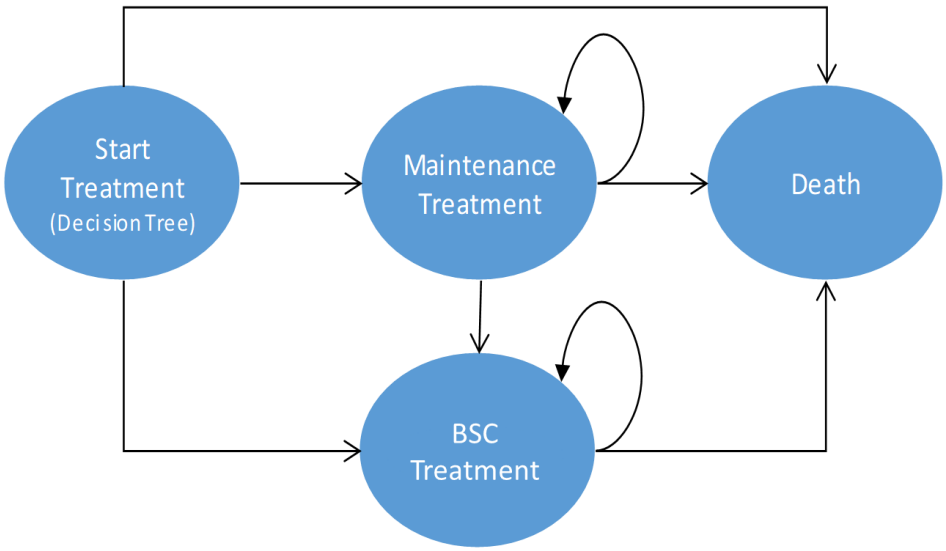
Patients are assessed again at 52 weeks. If response with dupilumab is maintained patients enter the Markov 'Maintenance Treatment' state, if response is lost patients move to the 'BSC' Markov Treatment state. All patients who started the decision tree on BSC stay on BSC those who switched to BSC due to lack of response at the 16-week assessment point enter the Markov in the BSC Treatment State. For all branches (not shown for simplicity), mortality is integrated into the decision tree payoffs with an assumption that death occurs at 6 months. A limitation of this model is that patients responding at 52 weeks that did not respond at 16 weeks are not captured in the Maintenance Treatment state. Although in the CHRONOS 52-week study all patients continued on treatment regardless of clinical assessment at 16 weeks. A further limitation is that the trial outcome point is at 16 weeks, while in clinical practice 24 weeks may be more appropriate for some patients we have learnt from EAMS clinicians. They have shared that patients with extensive BSA involvement or with head and face AD take longer to respond.

Figure 3.3. Short-term decision tree



Within the Markov portion of the model, at the end of each year-long Markov cycle, patients may remain in the Maintenance treatment state, discontinue to BSC treatment, or die. Discontinuation to BSC may be due to lack of long-term efficacy, adverse events, patient preference, or physician preference. Patients in the BSC treatment health state may remain on BSC or die. No patient may transition from BSC to the Maintenance treatment state. A half-cycle correction for efficacy measured at Week 16 is applied at Week 8 in the decision tree.

Figure 3.4. Long-term Markov model



In the decision tree part of the model each 'branch' collects specific utilities and costs based on the assumptions associated with that branch. For example, the branch 'Response, Continue dupilumab' accrues costs associated with: dupilumab acquisition, visits to GPs and dermatologists, background treatments (emollients and TCS). Costs associated with adverse events are also accrued. Adverse events do not accrue disutilities in this model for two reasons, firstly AEs were largely mild and transient and secondly utilities were measured every two weeks for the 16 week portions of the CHRONOS, CAFÉ and SOLO1 and 2 trials. It is assumed that utility collection with this frequency means the negative impact of AEs will be largely captured, adding in additional disutility for the AEs recorded in the trials risks double counting.

In the Markov model, each treatment state captures the costs and utilities associated with that state. The Maintenance Treatment State captures patients on dupilumab treatment, both responders and non-responders. The dupilumab responders accrue the costs and utilities asscoaited with dupilumab treatment and response. The dupilumab non-responders are assumed to stop active treatment and accrue the costs and utilities associated with BSC. In the BSC Treatment State the cost and utilities associated with BSC treatment. BSC costs reflect whether the patient is a BSC responder or non-responder. The aggregate BSC utility weight is applied. These utility data are populated directly from the trials (with adjustments described later) and therefore represent the true utilities experienced by these patients.

See Section B 3.2.2 for a discussion of how response is implemented in the economic model based on the trial data and Section B 3.3.3 for an explanation of the cacluation and implementation of utility weights in the model.

Costs and QALY benefits accrued after the first year have the annual discounting rates of 3.5% applied[194]. The model estimates total lifetime costs for each treatment arm, total lifetime QALY gains for each treatment arm. The results for BSC are compared with those for dupilumab and an ICER is reported.

B 3.2.4 Intervention technology and comparators

The base case presented here is for a subgroup of the licenced population. The comparator technology for this population is BSC. In routine UK clinical practice, BSC for the base case population is uncertain and variable. Clinicians work hard to manage these AD patients however, there is not an established treatment at this point in the treatment pathway. Baseline data from the Early Access to Medicines Scheme (EAMS) patient population indicates that 96.4% of patients had prior exposure to immunosuppressants and 75.2% were exposed to three or more. (See Section B 2.11.1). This is a heavily pre-treated population. Unfortunately, the data were not available in time for us to incorporate the broad range of treatments reported in EAMS, in the economic model. Instead BSC in the economic model is based on the treatment regimens prescribed for the placebo (BSC) arm in the dupilumab trials, in this case BSC is a combination of emollients, low-to-mid potency TCS and rescue therapy (such as higher potency topical or oral corticosteroids or topical calcineurin inhibitors [TCIs]).

In scenario analysis the full licence population is modelled comparing dupilumab against both BSC and the immunosuppressant ciclosporin. For the purposes of modelling ciclosporin treatment is assumed to continue for 12 months, the maximum duration of treatment recommended in guidelines. However it should be noted that the average length of a course of treatment according to a recent treatment pattern survey by Taylor estimates that dermatologists try to minimise exposure to ciclosporin and the average length of a course of treatment is limited to 5.8 months although repeated courses may be prescribed[116]. Given that ciclosporin is the only systemic immunosuppressant licenced for AD it is used here as a proxy for all systemic immunosuppressants.

B 3.2.5 Clinical parameters

B 3.2.5.1 Model baseline patients characteristics

The baseline characteristics of the patients in the LIBERTY AD trial programme that reflect the UK base case for dupilumab are presented in full in Table 2.34. The key demographic data used in the model are presented in Table 3.3. Demographics for the studies are all similar but the CHRONOS CAFÉ-like and SOLO-CAFÉ-like populations have slightly higher severity scores for signs and symptoms and lower quality of life as recorded by DLQI and EQ-5D.

Table 3.3. Patient characteristics at baseline for the base case, SOLO CAFÉ-like and CAFÉ+CHRONOS CAFÉ-like populations.

	CAFÉ + CHRONOS CAFÉ-like	SOLO CAFÉ- like
	N=462	N=288
Mean age – years (SD)	38.1 (12.9)	38.1 (13.0)
Gender (male) n (%)	277 (60.0%)	186 (64.6%)
Weight (kg), mean (SD)	74.8 (17.1)	75.0 (17.0)
EASI score, mean (SD)	34.2 (11.5)	36.1 (14.5)
Weekly average of peak daily Pruritus NRS, mean (SD)	6.8 (2.1)	7.6 (1.6)
EQ-5D utility, mean (SD)	0.663 (0.290)	0.547 (0.357)

EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; NRS, numerical rating scale; SD, standard deviation

In the real world previous treatment history (encompassing inadequately effective, not tolerated or contraindicated therapies i.e. medically inadvisable) coupled with physician opinion, serves as a holistic assessment for eligibility for treatment with dupilumab.

B 3.2.5.2 Efficacy response model inputs

The efficacy response criteria define which patients continue dupilumab treatment. In the base case, model response is based on patients achieving EASI-50 and DLQI ≥4 from the CHRONOS-CAFÉ like and SOLO-CAFÉ-like populations. All of whom have with prior history of ciclosporin treatment failure or contraindication. These are the likely dupilumab treated population in the UK.

It is noteworthy that the dupilumab clinical trial data suggests that many patients exhibit significant response earlier than week 8 and this is tested in sensitivity analysis at week 4 (See Section B 3.5.3). Sensitivity analysis is provided for other response criteria including the primary endpoint of EASI-75. No intermediate outcomes were linked to final outcomes, this is not relevant in this therapy area as the breadth of final outcomes can be directly measured.

Table 3.4. Response data used in the model to support UK base case (all observed)

			CAFÉ+CHRONOS-CAFÉ-LIKE		SOLO-CAFÉ LIKE	
Time point	**Criteria**	**Analysis method**	**DUP Q2W %**	**BSC %**	**DUP Q2W %**	**BSC %**
Base case						
Week 16	**EASI 50+DLQI≥4**	**All observed**	**73.1**	**27.8**	**58.7**	**23.9**
Week 52	**EASI 50+ DLQI≥4**	**All observed**	**68.6**	**21.3**	**55.1**	**18.3**
Sensitivity analysis						
Week 16	EASI 50+ DLQI≥4	Primary	68.5	20.7	51.9	11.4
Week 52	EASI 50+ DLQI≥4	Primary	64.3	15.9	48.8	8.7
Week 16	EASI 50	All observed	88.5	48.5	67.3	34.1
Week 52	EASI 50	All observed	83.6	39.4	63.6	27.7
Week 16	EASI 50	Primary	83.1	37.9	60.6	19.3
Week 52	EASI 50	Primary	78.5	30.8	57.2	15.7
Week 16	EASI 75	All observed	66.9	30.2	45.2	17.0
Week 52	EASI 75	All observed	54.9	21.3	37.1	12.0
Week 16	EASI 75	Primary	63.8	25.4	40.4	11.4
Week 52	EASI 75	Primary	52.4	18.0	33.1	8.0

BSC, best supportive care; DLQI, Dermatology Quality of Life Index; DLQI>4, DLQI score at least 4 point change from baseline; DUP Q2W, dupilumab 300mg every 2 weeks; EASI, Eczema Area and Severity Index; EASI-50, EASI, ≥50% response; IGA , Investigator Global Assessment; N/A , not applicable; Source: Sanofi, 2017[195]

B 3.2.5.3 Sustained response

It is critical to model the sustained efficacy of the dupilumab treatment effect to understand the long-term relative health benefit to BSC. In the CHRONOS trial, response at 52 weeks

was related to response at 16 weeks giving a probability of response at 52 weeks based on response rate at 16 weeks. This conditional response rate was applied to the other trials.

Table 3.5 summarises sustained response at 52 weeks modelled on the 16 week response data, with uncertainty values sampled via a beta distribution in the probabilistic sensitivity analysis also reported.

Table 3.5. Conditional probability of response at 52 weeks on 16-week response in CHRONOS (all observed data).

Efficacy Response	52-week Conditional Response Probability	SE
DUP Q2W		
EASI-50 AND DLQI ≥4	0.939	0.028
EASI-50	0.945	0.025
EASI-75	0.821	0.053
BSC		
EASI-50 AND DLQI ≥4	0.767	0.048
EASI-50	0.813	0.035
EASI-75	0.706	0.064

BSC, best supportive care; DLQI, Dermatology Quality of Life Index; DLQI≥4, DLQI at least 4 points change from baseline; DUP Q2W, dupilumab 300 every 2 weeks; EASI, Eczema Area Severity Index; EASI-50; EASI score at least 50% response; EASI-75; EASI score at least 75% response SE, standard error

The conditional response in the studies is discussed in Section B 2.7.1

B 3.2.5.4 Annual discontinuation rate

The model also includes an annual probability of discontinuation input that represents the annual rate at which patients discontinue dupilumab each year due to lack of long-term efficacy, adverse event, patient preference, or physician preference. The annual probability of discontinuation is applied to patients in the Maintenance Treatment health state starting at the second year of the model as first year data are based on sustained response data. Patients who discontinue dupilumab enter the BSC health state. The probability of discontinuation for SOLO trials is set to the number of patients who discontinued from the SOLO CONTINUE study[196]. In the case of CAFÉ or CHRONOS trials, the probability of discontinuation is set to the number of non-completers in the 52-week treatment period among the responders at week 16 estimated from CHRONOS by the specific response selected (EASI-50 AND DLQI ≥4) this is tested in the sensitivity analysis using EASI-50 or EASI-75) (Table 3.6).

Table 3.6. Annual probability of discontinuation.

Trial response	Annual Probability of discontinuation	alpha	beta
SOLO (all levels of response)	0.063	24	357
CHRONOS			
EASI 50 AND DLQI ≥4	0.037	24	357
EASI 50	0.055	5	86

Trial response	Annual Probability of discontinuation	alpha	beta
EASI 75	0.051	4	74

DLQI, Dermatology Quality of Life Index; EASI, Eczema Area Severity Index, Note: The CAFÉ trial utilises CHRONOS discontinuation by response data.

B 3.2.5.5 Adverse events

The adverse events considered in the model are based on those reported in the dupilumab clinical trials. Data are trial specific and the incidence of these events for the CAFÉ trial is shown in Table 3.7. The model assumes that injection site reaction is a one-time event, with the costs occurring in the first cycle for dupilumab. No injection site reaction has been accounted for in the BSC arm. The rates of allergic conjunctivitis, infectious conjunctivitis and oral herpes are per cycle rates. Adverse event rates for all trials are provided in Section B 2.10, and within the EPAR (see Appendix C).

The proportion of patients with events (see Section B 2.10) is not used as some patients may have more than one event which is not captured in the proportion metric. The actual number of events should be reflected in the costing. Hence for the purposes of the modelling the adverse event rates are calculated based on the number of events and adjusted per 100 patient years in order to derive a rate per person per year. The number of key adverse events per 100-patient years is presented in Table 3.7 below.

Table 3.7. Adverse event rates (number of events per 100 patient years) from the CHRONOS, CAFÉ and pooled SOLO studies (FAS)

Preferred Term	nE (nE/100PY)	nE (nE/100PY)	nE (nE/100PY)
CHRONOS nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	280.4	100.4	291.9
Injection site reaction	0	35 (34.870)	228 (78.112)
Allergic conjunctivitis	21 (7.488)	20 (19.926)	70 (23.982)
Infectious conjunctivitis	2 (0.713)	0	4 (1.370)
Oral herpes	13 (4.636)	7 (6.974)	28 (9.593)
CAFÉ nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	33.6	33.2	34
Injection site reaction	0	1 (3.010)	5 (14.723)
Allergic conjunctivitis	9 (26.771)	18 (54.178)	11 (32.391)
Infectious conjunctivitis	3 (8.924)	14 (42.138)	8 (23.557)
Oral herpes	0	3 (9.030)	5 (14.723)
SOLO nE (nE/100PY)	**BSC**	**Q2W**	**QW**
Total patient years	135.5	140.8	135.9
Injection site reaction	0	124 (88.098)	196 (144.187)
Allergic conjunctivitis	4 (2.952)	16 (11.367)	13 (9.563)
Infectious conjunctivitis	3 (2.214)	23 (16.341)	16 (11.770)

Preferred Term	nE (nE/100PY)	nE (nE/100PY)	nE (nE/100PY)
Oral herpes	8 (5.905)	19 (13.499)	16 (11.770)

BSC, best supportive care; FAS, full analysis set; QW, once every week; Q2W, once every two weeks; nE/110PY, number of events per 100 patient years

The adverse event rates used in the model are derived from the data above and tabulated below (

Table 3.8). The Q2W event rates are used to reflect the licenced dose.

Table 3.8. Adverse event rates used in the model

Preferred term	SOLO- CL		CAFÉ+CCL	
	BSC	Dupilumab	BSC	Dupilumab
Injection site reaction	0	0.881	0	0.091
Allergic conjunctivitis	0.03	0.114	0.188	0.401
Infectious conjunctivitis	0.022	0.163	0.033	0.255
Oral herpes	0.059	0.135	0.11	0.055

BSC, best supportive care; Q2W, once every two weeks

Ciclosporin is most often associated with long-term clinical events; however, based on UK clinical restrictions its use is limited to one year. Thus, for the scenario analysis a conservative approach is taken, and ciclosporin-related adverse events are not considered.

B 3.2.5.6 Mortality

All-cause mortality is estimated based on National Life Tables for the UK[197] with no adjustment for AD-specific mortality. The AD population reports high rates of suicidal ideation, completed suicide data is more ambiguous. A rare complication of AD is eczema herpeticum which has a mortality risk of 6-10%[81], however, its incidence in the adult AD population is rare and hard to determine. As such, no mortality adjustment has been made for these factors in this model. However, it is plausible that dupilumab could reduce the rate of these preventable deaths, particularly with emerging data indicating dupilumab reduces rates of eczema herpeticum.

B 3.3 Measurement and valuation of health effects

In this section we report the results of the HRQoL SLR, then the QoL measured in the LIBERTY trial programme used in the economic model.

B 3.3.1 Health-related quality of life studies

An SLR was conducted to identify relevant HRQoL data for adults with any severity of AD. This is described in full in Appendix H (including the search terms, list of included and excluded studies, full extraction tables and the risk of bias assessments). The results of this search are summarised below and inTable 3.9

The searches were conducted from 15-17 August 2017 and retrieved 2250 records. 1785 records were assessed after removal of duplicates.

16 studies (in 24 documents) were included in the utilities SLR:

- Eight cross-sectional studies or surveys[5, 61, 198-207]
- Three RCTs[2, 75, 208, 209]
- A pooled analysis of two RCTs[146]
- A report of an RCT and economic evaluation based on its findings[210, 211]
- An economic evaluation with Markov model[212-214]
- An open-label, single-arm study[215]
- A nested case-control study[216]

11 studies reported utilities and used the following instruments:

- Three studies used EQ-5D-3L[2, 75, 146, 216]
- Four studies used EQ-5D (version not stated, but assumed to be EQ-5D-3L)[206, 208, 210, 212, 213]
- One study used EQ-5D mapped from SF-36[209]
- Two studies used SF-6D[5, 199, 200, 210, 211]
- Two studies used standard gamble (SG)[203, 204, 212-214]
- Two studies used time-trade-off (TTO)[203, 204, 207]

Six studies reported SF-36 domain data and/or summary component domain data[5, 61, 198-204, 215]. The studies reporting utilities are tabulated overleaf for comparative purposes (Table 3.9). A summary of the included studies is reported in Appendix H.

Table 3.9. Comparison of the quality of life data by AD severity from the literature and previous technology appraisals

		Disease severity						
Study (Year)	**Instrument**	**Very mild**	**Mild**	**Mild to moderate**	**Moderate**	**Moderate-to-severe**	**Severe**	**Comment**
Akerstrom (2015)[208]	EQ-5D				0.812 – 0.960			Median disease severity of patients judged to be moderate
Eckert (2016, 2017)[5, 199, 200]	SF-6D	0.67						Mild, moderate or severe
Garside: utility panel Garside (2004), Garside (2005), Pitt (2006)[212-214]	SG		0.985		0.875		0.675	Panel of 15 lay people
Garside: expert advisory	The descriptive system of		0.691		0.689		-0.154	Expert panel of four people – rejected by the HTA for validity concerns

		Disease severity						
Study (Year)	**Instrument**	**Very mild**	**Mild**	**Mild to moderate**	**Moderate**	**Moderate-to-severe**	**Severe**	**Comment**
group (2004, 2005)[212, 213]	the EQ-5D							
Garside: industry submission - MERG[212, 213]	EQ-5D	0.89	0.76		0.71		0.60	Non-UK population
Lundberg (1999, 2000)[203, 204]	Rating scale	0.72 – 0.77						Swedish sample. Patients with AD, Psoriasis and comorbidities valued their own health using 3 instruments. Severity is not differentiated.
	TTO	0.93 – 0.95						
	SG	0.98 – 1.00						
Ock (2015)[206]	EQ-5D	0.68 – 0.98						Utilities stratified by age group and sex
Poole (2010)[209]	EQ-5D (mapped from SF-36)				0.768 – 0.773		0.655 – 0.676	Baseline patient characteristics in the 2 arms (TCS and Tacrolimus)
					0.72 – 0.88			Utilities stratified by treatment
Schmitt (2008)[207]	TTO (General population)		0.97				0.64	Patients were described as controlled and uncontrolled and we have assumed that uncontrolled is severe and controlled is mild
	TTO (AE patients)		0.96				0.65	
	TTO (Psoriasis patients)		0.90				0.47	
Simpson (2017)[146]	EQ-5D-3L					0.607 – 0.629		Utilities stratified by treatment
						+0.031 to +0.210		Utility increments after intervention stratified by treatment
Simpson (2016)[2, 75]	EQ-5D-3L					0.578 – 0.658		Utilities stratified by treatment
						+0.028 to +0.240		Utility increments after intervention stratified by treatment
Vinding (2014)[216]	EQ-5D-3L	0.842						
Woollenberg (2008)[211] **and Poole (2009)**[210]	SF-6D (Woollenberg 2008)[211]				0.72 – 0.79		0.71 – 0.75	
	EQ-5D (Poole 2009)[210]		0.848		0.796		0.760	Median scores
	SF-6D (Poole		0.800		0.800		0.754	Median scores

		Disease severity						
Study (Year)	**Instrument**	**Very mild**	**Mild**	**Mild to moderate**	**Moderate**	**Moderate-to-severe**	**Severe**	**Comment**
	2009)[210]							
	EQ-5D (Poole 2009)[210]		+0.045					Mean increments after 12 months of maintenance
	SF-6D (Poole 2009)[210]		+0.040					Mean increments after 12 months of maintenance

AE- Atopic Eczema, EQ-5D - EuroQol Five Dimensions, EQ-5D-3L- EuroQol Five Dimensions 3 Levels, SF- Short Form, SG - Standard Gamble, TTO -Time-Trade-off

The SLR described for utility found literature values for moderate-to-severe AD which largely ranged between 0.6 and 0.8 depending on the sources and instruments used. (Table 3.9). There were very few reports of utility measured directly using the EQ-5D instrument beyond the published dupilumab studies[2, 75, 146]. Of these the data used in the evaluation of tacrolimus and pimecrolimus is probably the most applicable[212, 213] and is in line with the utilities recorded in the dupilumab studies. The data collected in the dupilumab trials represents the best available evidence and is used in this evaluation.

B 3.3.2 Health-related quality of life data from clinical trials used in the cost-effectiveness analysis

The base case cost-effectiveness analysis incorporates utility data from the LIBERTY trial programme collected using the EQ-5D-3L instrument and valued using the UK tariff [217]. This is the most appropriate source of data since it is derived directly from patients with the condition and, in the subgroup of patients forming the base case, baseline characteristics and treatment history are consistent with the patients for whom use in the NHS is expected. These data are therefore consistent with the requirements of the reference case.

Utility data in the trials were collected every two weeks, up to the week 16 assessment point, and in CHRONOS every four weeks until the end of the study (see Section B 2.7 for details of the schedule in the trials).

B 3.3.3 Derivation of Health-related quality of life data for use in the modelling

Utility weights for all patients are used for dupilumab patients up to the 16-week response assessment period. At 16-weeks, dupilumab responders continue treatment and receive the utility weights for week 16 responders. In a conservative approach, non-responders switch immediately to BSC, rather than a slow reduction in QoL over time, and receive the BSC utility weight. The utility weight for all patients in the BSC treatment arm is used throughout the model as BSC patients do not switch treatments.

For the base case analysis utility weights were estimated following best practice methods of using a mixed model regression based on the 'all observed' to adjust for baseline characteristics. In sensitivity analysis we use the data observed in the trial. Standard UK tariffs were used in the creation of utility weights.

Mixed models were fitted for each trial using a forward selection process, controlling for baseline age, gender and EQ-5D utility score using the following variables:

- Total EASI score change from baseline
- Total weekly average of peak daily pruritus NRS change from baseline
- Interaction between total EASI score change from baseline and total weekly average of peak daily pruritus change from baseline
- Treatment (dupilumab Q2W, dupilumab every week, or BSC)

Significant variables were kept in the regression and goodness-of-fit was assessed using diagnostic plots, Akaike's information criterion (AIC), and the Bayesian information criterion (BIC) statistics. (Lower AIC and BIC values indicate better fit). AICs and BICs for each model fit are shown in Table 3.10 and diagnostic plots for the best-fit models are shown in Figure 3.5, and Figure 3.6.

Table 3.10. Utility Weight Mixed Model Goodness-of-Fit

Covariates	AIC	BIC
EASI total score	−1964	−1956
Weekly average of peak daily pruritus	−2067	−2060
EASI total score, weekly average of peak daily pruritus	−2099	−2091
EASI total score, weekly average of peak daily pruritus, EASI-pruritus interaction	−2157	−2150
EASI total score, weekly average of peak daily pruritus, EASI-pruritus interaction, treatment	−2150	−2142

AIC, Akaike's information criterion; BIC, Bayesian information criterion; EASI, Eczema Area Severity Index

Based on the AIC and BIC, the best-fit model includes EASI total score, weekly average of peak daily pruritus, a EASI-pruritus interaction term. Additionally, the dupilumab Q2W treatment was significant while the weekly dose of dupilumab was not in the CAFÉ analysis. Thus, with similar AIC and BIC values and with dupilumab Q2W reaching significance, the model that included a treatment covariate was determined to be the best fit. The coefficients for covariates included in the final best-fit model are shown in Table 3.10. All models adjusted for age, gender, and baseline utility weight.

Table 3.11. CHRONOS Model Covariates

Covariate	Coefficient	Individual *P*-Value
Intercept	0.7870	<0.0001
Age	–0.0004	0.2922
Male	0.0130	0.1740
Baseline EQ-5D utility score	0.2240	<0.0001
Total EASI score	0.0005	0.2815
Weekly average of peak daily pruritus	–0.0146	<0.0001
EASI * pruritus	–0.0006	<0.0001
Treatment		
DUP Q2W	0.0312	0.0298
DUP QW	0.0242	0.0179

DUP Q2W = dupilumab 300 mg every 2 weeks; DUP QW = dupilumab 300 mg every week; EASI = Eczema Area Severity Index. Note: Group *P*-values not reported.

Figure 3.5 CHRONOS trial mixed model diagnostics without treatment covariate

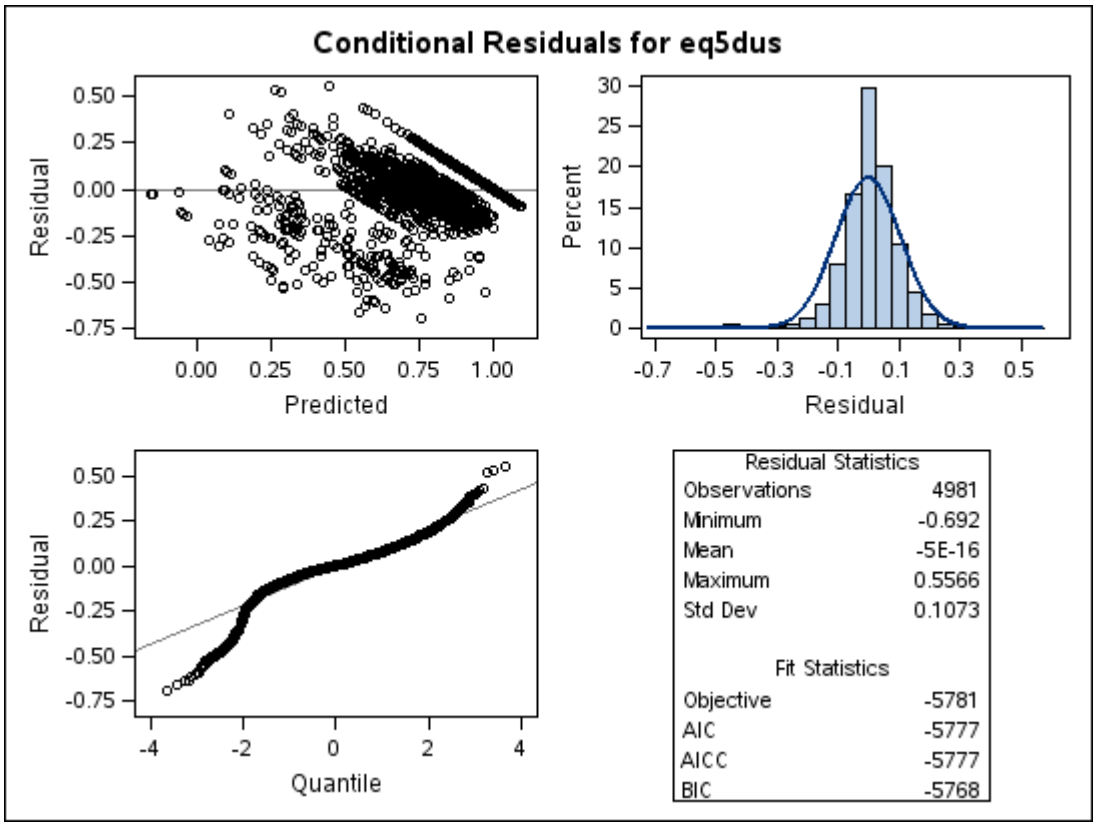


Figure 3.6. CAFÉ trial mixed model diagnostic with treatment covariate

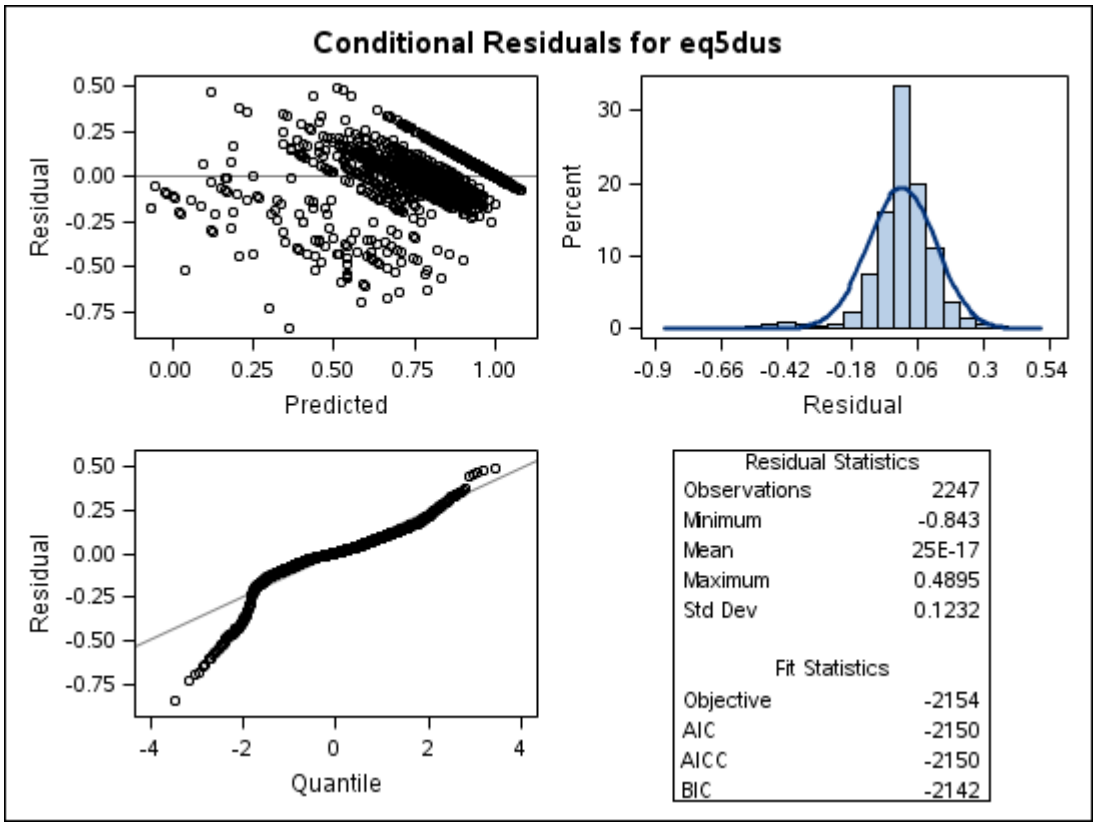


Table 3.12. CAFÉ Model Utility Regression Covariates

Covariate	Coefficient	Individual *p*-Value
Intercept	0.6906	<0.0001
Age	−0.0001	0.7949
Male	−0.0001	0.9955
Baseline EQ-5D utility score	0.3086	<0.0001
Total EASI score	0.0027	<0.0001
Weekly average of peak daily pruritus	−0.0119	<0.0001
EASI-pruritus interaction	−0.001	<0.0001
Treatment		
DUP Q2W	0.0365	0.0189
DUP QW	0.0144	0.3486

DUP Q2W = dupilumab 300 mg every 2 weeks; DUP QW = dupilumab 300 mg every week; EASI = Eczema Area Severity Index.Note: Group *p*-values not reported

Figure 3.7. SOLO trial mixed model diagnostic with treatment covariate

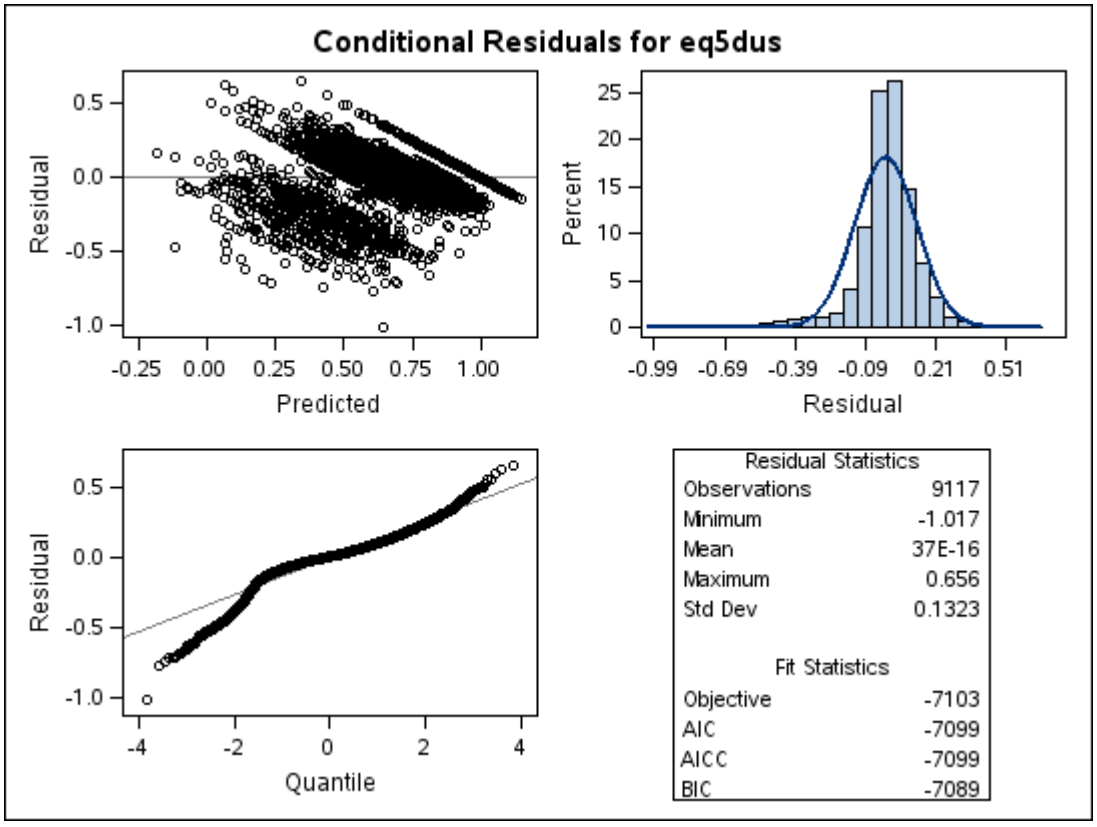


Table 3.13. SOLO model covariates

Covariate	Coefficient	Individual *P*-Value	Group *P*-Value
Intercept	0.7760	<0.0001	
Age	–0.0010	0.0215	0.0215
Male	0.0160	0.0369	0.0369

Baseline EQ-5D utility score	0.2630	<0.0001	<0.0001
Total EASI score	0.0020	<0.0001	<0.0001
Weekly average of peak daily pruritus	–0.0190	<0.0001	<0.0001
EASI * pruritus	–0.0010	<0.0001	<0.0001
Treatment			
DUP Q2W	0.0350	0.0002	0.0002
DUP QW	0.0340	0.0005	--

DUP Q2W = dupilumab 300 mg every 2 weeks; DUP QW = dupilumab 300 mg every week; EASI = Eczema Area Severity Index.

B 3.3.4 Utility Values used in the base case cost-effectiveness model

The regression analyses were conducted at the trial level using CAFÉ, CHRONOS and SOLO and not at the base case population level (CAFÉ+CCL, SOLO-CAFÉ Like). This is because quality of life is dependent on the EASI score and pruritus reduction and any differences in populations are adjusted for by taking into account the baseline utility weight. However, when utility weights are generated for the base case population, the mean change in EASI score and change in pruritus from the base case population are used in the regression to calculate the utility weights specific to the base case population. (Note that for the CAFÉ + CHRONOS CAFÉ-Like pooled population the covariates from the CAFÉ study are used).

The utility weights for the all observed dataset for the base case are shown below. These data (change in EASI score, change in pruritus) are calculated for the base case population and contained within the model. Baseline utilities are different from the utilities recorded for the health states.

Table 3.14. Base case utility weights used in the model (all observed)

Patient population (baseline utility)	Parameter	DUP Q2W	BSC
CAFE + CCL	All patients week 16	0.898	0.811
(0.66)	Week 16 EASI-50 +DLQI≥4 responder*	0.904	*
SOLO - CL	All patients week 16	0.830	0.718
0.55	Week 16 EASI-50 +DLQI≥4 responder*	0.855	*

*Utility is applied in aggregate for all BSC patients as they persist in the BSC health state and do not transfer according to reponse BSC, best supportive care; CCL, CHRONOS-CAFÉ-like; DLQI, Dermatology Life Quality Index; DLQI>4, DLQI score at least 4 point change from baseline; EASI, Eczema Area and Severity Index; EASI-50, EASI score ≥50% response; LOCF, Last Observation Carried Forward

Utility weights are applied in the model according to the decision points shown in Table 3.15.

Table 3.15 Application of utility weights in the economic model

Treatment	From 0 to 8 weeks	From 8 to 16 weeks	From 16 to 52 weeks	Markov (Year 2 – lifetime)
Dupilumab	Baseline utility (regardless of treatment)	Utility from all Dupilumab patients at 16 weeks (regardless	**Responder:** Utility from Dupilumab patients responders at 16 weeks	As for 16 to 52 weeks

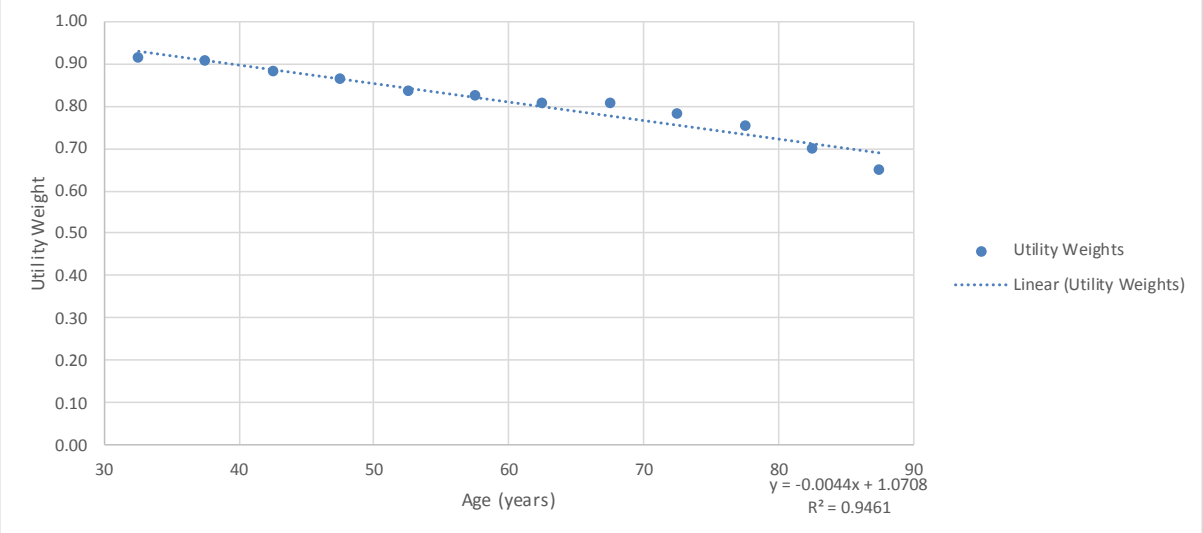
		of response)	**Non-Responder:** Utility from all BSC patients at 16 weeks	
BSC	Baseline utility (regardless of treatment)	Utility from all BSC patients at 16 weeks (regardless of response)	Utility from all BSC patients at 16 weeks	As for 16 to 52 weeks

BSC, Best supportive Care

B 3.3.5 Utility adjustments based on age

The model also includes options to consider adjustments to utility weights as patients age. In the base case, a general population age adjustment replaces the age coefficient from the mixed model. The base case population norm decline in utility weights by age was estimated using general population UK data from Ara et al. (2011)[218] by fitting a linear trendline to age-specific weights as shown in Figure 3.8.

Figure 3.8 Decline in utility weights due to age



B 3.3.6 Change in HRQoL over time

In all the studies in the LIBERTY AD trial programme, but particularly in CHRONOS and CAFÉ, a significant proportion of patients in the BSC arm met the primary end points, i.e. there was a high BSC response rate. These BSC responders accrued the BSC response utility and this continues to be applied at Week 52.

It is improbable that this effect size for BSC alone would persist once patients have completed the studies and are outside the protocol driven clinical trial setting where behaviours, particularly around the adherence to topical treatments, are mandated. Data to support this hypothesis are not available from the LIBERTY AD programme. There is an absence of NICE methodological guidance concerning the extrapolation of non-time to event outcomes such as utilities however, the NICE methods guide states that alternative scenarios should be routinely considered to examine treatment benefit in the extrapolated phase and these may include modelling reductions in benefit over the long-term[194]. In the

technical literature existing approaches have been reviewed recently by Bojke and four methodologies described 'Constant values', 'Profiles', 'Constant marginal change to moving baseline' and 'Regression' [219].

We used the 'Profiles' methodological approach to attempt to quantify utility progression after the end of the studies. We followed the approach reported in Health Technology Assessment by McKenna et al.[220] in which experts were asked to elicit their beliefs about QoL benefits over time. Our elicitation exercise was conducted using this individual expert method, with each expert completing the exercise independently and giving their own belief about the unknown quantities by completing an iterative questionnaire which included background information explaining the QoL benefits observed in the studies. This questionnaire is reproduced in Appendix Q. Five principle investigators from the dupilumab studies were chosen to complete the questionnaire as prior experience of the treatment of patients with severe AD and the use of dupilumab for these patients was considered important. A summary of the results is provided in Table 3.16

Table 3.16. Probability of Sustained Response for Years 2-5+

	Probability of Sustained Quality of Life (%)	
Year	**Dupilumab Q2W**	**BSC**
Year 2	98.0	37.0
Year 3	95.0	9.0
Year 4	93.0	0.0
Years 5+	92.0	0.0

BSC, best supportive care; Q2W, every two weeks

(Source: See Appendix T Persistence of the quality of life gain after the dupilumab trials have ended)

The data obtained in this elicitation exercise was tested and validated in an advisory board setting with eight clinicians and in a series of one-to-one interviews with consultant dermatologists.

The probability of not maintaining utility at the level achieved during the studies in the BSC arm is further supported by the TTO exercise presented in Section B 1.3.6.2.5 (see also Appendix R). In this study incremental disutilities associated with the use of topical treatments between different therapeutic regimens were elicited in a representative UK population (n = 484). Representative results are provided in Table 3.17 for the difference between emollients applied twice daily and three different steroid containing regimens which are typical for patients with moderate-to-severe AD depending on their current level of control. Ranges for these values are provided by sensitivity analysis according to exclusion of patients depending on their answers to the survey questions (see Table 3.17).

Disutility associated with the use of the most burdensome skin care regimen ranges between 0.14 and 0.19 and for the lightest steroid containing option between 0.08 and 0.10 depending on the analysis, indicating the very strong preference against these levels of continuous treatment burden.

Table 3.17. Representative disutilities for pairwise comparisons between various skin care regimens

Pairwise comparison between:		Base: Respondent level*	No exclusions†	Strict exclusion‡	Rules applied§
Steroid containing regimen	**Emollient regimen**				
Steroid twice daily and emollient four times daily	Emollient twice daily	0.1894	0.1356	0.1427	0.1547
Steroid twice daily and emollient twice daily	Emollient twice daily	0.1391	0.0944	0.0952	0.0979
Steroid once daily and emollient twice daily	Emollient twice daily	0.1027	0.0812	0.0802	0.0838

*Respondents with valid responses for both regimens, †No exclusions; ‡Strict exclusion, whereby any respondent with an invalid response for **any** skincare regimen was excluded from **all** calculations, §Rules applied, any respondent trading full 10 years, **and/or** who did not trade-off a greater number of years for steroid vs no steroid (indicates poor understanding of TTO)
TTO, Time-Trade-Off

Given these values, the burden associated with some regimens may be one factor that could prevent a sustained QoL benefit. It is likely that after completion of the study and withdrawal of the support provided by the trials, the burdensome and continuous nature of treatment will once again become an important aspect of the lives of patients. This is exemplified in the responses to the Allergy UK survey in which participants were asked about the impact of their therapeutic regimens on their quality of life. Patients cited time spent applying treatments, influence on usual activities, problems at work, impact on clothing and anxiety and depression among other things as key issues directly associated with the management of their condition (see Allergy UK survey, Appendix S[34]). QoL is influenced by a complex and varied set of factors for patients with AD (see Section B 1.3). The utility benefit BSC patients derived from inclusion in the trial from practical support and further optimisation of topical treatment, is unlikely to be solely removed by the disutility associated with the daily grind of management once patients return to their day-to-day lives. However, it is important to note the magnitude of the effect observed in Table 3.17 and the attitudes of patients towards their daily rituals expressed in the Allergy UK survey(see Appendix S[34]).

This effect may not be relevant to dupilumab treated patients. Clinical experts consulted in an advisory board suggested that patients with a good response to dupilumab treatment are likely to reduce their use of steroids to a minimum and use 50 to 80% less emollients as required. Hence any disutility associated with their daily rituals is likely to be minimal. (In CAFÉ there was a 50% reduction in steroid use in the dupilumab arm and a 19% reduction in the BSC arm at 16 weeks).

The results from the persistence of utility effect survey indicate that clinicians believe the incremental benefit for dupilumab vs. BSC is likely to increase over time because the quality of life observed for patients in the BSC arm will not persist beyond two years after the end of the trials.

In addition, published literature values suggest that utilities for severely affected patients may be as low as 0.6 (Table 3.9) This is consistent with or lower than the values we have observed in the clinical trials at baseline (

Table 3.14). Hence it is reasonable to expect that in real world clinical practice utility is unlikely to be sustained at levels seen in the clinical trials for BSC patients.

The aggregate results shown in Table 3.16 are implemented in the model to account for the expected divergence in utility between the dupilumab and BSC patients over time. These assumptions are tested in sensitivity analysis using different levels of sustained benefit and different rates for the return to baseline for BSC (see Section B 3.7.2).

B 3.3.7 Mapping

Mapping was not carried out as EQ-5D data was collected directly in the relevant studies.

B 3.3.8 Disutilities associated with adverse reactions

Disutilities due to adverse events are not included in the model. Adverse events arising from treatment during the LIBERTY trial program were generally mild and transient. (See Section B 2.10). Therefore, it is not expected that there would be a significant decrement to quality of life associated with these events.

Furthermore, utility data was captured every two weeks in the first 16 weeks of the trials (See Section B 2.3.2 above) and it is assumed that any quality of life decrements due to AEs would be encompassed by these measurements. AEs were generally balanced between the dupilumab and BSC arms and by not incorporating AE disutilities the possibility of double counting is avoided.

B 3.4 Cost and healthcare resource use identification, measurement and valuation

In order to identify resource utilisation rates and unit costs most appropriate to this submission we undertook a number of activities:

- A Systematic review of the literature to identify published and unpublished studies (See Section B 3.4.1 below and Appendix I-1).
- A retrospective UK case notes review of 30 patient records for adults with uncontrolled moderate-to-severe AD and history of immunosuppressant use or contraindication to establish current clinical practice (See Section B 3.4.2 below and Appendix I-2).
- An evaluation of the current treatment pathways and associated NHS resource use for the management of uncontrolled moderate-to-severe AD using the Salford Integrated Record (SIR). (See Section B 3.4.3 below and Appendix I-3).
- Market research to evaluate UK clinicians' perceptions of healthcare resource use among their patients. (See Section B 3.4.4 below and Appendix I-4).

B 3.4.1 Systematic review of the literature to identify published and unpublished studies.

An SLR was conducted to identify published and unpublished studies reporting costs and healthcare resource use data for with adults with any severity of AD in England. The review is reported in summary below and in Appendix I in full (including search strategy, included and excluded records with reasons and data extraction tables).

B 3.4.1.1 Results

After duplicates were removed 2,826 records were screened and 101 were identified for full text review. 12 studies (in 13 documents) were included in the qualitative synthesis. Seven studies (in eight documents) were economic evaluations [Green et al. 2004[221], Salo et al. 2004[187], Garside et al. 2005[213], Green et al. 2005[221], Pitt et al. 2006[214], Hjelmgren et al. 2007[222], Hjalte et al. 2010[223], Norrlid et al. 2016[224]], one was a costing study [Gieler et al. 1999[225]], one was a descriptive study of a single-centre [Garcia-Doval et al. 2002[226]], two were burden of disease/epidemiology reports [Gupta et al. 2004[227], Anandan et al. 2009[228]] and one was an analysis of the effects of a policy intervention [Schmitt, et al. 2009[229]]. Data extracted from the included publications are presented in Appendix I, Table I-2. The study selection process and identified studies are summarised in Appendix I, Figure I.1.

B 3.4.1.2 Summary of findings

Key parameters required for the cost-effectiveness evaluation such as the number and frequency of consultant and GP visits are reported in the literature, but these are from sources not relevant to the UK setting[213] or are estimated by clinical opinion[214]. In the more recent tacrolimus UK report by Healy (identified in the economic evaluations review) expert opinion was used extensively[230]. There is limited published evidence for hospital admissions for AD in England[227] at 0.7 to 1.4 episodes per 100,000 population per year although this data is from 2000 – 2001. Hjelmgren et al used a patient survey in Sweden but only report costs by health state, and not resource utilisation, which makes adaptation difficult[222]. There is no published data for length of stay in the UK.

Overall this SLR has demonstrated that there is little evidence upon which to base healthcare resource use estimates relevant to UK clinical practice today. A detailed summary of the studies found are provided in Appendix I.

However, it is worth noting that the NICE appraisal for pimecolimus and tacrolimus published by Garside (which used estimates taken from a 1997 Australian study) implemented 6.5 (non-responder) and 2.7 (responder) dermatologist visits and 11.7 (non-responder) and 4.0 (responder) GP visits per patient per year for the moderate cohort evaluated[212]. These estimates were accepted by the committee. While these estimates must be considered with caution given the historic and non-UK nature of them they are in line with the ranges for number of visits that we have observed in the research carried out for this assessment. We have tested these estimates in sensitivity analysis.

Given the paucity of information in the literature we have based our estimates for resource use implemented in the economic modelling on the sources below (Sections B 3.4.2 to B 3.4.4). Justification for the choice of the base case estimates is provided in Section B 3.4.5.

B 3.4.2 Case note review: Resource use for patients with AD

A study was undertaken to evaluate the current treatment pathways and associated NHS resource use for the management of uncontrolled moderate-to-severe AD in secondary care. A very brief description of the study design is provided below along with the key findings relevant to the economic modelling. See Appendix I-2 for a full description of the study including the study protocol and results.

This was an observational, multicentre retrospective descriptive research study conducted in five secondary/tertiary NHS Hospital Trusts selected to provide an even geographical spread across the United Kingdom.

B 3.4.2.1 Key findings

This study aims to collect data on 50 to 80 patients, but the study was not completed at the time of writing. A key results memo was issued on 9th October 2017 and the results applicable to the economic model are presented below for 30 patients. A full description of the study findings is presented in Appendix I-2.

Key resource use data pertinent to the modelling are provided in Table 3.18 and Table 3.19. Data is tabulated for year 3 of the study which provides the most complete and up to date estimates. For some patients records were either not complete or had not begun in earlier years.

Table 3.18. Resource use, per patient per year

Secondary / tertiary care visit to:	Total	N	Mean (per patient)	Range
Clinician	211	30	7.03	1-16
Nurse	17	30	0.57	0-6

Day case, A&E, hospital attendance is tabulated in Table 3.19 below.

Table 3.19. Day case, A&E and hospital admissions per person per year

	Number of events	Mean per patient per year
Day case	5	0.17
Accident and emergency	3	0.1
Hospitalisation	7	0.23

Of the hospitalisations one case was admitted for a stay of 23 days for an infection). Other admissions were between 2 and 3 days and were coded as for administration of treatment.

B 3.4.3 Integrated records review: resource used associated with AD patients

An evaluation of the current treatment pathways and associated NHS resource use for the management of uncontrolled moderate-to-severe AD was undertaken using the Salford Integrated Record (SIR). See Appendix I-3 for a full description of the evaluation and results.

This evaluation was conducted to provide complementary information to that reported above in B 3.4.2. To further describe the moderate-to-severe population who may be candidates for dupilumab in terms of counts for consultant dermatology visits, general practitioner visits (not available from the secondary care case notes review), accident and emergency visits and hospital in-patient stays. Two analyses were undertaken looking at populations with slightly different baseline characteristics. Analysis 2 aligns with the base case population and is reported below.

B 3.4.3.1 Key findings

Results for the key components of resource use included in the model are tabulated below (Table 3.20).

Table 3.20. Primary and secondary care resource use.

	Primary Care encounters	Dermatology Clinic Outpatient visits	Dermatology related Hospital admissions	A&E dermatology related visits
Analysis 2: (n = 37)				
Mean Number per Subject per Year (±SD)	17.72 (±9.04)	7.53(±9.77)	0.14 (±0.29)	0.00
Min	3.00	0.75	0.00	0.00
Max	41.63	50.88	1.50	0.00
25th percentile	11.50	1.91	0.00	0.00
Median	15.50	3.90	0.00	0.00
75th percentile	23.75	8.83	0.40	0.00

B 3.4.4 Market research to evaluate UK clinicians' perceptions of healthcare resource use by their patients.

A very brief description of the market research is provided below along with the key findings relevant to the economic modelling. See Appendix I-5 for a full description of the questionnaire including the results.

The key results relevant to the economic model for the survey completed by dermatologists are provided in Table 3.21 below, these are used to test the resource utilisation data above in the sensitivity analysis.

Table 3.21. Mean number of visits per patient per year (Dermatologist responses)

	Responding to SI	Not responding to SI/ intolerant/ contraindicated	Multiplier
Total number of patients	**560**	**290**	
OP visits to dermatologist (total pt visits/yr)	3.53	4.92	0.72
OP visits to dermatology nurse (total pt visits/yr)	1.84	2.39	0.77
Visits to the GP (total pt visits/year)	2.30	4.78	0.48
A&E attendance (total pt visits/ year)	0.43	1.74	0.25
Hospital admissions (total pt admissions/year)	0.15	1.16	0.13

SI: Systemic Immunosuppressant

In order to implement these data in the economic model where necessary a factor was derived from the difference between the responder and non-responder patients.

B 3.4.5 Choice of resource use data for the economic model.

The data implemented in the base case are discussed below with justifications.(Table 3.22) .

Where available the healthcare resource use data implemented in the base case have been taken from the secondary care case notes review described in B 3.4.2 above to characterise resource use in patients uncontrolled by current therapy. This is the most appropriate source for these data as the participants were selected by their clinicians because they were uncontrolled on current systemic therapies and could be potential candidates for dupilumab. If data are not available from this secondary care data other sources are used. For example the number of GP visits per patient per year are taken from the analysis of the SIR (see Section B 3.4.3).

The healthcare resource use inputs define the annual number of each resource used by patients per year. These numbers are applied to the respective unit costs in the model for each resource to estimate total annual health care resource costs. See section B 3.4.6 below for a explanation of the costs used.

Resource use for patients who respond to dupilumab is not currently available. The market research described in Section B 3.4.4 collected clinician's perceptions of resource use for patients who could be characterised as well controlled (proxy for dupilumab responder) or uncontrolled (proxy for non-responder) on currently available systemic immunosuppressant therapy. Therefore where necessary we have used multipliers derived from the controlled and uncontrolled patients in the market research applied to the directly collected data in order to estimate the effect of successful treatment in the model on resource use (Table 3.21)

The number of dermatology visits and specialist nurse visits were discussed in an advisory board. In addition these inputs have been validated with two UK dermatologists who have experience of dupilumab either through the clinical trial program or EAMS. With the exception of GP visits these resource use estimates for patients uncontrolled on current therapy were considered to be conservative. In particular, the number of hospitalisations, nurse attendances and A&E visits. The difficulty of characterising the number of GP visits, not least due to coding issues was recognised but on reflection felt that the apparently high number could be representative of a population with high disease burden. The aplication of factors to dervive resource use estimates for dupilumab responders was accepted.

Table 3.22. Resource use data used in the economic model

Resource	Dupilumab		BSC		Source and justification
	Year 1	Years 2+	Year 1	Years 2+	
Dermatologist outpatient consultation (per patient per year)					
Responder	4	2	2	2	Advisory board. Expert opinion stated that dupilumab patients would be seen every three months for the first year and if well controlled every 6 months thereafter. For patients responding well on BSC a conservative assumption of 2 visits per year is implemented in line with the dupilumab estimate. This is in line with the value implemented in TA82 of 2.7[212].
Non-responder	7.03	7.03	7.03	7.03	B 3.4.2 The number of dermatologist visits is similar between B 3.4.2 and the retrospective database review described in B 3.4.3 (7.53) respectively. This is also consistent with the value implemented in TA82 of 6.5[212], although the latter was in a moderate population.
Dermatology related GP consultation (per patient per year)					
Responder	2	2	2	2	Assumption. During validation it was suggested that no attendances to the GP were made by patients responding to dupilumab. In the absence of any other data a figure of 2 attendances per year over and above attendance for other reasons (See below) was suggested by the expert. This is in line with the estimate provided by the clinicians collected during the market research. B 3.4.4.
Non-responder	12.81	12.81	12.81	12.81	GP visits are not in the secondary care record (B 3.4.2) and so they are taken from the next most robust source, the retrospective database review. B 3.4.3. The number of visits recorded was 17.72. The reason for consultations is not given and so this number represents all visits. The average number of contacts per registered patient per year has been estimated recently to range from 3.64 to 9.88 with a mean of 4.91[231]. In the absence of other data we have reduced the number of GP consultations observed in the database review by 4.91 to 12.81 in order to avoid over counting. The number of visits accepted in TA82 was 11.7 which is slightly lower but TA82 examined a less severe population[212].
Dermatology Nurse visit (per patient per year)					
Responder	1	0.44	0.44	0.44	Advisory board. A nurse visit at 4 weeks after initiation would be expected for dupilumab. Thereafter the number of visits observed in B 3.4.2 is reduced by the multiplier (0.77) derived from the market research. B 3.4.4 Likely to be underestimated.
Non-responder	1	0.57	0.57	0.57	Number of visits per person observed in the case notes review. B 3.4.2. Likely to be

					underestimated.
Accident and emergency visit (per patient per year)					
Responder	0.06	0.06	0.06	0.06	The number of visits observed in B 3.4.2 is reduced by the multiplier (0.25) derived from the market research B 3.4.4. Likely to be overestimated.
Non-responder	0.25	0.25	0.25	0.25	Number of visits per person observed in the care notes review B 3.4.2.
Hospitalisation					
Responder	0.03	0.03	0.03	0.03	The number of hospitalisations observed in B 3.4.2 is reduced by the multiplier (0.13) derived from the market research B 3.4.4. Likely to be overestimated.
Non-responder	0.23	0.23	0.23	0.23	Number of hospitalisations per person observed in the care notes review B 3.4.2.
Tests and investigations (per patient per year)					
Responder	0	0	4	4	The SmPC for dupilumab states that no tests are required (see Appendix C). During validation expert opinion stated that testing for patients on current therapies would be carried out on a quarterly basis. Conservative estimate (See Table 3.21).
Non-responder	4	4	4	4	During validation expert opinion stated that testing for patients on current therapies would be carried out on a quarterly basis. Conservative estimate (See Table 3.21).
Day case					
Responder	0.00	0.00	0.00	0.00	Assumption based on feedback obtained from UK clinicians at an advisory board
Non-responder	0.17	0.17	0.17	0.17	The number of day-cases observed in B 3.4.2

B 3.4.6 Intervention and comparators' costs and resource use

The cost of treatment comprises the cost of specific medications, administration costs, monitoring and the cost of adverse events.

B 3.4.6.1 Drug unit and administration costs

The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg once every 2 weeks (Q2W)[11]. During the maintenance phase patients receive 26 doses per year. The additional loading dose is included in the economic model.

The annual cost for dupilumab is £16,500. [redacted] The annual PAS adjusted cost and cost per dose are tabulated below. (Table 3.23).

Table 3.23. Cost per dupilumab dose

Treatment	Annual PAS adjusted cost	PAS adjusted cost per dose	Source
[redacted]	[redacted]	[redacted]	Sanofi Genzyme
[redacted]	[redacted]	[redacted]	

PAS, patient access scheme

Patients are assumed to be 100% compliant with treatment and costs for all scheduled doses are incurred in the model.

Dupilumab is assumed to be self-administered following half an hour of instruction from a nurse and there is no training required for the administration of BSC. Subcutaneous training cost for nurse time is applied once for patients receiving a dupilumab treatment regimen. The unit cost for subcutaneous training (£54) was obtained from the Unit Costs of Health and Social Care 2016[232] as the cost of 30min of patient contact with a Band 6 (Nurse specialist/team leader, £108/hour) with qualifications.

B 3.4.6.2 Background treatments (concomitant medications)

In the dupilumab studies all patients were required to apply moisturisers at least twice daily in line with European guidelines[88, 233]. Clinical opinion provided to us during an advisory board held on the 14th September 2017 suggested that wash products as well as moisturisers should be considered in the economic modelling and that several choices should be included. To represent choice, we have included the top five most widely prescribed bathing products according to the NHS Prescription cost analysis data 2016[234] in the modelling. These include the two bathing products suggested by the clinical experts (dermol and oilatum) and are tabulated below (Table 3.24). We have implemented treatment according to package labelling and assumed one application per day reduced by 50% for responders to dupilumab according to direction from the experts to calculate costs.

Table 3.24. List of bathing products used in the economic modelling.

				Non-responder		Responder
Bathing product	**Proportion of product prescribed ***	**Pack size**	**Cost per pack†**	**Amount per week**	**Cost per week**	**Cost per week assuming 50% reduction**

Aqueous Cream	33%	500 g	£0.86	Assume 1 pack per week	£0.86	£0.43
Dermol 200 Shower Emollient	25%	200 ml	£3.55	Use as a soap substitute. Assumed 1 pack per week	£3.55	£1.78
Aveeno Bath Oil	17%	500 ml	£7.12	30ml per bath	£2.99	£1.50
Dermol 600 Bath Emollient	15%	600 ml	£7.55	30ml per bath	£2.64	£1.32
Oilatum Bath Formulation	10%	300 ml	£5.02	140 ml (20ml per bath)	£2.34	£1.26
				Average cost per week	**£2.48**	**£1.36**

*Proportions of the top five most frequently prescribed wash and bathing products according to the Prescription cost analysis data 2016[234]. †All costs taken from the BNF September 2017[235] update except for aqueous cream which is taken from the eMIT costs

Similarly, the clinical experts suggested several emollients (Cetraben, Epiderm, 50/50 white soft paraffin, and hydramol) but recommended that choice was important. In addition to these products we have included the most widely prescribed emollient products according to the Prescription cost analysis data 2016[234] in the modelling.

The recommendations for emollient dose provided by Ring et al. were discussed with the clinical experts (250g to 500g of emollients per week)[88] ,who agreed that 500g of emollients is a plausible amount per week for patients unresponsive to treatment and that for responders to dupilumab there was likely to be a 50% to 80% reduction. Hence, we have assumed 500g for non-responders and a 50% reduction for responders in the base case. The products are prescribed in broadly equal proportions, so we have calculated the mean cost across all products. (Table 3.25).

Table 3.25. List of emollients products used in the economic modelling.

Emollient product	Pack size	Cost per pack*	Number of packs per week: non-responder	Cost per week: non-responder	Cost per week - responder with 50% reduction
Aveeno cream (Johnson & Johnson Ltd)	500 ml	£8.05	1	£8.05	£4.03
Cetraben ointment (Thornton & Ross Ltd)	450 gram	£5.39	1	£5.39	£2.70
Dermol cream (Dermal Laboratories Ltd)	500 gram	£6.63	1	£6.63	£3.32
Diprobase ointment (Bayer Plc)	500 gram	£5.99	1	£5.99	£3.00
Epaderm ointment (Molnlycke Health Care Ltd)	1000 gram	£12.02	0.5	£6.01	£1.50
Hydromol ointment (Alliance Pharmaceuticals Ltd)	1000 gram	£9.15	0.5	£4.58	£1.14
White soft paraffin 50% / Liquid paraffin 50% ointment	500 gram	£4.19	1	£4.19	£2.10

Emollient product	Pack size	Cost per pack*	Number of packs per week: non-responder	Cost per week: non-responder	Cost per week - responder with 50% reduction
(A A H Pharmaceuticals Ltd)					
Oilatum cream (GlaxoSmithKline Consumer Healthcare)	1050 ml	£9.98	0.5	£4.99	£1.25
Average cost per week	**£5.73**			**£2.38**	

*BNF September 2017 update[235]

According to the experts the most usually prescribed mid potency TCS in the UK is mometasone 0.1% ointment and we have assumed the this in the economic modelling. The number of grams per week was calculated based on BSA involvement from CAFÉ (55.7% at baseline) and the recommendation from the BNF that 500 mg of product from a tube with a standard 5 mm diameter nozzle is sufficient to cover an area that is twice that of the flat adult handprint (palm and fingers). One hand print has been calculated to be 0.87% of the area of an adult[236]. The amount of TCS required is therefore ~16 g per application or ~32g per day assuming twice daily application.

The amount and frequency of TCS used during the CAFÉ study were recorded at home by patients in a medication diary. For patients taking Q2W dupilumab the baseline weekly dose of TCS active ingredient was 34.18 mg and this fell to 17.3mg at study end representing a decline of 49%. We have applied this reduction in TCS use to the responder patients in the economic modelling. This is likely to be an underestimation of the reduction in TCS use on responding to treatment, given patient attitudes towards steroids and the potential fear of side effects[237]. This was confirmed by the clinical experts who felt that patients who responded well to dupilumab would reduce TCS to a minimum (perhaps 1 dose a week or would stop altogether). As above an average cost was derived for the TCS products. (Table 3.26).

Table 3.26. List of TCS products used in the economic modelling.

				Non-responder		Responder (49% reduction)	
Topical corticosteroid	**Grams per tube**	**Cost per tube***	**Cost per gram**	**Grams per week**	**Cost per week**	**Grams per week**	**Cost per week**
Mometasone 0.1% ointment	100	£3.10	£0.03	112.04	£3.47	56.70	£1.76

*Taken from the electronic market information tool [eMIT][238]

A similar approach has been taken to background TCIs for the modelling (Table 3.27). The clinical experts directed that for facial involvement TCIs are more appropriate than steroid treatments and that protopic 0.1% ointment, (Tacrolimus) is preferred. We have implemented this in the modelling according to the label which states that it should be applied thinly twice weekly, with an interval of 2–3 days between applications. Following the methodology above for TCS use we have estimated that 1.75g per week is sufficient for

maintenance treatment. The clinical experts concluded that for responders to treatment, TCI use could be stopped.

Table 3.27.Topical calcineurin inhibitor costs implemented in the modelling.

				Non-responder		Responder (49% reduction)	
Topical calcineurin inhibitor	**Grams per tube**	**Cost per tube***	**Cost per gram**	**Grams per week**	**Cost per week**	**Grams per week**	**Cost per week**
Protopic 0.1% ointment, tacrolimus (LEO Pharma)	60	£47.28	£0.79	1.75	£1.38	0	0

*Taken from the BNF September 2017 update[235]

The annual cost of all the background treatments described above is calculated for the responder and non-responders and applied in the model as an aggregate cost in each arm.

B 3.4.3.3. Treatment for flares

Rescue medications are often required for patients when they experience flares. In CHRONOS at 52 weeks there were approximately three times as many patients receiving placebo who required at least one rescue medication as for the dupilumab treated patients. The proportions of patients with various therapeutic classes of treatment over 2.5%(for the purposes of the calculation of cost) are shown in Table 3.28 below.

Table 3.28. Distribution of rescue therapy at 52 weeks in CHRONOS.

	Percentage of patients receiving at least on rescue medication	
Therapeutic class	**Placebo**	**Dupilumab Q2W**
At least one rescue medication	53.0%	17.3%
TCS: Potent	40.6%	11.8%
TCS: very potent	20.3%	6.4%
Systemic steroids	10.2%	8.2%
Immunosuppressants (TCI)	4.4%	0.0%

Flare was not an end point in the studies, but the receipt of rescue medication can be considered a proxy for flare. ‘Escalation of treatment’ or ‘use of topical anti-inflammatory medications’ have both been proposed in the literature as proxy indicators of AD flare[107].

The cost of representative products for each therapeutic class cited above in common use in the UK (advisory board recommendation) are presented in Table 3.29.

Table 3.29. Commonly used products for the treatment of flares.

Therapeutic class	Product	Indication	Pack size (g)	Cost per pack	Source
TCS: Potent	Betamethasone valerate cream	Apply 1–2 times a day, to be applied thinly	100	£3.22	eMIT
TCS: Potent	Cutivate 0.05% cream	Apply 1–2 times a day, to be applied thinly	30	£4.24	BNF Sept 17
TCS: Very potent	Eumovate 0.05% ointment	Max 50g per week up to 4 weeks	100	£5.44	BNF Sept 17
TCS: Very potent	Dermovate 0.05% cream	Max 50g per week up to 4 weeks	100	£7.90	BNF Sept 17
Systemic steroid	Predisolone 5mg packsize = 28	10mg per day for 2 weeks	28	£0.41	eMIT
TCI	Protopic 0.1% ointment	Apply twice weekly, 0.1% ointment to be applied thinly, with an interval of 2–3 days between applications	60	£47.28	BNF Sept 17

TCI=Topical calcineurin inhibitor; TCS= Topical corticosteroid

The average cost for 4 weeks of treatment according to label for the potent TCS's is £17.35 and for the 'very potent TCS's' it is £13.34 (assuming equal weight for all products). The cost for a 2-week course of prednisolone is £0.41. The cost for a 4-week course of TCI assuming 10% BSA coverage of flare and applying the same methodology as for TCS coverage above (11.49 handprints equating to 5.7 grams per dose every 3 days according to label) is £19.02.

Using the same proportions as observed in the CHRONOS study at 52 weeks and assuming one treatment per therapeutic class, the average medication cost to treat a flare from the 52-week CHRONOS data is shown below. (Table 3.30).

Table 3.30. Cost of medications to treat a flare (derived from 52-week data in CHRONOS*)

Therapeutic class	CHRONOS 52 weeks		Medication cost	
	Placebo	Dupilumab Q2W	Placebo	Dupilumab Q2W
TCS: Potent	0.54	0.42	£9.29	£7.26
TCS: very potent	0.27	0.23	£3.57	£3.03
Systemic steroids	0.13	0.29	£0.06	£0.12
Immunosuppressants (TCI)	0.06	0.00	£1.10	£0.00
		Total cost	**£14.03**	**£10.41**

The annualised rate for flares observed in CHRONOS was 0.78 for the placebo group and 0.18 for the dupilumab treated patients (Table 3.31).

Table 3.31. Annualised event rate for flares from CHRONOS.

Treatment	Total number of flares	Total patient years followed	Adjusted annualised rate (95% CI)*	Relative Risk (95% CI)[1]	P-value[1]
Placebo QW(N=315)	221	285.8	0.78 (0.643, 0.935)		
Dupilumab 300 mg Q2W(N=106)	18	99.2	0.18 (0.108, 0.301)	0.23 (0.136, 0.400)	<0.0001
Dupilumab 300 mg QW(N=319)	56	300.3	0.18 (0.138, 0.248)	0.24 (0.169, 0.336)	<0.0001

*Derived using negative binomial model with the total number of events onset starting from first dose date through week 52 visit as the response variable, treatment, region and baseline disease severity (IGA=3 vs. IGA = 4) as factors, and log-transformed standardised week 52 treatment duration as an offset variable.

The cost for flares calculated above has been applied as an annual cycle cost for these proportions of patients in each year in the model in the base case. (Data from CHRONOS are used in all cases as this study provides the longest duration of observation in the RCT program). It is very likely that this underestimates the cost of flares in the real world. Evidence from the literature suggests that the number of flares per patient per year could be between 7 to 15 with some patients experiencing a significant proportion of the year in a state of flare:

- Patients with moderate-to-severe AD experience significantly more exacerbations than those with mild disease, reporting an average of 15.5 exacerbations compared with 2.8 exacerbations per year (P<0.0001)[63]
- In a multinational study, patients (N=2,002) with moderate-to-severe AD reported 8.3 (moderate) to 11.1 (severe) exacerbations per year, most lasting at least 13.6 days (moderate) to 17.3 days (severe)[62]
- In a cross-sectional Spanish study, adult patients (N=159) reported seven exacerbations during the last year, most lasting 18 days[108]
- Furthermore, those with severe forms of AD report having exacerbations up to 192 days per year, thereby spending more than half of each year in a state of exacerbated disease[62]

This is tested in sensitivity analysis in the model using the rates from Simpson 2016 (15.5 for patients treated with placebo vs. 2.8 exacerbations per year for patients treated with dupilumab)[63] and the costs derived above.

B 3.4.6.3 Cost of tests and investigations

Full blood counts (FBC) are routinely ordered for patients with AD under currently available treatment regimens. The cost for a FBC is £3.10 (HS Reference Cost 2015-2016 [National schedule of reference costs: the main schedule, Currency Code: DAPS05] (Haematology)).

B 3.4.6.4 Cost associated with resource utilisation.

Sources for the estimates used in the economic model have been discussed in Section B 3.4.5 above.

B 3.4.6.5 Cost of physician appointments and monitoring

The costs of consultant appointments for dermatology services or allergy services were derived from the National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts for consultant led appointments[239] as shown in Table 3.32 below.

Table 3.32. Average cost of a consultant led appointment in dermatology and allergy clinics.

Currency code	Currency description	No. of attendances	National average unit cost
WF01A	Non-Admitted Face to Face Attendance, Follow-Up	1,169,536	£99
WF01B	Non-Admitted Face to Face Attendance, First	666,340	£112
WF01C	Non-Admitted Non-Face to Face Attendance, Follow-Up	8,103	£72
WF01D	Non-Admitted Non-Face to Face Attendance, First	4,533	£39
WF02A	Multi-professional Non-Admitted Face to Face Attendance, Follow-Up	14,085	£147
WF02B	Multi-professional Non-Admitted Face to Face Attendance, First	5,621	£157
WF02C	Multi-professional Non-Admitted Non- Face to Face Attendance, Follow-Up	2	£73
	Weighted average	**£104.24**	

During the market research described in Section B 3.4.4 12% of dermatologists said that their centre had a multi-disciplinary team (MDT). The costs associated with MDT are much higher than those captured in Table 3.32 above. Based upon an NHS example, the care provider negotiated MDT cost for an eczema new and follow-up appointment is around [redacted]. While these tariffs are not nationally negotiated or published it is important to reflect that higher costs are associated with MDTs. To model this variation, we have weighted the average of the NHS reference costs shown in Table 3.32 and the MDT cost according to the market research findings. The derived cost of an appointment is therefore [redacted]. This is tested in sensitivity analysis by removing the MDT component.

The cost of a general practitioner (GP) consultation lasting 9.22 minutes (With qualification costs including direct care staff costs) was taken from the Unit Costs of Health and Social Care 2016, Table 10.3b at £36[232]. The cost of a GP practice nurse visits is estimated on the basis of 15 minutes of nurse time taken from the PSSRU 2016: Chapter 10.6 Nurse GP practice at £10.75.

The cost of a day case visit is taken from National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts (Average of JD07A, JD07B, JD07C, JD07D, JD07F, JD07G, JD07H, JD07J and JD07K) and is estimated to be £492.19.

No additional tests or investigations are required for patients taking dupilumab[11].

B 3.4.6.6 Non-elective hospitalisation costs

To calculate the cost of a non-elective hospital stay specifically related to AD (and not other skin disorders), a data search was conducted on HES data extracted from www.HealthIQ.co.uk via the VANTAGE health intelligence platform for non-elective

admissions between 01/4/2016-31/3/2017 covering England with a primary diagnosis of L20 atopic dermatitis or secondary diagnosis L20 atopic dermatitis. HRG codes with PA prefix (Paediatric) were excluded and small number suppression (<10 patients) was implemented. The cost of an average stay is estimated in Table 3.33 below.

Table 3.33. Cost of average non-elective stay in hospital for atopic dermatitis (2016/17 cost year)

HRG	Admissions (count)	Total cost (sum)
Intermediate Skin Disorders Category 2, with Major CC (JD03A)	95	£271,638
Intermediate Skin Disorders Category 2, without CC (JD03C)	80	£73,552
Intermediate Skin Disorders Category 2, with Intermediate CC (JD03B)	50	£65,323
Intermediate Skin Disorders Category 1, with Intermediate CC (JD04B)	10	£9,788
Intermediate Skin Disorders Category 1, with Major CC (JD04A)	10	£19,801
Intermediate Skin Disorders Category 1, without CC (JD04C)	10	£13,629
Minor Skin Disorders Category 1, with CC (JD06A)	10	£22,020
Total	265	£475,752
	Weighted average	**£1,795**

B 3.4.6.7 Accident and Emergency costs

A visit to the emergency room was calculated at £137.82 and was the weighted average of currency codes VB01Z-VB09Z taken from the National Schedule of Reference Costs – Year 2015 to 2016 - NHS trusts and NHS foundation trusts for emergency medicine[239].

B 3.4.6.8 Adverse reaction unit costs and resource use

The adverse events considered in the model are based on those reported in the dupilumab clinical trials. Data are trial specific, and the incidence of these events is shown in Table 3.34. The model assumes that injection site reaction is a one-time event, with the costs occurring in the first cycle. The rates of allergic and infectious conjunctivitis and oral herpes are per cycle.

Table 3.34. Proportion of patients experiencing adverse event used in the model (Safety populations)

Preferred term	SOLO- CL*		CAFÉ+CCL		CHRONOS		CAFÉ		SOLO pool	
	BSC	Q2W	BSC	Q2W	BSC	Q2W	BSC	Q2W	BSC	Q2W
Injection site reaction	0	0.881	0	0.091	0	0.349	0	0.03	0	0.881
Allergic conjunctivitis	0.03	0.114	0.188	0.401	0.075	0.199	0.268	0.542	0.3	0.114
Infectious conjunctivitis	0.022	0.163	0.033	0.255	0.007	0	0.089	0.421	0.22	0.163
Oral herpes	0.059	0.135	0.11	0.055	0.046	0.07	0	0.09	0.059	0.135

*** SOLO-CL uses the safety analysis from the SOLO pooled analysis**

BSC, best supportive care; Q2W, once every two weeks

The adverse event costs (Table 3.35) are multiplied by the incidence rates to estimate treatment-specific adverse event costs. The cost of injection site reaction is assumed to be

the cost of a dermatologist visit based on the unit cost for consultant led dermatology, non-admitted face to face follow-up from the NHS reference costs 2014-15 [currency code WF01A] @ £104[240]. The costs of allergic conjunctivitis and oral herpes are assumed to be the cost of a cost of a GP visit lasting 9.22 minutes, including direct care staff costs with qualifications from the Unit Costs of Health and Social Care 2015[232] @ £36. The cost of infectious conjunctivitis was discussed at an advisory board held on the 14th of September. The experts advised that in about 10% of cases a visit to an ophthalmologist visit would be required. Medication for infectious conjunctivitis was expected to be a course of prednisolone eye drops. The cost is therefore the weighted average of a GP visit (90% @ £36) and an ophthalmologist visit (10% @ £93.50) along with the cost of 1% prednisolone eye drops (£3.66)[235].

Table 3.35. Adverse event costs implemented in the model.

Adverse Event	Cost	Source
Injection site reaction	£104	Table 3.32
Allergic conjunctivitis	£36.00	Unit Costs of Health and Social Care 2016, Table 10.3b[232]
Oral herpes	£36.00	Unit Costs of Health and Social Care 2016, Table 10.3b[232]
Infectious conjunctivitis	£45.41	Assumed to be the weighted average cost of a GP visit lasting 11.7 minutes, including direct care staff costs with qualifications from the Unit Costs of Health and Social Care 2015[241] (90% weight) @ £36 and the Cost of Ophthalmology WF01B Non-Admitted Face to Face Attendance, First' @£93.50 (10% weight) taken from National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts[239] plus the cost of 1% prednisolne eye drops. @ £3.66 (BNF 2017 September update[235])

BNF, British National Formulary

B 3.4.6.9 Miscellaneous unit costs and resource use

The model also includes an option to consider indirect costs, based on response status. The effect of these on the ICER is presented in scenario analysis. When indirect costs are included in the analysis, the productivity loss inputs (Table 3.36) are applied to the employment parameters (Table 3.37) to estimate the indirect costs. The average number of days lost to work through sickness in the UK in 2016 was 4.3[68]. Absenteeism reported in the 2013 national health and wellness survey for patients with moderate-to-severe AD was three times greater than those without AD[61]. Therefore, we have implemented 4.3 and 12.9 days per year lost productivity in the model for responders and non-responders respectively.

Table 3.36. Productivity Loss Inputs

Productivity loss	Responder (days per month)	Non-responder (days per month)	Source
UK population norm adjusted for moderate-to-severe AD using the National Health and Wellness Survey	0.36	1.08	ONS 2016, Whitely 2016 [61, 68]

AD=Atopic Dermatidis

Table 3.37. Employment Parameters

Employment Parameters	Input	Source
Value of productivity loss per hour	£15.13	Weighted average of full- and part-time employment wages per hour using data from the Office of National Statistics[242, 243]
Percentage employed	78.5%	Percentage of employed participants in the AWARE study[244]. Like the percentages in SOLO1+2 (72.4%), CHRONOS (76.6%), and CAFÉ (76.6%).
Working hours per day	6.67	Weighted average of full- and part-time employment hours per work day using data from the Office of National Statistics[243]

B 3.5 Summary of base case analysis inputs and assumptions

B 3.5.1 Summary of base case analysis inputs

A full summary of the inputs and variables used in the cost-effectiveness analysis for the base case is provided in Table 3.38.

Table 3.38. Summary of variables in the economic model for the two analyses presented in the base case.

	CAFÉ + CHRONOS CAFÉ-like pooled population			SOLO CAFÉ-like population		
Variable	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**
Patient characteristics at baseline						
Percentage male (%)	60.0	54.0 to 66.0	Table 2.34	64.6	58.1 to 71.1	Table 2.34
Age (years)	38.1	34.3 to 41.9	Table 2.34	38.1	34.3 to 41.9	Table 2.34
Utility at baseline	0.66	0.594 to 0.726	Table 2.34	0.55	0.495 to 0.605	Table 2.34
Response variables						
Efficacy response at 16 weeks (EASI50 AND DLQI ≥4): dupilumab (%)	73.1	65.5 to 80.7 (beta)	Table 2.37	58.7	49.2 to 68.1 (beta)	Table 2.37
52 week sustained response relative risk: dupilumab	0.939	0.889 to 0.992 (log-normal)	Table 3.5	0.939	0.889 to 0.992 (log-normal)	Table 3.5
Efficacy response at 16 weeks (EASI50 AND DLQI ≥4): BSC (%)	27.8	21.1 to 34.6 (beta)	Table 2.37	23.9	15.0 to 32.8 (beta)	Table 2-25
52 week sustained response relative risk: BSC	0.767	0.698 to 0.842 (log-normal)	Table 3.5	0.767	0.698 to 0.842 (log-normal)	Table 3.5
Efficacy response applied at week	8	Not varied in sensitivity analysis	Section B 3.2.5.2	8	Not varied in sensitivity analysis	Section B 3.2.5.2
Annual discontinuation rate (%)	3.7	3.3 to 4.0 (beta)	Section B 3.2.5.4	6.3	5.7 to 6.9 (log-normal)	Section B 3.2.5.4
Mortality increase for patients with AD	1.00	Not varied in sensitivity analysis	Section B 3.2.5.6	1.00	Not varied in sensitivity analysis	Section B 3.2.5.6
Dupilumab compliance (0 - 16 weeks) (%)	100	Not varied in sensitivity analysis	Section B 3.4.3.1	100	Not varied in sensitivity analysis	Section B 3.4.3.1
Dupilumab maintenance compliance (%)	100	Not varied in sensitivity analysis	Section B 3.4.3.1	100	Not varied in sensitivity analysis	Section B 3.4.3.1

	CAFÉ + CHRONOS CAFÉ-like pooled population			SOLO CAFÉ-like population		
Variable	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**
Drug costs						
Dupilumab acquisition cost per 300 mg dose (£)	[redacted]	Not varied in sensitivity analysis	Section B 3.4.6.1, Table 3.23	[redacted]	Not varied in sensitivity analysis	Section B 3.4.6.1, Table 3.23
Flare medication cost: dupilumab (£)	1.89	0.00 to 11.48 (gamma)	Table 3.30	1.89	0.00 to 11.48 (gamma)	Table 3.30
Flare medication cost: BSC (£)	7.46	0.00 to 14.08 (gamma)	Table 3.30	7.46	0.00 to 14.08 (gamma)	Table 3.30
Concomitant (background) medication cost – dupilumab responder (£)	306.50	153.25 to 306.50	Table 3.23	306.50	153.25 to 306.50	Table 3.23
Concomitant (background) medication cost – dupilumab responder (£)	730.20	365.10 to 730.20	Table 3.23	730.20	365.10 to 730.20	Table 3.23
Parameters used in the utility regression						
DUP Q2W EASI change from baseline (all patients)	−26.480	−24.306 to −28.654 (Normal)	Table 2.37	−23.540	−21.204 to −25.876 (normal)	Table 2.37
BSC EASI change from baseline (all patients)	−14.560	−12.643 to −16.477 (normal)	Table 2.37	−11.700	−9.232 to −14.168 (normal)	Table 2.37
DUP Q2W EASI change from baseline (responders)	−29.110	−27.813 to −30.407 (normal)	Table 2.37	−29.880	−28.334 to −31.426 (normal)	Table 2.37
DUP Q2W pruritus change from baseline (all patients)	−3.890	−3.473 to −4.307 (normal)	Table 2.37	−3.300	−2.822 to −3.778 (normal)	Table 2.37
BSC pruritus change from baseline (all patients)	−2.170	−1.803 to −2.537 (normal)	Table 2.37	−2.000	−1.498 to−2.502 (normal)	Table 2.37
DUP Q2W pruritus change from baseline (responders)	−4.270	−3.784 to −4.756 (normal)	Table 2.37	−3.830	−3.256 to −4.404 (normal)	Table 2.37
DUP Q2W utility change from baseline (all patients)	0.194	0.152 to 0.236 (normal)	Table 2.37	0.281	0.234 to 0.328 (normal)	Table 2.37
BSC utility change from baseline (all patients)	0.119	0.082 to 0.156 (normal)	Table 2.37	0.161	0.112 to 0.210 (normal)	Table 2.37
DUP Q2W utility change from baseline	0.257	0.216 to 0.298		0.313	0.258 to 0.368	

	CAFÉ + CHRONOS CAFÉ-like pooled population			SOLO CAFÉ-like population		
Variable	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**
(responders)		(normal)			(normal)	
Adverse event rates						
DUP Q2W injection site reaction rate	0.349	Not varied in sensitivity analysis	Table 3.8	0.881	Not varied in sensitivity analysis	Table 3.8
BSC injection site reaction rate	0.0			0.000		
DUP Q2W allergic conjunctivitis rate	0.199			0.114		
BSC allergic conjunctivitis rate	0.0			0.030		
DUP Q2W infectious conjunctivitis rate	0.075			0.163		
BSC infectious conjunctivitis rate	0			0.022		
DUP Q2W oral herpes rate	0.07			0.135		
BSC oral herpes rate	0			0.059		
Annualised event rate for flares: dupilumab	0.18	2.5. (Tested in one-way sensitivity analysis)	Table 3.31	0.18	2.5. (Tested in one-way sensitivity analysis)	Table 3.31
Annualised event rate for flares: SC	0.78	15.5. (Tested in one-way sensitivity analysis)	Table 3.31	0.78	15.5. (Tested in one-way sensitivity analysis)	Table 3.31
Adverse event costs						
Injection site reaction cost	104.24	Not varied in sensitivity analysis	Table 3.35	104.24	Not varied in sensitivity analysis	Table 3.35
Allergic conjunctivitis cost	36.00			36.00		
Infectious conjunctivitis cost	45.51			45.51		
Oral herpes cost	36.00			36.00		
NHS resource use parameters						
Average number of Primary care visits per year: Responder	2	The unit number of resource parameters is not	Table 3.22	2	The unit number of resource parameters is not	Table 3.22
Average number of Primary care visits	12.81			12.81		

	CAFÉ + CHRONOS CAFÉ-like pooled population			SOLO CAFÉ-like population		
Variable	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**
per year: Non-responder		tested separately from their associated costs in sensitivity analysis. In order to reflect the uncertainty in both of these parameters the unit costs are varied by 50% (see below). This is likely to be a conservative estimate. Other estimates are also tested in one way sensitivity analysis			tested separately from their associated costs in sensitivity analysis. In order to reflect the uncertainty in both of these parameters the unit costs are varied by 50% (see below). This is likely to be a conservative estimate. Other estimates are also tested in one way sensitivity analysis	
Average number of consultant dermatologist visits per year: Responder dupilumab	4 in first year followed by 2			4 in first year followed by 2		
Average number of consultant dermatologist visits per year: Responder BSC	2			2		
Average number of consultant dermatologist visits per year: Non-responder	7.03			7.03		
Average number of accident and emergency attendances per year: Responder	0.06			0.06		
Average number of accident and emergency attendances per year: Non-responder	0.25			0.25		
Average number of in patient hospitalisations per year: Responder	0.03			0.03		
Average number of in patient hospitalisations per year: Non-responder	0.23			0.23		
Resource use costs						
Primary care visit unit cost	£36.00	18.00 to 54.00 (gamma)	Section B 3.4.6.5	£36.00	18.00 to 54.00 (gamma)	Section B 3.4.6.5
Dermatologist visit unit cost	[redacted]	[redacted]	Section B 3.4.6.5	[redacted]	[redacted]	Section B 3.4.6.5
Emergency room visit unit cost	£137.82	68.91 to 206.73 (gamma)	Section B 3.4.6.7	£137.82	68.91 to 206.73 (gamma)	Section B 3.4.6.7
Hospitalisation unit cost	£1,795.29	897.65 to 2,692.94 (gamma)	Section B 3.4.6.6	£1,795.29	897.65 to 2,692.94 (gamma)	Section B 3.4.6.6
Day case unit cost	£492.19	246.10 to 738.29 (gamma)	Section B 3.4.6.5	£492.19	246.10 to 738.29 (gamma)	Section B 3.4.6.5

	CAFÉ + CHRONOS CAFÉ-like pooled population			SOLO CAFÉ-like population		
Variable	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**	**Value (reference to appropriate table or figure in submission)**	**Measurement of uncertainty and distribution: CI (distribution)**	**Reference to section in submission**
Full blood count unit cost	£3.10	1.55 to 4.65 (gamma)	Section B 3.4.6.3	£3.10	1.55 to 4.65 (gamma)	Section B 3.4.6.3
Dermatology nurse visit unit cost	£10.75	5.38 to 16.13 (gamma)	Section B 3.4.6.5	£10.75	5.38 to 16.13 (gamma)	Section B 3.4.6.5
Subcutaneous training cost	£56.00	50.40 to 61.60 (gamma)	Section B 3.4.6.1	£56.00	50.40 to 61.60 (gamma)	Section B 3.4.6.1
Other model parameters						
Discount rate for costs	3.5%	Not tested in sensitivity analysis	NICE ref case	3.5%	Not tested in sensitivity analysis	NICE ref case
Discount rate for benefits	3.5%		NICE ref case	3.5%		NICE ref case

AD, atopic dermatidis; BSC, best Supportive Care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; Q2W once every two weeks

B 3.5.2 Assumptions

The assumptions held in the model base case are summarised in Table 3.39.

Table 3.39 Assumptions in the model base case

Assumption	Implementation	Justification
Quality of life is not sustained indefinitely in the BSC arm	According to methodology reported in McKenna 2009*[220]	Response to BSC observed in the trial unlikely to be maintained after trial end. Therefore, placebo benefit is returned to baseline. Tested with HCP opinion.
BSC resource use estimates based on current dupilumab target patients. Dupilumab responder resource use based on clinician survey / validated by EAMS clinicians	As counts per patient-year multiplied by estimated cost element	Best available evidence. Data from retrospective case notes review supplemented by database analysis. The number of GP visits is based on an estimate for dermatology based visits only. The frequency of visits recorded in the database analysis is reduced by the average number of visits per adult in the UK.
All observed data are a better reflection of likely true impact on NHS costs/efficacy	Using the scenario analysis from the trials: 'All Observed' rather that the 'primary analysis'	Better approximation of likely impact in NHS
Response at 52 weeks for CAFÉ patients is conditional on the response at 16 weeks from CHRONOS	Response relative risk applied according to CHRONOS	Used the relationship between CHRONOS 16wk to 52 week as an approximation for the expected response for patients at 52 weeks, given all other trials have endpoints at 16 weeks.
Disutility associated with treatment of AD flares are already accounted for in the EQ-5D for both arms	Utility is captured by the average of EQ-5D over time within the treatment arms and Markov treatment states	To avoid double counting. Flares were relatively rare in the studies. The frequency of EQ-5D data collection ensured that flare disutility was captured as a matter of course during the trial.
No AE disutilities in model	Disutility set to 0 for AEs	To avoid double counting. Given frequency of EQ5D assessment assumed no need for further disutility due to AEs to be applied.
Post-IM treatment history is a proxy for uncontrolled moderate-to-severe disease	Moderate-to-severe AD patients that are immunosuppressant failures from the CAFÉ + CCL + Solo-CL	In the real world dupilumab patients would not be 'washed out' as they were in the trial therefore failure on prior treatment is a valid method for identification of target patients
Ciclosporin comparator use for 1 year in scenario analysis in line with scope	Ciclosporin included in 1 year decision tree	In line with guidelines which state it should not be used for more than 1 year. Recent treatment pattern survey suggested average duration of use is 5.8 months[116]. Tested in Sensitivity analysis.
100% compliance	Cost of dupilumab is set at 100%	Reflects the cost burden to the NHS. Compliance rates in the trial are high >95%
Dupilumab non-responders revert to BSC until death	Cost and utility as for BSC non-responder	Simplifying assumption in the model
Dupilumab is assumed to be self-administered	one off cost for injection training incurred	To reflect the cost to the NHS with dupilumab established as a treatment options; assumed use in real world
Dupilumab response at the end of year 1 is carried forward into Markov Model BSC patients retain the 16-week	Treatment- and response-specific utilities are continued from end of year 1 for dupilumab	Simplifying assumption

observed utility weights in the BSC Treatment health state		
Efficacy (change in EASI, NRS, and/or utility weights) is assumed to occur at 8 weeks (halfway through the clinical assessment of 16 weeks)	Payoffs for response category begins at week 8	Based on cumulative time to response plots from the clinical trials where 50% of patients who responded exhibited response before 8 weeks. Week 4 tested in scenario analysis

AD, atopic dermatidis; AE, adverse events; BSC, Best Supportive Care; EAMS, Early Access to Medicines Scheme; EASI, Eczema Area Severity Index HCP, health care professional; IM, immunotherapy; NRS, Numeric Rating Scale

B 3.5.3 Sensitivity analysis

To test the stability of the model and the robustness of assumptions and inputs in the model we carried out both probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA) and scenario analyses. In the OWSA the key drivers in the model were: efficacy response thresholds, timing of assessment (16 to 24 weeks), timing of efficacy onset, flare event rate, persistence of utility, resource utilisation rates and costs and time horizon. In the scenarios we explore the full licence population compared with both BSC and ciclosporin.

Assessment of dupilumab efficacy response at week 24

In line with the SmPC wording, ' *Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks*' we assessed efficacy response at 24 weeks based on CHRONOS trial data.

The assessment of efficacy at 24 weeks is supported by clinical opinion. Clinical experts informed us that for some patients achievement of efficacy targets in 16 weeks would be difficult due to the extent of their underlying disease and that it would be unethical to withdraw treatment on the basis of a short-term goal when these patients are clearly benefiting.

In the CHRONOS study all patients continued on treatment regardless of clinical assessment at 16 weeks.There were 106 Q2W dupilumab patients in CHRONOS. Of these there were 24 people who did not reach a response of EASI-50 and DLQI4+ at 16 weeks and 77 who met these criteria. Of the 24, seven went onto to be responders at 24 weeks (a further 6.6% (7/106)). In the base case with concomitant use of TCS (CAFÉ + CHRONOS CAFÉ-like) 73.1% of patients were responders at 16 weeks (EASI-50 and DLQI4+). For the purposes of modelling a 24 week assessment point it is assumed that all the 16 week responders would continue on treatment without further assessment and that patients deemed 'partial responders' by their clinicians are reassessed at 24 weeks. Using the proportion of patients from CHRONOS who went on to respond the overall proportion of patients deemed responders at 24 weeks in CAFÉ + CHRONOS CAFÉ-like is estimated to be 73.1% + 6.6%. = 79.7%. The model includes a single assessment point and so for this sensitivity analysis a simplifying assumption is made that efficacy assessment is at 24 weeks for all patients.

However, in order to assess response for partial responders at 24 weeks an additional dermatologist visit would be required. A fraction of a dermatologist visit cost is added to account for the additional visit by partial responders. In order to be conservative and to capture the possibility that some patients judged partial responders at 16 weeks may not

reach the efficacy end point of EASI-50 and DLQI4+ at 24 weeks, 0.1 (vs. 0.066 as pre-responder proportion) additional dermatologist visits are included.

B 3.6 Base case results

B 3.6.1 Base case incremental cost-effectiveness analysis results

The expected position for dupilumab in clinical practice in the UK is for use in patients who have been optimised on topical therapies and an immunosuppressant but for whom these therapies have failed, are contraindicated or are not tolerated (see Figure 1.6). For this population there remain no other treatment options. This population is exemplified by the CAFÉ study in the LIBERTY trial program. However, in both CHRONOS and SOLO there were a proportion of patients with experience of ciclosporin, the 'CAFÉ-like populations'.

In line with this positioning and to include the entire available data set for these patients we present results for the full analysis sets for the CAFÉ + CHRONOS-CAFÉ-like and SOLO CAFÉ-like pooled populations below. All the CAFÉ-like patients are not pooled for the basecase as the trial methodology differs with respect to use of concomitant TCS as required between SOLO and the other two studies.

The base case results are calculated on the following key parameters (Table 3.40)

Table 3.40. Parameter settings in the base case

Parameter	Setting
Perspective	NHS England
Time horizon	Lifetime
Trial population	CAFÉ+ CCL , SOLO-CL Q2W
Comparator	BSC (placebo)
Analysis method for efficacy	All observed data
Utility calculation	Regression
Time point for efficacy application	Week 8
Efficacy evaluation @ 16 weeks	EASI50 and DLQI≥4 points change
Probability of sustained response	According to clinician survey
Discontinuation	For CAFÉ+CCL: according to CHRONOS 52 week rates For SOLO-CL: according to SOLO CONTINUE

BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area Severity Index; Q2W once every two weeks

Table 3.41 Base case results for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,874

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 3.42 Base case results for the SOLO CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,703

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

This result would demonstrate that dupilumab is an appropriate use of NHS resources for monotherapy and in combination with TCS. What is notable is the scale of QALY gain given this is a therapy that does not impact life expectancy, as such this gain represents a substantial and long-term improvement in patient quality of life, both reflective of the benefit of dupilumab and the very poor starting health state for patients with moderate-to-severe AD for whom systemic immunosuppressants are medically inadvisable. Disaggregated results are provided in Appendix J

B 3.7 Sensitivity analyses

B 3.7.1 Probabilistic sensitivity analysis[220]

The parameters and their distributions used in the probabilistic sensitivity analysis are specified in Table 3.38. The probabilistic results for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC are presented in Figure 3.9 and Figure 3.10.

Figure 3.9. Cost-effectiveness Acceptability Curve (CEAC)[116] for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations)

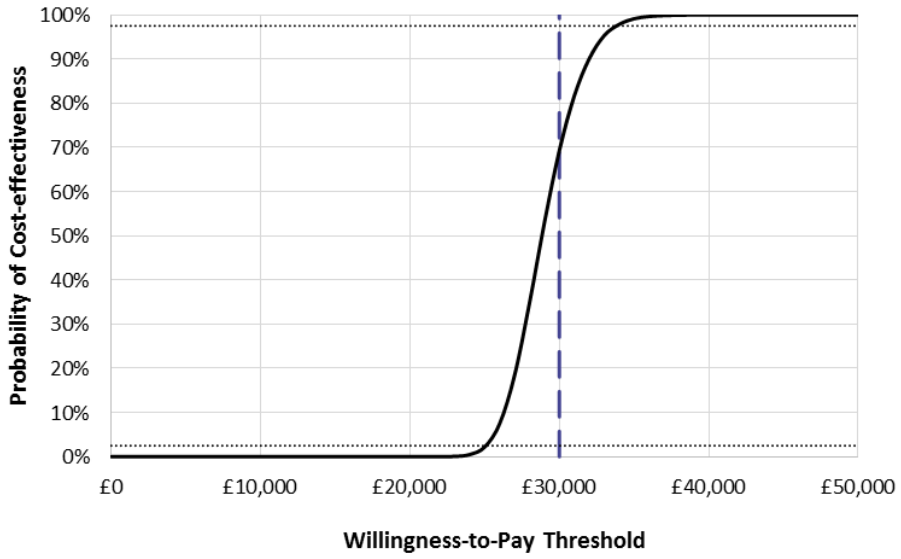


Figure 3.10. Scatter plot for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations)

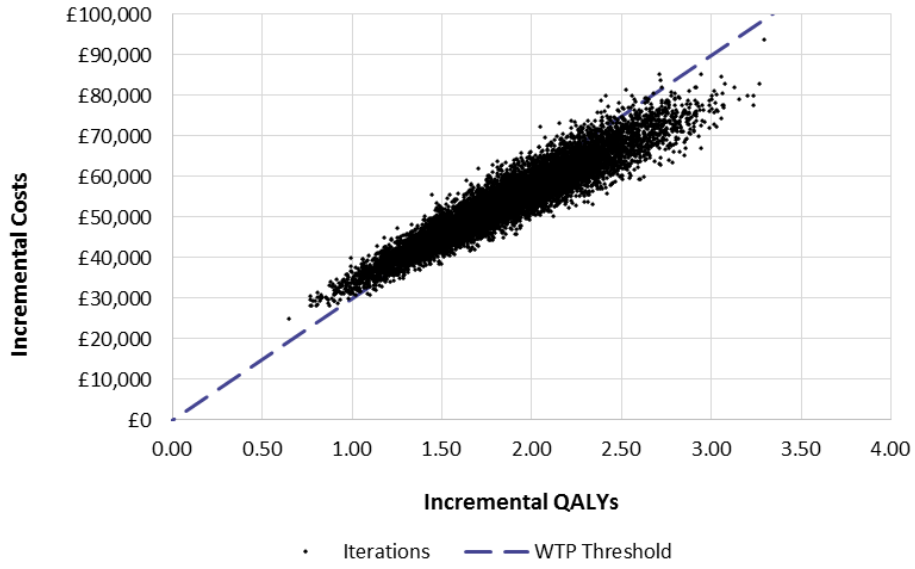
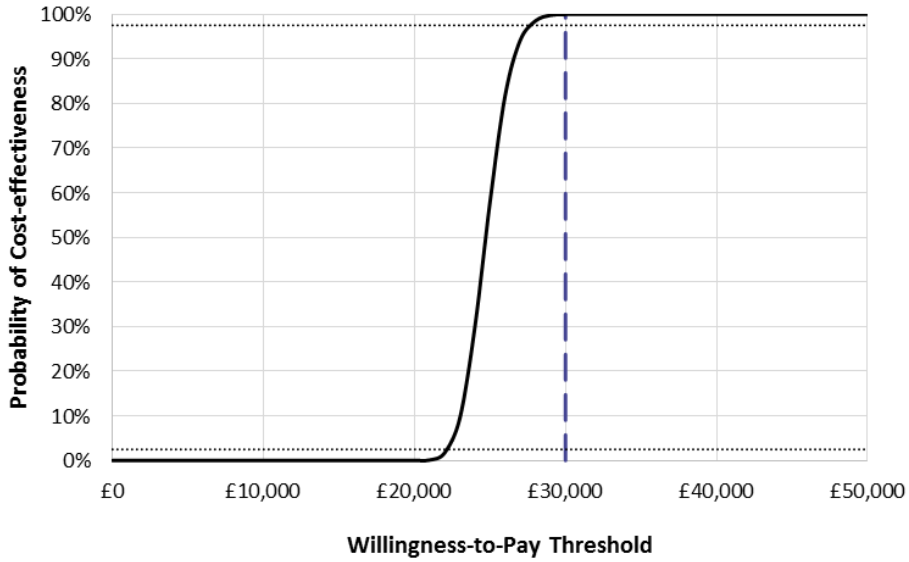


Figure 3.11. Cost-effectiveness Acceptability Curve (CEAC) for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations)



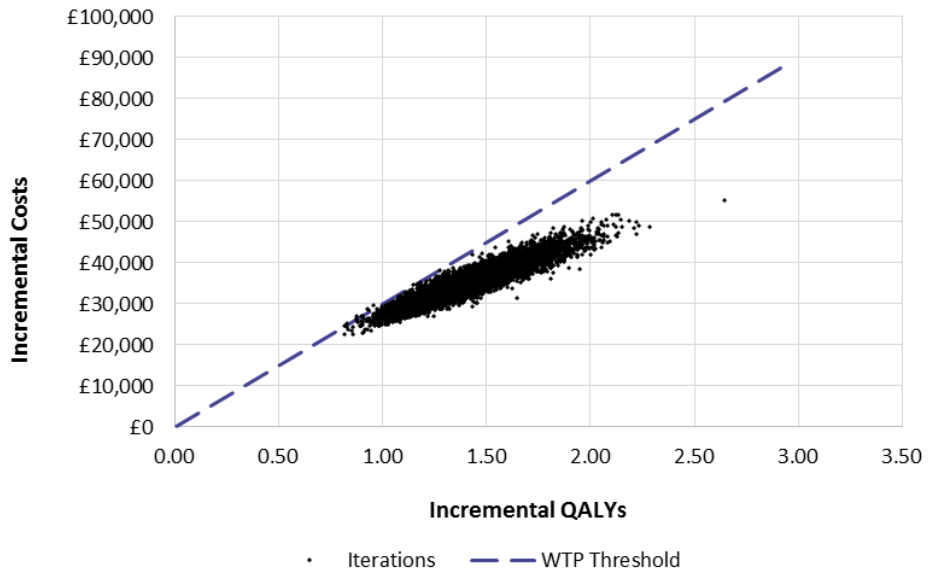
BSC, Best Supportive care; Q2W, every two weeks

Table 3.43. Base case results (probabilistic) for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	£28,686

BSC= Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 3.12. Scatter plot for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations).



BSC, Best Supportive care; QALY, quality-adjusted life year; Q2W, every two weeks; WTP, willingness to pay

Table 3.44. Base case results (probabilistic) for the SOLO CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	£24,640

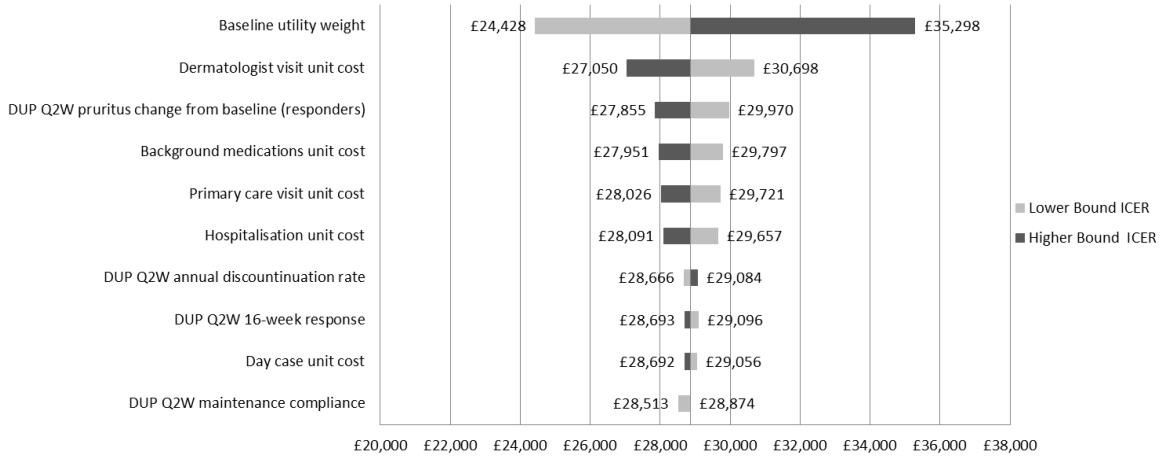
BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Q2W, every two weeks

For the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC the probabilistic ICER is £28,686/QALY and at a WTP of £30,000 the probability of being cost-effective is 70% at £20,000 it is 0%.

For the comparison of SOLO-CAFÉ-like with BSC the probabilistic ICER is £24,640/QALY and at a WTP of £30,000 the probability of being cost-effective is 100% and at £20,000 WTP it is 0%.

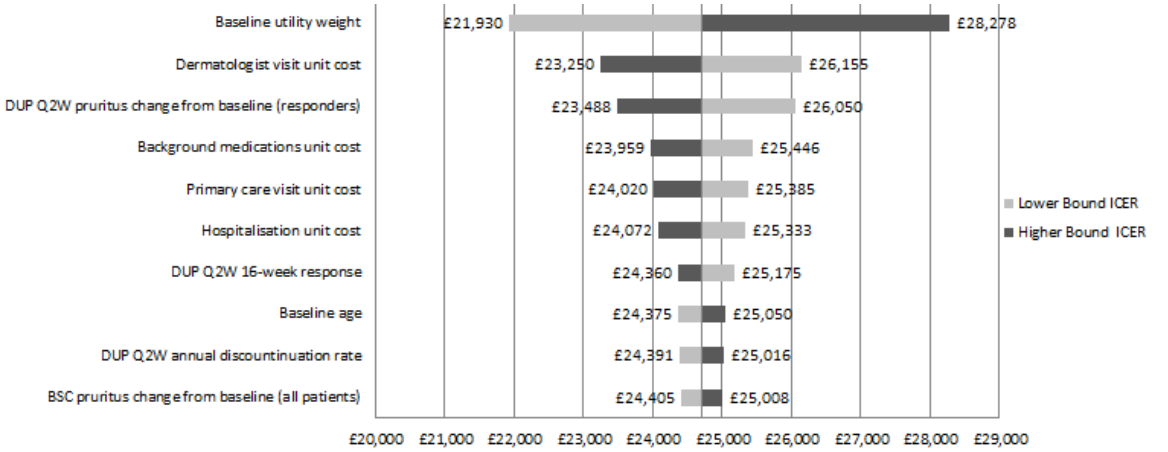
B 3.7.2 Deterministic sensitivity analysis

Figure 3.13. Tornado diagram for one-way sensitivity analyses for the comparison CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC.



BSC, Best Supportive Care; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; DUP Q2W, dupilumba 300 mg every two weeks

Figure 3.14. Tornado diagram for one-way sensitivity analyses for the comparison SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC.



BSC, Best Supportive Care; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; DUP Q2W, dupilumba 300 mg every two weeks

Further sensitivity analyses were carried out to account for factors not included in the calculations for the tornado diagrams above. (**Table 3.45** and Table 3.46).

Table 3.45. One-way sensitivity analyses for the comparison CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC

	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	**£28,874**
Utility				
Methodology: Obs change from baseline.	[redacted]	[redacted]	[redacted]	£26,436
Maintenance of utility benefit post trial period				
Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£36,378
No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£28,127
Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£30,456
Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£29,313
No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£39,567
Time horizon				
5 years	[redacted]	[redacted]	[redacted]	£40,823
10 years	[redacted]	[redacted]	[redacted]	£33,110
20 years	[redacted]	[redacted]	[redacted]	£29,993
Measure of response				
Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£30,903
Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£30,445
Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£28,730
Primary analysis method for response	[redacted]	[redacted]	[redacted]	£28,945
Additional efficacy assessment at 24 weeks	[redacted]	[redacted]	[redacted]	£29,206
Resource use				
TA82 [Garside 2004] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£30,157
Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC) GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92) A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)	[redacted]	[redacted]	[redacted]	£25,770
Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£30,316
Number of flares increased in accordance with Simpson 2016[63] (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£28,052
Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£29,797
No nurse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£28,844
Societal costs,				
Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 (National Health and Wellness Survey, Whitely, 2016)[61]	[redacted]	[redacted]	[redacted]	£26,474

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; ICER, incremental cost-effectiveness ratio; LOCF, last oberservation carrier forward; LYG, life years gained; QALYs, quality-adjusted life years; QoL, quality of life

Table 3.46. One-way sensitivity analyses for the comparison SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC.

	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	**£24,703**
Utility				
Methodology: Obs change from baseline	[redacted]	[redacted]	[redacted]	£23,349
Maintenance of utility benefit post trial period				
Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£29,773
No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£24,036
Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£26,153
Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£25,108
No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£31,711
Time horizon				
5 years	[redacted]	[redacted]	[redacted]	£33,762
10 years	[redacted]	[redacted]	[redacted]	£27,723
20 years	[redacted]	[redacted]	[redacted]	£25,376
Measure of response				
Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£25,544
Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£25,052
Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£24,514
Primary analysis method for response	[redacted]	[redacted]	[redacted]	£26,092
Additional efficacy assessment at 24 weeks	[redacted]	[redacted]	[redacted]	£25,544
Resource use				
TA82 [Garside 2004] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£25,701
Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC) GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92) A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)	[redacted]	[redacted]	[redacted]	£22,164
Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£25,851
Number of flares increased in accordance with Simpson 2016 (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£24,025
Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£25,446
No nurse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£24,664
Societal costs,				
Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 NHWS, Whitely, 2017	[redacted]	[redacted]	[redacted]	£22,690

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; ICER, incremental cost-effectiveness ratio; LOCF, last oberservation carrier forward; LYG, life years gained; QALYs, quality-adjusted life years; QoL, quality of life

In addition to the analyses above, the further sensitivity analysis was carried out on the FAS population from CAFÉ also using the base case settings. The results are tabulated below (Table 3.47).

Table 3.47. Incremental cost-effectiveness results for CAFÉ FAS, including dupilumab Q2W patients.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,441

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; FAS, full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W, once every two weeks; QALYs, quality-adjusted life years

The QALY gain for the CAFÉ FAS population is 1.61 which is a significant benefit for a non-life extending therapy. The ICER of £32,441/QALY reflects the higher baseline EQ-5D in this patient population and lower QALY gain in comparison with CAFÉ + CCL. However all other clincal and patient reported measures are similar to those recorded in the LIBERTY AD studies overall.

B 3.7.2.1 Discussion of sensitivity analysis results

This economic model was tested against a range of assumptions and inputs. As would be expected varying the structural assumptions around time horizon and perspective had a significant impact on the ICER. Assumptions relating to the persistence of utility benefit in the post-trial period were also a significant driver of the ICER. With these exceptions the sensitivity analysis indicates that the economic model is stable, providing consistent ICER estimates.

Of the other assumptions and inputs tested, the key drivers of the ICER results include the assumption relating to loss of utility in the best supportive care (BSC) arm, baseline patient utility score and the total cost of dermatology visits (both unit cost and frequency of visit).

It is important to note that a number of conservative assumptions are made in the model base case. This includes the loss of persistence of utility in the dupilumab arm from year 2. This was based on clinician opinion however, data from the phase IIb, CHRONOS 52 week and MAINTAIN 104-week trials indicate response will persist while on treatment. In contrast the gradual loss on the BSC arm may be an over estimate, given that once the 'trial effect' is removed patients are likely to return to baseline utility scores within less than 3 years.

The costs assigned to BSC well describe the cost of routine background therapies however, they are likely to underestimate the true cost of BSC in the expected patient population, as this is the popuation that cycles through multiple systemic immunosuppressants, requires rescue treatment more frequently and is more at risk of hospital admission. Costs on the dupilumab arm are slightly overestimated as we assign 100% of nurse training for self-injection as an NHS costs, however it is likely some patients will choose to initate treatment at home via a Patient Support Programme nurse.

There is disutility asscociated with flare. However the frequency of measurement of EQ-5D in the LIBERTY trial programme means that this is likely to be captured in the QALY. A conservative assumption was made to not add a further decrement for flares in order to avoid double counting. However this may underestimate the benefit of dupilumab vs BSC in in the reduction of flares (See Figure 2.12, Figure 2.18 and Figure 2.26). Aspects of dupilumab that are currently uncertain but could under-value the drug because they are not included in the current model are reduction in skin infections and the long-term benefit this would have on patients and the NHS, (including reduced use of antibiotics, topical and oral steroids), reduced rates of anxiety and depression. While the relationship with mortality is uncertain improved mental health may reduce suicidal ideation. Data also indicate a reduced risk of eczema herpeticum[182], which while very rare, carries with it a risk of mortality.

24 week responders

The ICERs calculated for the base case populations which include an additional assessment for partial responders at 24 weeks, do not differ substantively from the ICER calculated at 16 weeks (Table 3.48 and Table 3.49)

Table 3.48 Incremental cost-effectiveness results for Cafe + CCL including dupilumab Q2W patients vs, BSC with efficacy assessment at 24 weeks.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,206

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

Table 3.49 Incremental cost-effectiveness results for SOLO-CL including dupilumab Q2W patients vs, BSC with efficacy assessment at 24 weeks.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,544

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

These are likely to be conservative estimates because all patients continue on dupilumab until 24 weeks in this scenario. In real world clinical practice, in line with the SmPC consideration should be given to discontinuing treatment for, *'patients who have shown no response after 16 weeks'*. In this analysis all patients continue to 24 weeks accruing dupilumab cost.

B 3.7.3 Scenario analysis

B 3.7.3.1 Scenario analysis 1:

The full licence population as defined in the dupilumab licence. This includes moderate-to-severe AD patients who are eligible for systemic therapy. This scenario analysis includes patients from the CHRONOS FAS and SOLO pooled FAS analyses. The SOLO analysis reflects dupilumab monotherapy whereas the CHRONOS analysis reflects concomitant (background) use of TCS/TCI as required. These analyses are not restricted based on prior systemic therapy history.

Scenario analysis was carried out on the FAS populations from CAFÉ and from CHRONOS using the base case settings. The results are tabulated below Table 3.50 and Table 3.51) and disaggregated costs and outcomes are provided in Appendix J.

Table 3.50. Incremental cost-effectiveness results for CHRONOS FAS, including dupilumab Q2W patients.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,188

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; FAS, full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W, once every two weeks; QALYs, quality-adjusted life years

Table 3.51. Incremental cost-effectiveness results for SOLO FAS, including dupilumab Q2W patients.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,729

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; FAS, full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W, once every two weeks; QALYs, quality-adjusted life years

B 3.7.3.2 Scenario analysis 2 - Cost-effectiveness compared to ciclosporin.

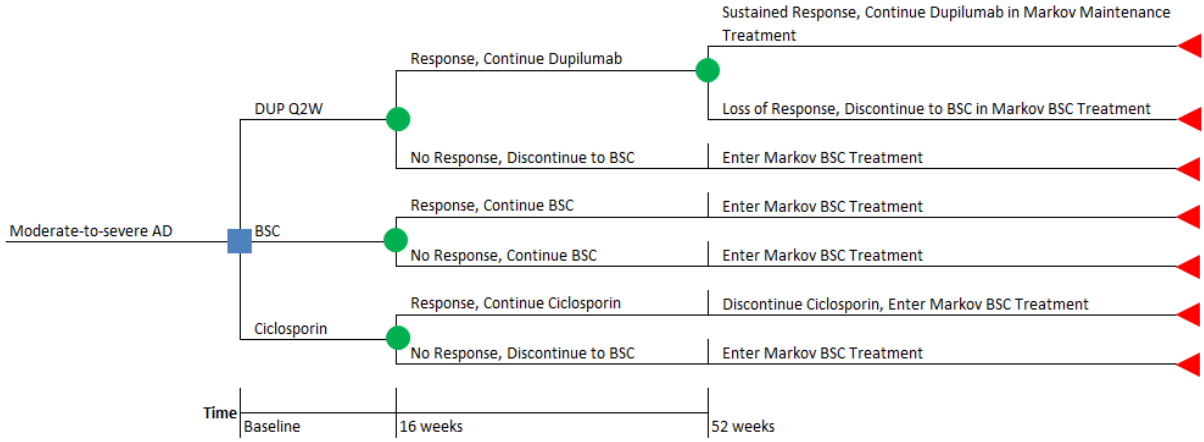
A cost-effectiveness analysis comparing dupilumab versus currently available systemic immunosuppressants (IM) is presented below. This analysis was requested within the scope of this appraisal however according to UK clinician opinion; dupilumab would not be used instead of currently available systemic immunosuppressants but rather after these have failed.

According a survey of 61 consultant-level dermatologists in the UK, the most common systemic treatments include azathioprine being used as first line followed by oral corticosteroids, ciclosporin and methotrexate[116]. However, only ciclosporin is licenced in severe AD. Further differences in the average duration of treatment between agents were reported by the authors. On average, azathioprine treatment was continued for 13.8 months, compared with 5.8 months for ciclosporin. Methotrexate was continued for 15.1 months on average, similarly to azathioprine. Majority of respondents reported using ciclosporin for a

maximum of 7–12 months, compared with > 24 months for azathioprine and methotrexate. As shown in B 2.9, no data were available for azathioprine and methotrexate and limited data are available for ciclosporin.

Figure 3.15 below illustrates the decision tree used for this scenario analysis. At the end of the tree patients transition to the Markov model as shown in Figure 3.4 previously. Patients with moderate-to-severe AD can either be treated with dupilumab, BSC, or ciclosporin at the blue decision node. At the 16-week assessment point, those on active treatment (dupilumab or ciclosporin) without response discontinue to BSC.

Figure 3.15. Decision tree including ciclosporin.



In a recent treatment pattern survey, 61 clinicians from more than 30 centres around the UK reported the average time spent on ciclosporin for patients with moderate-to-severe AD was 5.8 months and the maximum duration of treatment allowed was 7 -12 months[116]. This is in line with guidelines which state that use beyond one year should be avoided due to concerns over long-term safety. In the model ciclosporin-treated patients who had response at 16-weeks must discontinue treatment at the end of the year. At this point, they enter the Markov in the SC Treatment health state. For all branches (not shown for simplicity), mortality is integrated into the decision tree payoffs and an assumption is made that death occurs at 6 months. Those that die enter the Markov in the Death health state.

B 3.7.3.2.1 *Model inputs*

Unless described here, all other model inputs used for this analysis are as reported in Section B 3.5.

B 3.7.3.2.2 *Efficacy outcomes*

Ciclosporin efficacy is based on the results from the MAIC vs. DUP Q2W reported in Section B 2.9 based on the efficacy outcome EASI-50

Table 3.52. Efficacy outcomes for CSA based on MAIC

Time Point	Criteria	Analysis Method	Ciclosporin (MAIC)
Week 16	EASI-50	All observed	57.0%
Week 52	EASI-50	All observed	N/A

Time Point	Criteria	Analysis Method	Ciclosporin (MAIC)
Week 16	EASI-50	Primary	57.0%
Week 52	EASI-50	Primary	N/A

CSA, ciclosporin A; EASI, Eczema Area Severity Index; MAIC, Matching-adjusted indirect comparison

The unit price for ciclosporin was based on the lowest package cost of 30 x 25-mg capsules from the BNF September 2017 update (Capimune £13.05) at £0.44 per 25mg tablet.

The ciclosporin dosing inputs define the dosing pattern for ciclosporin for the first 6 weeks of therapy and for weeks 6-52. The default ciclosporin doses for each time-period are based on the MAIC used to estimate ciclosporin efficacy, where the Haeck et al. (2011) study[150] dosed patients at 5 mg/kg daily for 6 weeks followed by 3 mg/kg daily (Table 3.53).

Table 3.53 Ciclosporin dosing inputs

Treatment	Dose or weight	Source
Ciclosporin dosing baseline to week 6	5 mg/kg daily	Haeck, 2011[150]
Ciclosporin dosing week 6 to 52	3 mg/kg daily	
Average patient weight	76kg	Weighted average in LIBERTY programme at baseline

B 3.7.3.2.3 *Resource use*

In the absence of any other data, resource use for ciclosporin is considered equivalent to dupilumab use with the exception of testing and monitoring.
The monitoring requirements specific for AD with systemic use of ciclosporin are as follows (taken from the BNF September 2017 update[235]).

- Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting treatment for psoriasis or AD.
- Monitor liver function.
- Monitor serum potassium, especially in renal dysfunction (risk of hyperkalaemia).
- Monitor serum magnesium.
- Measure blood lipids before treatment and after the first month of treatment.
- In psoriasis and AD monitor serum creatinine every two weeks for first three months then every month.
- Investigate lymphadenopathy that persists despite improvement in AD.

To reflect this increased burden of monitoring exemplified by the requirement for *'serum creatinine every two weeks for first three months then every month for one year'* we have assumed that 15 full blood counts are required within year (

Table 3.54). Each blood count requires at least one nurse visit. It is likely that some testing will be combined with routine dermatology appointments and, so we have estimated the number of additional nurse visits required at 7.5 (0.5 *15 = 7.5).

Table 3.54. Estimated resource use for ciclosporin patients

Resource	Year 1	Years 2+
Primary care visit		
Responder	2.00	2.00
Non-responder	12.81	12.81
Dermatologist visit		
Responder	4.00	2.00
Non-responder	7.03	7.03
Emergency room visit		
Responder	0.06	0.06
Non-responder	0.25	0.25
Hospitalisation		
Responder	0.03	0.03
Non-responder	0.23	0.23
Day case		
Responder	0.00	0.00
Non-responder	0.17	0.17
Full blood count		
Responder	15.00	4.0
Non-responder	15.00	4.0
Dermatology nurse visit		
Responder	7.50	0.44
Non-responder	7.50	0.57

Ciclosporin is most often associated with long-term clinical events; however, based on UK clinical restrictions its use is limited to 1 year. Thus, ciclosporin-related adverse events are not considered. Utility weights for ciclosporin are assumed to be equivalent to DUP Q2W in the first year.

B 3.7.3.2.4 *Results*

The results for the comparison of 1 year of ciclosporin use are presented in Table 3.55 and Table 3.56.

Table 3.55. Incremental cost-effectiveness results for CHRONOS FAS including dupilumab Q2W patients vs, ciclosporin.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,638

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

Table 3.56. Incremental cost-effectiveness results for SOLO FAS including dupilumab Q2W patients vs, ciclosporin.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,092

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

Ciclosporin can be used for more than one cycle in some patients in the real world. The analysis above represents 1 year of continuous treatment. However it should be noted that the average length of a course of treatment according to the treatment pattern survey by Taylor estimates 5.8 months[116]. Therefore, the analysis above can be interpreted as equivalent to two courses of treatment.

B 3.8 Validation

B 3.8.1 Validation of cost-effectiveness analysis

The model was subjected to a thorough validation process in accordance with guidelines for validation put forth by the International Society for Pharmacoeconomics and Outcomes Research Society and the Society for Medical Decision-Making Joint Task Force for Modelling Good Research Practices[245]. These guidelines stress the importance of face validity (confirming the model approach, data sources, and assumptions with experts), internal validity (quality-checking of parameter values and calculations), and external validity (comparing model results with other published studies).

Face validity was tested throughout model development with external health economic and clinical experts. Internal validity was tested during which researchers not involved in model development checked the accuracy of all data extracted from the literature, the logical structure of the model, and the accuracy of all calculations and programming. Additionally, the researchers conducting the quality control review, in collaboration with the model developers, subjected the model to a series of diagnostic tests to ensure that the model reacts as expected. External validation was not possible as this is the first cost-effectiveness model for long-term treatment with a biologic in AD. All other cost-effectiveness models identified, were for short-term treatment of AD and were not relevant comparisons to this model.

Please see Appendix U for more details on the validation process.

B 3.9 Interpretation and conclusions of key economic evidence

B 3.9.1 Conclusions from the cost-effectiveness analysis

The economic analysis for the base case relevant to the UK demonstrates that dupilumab is a cost-effective treatment as monotherapy and in combination with TCS when compared to BSC in patients with moderate-to-severe AD who have been optimised on topical treatments and who were contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic

immunosuppressant. The ICER is £24,703/QALY in monotherapy and £28,874/QALY with TCS, both of which are below £30,000/QALY. According to NICE guidance judgement relating to a technology with an ICER above a plausible ICER of £20,000 per QALY gained should take account of the following factors:

The degree of certainty around the ICER. As demonstrated in the sensitivity analysis the base case ICERs are stable and robust to variation in inputs and structural assumptions. According to the probabilistic sensitivity analysis there is a high likelihood that dupilumab is cost-effective (70% to 100%) vs. BSC with a WTP threshold of £30,000.

Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been fully captured, and may therefore misrepresent the health utility gained. Dupilumab offers significant benefits to patients and society that are not captured in the QALY. Social functioning is not included in the descriptive system in EQ-5D but is an important aspect of disease burden. It is likely that dupilumab which significantly reduces pruritus and sleep loss, will enable patients to return to work or take fewer days off with associated productivity gains (the proportion of patients with no missed work days at week 16 in CAFÉ was 83% for placebo vs. 92% for dupilumab patients). This will impact the associated psychological burden of joblessness and feelings of social isolation/depression[62][62][62][62][62][62][62][62](62)[62]. AD has an impact on the families of patients and on relationships[205]. It is likely that improvements in symptoms and QoL for patients may improve QoL for those close to them**.**

The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure. Dupilumab was the first medicine for a chronic, non-life-threatening condition to be recognised in EAMS[246]. This highlights the innovative nature of dupilumab, and the rapid enrolment of 244 patients reflects high unmet need associated with moderate-to-severe AD. There are no effective treatments for AD patients with intolerance, inadequate response or contraindication to current immunosuppressant therapies. The only licenced immunosuppressant for AD, ciclosporin, is recommended for short-term use and has an unfavourable benefit risk profile for long-term management of this chronic relapsing condition[7, 117]. Significant numbers of patients have an inadequate response despite treatment with a systemic immunosuppressant[247] and episodic management of symptoms with these (on- and off-label) is not a satisfactory approach to target underlying inflammation in the longer-term. Dupilumab is the first targeted biologic therapy for AD, which is suitable for long-term use. It is a translational medicine developed through a robust understanding of the pathophysiology of AD, leading to specific targeting of the underlying inflammatory pathway[15-18].

Scenario and sensitivity analyses support the results of the base case. In the full licenced population which incorporates the full analysis set (FAS) the ICER for dupilumab vs BSC is £25,188/QALY (CHRONOS), £26,729/QALY (SOLO 1 & 2) and £32,441/QALY (CAFÉ). Although published evidence for current systemic immunosuppressants is very limited, a cost-effectiveness analysis vs. ciclosporin (a licenced proxy for currently systemic therapy) shows the ICERs are £25,638/QALY: CHRONOS FAS and £28,092/QALY: SOLO 1 & 2 FAS.

These results are stable and robust. The ICER is most affected by assumptions relating to baseline utility and maintenance of QoL over time. There are a number of strengths of this economic analysis highlighted below; as a result, the incremental cost-effectiveness ratios are based on best available evidence (in absence of published literature), accepted NICE methodology but specific to the dupilumab place in UK treatment path.

B 3.9.2 Generalisability to clinical practice

The base case population reflects the anticipated UK population and is derived directly from RCT evidence

The patient population included in the dupilumab studies and in the economic analysis reflect patients expected in clinical practice. The dupilumab studies comprised adults with AD with moderate-to-severe AD affecting a large portion of their BSA. They experienced high levels of AD symptoms, including pruritus. Their disease could not be adequately controlled with topical prescription medications, or otherwise topical mediations were not advised due to important side effects or safety risks. This population included patients who had been, or would typically be, candidates for systemic AD therapies. In the real wordl previous treatment history (encompassing inadequately effective, not tolerated or contraindicated therapies i.e. medically inadvisable) coupled with physician opinion, serves as a holistic assessment for eligibility for treatment with dupilumab.

Holistic assessment of effiacy response in the model

We have implement the outcomes measured in the study programme in the economic model while capturing improvements in the key disease characteristics important to patients and clinicians in order to support clinical decision making. According to UK clinicians a measure of response which captures clinical signs alongside quality of life improvement is required Improvement in clinical signs (such as skin clearance) alone is not comprehensive enough. EASI-50 is generally regarded as a distinct clinical benefit particularly in patients with moderate-to-severe AD for whom topical therapy has failed and for whom systemic immunosuppressants are contra-indicated, intolerable, provide inadequate response or are otherwise medically inadvisable. Clinically meaningful improvement in DLQI is also needed. The model uses an improvement in DLQI of 4 or more points to capture significant quality of life benefit for patients with AD. Hence EASI-50 and DLQI 4 or more points is used as a proxy for holistic assessment of efficacy response in the modelling. This is a *post-hoc* endpoint developed to reflect UK practice. It is statistically significant in both the full licence population and the base case population versus BSC, justifying its use in the economic case.

Strength - use of RCT evidence to reflect clinical practise

A key feature of the LIBERTY trial programme was that the study designs closely reflect allowed trial participants to receive rescue therapy in response to an exacerbation. In addition in CHRONOS and CAFÉ TCS as required was also permitted. We have used the ‘all observed’ data from the trial in the economic analysis (including patients requireing rescue treatment and using TCS) as this retains as much of the trial data as possible. This most closely reflects expected real world clinical practice.

Limitation – 16 weeks primary endpoint

In all the studies in the LIBERTY trial programme the primary endpoint was measured at 16 weeks, according to regulatory requirements, however a number of patients, and patients with the greatest potential to benefit, may require a longer treatment to reach specified threshold. However, CHRONOS provides data out to 52 weeks in the full licence population.

Limitation - Lack of robust data for indirect comparison with immunosuppressant therapies

The evidence base for comparison with currently available systemic immunosuppressants is not robust and lacks common comparators and endpoints that can be used to compare dupilumab to them. To address the requirement in the NICE Final Scope to assess the the full licence indication (adult patients eligible for immunosuppressant therapies) against an immunosuppressant we carried out a MAIC. However, the results from this analysis are associated with uncertainty due to small sample sizes, trial heterogeneity and the low number of prognostic factors available to us and should be interpreted with caution. However, it is likely that dupilumab would be used after systemic immunnosupppressants.

Conclusion

Dupilumab has been designated a “breakthrough therapy” for the treatment of moderate-to-severe AD by the United States Food and Drug Administration (FDA) and designated as a Promising Innovative Medicine by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA). Dupilumab is being used in the UK as part of EAMS programme.

For the expected population, dupilumab is a cost-effective medicine at a WTP threshold of £30,000, based upon the innovative nature of the medicine and represents a good use of NHS resources compared with current treatments. ICER results were consistent and robust when tested against a range of key model inputs and assumptions. Incremental QALY gains were generally in the range of 1.2 to 1.9, with incremental ICERs clustered just below the £30,000 WTP threshold at the PAS price. It should be emphasised that a QALY gain above 1.0 in a treatment that is not life extending is a remarkable result.

When asked, an EAMS clinician told us:

‘Initiation of dupilumab has resulted in dramatic improvement in QoL with cessation of steroids/ciclosporin. For some patients it has been transformational’.

B 4 References

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B 5 Appendices

Appendix C: Summary of product characteristics or information for use, European Public Assessment Report, scientific discussion or drafts

Appendix D: (see sections 2.1, 2.4, 2.5 and 2.9)

Appendix E: Subgroup analysis (see section 2.7) Identification, selection and synthesis of clinical evidence

Appendix F: Adverse reactions (see section 2.10)

Appendix G: Published cost-effectiveness studies (see section 3.1)

Appendix H: Health-related quality of life studies (see section 3.4.3)

Appendix I: Cost and healthcare resource identification, measurement and valuation (see section 3.5)

Appendix J: Clinical outcomes and disaggregated results from the model (see sections 3.7.1–3.7.2)

Appendix K: Checklist of confidential information

Appendix L: Commonly used assessment tools for atopic dermatitis

Appendix M: Clinical guidelines for AD

Appendix N: Phase IIb Study (R668-AD-1021)

Appendix O: Studies included in the economic model – additional information

Appendix P: MAINTAIN and CONTINUE efficacy evaluations

Appendix Q: Early Access to Medicines Scheme (EAMS)

Appendix R: Other studies

Appendix S: Verbatim from the Allergy UK survey

Appendix T: Persistence of the quality of life gain after the dupilumab trials have ended

Appendix U Economic model – quality control

Appendix V: Appendix References

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Single technology appraisal

Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

Dear Company

The Evidence Review Group, Aberdeen HTA, and the technical team at NICE have looked at the submission received on Monday 27th November 2017 from Sanofi Genzyme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by the end of **11 January**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sharlene Ting, Technical Lead (Sharlene.Ting@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

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Literature search

A1. Company submission (CS), section B2.1, table 2.2 (page 51). 4 articles were identified after the updated literature search (Blauvelt 2017, de Bruin-Weller 2017, Deleuran 2017, Simpson 2017) using 'Sanofi Genzyme internal processes'. Please provide details on how these articles were identified.

Clinical trials

CAFÉ, CHRONOS, SOLO 1 and SOLO 2 follow-up period data

A2. PRIORITY QUESTION. CS, section B2.2.1, tables 2.3 to 2.5 (pages 54-56). Within the study design, CHRONOS, SOLO 1 and SOLO 2 state that there were 12-week follow-up periods after treatment was stopped, while CAFÉ refers to a 16-week follow-up period after treatment was stopped. However, no data for these follow-up periods from all 4 trials were included in the company submission. Please clarify whether any efficacy measures, such as the Eczema Area Severity Index (EASI) and Dermatology Life Quality Index (DLQI), were collected during these follow-up periods. If data are available, please provide:

a. The proportion of participants responding in each arm (based on the definition used in the economic model) at week 64 for CHRONOS, and at week 28 for CAFÉ, SOLO 1 and SOLO 2.

b. The proportion of responders at week 16 who maintained their response at week 64 for CHRONOS and at week 28 for CAFÉ, SOLO 1 and SOLO 2.

CHRONOS adverse events

A3. CS, section B2.10.3, table 2.50 (pages 143-145). Several cells (such as pruritus, abdominal pain, gastroenteritis, herpes simplex and folliculitis) appear to have textual or typographic errors. Please clarify whether the data are correct. If the data are inaccurate, please provide correct information.

SOLO 1 and 2 adverse events

A4. CS, section B2.10.5, table 2.52 (pages 148-149). Several cells (such as exacerbations of atopic dermatitis and headache) appear to have errors. Please clarify whether the data are correct. If the data are inaccurate, please provide correct information.

CAFÉ + CCL and SOLO CL sample sizes

A5. CS, section B2.11.2.3, table 2.59 (page 153). Please provide the sample sizes for CAFÉ+CCL and SOLO CL.

Matched-adjusted indirect comparison

A6. CS, section B2.9, tables 2.39 and 2.40 (pages 127-129). Numerous cells contain duplicate data. For example, in Table 2.40, columns labelled "dupilumab (ESS=61)" and "ciclosporin (N=17)" contain identical information in many of the baseline characteristics.

a. Please clarify whether the data in Tables 2.39 and 2.40 are correct.

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b. If the data are correct, please provide the rationale for comparing 40.1 year old patients on dupilumab with 19.5 year old patients on ciclosporin (Table 2.40).

Early Access to Medicines Scheme (EAMS)
A7. CS, section B2.11.2 (page 152). Please clarify whether the EAMS study is still ongoing.

A8. CS, section B2.3.2, table 2.9 (page 61) and section B2.11.2.2, table 2.55 (page 153). Table 2.9 (CS, page 61) define moderate to severe atopic dermatitis as "… baseline AD severity scores of IGA ≥3 (SOLO 1 and 2, CHRONOS, CAFÉ), EASI ≥16 (CHRONOS), EASI ≥ 20 (CAFÉ) …". Table 2.55 (CS, page 153) provide a range of values (EASI lower value 0.6 and IGA lower value 1) that suggest patients with less severe disease were included in the dupilumab EAMS compared with patients in CHRONOS, CAFÉ, SOLO-1 and SOLO-2. Please clarify the reason for this difference.

Section B: Clarification on cost-effectiveness data

Model structure
B1. CS, section B3.2.3 (pages 173-175). The company model utilises three Markov states: on-treatment, best supportive care (BSC) and dead. Only treatment responders are maintained on-treatment in the Markov model, and are assumed to have a relatively stable response whilst on treatment. The chosen structure may lack the flexibility to capture the waxing and waning nature of atopic dermatitis. A state transition model with defined states such as clear, mild, moderate and severe might better reflect the natural variation in severity over time. Please provide further rationale for the chosen model structure compared to other alternative options

Utility adjustments based on age
B2. CS, section B3.3.5 (page 188). The age adjustment to utility weights in the model appears be follow a constant "additive" approach that has a zero impact on the ICER. The NICE DSU appears to recommend a "multiplicative" adjustment method for reasons of consistency (NICE TSD 12, page 5). Please explore the impact of age adjusting the utility multipliers and then applying a multiplicative approach to age adjustment using age specific general population utilities, as described in NICE TSD 12.

Resource use and costs

Administration training costs
B3. CS, section B3.4.6.1 (page 196). The company assumes that dupilumab will be self-administered with only a single training session resulting in costs to the NHS. Please clarify the prescribing, delivery and administration model for dupilumab. In particular:

a. Will dupilumab be distributed from hospital pharmacies, or delivered directly to patients' homes?

b. What is the intended frequency of prescription and delivery to patients?

c. How many vials can be stored at the patient's home?

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d. Are any mechanisms in place to guarantee patients receive and correctly self-administer the drug in the long run?

Medical costs

B4. PRIORITY QUESTION. CS, table 3.38 (pages 211-212) and section B3.4.6.2 (pages 198-201). Please provide further disaggregation of the following medical costs for the base-case analysis: physician, dermatologist, emergency, hospitalization, day case, full blood count, dermatology nurse visit and background medications.

Tests and investigations costs

B5. CS, table 3.22 (pages 196-197). Dupilumab responders are assumed to have 0 diagnostic/monitoring tests, whereas best supportive care responders have 4 tests per year. This implies that no testing is required for the ongoing safety monitoring of dupilumab.

a. Please provide further rationale for this assumption.

b. Please clarify whether monitoring of liver function, renal function, blood counts and drug levels is not necessary with dupilumab.

Adverse reaction unit costs and resource use

B6. CS, section B3.4.6.8 (page 205). Please provide further rationale for assuming that injection site reactions are a one-time event "with the cost occurring in the first cycle". In what proportion of patients experiencing an injection site reaction did it occur only once or more than once?

Excel model

B7. PRIORITY QUESTION. The tornado diagram provided in the company's model ("One-Way SA" sheet) shows that the incremental cost-effective ratio (ICER) is most sensitive to baseline utility weight. However, the deterministic sensitivity analysis only varies this parameter through ±10% of the mean and no distribution is assigned in the probabilistic analysis.

a. Please provide a sensitivity analysis showing the impact of varying this parameter estimate through its full 95% confidence limits.

b. Please provide a probabilistic sensitivity analysis that appropriately incorporates the uncertainty surrounding the baseline utility parameter.

Jeremy Powell,
National Institute for Health and Care Excellence,
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11th January 2017.

Dear Jeremy,

Re Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

Thank you for the opportunity to provide our answers to the clarification questions posed by the Evidence Review Group and technical team at NICE for this appraisal. Please find our responses attached. As requested we provide two versions of our written response; one with commercial-in-confidence information clearly marked and one with this information redacted. We also provide a checklist of confidential information and an updated economic model.

If you have any queries or require further clarifications please don't hesitate to contact me.

Yours Sincerely,

Claire GRANT
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UK & Ireland
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Section A: Clarification on effectiveness data

Literature search

A1. Company submission (CS), section B2.1, table 2.2 (page 51). 4 articles were identified after the updated literature search (Blauvelt 2017, de Bruin-Weller 2017, Deleuran 2017, Simpson 2017) using 'Sanofi Genzyme internal processes'. Please provide details on how these articles were identified.

The systematic literature review (SLR) carried out in accordance with the requirements for a submission covered the period January 1, 1980 – April 11, 2017 was carried out in two parts.

The SLR literature review was conducted in 2016 and covered the period January 1st 1980 to July 31st 2016. The update was carried out in April 2017 and covered the period January 1st 2016 to April 11th 2017. The Sanofi Genzyme internal process referred to in the company submission was used for dates later than April 11 2017. It is a weekly literature search that the Sanofi European Medical Affairs team run routinely. The search is run via MEDLINE using defined search terms, strings and MeSH terms. These terms are provided below:

Step 1 of the search identifies literature related to AD:

"dermatitis, atopic"[MeSH Terms] OR ("dermatitis"[All Fields] AND "atopic"[All Fields]) OR "atopic dermatitis"[All Fields] OR ("atopic"[All Fields] AND "dermatitis"[All Fields])

Step 2 of the search identifies literature directly related to dupilumab:

"SAR231893"[Supplementary Concept] OR "SAR231893"[All Fields] OR "dupilumab"[All Fields] OR "REGN668"[All Fields] OR "dupixent"[All Fields]

In addition to these weekly searches, 'in-press' Sanofi sponsored articles are circulated for review to the UK medical team, so we are made aware of forthcoming key publications before they are abstracted by the search engines.

Clinical trials

CAFÉ, CHRONOS, SOLO 1 and SOLO 2 follow-up period data

A2. PRIORITY QUESTION. CS, section B2.2.1, tables 2.3 to 2.5 (pages 54-56). Within the study design, CHRONOS, SOLO 1 and SOLO 2 state that there were 12-week follow-up periods after treatment was stopped, while CAFÉ refers to a 16-week follow-up period after treatment was stopped. However, no data for these follow-up periods from all 4 trials were included in the company submission. Please clarify whether any efficacy measures, such as the Eczema Area Severity Index (EASI) and Dermatology Life Quality Index (DLQI), were collected during these follow-up periods. If data are available, please provide:

a. **The proportion of participants responding in each arm (based on the definition used in the economic model) at week 64 for CHRONOS, and at week 28 for CAFÉ, SOLO 1 and SOLO 2.**

b. The proportion of responders at week 16 who maintained their response at week 64 for CHRONOS and at week 28 for CAFÉ, SOLO 1 and SOLO 2.

The data requested was collected at week 64 for CHRONOS and at week 28 for CAFÉ, SOLO 1 and SOLO 2. However, low completion rates, confounding by transition into the extension studies and difficulty in retrieving and supplying complete data for patients transitioning between two studies means that interpretation of these existing data is difficult.

For the purposes of the discussion below, End of Treatment (EoT) refers to week 16 (SOLO and CAFÉ) or week 52 (CHRONOS) and End of Study (EoS) refers to the end of the 12 week follow-up periods (which occurred at 28 weeks for SOLO and CAFÉ and 64 weeks for CHRONOS). The duration of the 12-week follow-up period was based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. Patients completing the trials had the option to transition to one of the extension studies (Open-label extension (OLE) or SOLO-CONTINUE) or continue to EoS. In addition, some patients were lost to follow-up after EoT.

A description of the patient flow for CAFÉ, CHRONOS and SOLO 1&2 is provided below followed by results from the CHRONOS study.

Patient flow

The majority of patients in the CAFÉ, CHRONOS and SOLO trials transitioned to one or other of the extension studies, see Table 1 to Table 3 below. It is critical to understand that the data at EoS (week 28 for SOLO and CAFÉ or at week 64 for CHRONOS) includes patients who transitioned to the extension studies and also those who completed to EoS but did not transition to the extension studies. The number of patients followed to EoS without entering an extension study was low in all cases and it is difficult to draw meaningful conclusions about the response or efficacy endpoints for the trial cohorts at EoS after cessation of treatment with dupilumab or placebo 12 weeks earlier given that we do not currently have patient characteristics for these groups.

The total number and proportion of patients with EoS data is emboldened in Table 1 to Table 3 below.

Table 1. Destination of patients after EoT in CAFÉ.

	Placebo QW + TCS (N=108)	**300 mg Q2W + TCS (N=107)**	**300 mg QW + TCS (N=110)**	**Combined + TCS (N=217)**	**Total (N=325)**
Completed Week 28 (End of Study), n (% calculated based on the total number of patients with EoS data)	**7 (6.5)**	**8 (7.5)**	**8 (7.3)**	**16 (7.4)**	**23 (7.1)**
Transitioned into open label extension study, n(%)	99 (91.7)	98 (91.6)	100 (90.9)	198 (91.2)	297 (91.4)
Did not transition into open label extension study, n(%)	9 (8.3)	9 (8.4)	10 (9.1)	19 (8.8)	28 (8.6)
Lost to follow up, n(%)	2 (1.9)	1 (0.9)	2 (1.8)	3 (1.4)	5 (1.5)

EoT: End of Treatment, EOS: End of study, Q2W: every other week; QW: every week; TCS: Topical corticosteroid

In the CAFÉ study, a total of nine patients on placebo and nine patients on the licenced dupilumab dose (300mg Q2W +TCS) did not enter the open-label study. At week 28 there are only seven (6.5%) patients on placebo and eight (7.5%) on dupilumab Q2W arm for whom data are available in the study follow-up period.

Table 2. Destination of patients after EoT in CHRONOS.

	Placebo QW + TCS (N=315)	300 mg Q2W + TCS (N=106)	300 mg QW + TCS (N=319)	Combined + TCS (N=425)	Total (N=740)
Total number of patients with EoS data* (% calculated based on the total number of patients with EoS data)	**119 (37.8)**	**58 (54.7)**	**203 (63.6)**	**261 (61.4)**	**380 (51.4)**
Transitioned into open label extension study, n(%)	237 (75.2)	90 (84.9)	255 (79.9)	345 (81.2)	582 (78.6)
Completed week 52 and week 64, n (%)	96 (30.5)	51 (48.1)	176 (55.2)	227 (53.4)	323 (43.6)
Completed week 52. Did not complete week 64, n (%)	108 (34.3)	35 (33.0)	74 (23.2)	109 (25.6)	217 (29.3)
Did not complete week 52 Did complete week 64, n (%)	4 (1.3)	0	2 (0.6)	2 (0.5)	6 (0.8)
Did not complete week 52 Did not complete week 64, n (%)	29 (9.2)	4 (3.8)	3 (0.9)	7 (1.6)	36 (4.9)
Did not transition into open label extension study, n(%)	78 (24.8)	16 (15.1)	64 (20.1)	80 (18.8)	158 (21.4)
Lost to follow up, n(%)	59 (18.7)	9 (8.5)	39 (12.2)	48 (11.3)	107 (14.5)
Completed Week 64 (EoS) but did not transition to OLE, n (%)	19 (6.0)	7 (6.6)	25 (7.8)	32 (7.5)	51.9)

*Includes patients who entered the extension studies but who also completed. EoT: End of Treatment, EoS. EOS: End of study, OLE: Open Label Extension, Q2W: every other week; QW: every week; TCS: Topical corticosteroid

In the CHRONOS study, a total of 78 patients on placebo and 16 patients on the licenced dupilumab dose (300mg Q2W) +TCS arm did not enter the open-label study. At week 64, there were only 19 (6.0%) and 7 (6.6%) patients remaining who did not enter the open label study respectively who had data available in the study follow-up period. A proportion of patients who entered the open-label study also completed to week 64 meaning that there are 119 (37.8%) and 58 (54.7%) patients with EoS data in total.

Table 3. Destination of patients after EoT in SOLO 1 & 2 pool.

	Placebo QW (N=224)	300 mg Q2W (N=224)	300 mg QW (N=223)	Combined (N=447)	Total (N=671)
Total number of patients with EoS data* n, (% calculated based on the total number of patients with EoS data)	**24 (5.2)**	**32 (7.0)**	**32 (6.9)**	**64 (7.0)**	**88 (6.4)**
Transitioned into another study, n(%)	388 (84.3)	402 (87.9)	393 (85)	795 (86.5)	1183 (85.7)
OPEN LABEL EXTENSION, n(%)	335 (72.8)	203 (44.4)	170 (36.7)	373 (40.5)	708 (51.3)
SOLO-CONTINUE STUDY, n(%)	53 (11.5)	199 (43.5)	223 (48.2)	422 (45.9)	475 (34.4)
Did not transition into another study, n(%)	72 (15.6)	55 (12)	69 (14.9)	124 (13.4)	196 (14.2)

Lost to follow up, n(%)	58 (12.6%)	33 (7.2%)	46 (9.9%)	79 (8.5%)	137 (9.9%)
Completed Week 28 (End of Study), n (%)	14 (3)	22 (4.8)	23 (4.9)	45 (4.8)	59 (4.2)

*Includes patients who entered the extension studies but who also completed. EoT: End of Treatment, EoS. EOS: End of study, Q2W: every other week; QW: every week; TCS: Topical corticosteroid

Only patients meeting the primary endpoint in SOLO 1 & 2 were eligible for entry to SOLO-CONTINUE. In this study dupilumab patients were re-randomised to receive placebo, QW, Q2W, Q4W or Q8W. Responding patients from the placebo arm persisted on placebo but data from these patients were not analysed.

In the pooled SOLO 1 & 2 studies, a total of 72 patients on placebo and 55 patients on the licenced dupilumab dose (300mg Q2W) did not enter an open label extension (OLE) study. At week 28, there were only 14 (6.0%) and 22 (6.6%) patients respectively who did not enrol into the maintenance study for whom data are available. A small proportion of patients who entered the OLE studies also completed to week 28 meaning that there are 24 (5.2%) and 32 (7.0%) patients with EoS data in total. (It is worth noting that for patients who did not enrol into the maintenance study, the follow-up period was variable between 4 and 12 weeks further complicating any interpretation of results).

As can be seen, the number of patients with EoS data in all the studies who did not participate in extension studies was low. In addition the proportions of patients with EoS data in the placebo and dupilumab Q2W populations are different. For example, in CHRONOS, EoS data were collected from 36.5% of participants who originally were in the placebo arm. This is statistically different from the 54.7% available from dupilumab Q2W arm (Chi2 test, $p<0.01$). On this basis, and given we present sub-groups in the base case, it is likely that the characteristics of these EoS patients will not be balanced, randomisation is not maintained and the results are likely to be biased so interpretation of the data is difficult. It should also be remembered that there is transition from Q2W (and placebo) to QW dupilumab dosing in the OLEs and so the data are further confounded by off label dosing.

Data collected at EoS

The question asks specifically about the outcomes for patients who completed EoT and EoS. Given the low patient numbers who meet this definition without confounding by entry into another study (eg 19 placebo and 7 dupilumab Q2W for CHRONOS) which may include the use of unlicensed doses, we do not believe that meaningful conclusions should be drawn from these data.

We present the data available for the CHRONOS study overleaf (Table 4) because this study has the largest available amount of patient data at EoS and also includes TCS as part of the treatment regimen. The results for this analysis are not available for CAFÉ and SOLO, however the patient numbers completing to EoS in the CAFÉ study were low and the data from the SOLO studies represent less than 10% of the patient population in each arm and are unlikely to be balanced. In addition the analysis for the economic modelling considered only the SOLO CAFÉ-like patients which were a sub-set of the SOLO cohort.

Table 4. CHRONOS – response under treatment (week 16 and 52) and off treatment (week 64). All observed values regardless of rescue medicine use with missing treated as Non-Responder.

	Placebo N=315	Q2W N=106
Responders according to: EASI-50 and DLQI≥4		
Data collected to EoT		
At week 16, n (%)	133 (42.2)	82 (77.4)
At week 52 (EOT), n (%)	143 (45.4)	87 (82.1)
Data collected at EoS		
At week 64 (EOS), n (% calculated from N)	115 (36.5)	58 (54.7)
Maintenance of response from week 16 to week 64 (EOS), n (% calculated from responder n at 16 weeks)	86 (64.7)	54 (65.9)
Responders according to: EASI-75		
Data collected to EoT		
At week 16, n (%)	102 (32.4)	78 (73.6)
At week 52 (EOT), n (%)	127 (40.3)	72 (67.9)
Data collected at EoS		
At week 64 (EOS), n	91 (28.9)	48 (15.2)
Maintenance of response from week 16 to week 64 (EOS), n	55 (53.9)	43 (55.1)
Responders according to: EASI-50		
Data collected to EoT		
At week 16, n (%)	176 (55.9)	91 (85.8)
At week 52 (EOT), n (%)	192 (61.0)	92 (86.8)
Data collected at EoS		
At week 64 (EOS), n	150 (47.6)	71 (67.0)
Maintenance of response from week 16 to week 64 (EOS), n	120 (68.2)	69 (75.8)

EoS: End of study; EoT: End of Treatment; EASI: Eczema Area Severity Index (for example EASI-75, EASI score 75% response); DLQI: Dermatology Quality of Life Index (for example DLQI≥4: response with 4 or more points change from baseline).

From these data we see, as expected, that week 52 EoT data show superiority for dupilumab vs. placebo. It is not clear what is driving the difference at week 64 and these data should be interpreted with caution due to confounding. The majority of patients with data at EoS had transitioned to the OLE. Furthermore we do not believe that these data are made up of balanced cohorts between the placebo and the dupilumab patients and have not been able to establish treatment regimens during the period EoT to EoS. We are seeking further clarification on the characteristics and outcomes for these patients.

CHRONOS adverse events

A3. CS, section B2.10.3, table 2.50 (pages 143-145). Several cells (such as pruritus, abdominal pain, gastroenteritis, herpes simplex and folliculitis) appear to have textual or typographic errors. Please clarify whether the data are correct. If the data are inaccurate, please provide correct information.

We apologise for the typographical errors in Table 2.50 from section B2.10.3. These have been corrected and all other values double-checked in this section. The full, corrected table is provided below (Table 5).

Table 5 CHRONOS summary of TEAE with incidence ≥2% in any treatment group during the 52-Week treatment period — SAF

Event n (%)	16 weeks			52 weeks		
	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N = 315)	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N =315)
TEAE or TE SAE						
At least 1 TEAE	215 (68.3)	81 (73.6)	228 (72.4)	268 (85.1)	97 (88.2)	263 (83.5)
At least 1 TE SAE	6 (1.9)	3 (2.7)	4 (1.3)	16 (5.1)	4 (3.6)	10 (3.2)
Death†	0	0	0	0	0	1 (0.3)
TEAE leading to treatment discontinuation	15 (4.8)	1 (0.9)	8 (2.5)	25 (7.9)	2 (1.8)	9 (2.9)
Non-infectious TEAE						
Injection site reaction	18 (5.7)	11 (10.0)	51 (16.2)	25 (7.9)	16 (14.5)	61 (19.4)
Fatigue	7 (2.2)	1 (0.9)	6 (1.9)	10 (3.2)	1 (0.9)	11 (3.5)
Pyrexia	4 (1.3)	2 (1.8)	1 (0.3)	7 (2.2)	4 (3.6)	7 (2.2)
Exacerbation of atopic dermatitis	86 (27.3)	12 (10.9)	25 (7.9)	147 (46.7)	22 (20.0)	55 (17.5)
Erythema	1 (0.3)	1 (0.9)	6 (1.9)	2 (0.6)	1 (0.9)	10 (3.2)
Acne	6 (1.9)	0	6 (1.9)	8 (2.5)	1 (0.9)	7 (2.2)
Pruritus	5 (1.6)	1 (0.9)	1 (0.3)	9 (2.9)	1 (0.9)	4 (1.3)
Urticaria	8 (2.5)	1 (0.9)	3 (1.0)	10 (3.2)	1 (0.9)	3 (1.0)
Headache	15 (4.8)	4 (3.6)	20 (6.3)	19 (6.0)	5 (4.5)	25 (7.9)
Arthralgia	8 (2.5)	2 (1.8)	4 (1.3)	15 (4.8)	5 (4.5)	10 (3.2)
Back pain	6 (1.9)	1 (0.9)	2 (0.6)	11 (3.5)	2 (1.8)	8 (2.5)
Pain in extremity	0	0	5 (1.6)	2 (0.6)	0	8 (2.5)
Osteoarthritis	0	1 (0.9)	1 (0.3)	3 (1.0)	3 (2.7)	2 (0.6)
Muscle spasms	4 (1.3)	0	0	7 (2.2)	0	1 (0.3)
Cough	5 (1.6)	2 (1.8)	6 (1.9)	8 (2.5)	3 (2.7)	10 (3.2)
Oropharyngeal pain	7 (2.2)	1 (0.9)	4 (1.3)	12 (3.8)	3 (2.7)	10 (3.2)
Asthma	11 (3.5)	3 (2.7)	0	19 (6.0)	5 (4.5)	2 (0.6)
Allergic conjunctivitis	9 (2.9)	7 (6.4)	19 (6.0)	15 (4.8)	12 (10.9)	47 (14.9)
Blepharitis	2 (0.6)	5 (4.5)	8 (2.5)	3 (1.0)	6 (5.5)	11 (3.5)
Eye pruritus	2 (0.6)	2 (1.8)	9 (2.9)	4 (1.3)	4 (3.6)	14 (4.4)
Dry eye	1 (0.3)	2 (1.8)	3 (1.0)	4 (1.3)	3 (2.7)	6 (1.9)
Diarrhoea	7 (2.2)	0	5 (1.6)	13 (4.1)	1 (0.9)	12 (3.8)

Event n (%)	16 weeks			52 weeks		
	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N = 315)	Placebo (N = 315)	Dupilumab Q2W (N = 110)	Dupilumab QW (N =315)
Nausea	7 (2.2)	2 (1.8)	6 (1.9)	12 (3.8)	2 (1.8)	9 (2.9)
Abdominal pain	2 (0.6)	0	3 (1.0)	4 (1.3)	0	7 (2.2)
Toothache	3 (1.9)	1 (0.9)	3 (1.0)	8 (2.5)	1 (0.9)	4 (1.3)
Blood creatine phosphokinase increased	6 (1.9)	1 (0.9)	8 (2.5)	9 (2.9)	3 (2.7)	11 (3.5)
Blood lactate dehydrogenase increased	4 (1.3)	4 (3.6)	1 (0.3)	5 (1.6)	4 (3.6)	1 (0.3)
Seasonal allergy	4 (1.3)	2 (1.8)	5 (1.6)	6 (1.9)	2 (1.8)	9 (2.9)
Psychiatric disorders	7 (2.2)	5 (4.5)	4 (1.3)	18 (5.7)	9 (8.2)	11 (3.5)
Infectious TEAE						
Infections and infestations	111 (35.2)	39 (35.5)	109 (34.6)	182 (57.8)	64 (58.2)	167 (53.0)
Nasopharyngitis	33 (10.5)	15 (13.6)	37 (11.7)	62 (19.7)	25 (22.7)	62 (19.7)
Upper respiratory tract infection	20 (6.3)	7 (6.4)	21 (6.7)	32 (10.2)	11 (10.0)	43 (13.7)
Sinusitis	3 (1.0)	0	10 (3.2)	9 (2.9)	2 (1.8)	18 (5.7)
Urinary tract infection	2 (0.6)	0	2 (0.6)	13 (4.1)	2 (1.8)	13 (4.1)
Influenza	6 (1.9)	1 (0.9)	2 (0.6)	16 (5.1)	4 (3.6)	9 (2.9)
Viral upper respiratory tract infection	4 (1.3)	2 (1.8)	7 (2.2)	9 (2.9)	3 (2.7)	9 (2.9)
Conjunctivitis bacterial	2 (0.6)	1 (0.9)	6 (1.9)	5 (1.6)	2 (1.8)	9 (2.9)
Conjunctivitis	2 (0.6)	0	3 (1.0)	5 (1.6)	1 (0.9)	8 (2.5)
Gastroenteritis	5 (1.6)	1 (0.9)	1 (0.3)	9 (2.9)	5 (4.5)	4 (1.3)
Oral herpes	5 (1.6)	3 (2.7)	8 (2.5)	9 (2.9)	4 (3.6)	15 (4.8)
Herpes simplex	1 (0.3)	0	4 (1.3)	2 (0.6)	3 (2.7)	5 (1.6)
Pharyngitis	2 (0.6)	0	3 (1.0)	8 (2.5)	3 (2.7)	5 (1.6)
Rhinitis	2 (0.6)	1 (0.9)	5 (1.6)	4 (1.3)	1 (0.9)	7 (2.2)
Folliculitis	5 (1.6)	1 (0.9)	2 (0.6)	7 (2.2)	2 (1.8)	4 (1.3)
Impetigo	3 (1.0)	0	1 (0.3)	10 (3.2)	1 (0.9)	4 (1.3)
Skin infection	7 (2.2)	0	1 (0.3)	7 (2.2)	0	1 (0.3)

AE, Adverse event; TEAE, Treatment-emergent adverse event; TE SAE, Treatment-emergent serious adverse event; SAF, safety analysis set; Q2W, every other week; QW, every week

† There was one death during the study of a 27-year-old female patient in the dupilumab QW group who died in a car accident.

SOLO 1 and 2 adverse events

A4. CS, section B2.10.5, table 2.52 (pages 148-149). Several cells (such as exacerbations of atopic dermatitis and headache) appear to have errors. Please clarify whether the data are correct. If the data are inaccurate, please provide correct information.

The identified typographical errors in Table 2.2 from section B2.10.3 have been corrected and all other values double checked in this section. The full corrected table is provided below (Table 6).

Table 6. SOLO1 and SOLO 2 Summary of TEAE with incidence ≥2% in any treatment group during the 16-Week treatment period — SAF

Event n (%)	SOLO 1			SOLO 2		
	Placebo (N=222)	Dupilumab Q2W (N=229)	Dupilumab QW (N=218)	Placebo (N=234)	Dupilumab Q2W (N=236)	Dupilumab QW (N=237)
AE or SAE						
At least 1 AE	145 (65.3)	167 (72.9)	150 (68.8)	168 (71.8)	154 (65.3)	157 (66.2)
At least 1 SAE	11 (5.0)	7 (3.1)	2 (0.9)	13 (5.6)	4 (1.7)	8 (3.4)
Death†	0	0	0	0	1 (0.4)	1 (0.4)
AE leading to treatment discontinuation	2 (0.9)	4 (1.7)	4 (1.8)	5 (2.1)	2 (10.8)	3 (1.3)
Non-infectious AE						
Injection site reaction	13 (5.9)	19 (8.3)	41 (18.8)	15 (6.4)	32 (13.6)	31 (13.1)
Fatigue	1 (0.5)	5 (2.2)	2 (0.9)	3 (1.3)	6 (2.5)	5 (2.1)
Exacerbation of atopic dermatitis	67 (30.2)	30 (13.1)	21 (9.6)	81 (34.6)	32 (13.6)	38 (16.0)
Pruritus	5 (2.3)	0	1 (0.5)	5 (2.1)	1 (0.4)	3 (1.3)
Alopecia	1 (0.5)	2 (0.9)	0	3 (1.3)	1 (0.4)	7 (3.0)
Headache	13 (5.9)	21 (9.2)	11 (5.0)	11 (4.7)	19 (8.1)	22 (9.3)
Dizziness	3 (1.4)	3 (1.3)	0	6 (2.6)	3 (1.3)	4 (1.7)
Allergic conjunctivitis	2 (0.9)	12 (5.2)	7 (3.2)	2 (10.9)	2 (10.8)	3 (1.3)
Diarrhoea	4 (1.8)	7 (3.1)	7 (3.2)	3 (1.3)	9 (3.8)	3 (1.3)
Nausea	1 (0.5)	5 (2.2)	2 (0.9)	3 (1.3)	5 (2.1)	7 (3.0)
Arthralgia	3 (1.4)	6 (2.6)	1 (0.5)	6 (2.6)	6 (2.5)	2 (0.8)
Back pain	4 (1.8)	2 (0.9)	5 (2.3)	5 (2.1)	7 (3.0)	5 (2.1)
Blood creatine phosphokinase increased	4 (1.8)	5 (2.2)	2 (0.9)	3 (1.3)	4 (1.7)	1 (0.4)
Oropharyngeal pain	1 (0.5)	2 (0.9)	3 (1.4)	4 (1.7)	5 (2.1)	4 (1.7)
Depression	2 (0.9)	1 (0.4)	1 (0.5)	5 (2.1)	0	0
Hypertension	2 (0.9)	3 (1.3)	3 (1.4)	4 (1.7)	5 (2.1)	2 (0.8)
Infectious AE						
Infections and infestations	63 (28.4)	80 (34.9)	74 (33.9)	76 (32.5)	65 (27.5)	68 (28.7)
Nasopharyngitis	17 (7.7)	22 (9.6)	25 (11.5)	22 (9.4)	20 (8.5)	20 (8.4)
Upper respiratory tract infection	5 (2.3)	6 (2.6)	11 (5.0)	5 (2.1)	7 (3.0)	9 (3.8)
Conjunctivitis	2 (0.9)	11 (4.8)	7 (3.2)	1 (0.4)	9 (3.8)	9 (3.8)
Oral herpes	4 (1.8)	9 (3.9)	4 (1.8)	4 (1.7)	8 (3.4)	9 (3.8)
Herpes simplex	3 (1.4)	7 (3.1)	2 (0.9)	1 (0.4)	0	1 (0.4)
Skin infection	2 (0.9)	2 (0.9)	1 (0.5)	5 (2.1)	1 (0.4)	1 (0.4)

AE, Adverse event; TEAE, Treatment-emergent adverse event; TE SAE, Treatment-emergent serious adverse event; SAF, safety analysis set; Q2W, every other week; QW, every week

†Two deaths were reported in SOLO 2: a 31-year-old man with a history of depression, including hospitalisation for depression, and suicidal ideation completed suicide, an event that occurred 8 days after the most recent dose of dupilumab and a 49-year old asthmatic woman who was not receiving an asthma-control medication died of an asthma attack, 84 days after the last dose of dupilumab and after study completion.

CAFÉ + CCL and SOLO CL sample sizes

A5. CS, section B2.11.2.3, table 2.59 (page 153). Please provide the sample sizes for CAFÉ+CCL and SOLO CL.

A full breakdown of the sample sizes for the CAFÉ+CCL and SOL CL populations are provided below in Table 7.

Table 7. Population size in the CAFÉ+CCL and SOLO CL populations

Population	Placebo	Dupilumab 300 mg			All
		Q2W	QW	Q2W+QW	
CAFE + CCL (n)	169	130	163	293	462
SOLO-CL (n)	88	104	96	200	288

Matched-adjusted indirect comparison

A6. CS, section B2.9, tables 2.39 and 2.40 (pages 127-129). Numerous cells contain duplicate data. For example, in Table 2.40, columns labelled "dupilumab (ESS=61)" and "ciclosporin (N=17)" contain identical information in many of the baseline characteristics.

a. Please clarify whether the data in Tables 2.39 and 2.40 are correct.

The data in tables 2.39 and 2.40 are correct. The cells which report the identical data refer to the baseline characteristics after matching and so it is expected that they should be the same or very similar. For further description of the methodology see Appendix D of the company submission.

b. If the data are correct, please provide the rationale for comparing 40.1 year old patients on dupilumab with 19.5 year old patients on ciclosporin (Table 2.40).

As stated in Section B 2.9, there are very limited data upon which an indirect analysis can be made with immunosuppressants currently used in the treatment of AD. Therefore, we have taken a pragmatic approach and chosen the best available evidence according to an assessment of relevance detailed in section B 2.9. In the Jin 2015 study, the average age was 19.5 years, which is lower than the age of patients recruited into the dupilumab trials. However, inspection of all the Forest plots from the Liberty program suggests that age is not a confounding variable for dupilumab efficacy (See Figure 1 to Figure 4). The percentage of patients achieving the primary endpoint of EASI-75 across all age groups was broadly comparable in the LIBERTY program. We have no insight into the effect of age on ciclosporin efficacy and patient outcomes, but given the results shown below, it is unlikely that the results from the MAIC would be strongly biased by the difference in ages.

Figure 1. SOLO 1: Percentage of patients Achieving EASI-75 (>=75% Improvement from Baseline) by subgroup at week 52. Patients were considered non-responders after rescue treatment use (Full Analysis Set)

Subgroup	Placebo Rate	Duilumab Rate
Overall		
300 mg QW vs Placebo	33/224(14.7)	117/223(52.5)
300 mg Q2W vs Placebo	33/224(14.7)	115/224(51.3)
Age		
>=18-<40		
300 mg QW vs Placebo	19/114(16.7)	59/113(52.2)
300 mg Q2W vs Placebo	19/114(16.7)	59/116(50.9)
>=40-<65		
300 mg QW vs Placebo	13/102(12.7)	54/102(52.9)
300 mg Q2W vs Placebo	13/102(12.7)	46/92(50.0)
>=65		
300 mg QW vs Placebo	1/8(12.5)	4/8(50.0)
300 mg Q2W vs Placebo	1/8(12.5)	10/16(62.5)

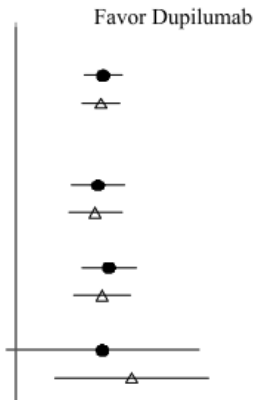


Figure 2. SOLO 2: Percentage of patients Achieving EASI-75 (>=75% Improvement from Baseline) by subgroup at week 52. Patients were considered non-responders after rescue treatment use (Full Analysis Set)

Subgroup	Placebo Rate	Duilumab Rate
Overall		
300 mg QW vs Placebo	28/236(11.9)	115/239(48.1)
300 mg Q2W vs Placebo	28/236(11.9)	103/233(44.2)
Age		
>=18-<40		
300 mg QW vs Placebo	16/140(11.4)	70/146(47.9)
300 mg Q2W vs Placebo	16/140(11.4)	70/151(46.4)
>=40-<65		
300 mg QW vs Placebo	12/87(13.8)	40/80(50.0)
300 mg Q2W vs Placebo	12/87(13.8)	27/72(37.5)
>=65		
300 mg QW vs Placebo	0/9(0.0)	5/13(38.5)
300 mg Q2W vs Placebo	0/9(0.0)	6/10(60.0)

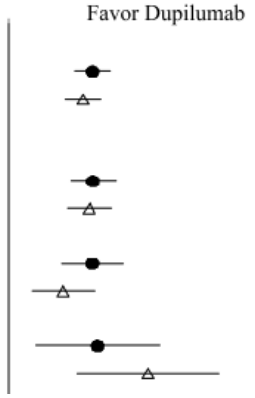


Figure 3. CHRONOS: Percentage of patients Achieving EASI-75 (>=75% Improvement from Baseline) by subgroup at week 52. Patients were considered non-responders after rescue treatment use (Full Analysis Set)

Subgroup	Placebo Rate	Duilumab Rate
Age		
>=18-<40		
300 mg QW + TCS vs Placebo + TCS	43/189(22.8)	124/193(64.2)
300 mg Q2W + TCS vs Placebo + TCS	43/189(22.8)	33/52(63.5)
>=40-<65		
300 mg QW + TCS vs Placebo + TCS	23/117(19.7)	73/113(64.6)
300 mg Q2W + TCS vs Placebo + TCS	23/117(19.7)	29/49(59.2)
>=65		
300 mg QW + TCS vs Placebo + TCS	3/9(33.3)	7/13(53.8)
300 mg Q2W + TCS vs Placebo + TCS	3/9(33.3)	4/5(80.0)

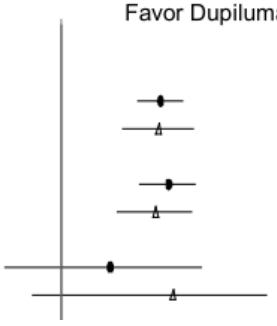
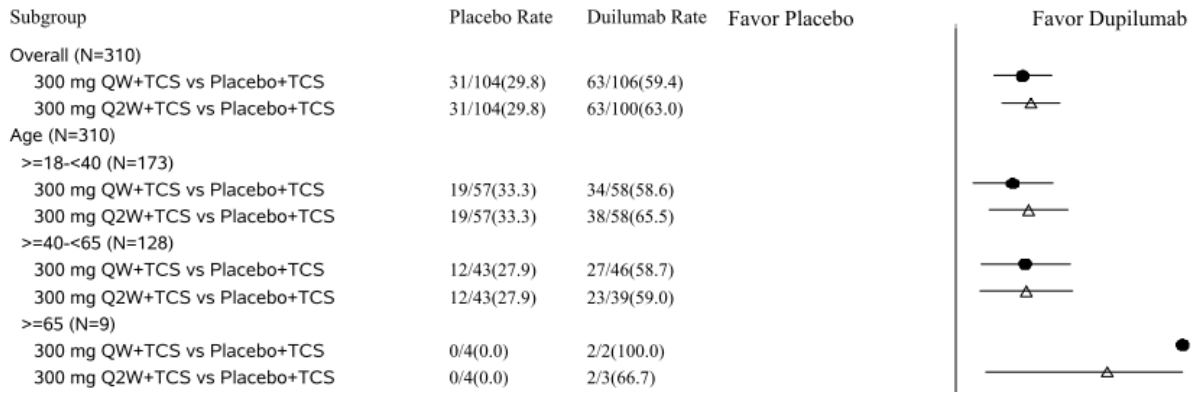


Figure 4. CAFE: Percentage of patients Achieving EASI-75 (>=75% Improvement from Baseline) by subgroup at week 52 Patients were considered non-responders after rescue treatment use (Full Analysis Set)



The MAIC indicated that dupilumab may be a superior treatment vs. ciclosporin for patients with moderate to severe AD. However, in the light of the uncertainty and lack of an equivalent EASI-50 and DLQI≥4 endpoints for the ciclosporin studies, a conservative approach was taken in modelling in which the efficacy of ciclosporin was set to be equal to dupilumab.

Early Access to Medicines Scheme (EAMS)

A7. CS, section B2.11.2 (page 152). Please clarify whether the EAMS study is still ongoing.

It is important to note that the Early Access to Medicines Scheme (EAMS) is not a formal study, however the data capture requirements and opportunities for data collection are described fully below. According to the terms of the scheme an EAMS may run up to the point of marketing authorisation after which no new patients may enter. The EAMS for dupilumab closed to new entrants at the point of on the 28th September 2017.

The Early Access to Medicines Scheme was launched by the Medicines and Healthcare Products Regulatory Agency (MHRA) in order *'…to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.'*

In MHRA guidance '*EAMS can provide an opportunity to generate real world patient data in the NHS – the expectation is that medicines with a positive scientific opinion could be made available to patients up to 12 to 18 months ahead of formal marketing authorisation*.' To date, there have been 19 positive scientific opinions granted since May 2015 including dupilumab, of which three are ongoing. In general the patient access periods for EAMS-approved products have been short with limited opportunity to collect real world data. (Mean (days) 97.6, Standard Deviation (days) 78.8, Median (days) 78.5, Min (days) 18, Max (days) 327). We are unaware of any scheme to date where EAMS outcomes data have been published.

Dupilumab was granted Promising Innovative Medicine (PIM) designation by the MHRA on the 23rd December 2015 and the MHRA granted positive scientific opinion for dupilumab on the 10th of March 2017. The dupilumab EAMS ran between the 10th of March and the 28th of September

corresponding to the date of marketing authorisation whereupon no new patients were recruited to the scheme. Under the terms of the scheme, Sanofi is committed to providing dupilumab to the NHS free of charge for all EAMS patients until recommendation from NICE. All EAMS patients will receive at least one year of treatment.

Whilst the dupilumab EAMS is the second longest to date (210 days vs. pembrolizumab for lung cancer at 327 days) there was no pre-existing registry that could be used for data collection and so no formal vehicle existed to collect data. Sanofi is in discussion with an academic group that is in the process of initiating an AD registry but unfortunately this was not available for EAMS patients.

Sanofi collected a baseline demographics, previous medical history, previous drug history and DLQI, IGA and EASI scores during assessment of entry criteria before patients were admitted to the scheme (See CS Section B2.11.2). No further data collection was carried out. (See above for the availability of a suitable registry). Proactive safety data collection was a requirement of the MHRA, and the safety reports were submitted to the MHRA as mandated in the EAMS protocol. Because EAMS is not a study, no formal EAMS outcomes data collection is planned. However, we are in discussion with the participating sites to understand what data was collected locally and may be analysed retrospectively.

A8. CS, section B2.3.2, table 2.9 (page 61) and section B2.11.2.2, table 2.55 (page 153). Table 2.9 (CS, page 61) define moderate to severe atopic dermatitis as "… baseline AD severity scores of IGA ≥3 (SOLO 1 and 2, CHRONOS, CAFÉ), EASI ≥16 (CHRONOS), EASI ≥ 20 (CAFÉ) …". Table 2.55 (CS, page 153) provide a range of values (EASI lower value 0.6 and IGA lower value 1) that suggest patients with less severe disease were included in the dupilumab EAMS compared with patients in CHRONOS, CAFÉ, SOLO-1 and SOLO-2. Please clarify the reason for this difference.

There is an ongoing debate about what the most appropriate tool for the assessment of disease is. Recently an expert panel of the International Eczema Council recommended that severity-based scoring systems alone cannot determine the need for systemic therapy and that holistic assessment is needed.(1) This includes consideration of signs and symptoms along with the impact on QoL, together with emotional and social functioning. Recognition of these limitations with the AD severity tools is one of the reasons why a holistic assessment of AD is recommended by NICE (in the under 12 year Atopic Eczema Guideline(2)).

According to the EAMS indication, dupilumab should be restricted to patients with severe AD. For the purpose of EAMS, the indication was as follows:

> *'Dupilumab is being made available to adult patients with severe atopic dermatitis who have failed to respond, or who are intolerant of or ineligible for all other approved therapies. Dupilumab can be used with or without topical corticosteroids'*

This is different to the final label wording and reflects the goal of the EAMS to provide medicine to patients with '*seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need'*. The mean and median

baseline EASI and IGA scores are numerically lower than those reported in the clinical trials. In isolation these clinical disease severity scores would suggest the EAMS patients are less severe than in dupilumab clinical trials. However, these are real world data. The aim of treatment is to reduce the burden of AD and patients are often treated with a range of systemic and topical therapies. Despite this, patients may continue to have a high unmet need. This means that the visible signs of AD on the day of an EASI assessment may be low, but a significant impact on quality of life remains. This is evident from the DLQI scores recorded at baseline in EAMS (Mean (SD): 16.65 (7.54) based on 165 patients with complete data and consent to analyse the data) which were equivalent to or higher than those observed at baseline in the LIBERTY program (For example, DLQI for the dupilumab Q2W patients in the base case populations: CAFÉ+CHRONOS CAFÉ-like: 14.6 (7.5) and SOLO CAFÉ-like: 15.7 (6.8)).

We believe the EAMS data are useful real-world evidence demonstrating a disconnect between scoring systems and disease severity in AD and highlights the need for a holistic approach to management of AD patients.

IGA and EASI assess severity and extent of the disease using signs and symptoms. Neither tool considers the impact of quality of life. Assessment of the visible signs of AD on the day of an EASI assessment may be low, but a significant impact on quality of life remains. For example body surface area (BSA) involvement can be low but affect high impact sites such as the face and genital regions. This results in lower EASI or IGA scores but impact on quality of life can be extremely high. For these patients their disease may be characterised as mild or moderate by score but is severe by nature.

Similarly the waxing and waning of disease symptoms in AD means that point assessment of disease severity by EASI score can be misleading. This is evident from the DLQI scores recorded at baseline in EAMS (Mean (SD): 16.65 (7.54)) which were equivalent or higher than those observed at baseline in the LIBERTY program (For example DLQI for the dupilumab Q2W patients in the base case populations: CAFÉ+CHRONOS CAFÉ-like: 14.6 (7.5) and SOLO CAFÉ-like: 15.7 (6.8)). Using DLQI scores, EAMS patients report a poorer quality of life than in dupilumab trials.

As part of the eligibility criteria for EAMS, participating physicians provided IGA, DLQI and EASI scores at baseline for patients entering the scheme. In addition, patients' previous medical history and AD drug treatment history were provided.

Given the EAMS indication for severe patients, we sought clarification from EAMS clinicians for patients who had "low" baseline scores. In particular we wanted to understand how severity had been determined, and why dupilumab was deemed an appropriate treatment given their scores. The reasons provided for 'low' EASI scores included:

- Currently on a systemic therapy (immunosuppressant or prednisolone)
- Small body surface area (BSA) involvement but high impact sites
- In between severe flares on the day of assessment

The clinicians described factors for the appropriateness of initiating dupilumab despite low scores with a systemic therapy such as:

- adverse effects emerging
- serious concerns about long term use and potential for adverse events
- less than “optimal” response
- skin infections

In the table below we have included some representative examples of the data we collected on a couple of EAMS patients who report a low EASI score, but follow up with their clinicians confirms that they do have severe AD.

42 year old Male. Lifelong, severe AD. EASI score 9.7; DLQI 15 2013 ciclosporin lack of efficacy. 2015-16 azathioprine (up to max dose 150mg) stopped due to lack of efficacy. 2017 methotrexate trialled and stopped due to acute macrocytosis. Intermittent high dose tapering regimens of prednisolone since then, score taken whilst on prednisolone.	24 year old female, longstanding AD. EASI score 7.9. DLQI 15 2007-08 Azathioprine– no effect 2008 Ciclosporin discontinued due to severe paraesthesia. 2008-12 methotrexate 15 mg weekly discontinued due to alopecia, gastris and nausea. Multiple courses of prednisolone . Since May 2017 Mycophenolate Mofetil 2.5g per day partial efficacy, develops flares episodes of exacerbation. Since starting had inter-menstrual bleeding.

In the light of these considerations and in line with advice we received from clinicians at an advisory board alongside published guidelines(1, 3), we suggest a holistic approach is needed when assessing severity, quality of life (including everyday activities and sleep) and psychosocial wellbeing (for example see Sections B1.3.4 and B1.3.9). A score from one of the AD assessment tools alone at a static point is unlikely to estimate true AD severity.

Section B: Clarification on cost-effectiveness data

Model structure

B1. CS, section B3.2.3 (pages 173-175). The company model utilises three Markov states: on-treatment, best supportive care (BSC) and dead. Only treatment responders are maintained on-treatment in the Markov model, and are assumed to have a relatively stable response whilst on treatment. The chosen structure may lack the flexibility to capture the waxing and waning nature of atopic dermatitis. A state transition model with defined states such as clear, mild, moderate and severe might better reflect the natural variation in severity over time. Please provide further rationale for the chosen model structure compared to other alternative options

AD is a complex and dynamic disease. In determining the final model structure we considered previously published models, dupilumab and comparator data availability and model complexity (in terms of transparency and number of health states). We took a pragmatic approach when specifying our model structure in which the disease is sufficiently described for the purposes of the decision problem but complexity is minimised. We acknowledge that the model may lack the sensitivity afforded by a more complex structure but given the available data we believe that uncertainty is minimised and our approach is robust. Indeed the results are likely to be conservative with respect to the benefit delivered by dupilumab. We provide further rationale for our chosen model structure below.

Evidence from the literature

For the purposes of this assessment we carried out a full systematic literature review which searched for economic models in the area of AD (See appendix G of the submission documents). This review revealed that all the previously published economic models (with the exception of the US adaptation of the dupilumab model published in 2017 (4)) focused on topical treatments for adults and children. These models have typically employed short cycle lengths and time horizons due to the nature of the treatments being modelled(5-10) .We took the view that it was inappropriate to base the dupilumab health economic model structure on any of the previously published models.

As dupilumab is the first biologic for the treatment of AD there are no other published economic models for biologics in this area. Given this gap in the literature and paucity of modelling approaches for AD in general, we conducted a pragmatic search to find other cost-effectiveness models focusing on biologic therapies indicated for long-term chronic use in related inflammatory skin conditions, such as psoriasis, psoriatic arthritis, and chronic spontaneous urticaria. Whilst there are differences between these diseases and AD, the following features are common to all of the diseases including AD:

- Are chronic in nature.
- Have a substantial skin component.
- Use efficacy scales similar to those used in AD.
- Have recent HTAs considering biologic treatment.

Overall, the models identified in this review contained several consistent themes. Treatment response is assessed in a short-term decision tree structure (generally 12-24 weeks) corresponding to study endpoints. After which consideration is given for continuation or discontinuation of patients from treatment. Long-term treatment is generally handled via a Markov model, with patients remaining in the disease severity state from the short-term model.

The most commonly used and most widely validated of the models identified in this context are based on a model developed at the University of York for the assessment of biologic therapies in psoriasis.(11) The ‘York’ model utilises data from published randomized clinical trials to define treatment response after an initial treatment period. Patients who respond to therapy after the initial treatment period are assumed to continue on therapy, while patients who do not respond are assumed to discontinue and transition to non-targeted therapy or supportive care. Allowing for such an efficacy assessment is a core element of HE models in various other immunological conditions. The York model also allows for extrapolation of clinical and economic outcomes over a lifetime time horizon.

Design of the dupilumab model.

These structural elements are important for the assessment of a chronic treatment in AD and on this basis we chose to adapt the ‘York’ model for use in our submission. When designing the model structure we considered the differences between psoriasis and AD and whether it would

be appropriate to partition the 'York' model structure model into response states such as mild, moderate or severe to provide more nuanced results. As noted in the question this might allow the model to capture the waxing and waning signs and symptoms of AD.

Moderate to severe AD is a lifelong illness for most patients. The mean disease duration ranged from 27 to 30 years for patients in the clinical trials and past medical histories for EAMS patients suggest similarly long durations of disease. In the target patient population many patients often spend a considerable amount of time in a state of 'exacerbation' and so these symptoms could be regarded as chronic(12) and ongoing, unlikely to be usefully described in an episodic model.

The evidence base to populate multiple states is not available from the dupilumab studies. The primary end points were recorded at 16 weeks and flares were not captured as an outcome. Nonetheless, the high frequency of outcome assessment and low missing data for EQ-5D collection during the studies means that utility associated with changes in disease status, if they occurred, are likely to be captured in aggregate. Hence the addition of further health states might add complexity without increasing accuracy or decreasing uncertainty.

Dupilumab should be used chronically which reinforces the need to use a structure that models chronic, rather than episodic disease.

A simple, robust and holistic treatment response assessment which accounts for signs, symptoms and quality of life is undertaken in the model using a set of criteria suggested to us by clinical experts. This encompasses both physician (EASI) and patient perspectives (DLQI). Such an assessment must be meaningful to patients, physicians and decision makers alike and applicable to real world clinical practice. In this context, the implementation of further health states not fully supported by evidence is likely to complicate the decision making process and introduce uncertainty.

Validation of the chosen dupilumab model structure.

When developing the model we sought to develop a simple structure that reflected the disease and treatment paradigm introduced by the first biologic in this area. With the considerations above in mind we discussed the proposed structure, management of patients, current patterns of care (standards of care) and expected use of dupilumab with several clinical and health economics experts in AD in the UK.

The AD experts we spoke to indicated that the majority of patients would respond to dupilumab and maintain this response. The clinical data support this assumption in terms of both EASI response and quality-of-life data (DLQI and EQ-5D). For those duplimab patients who do not continue to respond we have taken a conservative stance. The model assumes that there will be a total loss of response on discontinuation with return to standard of care (SoC) outcomes. Whilst patients are likely to eventually return to previous disease status as shown in the early studies an immediate return is unlikely and so the ICERs generated by the model are conservative in this respect.

Conversely the clinical experts felt that patients on SoC who respond in the studies would return quickly to baseline levels of AD after the support afforded by an RCT was withdrawn, and thus no further delineation of response was needed.

We received advice from health economic experts who cautioned that a complex model unsupported by robust evidence will not provide results useful to decision makers and that the simple structure proposed is likely to meet the needs of the assessment. Based on our findings the 3 state model exemplified by the 'York' structure was selected.

Conclusion

When faced with the choice between multiple different model structures we decided to use the simpler more transparent and familiar structure that was able to make best use of the available dupilumab data. Our concern was that a more complex model would lack transparency and we would not be able to populate it with meaningful data. Therefore what may be gained in a more complete description of the disease would not result in more accurate assessment of the economics of dupiluamb or reduce uncertainty.

Utility adjustments based on age
B2. CS, section B3.3.5 (page 188). The age adjustment to utility weights in the model appears be follow a constant "additive" approach that has a zero impact on the ICER. The NICE DSU appears to recommend a "multiplicative" adjustment method for reasons of consistency (NICE TSD 12, page 5). Please explore the impact of age adjusting the utility multipliers and then applying a multiplicative approach to age adjustment using age specific general population utilities, as described in NICE TSD 12.

The economic model has been modified to include the option to use a multiplicative approach. A switch is included on the 'Utility' worksheet in cell F48. Calculations are found in Lines 113 to 287 on the 'Utility Calcs' worksheet in the attached model.

The base case results using the multiplicative approach are summarised overleaf in Table 8 Table 8and Table 9 adapted from Tables 3.41 and 3.42 from the company submission.

Table 8. Base case results (including the multiplicative approach for calculating utility) for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	Redacted: Commercial in confidence						-
Dupilumab Q2W							£30,419

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 9. Base case results (including the multiplicative approach for calculating utility) for the SOLO CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	**Redacted: Commercial in confidence**						-
Dupilumab Q2W							£25,749

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

In both cases the ICER rises with respect to the approach using the additive methodology (**Redacted CIC** and **Redacted CIC** for the CAFÉ FAS + CHRONOS CAFÉ-like patients and the SOLO CAFÉ-like patients respectively).

This is because the multiplicative approach for calculating utility reduces the incremental QALY from **Redacted CIC** to **Redacted CIC** for the CAFÉ FAS + CHRONOS CAFÉ-like patients and from **Redacted CIC** to **Redacted CIC** for the SOLO CAFÉ-like patients. However, it is worth noting that the total QALYs in both arms increases by **Redacted CIC** (Dupilumab) and **Redacted CIC** (BSC) for the CAFÉ FAS + CHRONOS CAFÉ-like patients and by **Redacted CIC** (Dupilumab) and **Redacted CIC** (BSC) for the SOLO CAFÉ-like patients.

We have emphasised in the company submission that an incremental QALY gain above 1.0 in a treatment that is not life extending is a remarkable result.

The impact of starting age in the model on the ICER including the multiplicative approach is explored in Table 10 below.

Table 10. Impact of starting age on the ICER including the multiplicative approach for calculating utility.

Starting age (years)	ICER	
	CAFÉ + CHRONOS CAFÉ-like	SOLO CAFÉ-like
30	**Redacted: Commercial in confidence**	
35		
38.1 (Base case)	£30,419	£25,749
40	**Redacted: Commercial in confidence**	
45		
50		
55		
60		
65		
70		

Resource use and costs

Administration training costs

B3. CS, section B3.4.6.1 (page 196). The company assumes that dupilumab will be self-administered with only a single training session resulting in costs to the NHS. Please clarify the prescribing, delivery and administration model for dupilumab. In particular:

a. **Will dupilumab be distributed from hospital pharmacies, or delivered directly to patients' homes?**

In line with the label wording, it is anticipated that dupilumab will be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis. Over time it is likely that initiation will occur via homecare providers as has been the case for many other biologics. However we have taken a conservative approach in the modelling and assumed costs associated hospital initiation exclusively.

All NHS hospitals will be offered deliveries directly to patients' homes through homecare delivery at no cost to the NHS. It is anticipated that this will be the predominant supply route for patients however dupilumab will be available to hospital and out-sourced NHS trust pharmacies.

b. What is the intended frequency of prescription and delivery to patients?

Sanofi Genzyme will fund 4 weekly deliveries for the first 12 weeks. Deliveries will then be made every 12 weeks for the duration of treatment. We understand that clinicians may identify a small number of patients who will require more frequent deliveries and we will work with the National Homecare Medicines Committee (NHMC) to ensure the appropriate exceptions request documentation has been created and implemented.

The frequency of prescriptions will be left to the clinical team to determine. We are aware that some centres write a prescription for each delivery and some prefer to write prescriptions to cover a longer time period. For example, if a clinician wrote a 12-week prescription for a new patient, our homecare provider would still perform 4 weekly deliveries until the second prescription came in (unless expressly advised not to). This approach is aimed at reducing the administrative burden on the NHS, whilst simultaneously minimising exposure to financial risk, should a patient stop therapy in the first 12 weeks.

c. How many vials can be stored at the patient's home?

Dupilumab is provided in prefilled syringes not in vials. Assuming a 12 weekly delivery cycle with a 14 day 'buffer stock', the maximum number of syringes a patient should need to store at any time is 7 (6 for the 12 weekly delivery + 1 unit buffer stock).

The level of 'buffer stock' is agreed between the homecare provider and NHS centre.

In exceptional circumstances, should it be identified that a patient cannot safely or practically hold the amount of product required in their own refrigerator (for example a university student with a shared refrigerator and limited space), a small refrigeration unit will be provided by the homecare company. In these circumstances, the cost of the refrigerator will be covered by Sanofi Genzyme and, in order to comply with the ABPI code (clause 18.2 prohibiting the

provision of items above £6), the item will be leased, free of charge to the patient. The refrigerator will be collected by the homecare company should a patient finish or stop the therapy.

d. Are any mechanisms in place to guarantee patients receive and correctly self-administer the drug in the long run?

All NHS hospitals will be offered access to additional patient support, including:

- Home nurse training (3 sessions per patient)
- Text messages: Delivery & Injection Reminders for the duration of therapy
- Structured, HCP-led telephone support pathways tailored to their level of need (programme to be developed) for the duration of therapy
- Patient Welcome Pack & Injection Calendar

Homecare providers will provide stock checks at the point of arranging each delivery and if any issues arise, they will be discussed with the patient's clinical team.

Medical costs

B4. PRIORITY QUESTION. CS, table 3.38 (pages 211-212) and section B3.4.6.2 (pages 198-201). Please provide further disaggregation of the following medical costs for the base-case analysis: physician, dermatologist, emergency, hospitalization, day case, full blood count, dermatology nurse visit and background medications.

Disaggregation of the medical costs is provided in Table 11 and Table 12

Table 12overleaf. Within the tables, the entry titled 'Other medical costs' includes the required elements with disaggregation into: Primary care visit, Dermatologist visit, Emergency room visit, Hospitalisation, Day case, Full blood count, Dermatology nurse visit and Background medications.

Table 11. Disaggregated costs by health state for the comparison of the CAFE FAS + CHRONOS CAFE-like pool including dupilumab Q2W patients with BSC

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Decision Tree					
Active Treatment Costs	**Redacted: Commercial in confidence**				
Concomitant Medication Costs					
Other Medical Costs:					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation					
Day case					
Full blood count					

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Dermatology nurse visit					
Background medications					
Administration Costs					
Indirect Costs					
Maintenance Treatment Health State					
Active Treatment Costs					
Concomitant Medication Costs					
Other Medical Costs					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation	**Redacted: Commercial in confidence**				
Day case					
Full blood count					
Dermatology nurse visit					
Background medications					
Administration Costs					
Indirect Costs					
BSC Health State					
Active Treatment Costs	£0	£0	£0	£0	0.0%
Concomitant Medication Costs					
Other Medical Costs					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation	**Redacted: Commercial in confidence**				
Day case					
Full blood count					
Dermatology nurse visit					
Background medications					
Administration Costs					
Indirect Costs					
Adverse Event Costs					
Total Costs	**Redacted: Commercial in confidence**				**100.0%**

BSC=Best Supportive Care; FAS= full set analysis; QALY= Quality Adjusted Life Year; Q2W = once every two weeks

Table 12. Disaggregated costs by health state for the comparison of the SOLO CAFE-like pool including dupilumab Q2W patients with BSC

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Decision Tree					
Active Treatment Costs	**Redacted: Commercial in confidence**				
Concomitant Medication Costs					
Other Medical Costs					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation					
Day case					
Full blood count					
Dermatology nurse visit					
Background medications					
Administration Costs					
Indirect Costs					
Maintenance Treatment Health State					
Active Treatment Costs	**Redacted: Commercial in confidence**				
Concomitant Medication Costs					
Other Medical Costs					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation					
Day case					
Full blood count					
Dermatology nurse visit					
Background medications					
Administration Costs					
Indirect Costs					
BSC Health State					
Active Treatment Costs	**Redacted: Commercial in confidence**				
Concomitant Medication Costs					
Other Medical Costs					
Primary care visit					
Dermatologist visit					
Emergency room visit					
Hospitalisation					
Day case					
Full blood count					
Dermatology nurse visit					
Background medications					

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Administration Costs					
Indirect Costs					
Adverse Event Costs					
Total Costs	**Redacted: Commercial in confidence**				**100.0%**

BSC=Best Supportive Care; Q2W = once every two weeks

During these calculations, a marginal difference (~£10) was found in the absolute increment for 'Other medical costs' within the decision tree component of the model with respect to the originally submitted disaggregated costs (see columns Increment and Absolute Increment in Table 8 that report **Redacted CIC** and **Redacted CIC** respectively) using the approach described in the methods guide (i.e., using the modulus of the increment).

These differences do not affect the ICERs.
Note that disaggregated costs and outcomes are presented in Section J of the appendices according to the user guide to the submission template and can be found in Tables J-4 and J-8.

Tests and investigations costs

B5. CS, table 3.22 (pages 196-197). Dupilumab responders are assumed to have 0 diagnostic/monitoring tests, whereas best supportive care responders have 4 tests per year. This implies that no testing is required for the ongoing safety monitoring of dupilumab.

a. Please provide further rationale for this assumption.

The results of the pooled safety analyses and safety analyses from individual studies demonstrate that dupilumab is well tolerated with an acceptable safety profile largely comparable to placebo.

Dupilumab monitoring

Following regulatory assessment, no stipulation for blood testing was made before initiation of, or during, treatment. This was based on the clinical trial results, and the EPAR section of laboratory testing is below.(13)

> ***'Laboratory findings***
> *The results for the groups of patients treated with dupilumab, both as monotherapy and with concomitant TCS, showed a trend toward modestly greater mean decrease from baseline in the numbers of platelets and neutrophils than did the placebo group from baseline to week 16, with a similar trend extending to week 52. The changes in these 2 hematology parameters appeared to be due to patients with high values at baseline decreasing to normal, observed with dupilumab but not with placebo treatment. Of note, a fraction of patients had high baseline values in platelet and neutrophil counts and many of these patients shifted to normal values by the end of the treatment period. The incidences of TEAEs related to platelets (Thrombocytopenia and Platelet Count Decreased) were low overall and there did not*

appear to be any clinical consequence of this modest decrease in platelet count. The modest decrease in neutrophil count was not associated with an increased incidence of Infections and Infestations

The dupilumab monotherapy groups had a transient increase from baseline in eosinophil count, and the mean increase from baseline was modestly greater in the dupilumab groups than in the placebo group at all post-baseline assessments to week 16, with a similar trend extending through week 52. A high proportion of patients had high eosinophil levels at baseline, with more patients in the placebo group shifting to normal values by the end of treatment, compared with patients in the dupilumab groups.

Lactate dehydrogenase (LDH) levels clearly showed a progressive and greater decrease from baseline in the dupilumab treatment groups than in the placebo treatment group from baseline to week 16, with a similar trend extending through week 52. Consistent with this result, greater proportions of the dupilumab groups showed a shift in Lactate dehydrogenase levels from high to normal. Given the direct correlation between LDH levels with AD disease activity and severity reported from other studies, the greater decrease in LDH in the dupilumab group, compared with the placebo group, may be related to the greater efficacy of dupilumab in decreasing AD severity. The analyses found no evidence of drug-induced liver toxicity in any patient.'

As with all therapeutic proteins, there is a potential for immunogenicity. Accordingly, serum samples were collected in all the clinical studies for immunogenicity assessments using validated Anti-drug antibody (ADA) assays and the potential effects of anti-drug antibodies on safety and efficacy were evaluated.

ADA responses were not generally associated with dupilumab exposure, safety, or efficacy. For example in CHRONOS, approximately 3 % of patients in the placebo group and 2 % of patients in the dupilumab group had ADA responses lasting more than 12 weeks. Among these patients, 0.7 % on placebo and 0.2 % treated with dupilumab also had neutralizing antibody responses, but these were not associated with loss of efficacy. In the overall exposure pool, less than 0.1 % of patients exhibited high-titer ADA responses associated with reduced exposure and efficacy.

Hence no testing or examinations are recommended in the SmPC during treatment with dupilumab and no testing is implemented in the model.

Comparator monitoring

The assumptions relating to the frequency of comparator monitoring are based on the SmPC for ciclosporin(14) and supported by clinical opinion for SOC. Given the lack of effective treatment options for the target patient population (defined as patients with a history of intolerance, inadequate response or contraindication to topical therapies (emollients, TCS, TCI) and for whom current systemic immunosuppressants have been deemed inappropriate due to contraindication, intolerance or they were otherwise medically inadvisable) we have assumed SOC for these patients in the base case.

In the real world clinical treatment (SOC) includes a range of topical and systemic treatments some of which have monitoring requirements. (See section B 2.11.2 of the company submission for a description of treatments received by EAMS patients in routine care). During validation of

the model inputs, the clinicians we spoke to suggested that, on average, patients would probably receive full blood tests on a quarterly basis. This is likely to be a conservative estimate as any patient on a systemic immunosuppressant would be tested more regularly than this. (See below for a discussion of testing required for ciclosporin).

b. Please clarify whether monitoring of liver function, renal function, blood counts and drug levels is not necessary with dupilumab.

No monitoring of hepatic or renal function, drug levels or blood testing (see above) is recommended in the SmPC during treatment with dupilumab.

No clinical studies have been conducted to evaluate the effect of hepatic or renal impairment on the PK of dupilumab. Importantly, as a therapeutic protein, dupilumab is not expected to undergo significant hepatic or renal elimination (or to interact directly with cytochrome P450). This is because the metabolism of dupilumab is likely to be limited to proteolytic catabolism to small peptides and individual amino acids. Population PK analysis did not identify mild or moderate renal impairment (predicted creatinine clearance of >30 ≤ 80 mL/min) as having a clinically meaningful influence on the systemic exposure of dupilumab (Very limited data are available in patients with severe renal impairment).

This is in direct contrast to recommendations for the use of ciclosporin in AD, which is limited by commonly recognized toxicities, including hypertension, impaired renal and hepatic function, and the potential for greater susceptibility to infections and cancer, particularly to skin cancer. The use of ciclosporin requires intensive safety monitoring, especially of renal and liver function. Due to this high toxicity, ciclosporin use in AD is limited only to treatment of patients with severe AD, with a maximum duration of 1 year. (Walling 2010; Sandimmune® PI 2015)

No dose adjustments are recommended for any special populations in the SmPC and no monitoring of dupliumab drug levels is specified.

Adverse reaction unit costs and resource use

B6. CS, section B3.4.6.8 (page 205). Please provide further rationale for assuming that injection site reactions are a one-time event "with the cost occurring in the first cycle". In what proportion of patients experiencing an injection site reaction did it occur only once or more than once?

It is worth noting that during the trials, study drug was administered only into areas of normal-looking skin. This ensured that adequate assessment of possible injection site reactions could be made.

The occurrence of injection site reactions was examined for the purposes of answering this question (Table 13). As can be seen the majority of ISRs occurred only once for those patients with any ISR. For example in the base case population including CAFÉ + CHRONOS CAFÉ-like there were three patients with ISRs of whom only one patient had more than one ISR.
Hence injections site reactions are assumed to occur once in the model during the first cycle.

Table 13. Occurrence of injection site reactions in the LIBERTY trial program.

No. of ISRs	CAFÉ + CHRONOS CAFÉ-like		SOLO CAFÉ-like		CHRONOS		CAFÉ		SOLO 1 & 2 pool	
	Placebo	DUP Q2W	Placebo	DUP Q2W	Placebo	DUP Q2W	Placebo	DUP Q2W	Placebo	DUP Q2W
	Number of patients with injection site reactions (ISR) [n (%)]									
1	5 (50.0%)	2 (66.7%)	2 (40.0%)	7 (63.6%)	10 (41.7%)	8 (50.0%)	0	1 (100%)	22 (78.6%)	29 (56.9%)
2	1 (10.0%)	0	2 (40.0%)	1 (9.1%)	5 (20.8%)	3 (18.8%)	0	0	4 (14.3%)	7 (13.7%)
3	1 (10.0%)	1 (33.3%)	1 (20.0%)	2 (18.2%)	2 (8.3%)	3 (18.8%)	0	0	2 (7.1%)	5 (9.8%)
4	2 (20.0%)	0	0	1 (9.1%)	3 (12.5%)	1 (6.3%)	0	0	0	3 (5.9%)
5	0	0	0	0	0	0	0	0	0	3 (5.9%)
6	0	0	0	0	1 (4.2%)	0	0	0	0	1 (2.0%)
7	0	0	0	0	0	0	0	0	0	0
8	1 (10.0%)	0	0	0	0	0	0	0	0	1 (2.0%)
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	1 (4.2%)	1 (6.3%)	0	0	0	1 (2.0%)
12	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	1 (2.0%)
15	0	0	0	0	0	0	0	0		
16	0	0	0	0	1 (4.2%)	0	0	0	0	0

DUP: Dupilumab, Q2W: dosing every other week, ISR: Injection Site Reaction.

We have taken a conservative approach to assigning frequency for use in the modelling by including the total number of events adjusted for patient years. In this way *all injection site reactions observed* are accounted for in the modelling. A complete description of the injection site reaction frequency per 100 years for the studies is provided in Table 14. The annual rate

used in the model for cycle 1 is (nE/100PY)/100. See table 3.8 in document B. For the purposes of the modelling, the Q2W event rates were used to reflect the license.

Table 14. Number of treatment-emergent adverse events (TEAE) per 100 patient-years during the treatment period

Study		Placebo	DUP Q2W
CAFÉ+ CHRONOS CAFÉ-like	Total patient years	90.2	54.8
	nE (nE/100PY)	26 (28.810)	5 (9.124)
SOLO CAFÉ-like	Total patient years	26.00	32.34
	nE (nE/100PY)	9 (34.614)	19 (58.752)
CHRONOS	Total patient years	280.4	100.4
	nE (nE/100PY)	104 (37.084)	35 (34.870)
SOLO (1&2)	Total patient years	135.5	140.8
	nE (nE/100PY)	36 (26.571)	124 (88.098)

DUP: Dupilumab, Q2W: dosing every other week, nE: number of events, PY: patient years

Excel model

B7. PRIORITY QUESTION. The tornado diagram provided in the company's model ("One-Way SA" sheet) shows that the incremental cost-effective ratio (ICER) is most sensitive to baseline utility weight. However, the deterministic sensitivity analysis only varies this parameter through ±10% of the mean and no distribution is assigned in the probabilistic analysis.

a. Please provide a sensitivity analysis showing the impact of varying this parameter estimate through its full 95% confidence limits.

The sensitivity analysis for baseline utility weight has been updated in the model to reflect the 95% confidence intervals associated with these values. These are reflected on the 'Sensitivity analysis' worksheet and are reproduced below in Table 15 for the base case CAFÉ FAS + CHRONOS CAFÉ-like and SOLO CAFÉ-like populations.

Table 15. Baseline utility weights for the CAFÉ FAS + CHRONOS CAFÉ-like and SOLO CAFÉ-like populations including 95% CI for the upper and lower bounds and beta distribution for the probabilistic sensitivity analysis

Population		One-Way Bounds		Probabilistic Sensitivity Analysis					
	Current Value	Lower	Upper	Distribution	SE	Alpha	Beta	Sampled Value	Analysis Value
CAFÉ + CCL	0.66	0.6336	0.6864	Beta	0.0135	812.9	418.8	0.649	0.66
SOLO CL	0.550	0.508	0.592	Beta	0.021	300.9	246.2	0.565	0.550

CCL: CHRONOS CAFÉ-like, CL: CAFÉ-like, SE: Standard Error

The one way sensitivity analysis has been re-run for the base case populations including both the additive and multiplicative utility calculations as described in Question B2 above. Tornado diagrams for each analysis are provided overleaf.

Figure 5. Tornado diagram for one-way sensitivity analyses for the comparison CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC. Utility calculated by the additive approach.

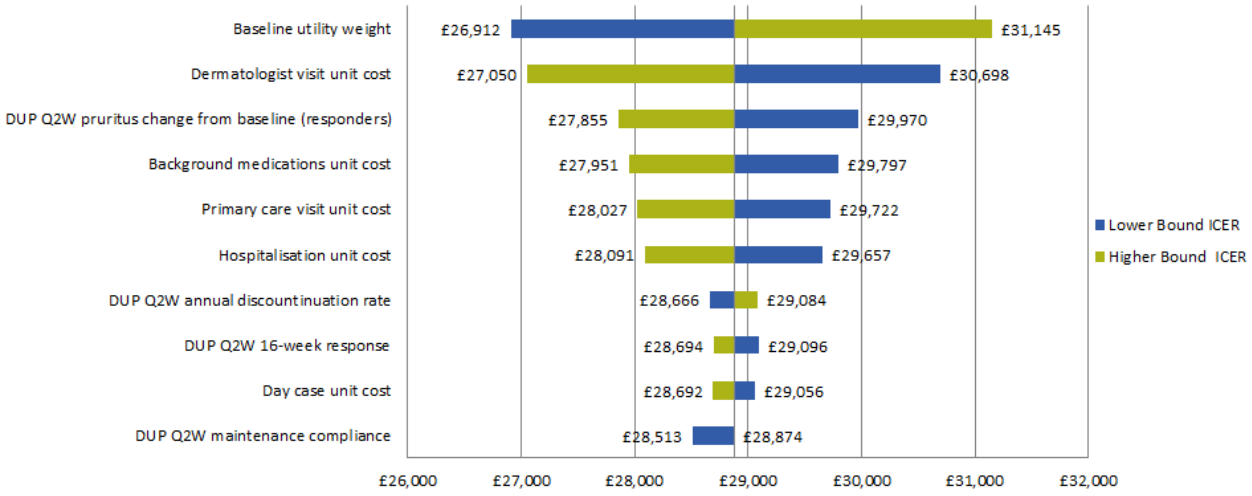


Figure 6. Tornado diagram for one-way sensitivity analyses for the comparison CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC. Utility calculated by the multiplicative approach.

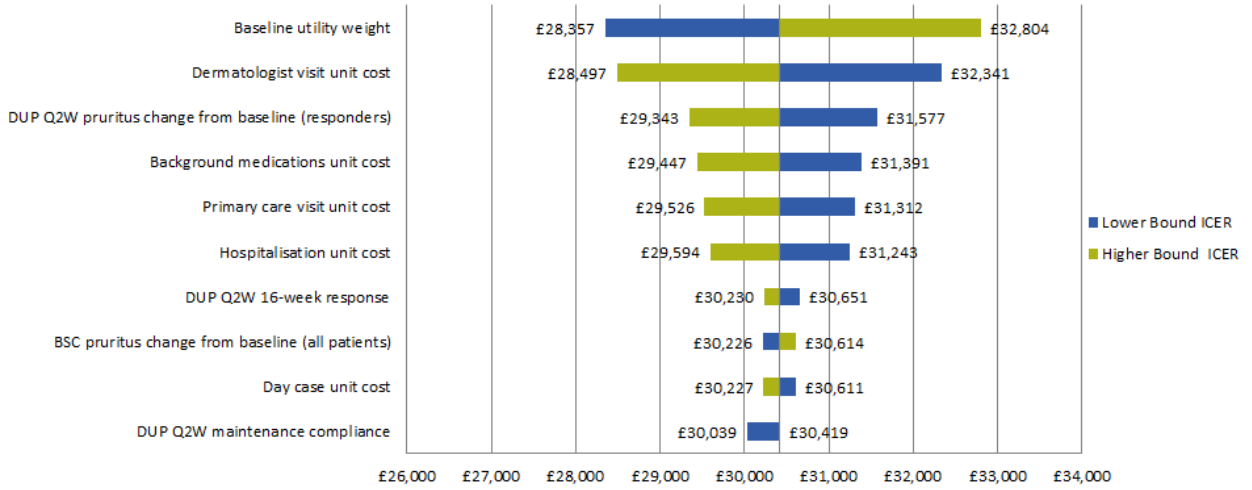


Figure 7. Tornado diagram for one-way sensitivity analyses for the comparison SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC. Utility calculated by the additive approach.

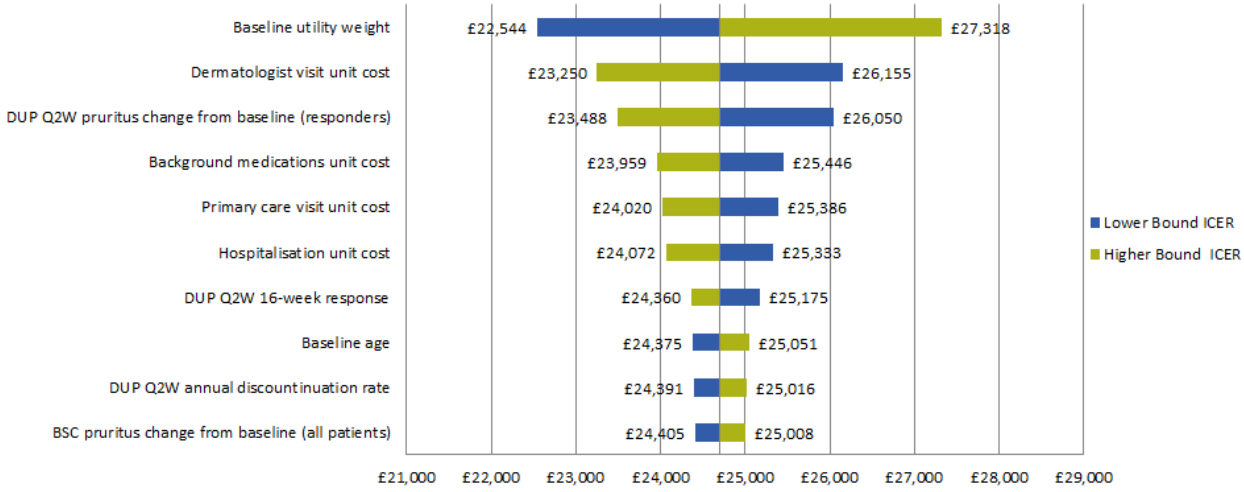
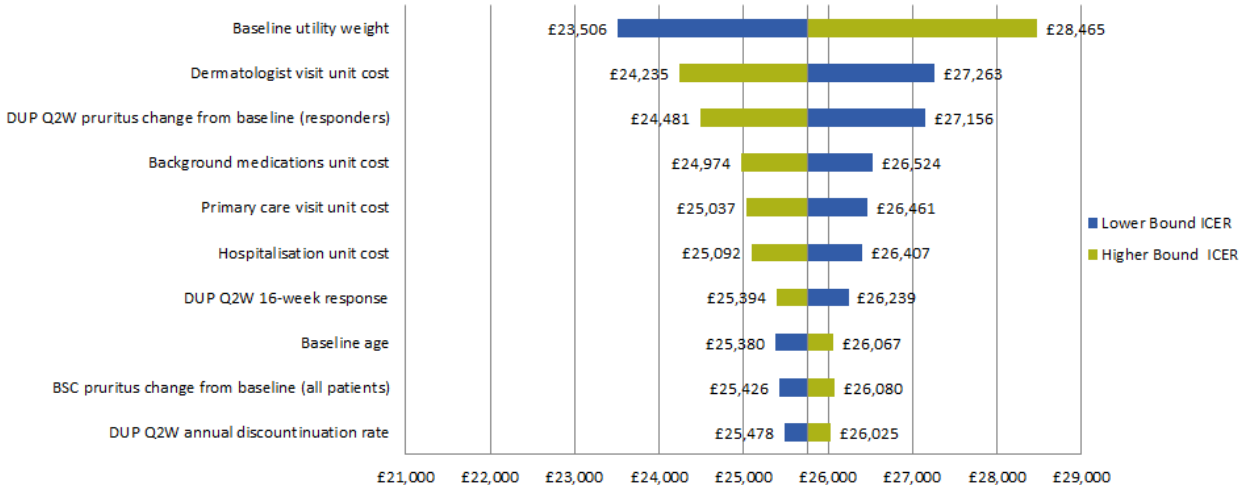


Figure 8. Tornado diagram for one-way sensitivity analyses for the comparison SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC. Utility calculated by the multiplicative approach.



b. Please provide a probabilistic sensitivity analysis that appropriately incorporates the uncertainty surrounding the baseline utility parameter

Probabilistic sensitivity analysis incorporating the additive and multiplicative methodologies for calculation of utility decrements over time are presented below for the base case populations of CAFÉ + CHRONOS CAFÉ-like and SOLO CAFÉ-like patients.

Probabilistic results for the CAFÉ FAS + CHRONOS CAFÉ-like population

Figure 9. Cost-effectiveness Acceptability Curve (CEAC)(15) for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the additive approach.

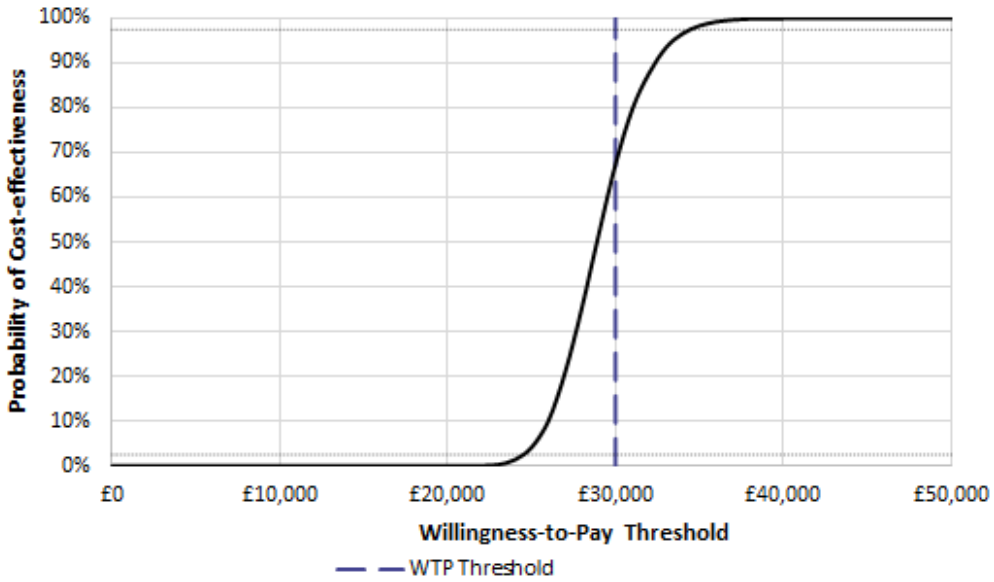


Figure 10. Scatter plot for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the additive approach.

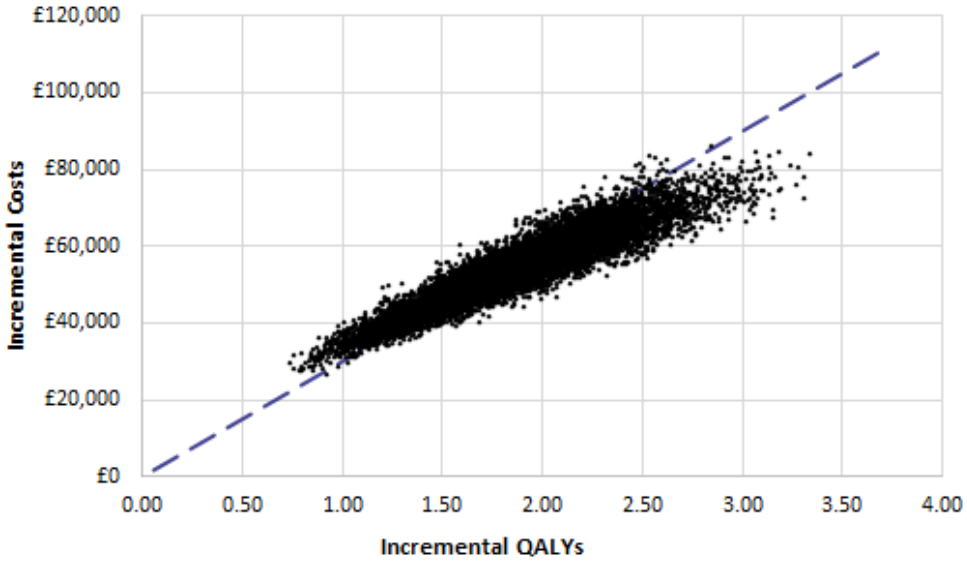


Table 16. Base case results (probabilistic) for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations). Utility calculated by the additive approach.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	Redacted: Commercial in confidence				
Dupilumab Q2W					£28,661

BSC= Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 11. Cost-effectiveness Acceptability Curve (CEAC)(15) for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the multiplicative approach.

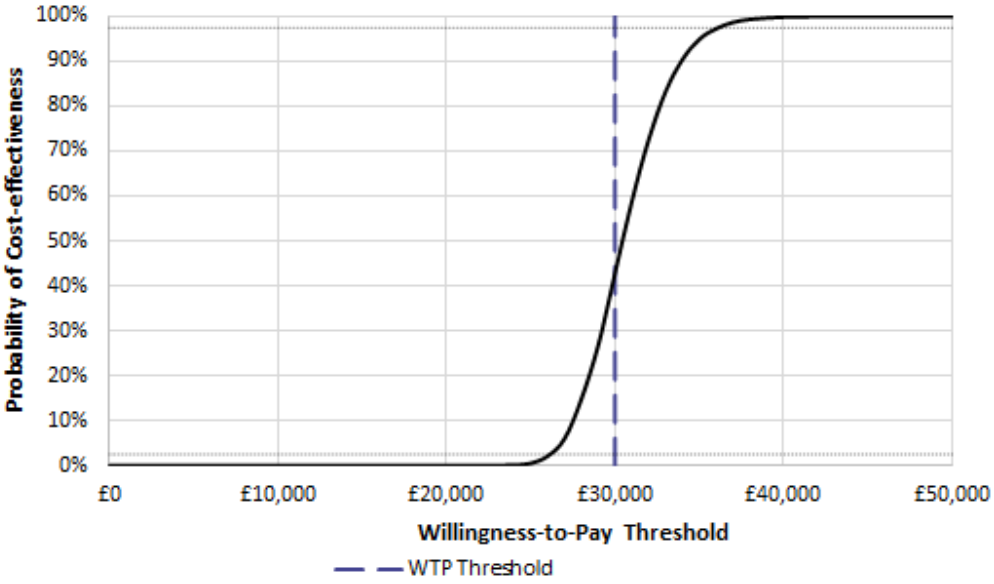


Figure 12. Scatter plot for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the multiplicative approach.

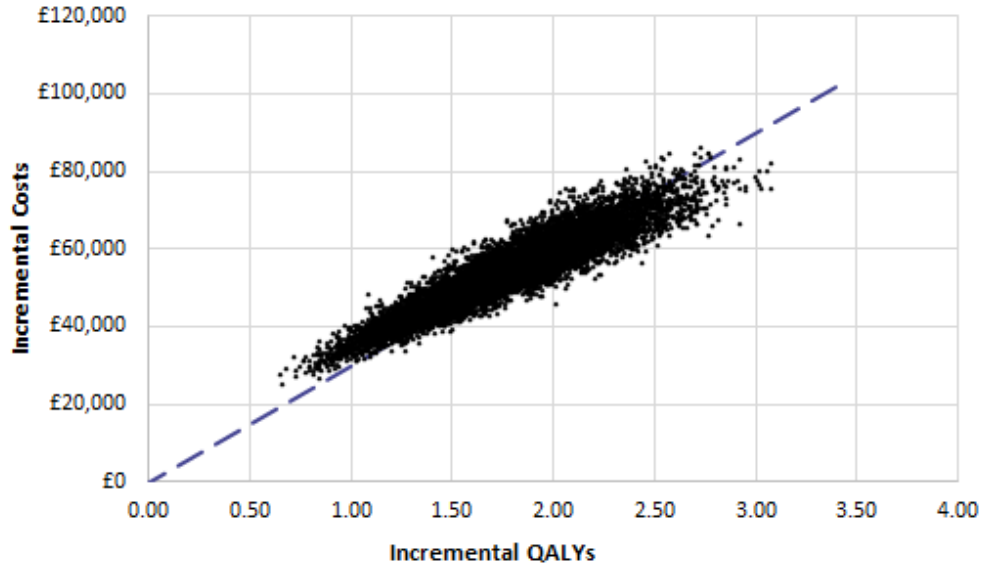


Table 17. Base case results (probabilistic) for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations). Utility calculated by the multiplicative approach.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	Redacted: Commercial in confidence				
Dupilumab Q2W					£30,283

BSC= Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Probabilistic results for the SOLO CAFÉ-like population

Figure 13. Cost-effectiveness Acceptability Curve (CEAC)(15) for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the additive approach.

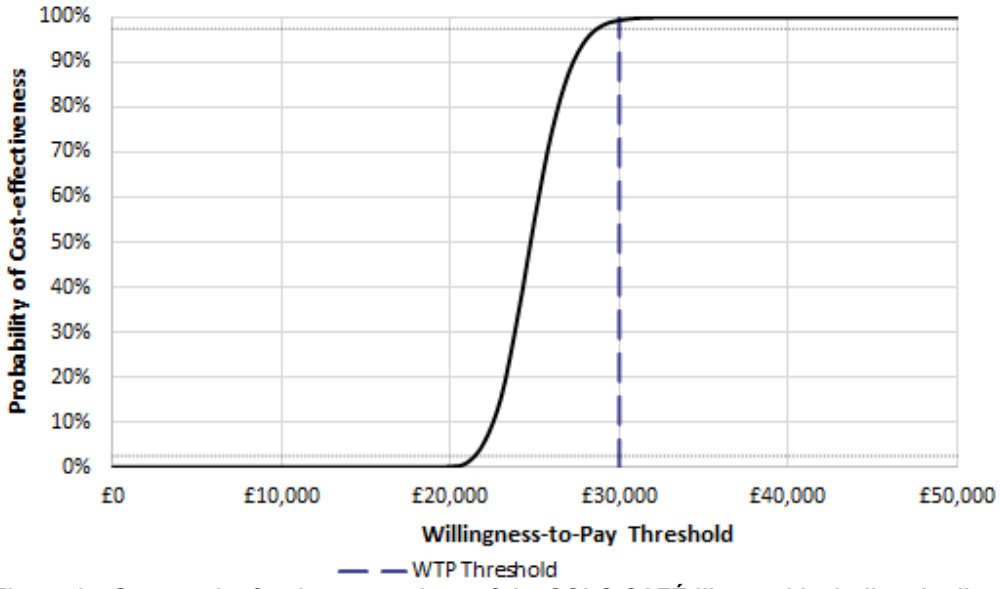


Figure 14. Scatter plot for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the additive approach.

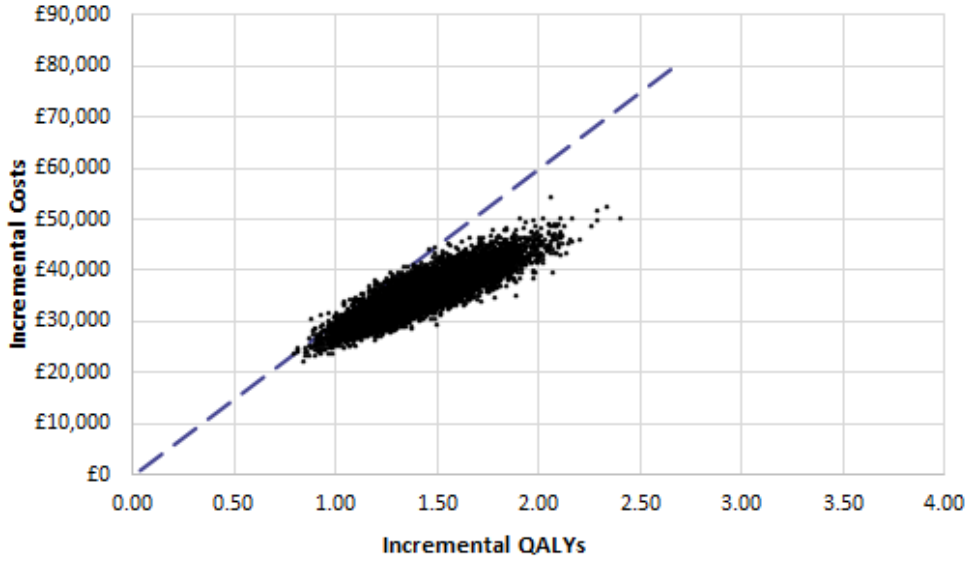


Table 18. Base case results (probabilistic) for the SOLO CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations). Utility calculated by the additive approach.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	Redacted: Commercial in confidence				
Dupilumab Q2W					£24,654

BSC= Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 15. Cost-effectiveness Acceptability Curve (CEAC)(15) for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the multiplicative approach.

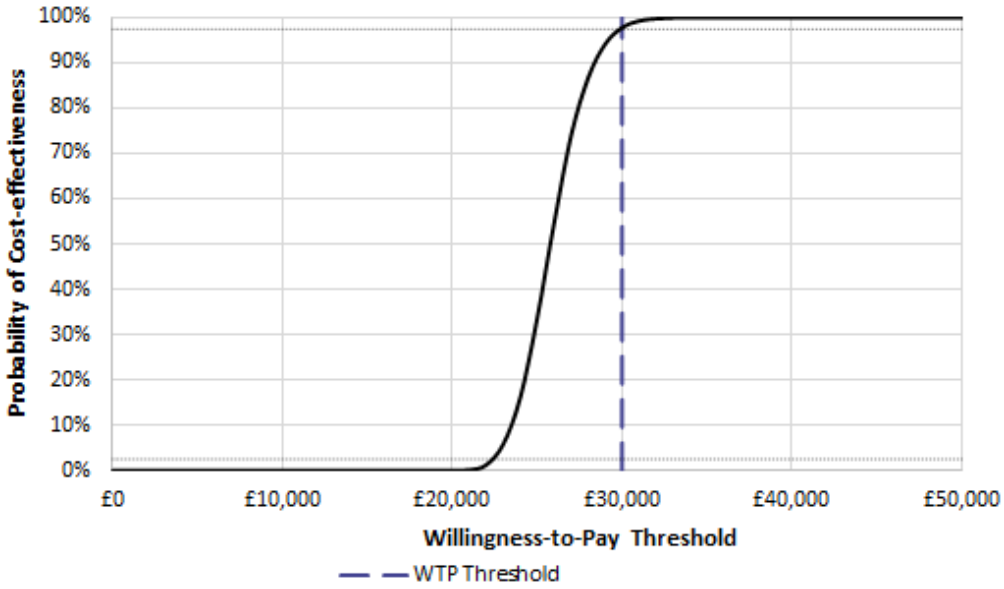


Figure 16. Scatter plot for the comparison of the SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (10,000 iterations). Utility calculated by the multiplicative approach.

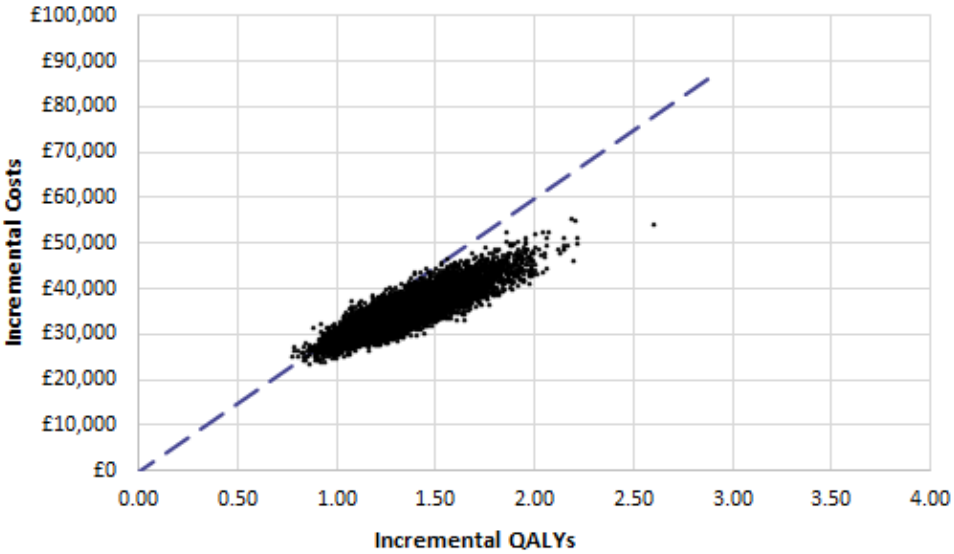


Table 19. Base case results (probabilistic) for the SOLO CAFÉ-like pool including dupilumab Q2W patients. (10,000 iterations). Utility calculated by the multiplicative approach.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	Redacted: Commercial in confidence				
Dupilumab Q2W					£25,687

BSC= Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Dupilumab for treating adults with moderate to severe atopic dermatitis

[ID1048]

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]

2. Name of organisation	**British Association of Dermatologists (the BAD)**
3. Job title or position	**Consultant Dermatologists**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD's 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. 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,	To reduce disease severity and burden, and improve quality of life. Clinical experience suggests that achieving good control of disease *may* be disease-modifying, inducing long-term remission, a reduced number of flares and preventing the development and/or reducing the severity of comorbidities including asthma, allergies and depression.

or prevent progression or disability.)	
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.)	Research studies have shown that the minimal clinically important difference in disease extent as measured by the Eczema Area and Severity Index (EASI) is a reduction of 6.6/72, and for disease symptom improvement as measured by the Patient Oriented Eczema Measure (POEM) is 3.4/28 [Schram et al. Allergy. 2012 Jan;67(1):99-106] However, for pragmatic reasons, we propose that in clinical practice a more conservative estimate of the benefit should be applied and suggest that the treatment should induce: • **A reduction in the Eczema Area and Severity Index (EASI) of 6 points** (the minimum clinically important difference), **at 16 weeks** or • **A reduction in the Eczema Area and Severity Index (EASI) of 50% (i.e. EASI50), at 16 weeks** (N.B. AD is a heterogenous disease and the response of some patients to dupilumab is much slower than others. These are usually the patients with the most severe AD who start with a very high absolute EASI score. In the SOLO dupilumab trial, some patients did not reach EASI50 at week 16, but described it as "life-changing" and "I am cured" compared to their previous life. Subsequently, these patients are cleared of their AD after approximately 9 months on dupilumab. We are in the era of stratified medicine where one size/rule does not fit all and this applies to the rate at which biologic drugs such as dupilumab exert their effect in different types of patients) or less critically • **A reduction in the Patient Oriented Eczema Measure (POEM) of 25% (i.e. POEM25), at 16 weeks**
8. In your view, is there an unmet need for patients and	There is an enormous unmet need for new therapies for patients with atopic dermatitis (AD). This is shown by evidence of high disease burden, increased healthcare resource utilisation and complications of ineffective treatment with current modalities [Eckert et al. J Am Acad Dermatol. 2017 Oct 7. Epub ahead of print].

healthcare professionals in this condition?	Current systemic treatments for severe AD, e.g. immunosuppression, are complicated by the significant risk of side effects. In some individuals, the disease burden is such that despite the documentation of toxicity, the immunosuppression needs to be continued. An alternative treatment with a good adverse event profile is to be welcomed for the treatment of severe AD.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	AD is a common inflammatory skin condition that effects approximately 5% of adults in industrialized countries, of which approximately 15-23% have moderate-to-severe disease (Flohr et al., 2014; Saeki et al., 2009). The mainstay of treatment in primary care remains topical steroids and emollients. Second-line therapies include topical calcineurin inhibitors and phototherapy; however, topical calcineurin inhibitors may not be suitable for widespread AD and phototherapy requires frequent hospital attendances. Systemic therapy is considered for patients who fail to respond, develop side effects or have moderate-to-severe disease. Despite the high prevalence of moderate-to-severe AD, there are limited systemic treatment options. Historically, ciclosporin has been the only systemic drug licensed for AD (short courses up to 8 weeks); however, other agents have been used off-license to treat moderate-to-severe AD, including methotrexate, azathioprine and mycophenolate mofetil (Roekevisch et al., J Allergy Clin Immunol. 2014 Feb;133(2):429-38). Therefore, there is very considerable unmet need in this severely disabling, life-affecting condition. In particular, ciclosporin cannot be used long-term; recommendations in NICE CG153 suggested treatment beyond 1 year is relatively contraindicated and there is no reason to indicate that the risk of renal impairment (the primary driver for this recommendation in psoriasis) should not be the same in AD. Recently, the International Eczema Council have published recommendations on when to consider systemic therapy, and this document also outlines the standard approach to management [Simpson et al., J Am Acad Dermatol. 2017 Oct;77(4):623-633]
• Are any clinical guidelines used in the treatment of the	SIGN guidelines – Management of atopic eczema in primary care

condition, and if so, which?	
• 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.)	The pathway of care is well defined (see above) and consensus amongst specialists about the optimal approach and treatment options [Taylor et al., Br J Dermatol. 2017 Jun;176(6):1617-1623]. There is, however, great variability in the delivery of care across the U.K. due to current pressures on dermatology departments, and variable access to secondary care.
• What impact would the technology have on the current pathway of care?	The reported adverse effects profile of dupilumab appears superior to all currently available systemic therapies for AD. Unlike all other options, this treatment does not immunosuppress. Current data suggest that dupilumab is likely to be at least as effective as currently available treatments. Clearly, for those patients where standard treatments have been ineffective or are relatively contraindicated, treatment with dupilumab is indicated. For those who tolerate the currently available systemic therapies for AD, the drugs have very different adverse effects profiles. It is currently accepted that after 1 year of therapy with: • ciclosporin, the risk of irreversible nephrotoxicity is significant. [Chakravarty et al., Rheumatology (Oxford) 2008 Jun;47(6):924-5] • azathioprine, the risk of skin malignancy is significant [Meggitt et al., Br J Dermatol. 2011 Oct;165(4):711-34] • methotrexate, the risk of significant complications (e.g. liver fibrosis) at 1 year is low, but is thought to be proportional to the cumulative dose and presence of other risk factors (evidence from other inflammatory diseases)

	The precise risks attached to extending time of immunosuppression (e.g. by cycling through different immunosuppressants) have not been determined but it is well established that with regard to malignancy the risk is proportional to the length of immunosuppression [Madeleine et al., Br J Dermatol. 2017 Oct 10. doi: 10.1111/bjd.15931.Epub ahead of print]. Additionally, the severity of AD can be a factor associated with an increased risk of lymphoma [Arellano et al., J Invest Dermatol. 2007 Apr;127(4):808-16]. Therefore, we suggest that dupilumab is indicated for treatment of moderate-to-severe* AD when: • standard systemic (immunosuppressive) therapies such as methotrexate, ciclosporin and azathioprine have failed to achieve an adequate improvement in disease severity and/or quality of life or • standard systemic (immunosuppressive) therapies such as methotrexate, ciclosporin and azathioprine are contraindicated at baseline or during treatment due to significant co-morbidities, such as renal or liver disease, or previous malignancy or • there is concern about a significantly increased risk of malignancy due to the cumulative use of immunosuppressive treatments, particularly azathioprine and ciclosporin, for longer than 1 year. *e.g. EASI score of 16 and Physician's Global Assessment (PGA) score of at least 3
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology is only currently available in selected centres via compassionate scheme and/or clinical trial. Use of biologic therapy is a well-established modality for other inflammatory conditions (psoriasis, urticaria, hidradenitis suppurativa) and therefore would be easily incorporated into current clinical practice.
• How does healthcare resource use differ	The healthcare resource used for moderate-to-severe disease currently involves phototherapy or systemic therapy that requires frequent monitoring, and, because it is of limited effectiveness in many patients, additional costs are often incurred due to management of poorly controlled disease (frequent GP/hospital visits, infections, hospital

between the technology and current care?	admissions). For patients who are controlled on dupilumab, these costs would be expected to be reduced significantly.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Dermatologists in a hospital setting
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of dermatologists and specialist nurses to prescribe and monitor the treatment. However, dermatologists and specialist nurses are familiar with biologic therapies (generally) and so this should not represent any major investment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes, life-saving in some patients because severe atopic dermatitis is associated with increased rates of depression and suicide [Yu et al., Journal of Investigative Dermatology (2015) 135, 3183–3186].
• Do you expect the technology to increase health-related quality of	Yes, substantially. Pooled results from two RCTs [Simpson, Dermatol Ther (Heidelb). 2017 Jun;7(2):243-248] reported that AD patients (n=1379) had significantly impaired baseline health-related quality of life (HRQoL), which was slightly worse than the HRQoL reported for moderate-to-severe psoriasis, as well as the general population norms for the UK and US. Patients treated with dupilumab at different dosing regimens reported significant

life more than current care?	improvements in HRQoL by week 16, compared to placebo. These increases resulted in scores that approached population norms, were in the same range as that of biologic agents for psoriasis and were clinically meaningful, as they exceeded the reported minimal clinically important difference outlined in the study.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, there are different ethnic groups that have different cytokine pathways in AD, so it may be more effective in some than others. The Th2 cytokines IL-4 and IL-13 predominate in most populations, however, in some Asian populations IL-17 predominates [Noda et al., J Allergy Clin Immunol. 2015 Nov;136(5):1254-64]
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	Easier to use as less monitoring required. Formal assessment methods of disease severity and treatment outcome will be needed. Some training of nurses will be required to be able to complete disease assessment and be aware of side effects.

or ease of use 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?	Response to therapy will be evaluated formally using validated tools for disease severity (e.g. EASI, POEM, DLQI). These are part of the normal clinical assessments used and no additional testing (over and above those done when starting any systemic therapy) would be required. For patients not responding to treatment then dupilumab would be stopped. Data from trials and clinical experience suggest that where there has been an initial response at 3 months, the full response (for example reduction in lichenification, return to normal skin) can take longer.
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, it has been shown to transform patients' lives from suicidal (been for euthanasia) – to very happy and from unemployable to successful career. Results from RCT [Tsianakas et al., Br J Dermatol. 2017 Aug 27. doi: 10.1111/bjd.15905. Epub ahead of print; Simpson et al., N Engl J Med. 2016 Dec 15;375(24):2335-2348; Bruin-Weller et al., Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY and CAFÉ)". British Journal of Dermatology, accepted] indicate that patients treated with dupilumab experienced rapid relief from clinical signs such as AD and their concomitant subjective symptoms, including sleep loss and pruritus. Importantly, dupilumab also significantly improved the HRQoL of patients as measured by Quality of life Index (QoLIAD). Of note, a significant improvement in QoLIAD score was already achieved after 4 weeks of dupilumab treatment, which was the earliest measured time point after baseline. Dupilumab was also found to reduce pruritus significantly and as a result leads to improvements in sleep, resulting in less daytime sleepiness and fatigue, which negatively affects functional activities, mood and overall mental and physical health. In both SOLO1 and SOLO2 trials, dupilumab q2w treatment has led to a significant ($p<0.001$) reduction (improvement) in the measure of anxiety and depression (HADS total score) at week 16 compared to placebo (mean ± SD: -5.2 ± 0.5

	vs. -3.0 ± 0.7, and -5.1 ± 0.4 vs. -0.8 ± 0.4 in SOLO1 and SOLO2, respectively). This has also been shown in the CAFÉ trial for dupilumab q2w + TCS vs. placebo + TCS (-6.1 ± 0.54 vs. -2.3 ± 0.56). In addition, the percentage of patients achieving HADS-A and HADS-D score of <8 at week 16 was significantly (p<0.001) higher in dupilumab q2w-treated patients vs. placebo-treated ones (41% vs. 12%, and 40% vs. 6% in SOLO1 and SOLO2, respectively). For the same parameter, in CAFÉ trial for dupilumab q2w + TCS vs. placebo + TCS-treated patients (62.5% vs. 36.7%), a statistical level of significance of p=0.0072 has been reached [Simpson et al., N Engl J Med. 2016 Dec 15;375(24):2335-2348; Bruin-Weller et al., Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY and CAFÉ)". British Journal of Dermatology, accepted]
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?	Yes, this is a highly innovative therapy – the first, targeted biologic mAb in AD, and targets a highly relevant pathway in the disease.
• Is the technology a 'step-change' in the management of the condition?	This therapy is the greatest advance in the treatment of AD since the introduction of topical corticosteroids.

• Does the use of the technology address any particular unmet need of the patient population?	Yes; it treats patients with AD who could not be treated with any currently available systemic therapy. This includes patients who have failed to respond to all current systemic therapies and /or had adverse events precluding their further use.
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 are few side-effects. Conjunctivitis is reported in around 10% of the trial population and may require temporary treatment cessation and/or review with an ophthalmologist for severe cases. Part of the mechanism is that IL-13 is required for lacrimal secretions production and blocking IL-13 therefore results in reduced lacrimal secretions and a dry eye syndrome. The use of prophylactic tears can be used to reduce/prevent this problem in some patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The core trial reflects UK practice.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	• EASI (physician-assessed) • POEM (patient-assessed) Both are measured in the clinical trials.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
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 [TAXXX]? [delete if there is no NICE guidance for the comparator(s)	No HTA

and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	The real-world experience is much better than the impression given by trial data. The most severe patients take much longer to clear than the 16-week primary efficacy endpoint in the trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions	

will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This therapy is the greatest advance in the treatment of AD in the past 50 years.
- This therapy effectively controls patients' AD in the majority of cases, often even when it has been unresponsive to all conventional systemic therapies.
- The adverse effect profile of the new therapy is substantially better than existing systemic treatments.
- For some of those who have been treated with the new therapy who also have severe depression (and have attempted suicide) it has been life-saving.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

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.

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
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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Eczema Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The National Eczema Society is a charity registered in England and Wales also in Scotland. Our role is to support people living with eczema and those who care for them in order to improve their quality of life. We do this by offering information and support about the condition and management and treatment options. We do this through publications, a free to access telephone and email helpline our website and social media also by holding and exhibiting at public information events. We also provide some training for healthcare professionals. We have approximately 2,800 members who subscribe to our quarterly magazine and an email supporter base of approximately 7,500.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	From discussion and email with members and supporters who are living with more severe eczema also though feedback from our helpline calls and email.

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?	Living with eczema can be significantly life challenging. More severe eczema can be very painful as damaged skin cracks and bleeds. Waking to find yourself stuck to your sheets is a common experience during a bad flare. Simply getting dressed (and finding skin friendly clothing which is acceptable in a school or work environment) can be very difficult. Moving your limbs when your skin is so sore can be almost impossible. Holding a pencil or typing on a key board or just holding your baby will be extraordinarily painful if your hands are affected. The skin can also become infected regularly exacerbating the problem. The incessant itch of eczema can be intolerable. The urge to scratch can't be resisted and then guilt sets in at the resultant further skin damage. Sleeping can be impossible as the itch is often much worse at night and many patients and parents to report poor sleep patterns over many years, often lifelong. That in turn leads to difficulties with concentration and carrying out day to day tasks. Eczema is also a visible condition and sadly still often perceived as infectious or a result of poor personal hygiene. In consequence for many "facing the world" is something they try to avoid. Many people with more severe eczema isolate themselves or if they do go out will cover themselves in clothing head to toe whatever the weather. Parents are equally challenged by this aspect of the condition. In part the concern relates to potential bullying at school (which does occur) and in part to accusations of poor parenting because of the visible eczema. The link between atopic eczema and depression has been documented (Yu et al Journal of Investigative Dermatology 2015 135(12):3183-3186)
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers have considerable concerns around the lack of a treatment for moderate to severe eczema that doesn't respond to topical management which has been shown to be effective in clinical trials without potentially severe adverse effects. While they worry about the potential adverse effects of topical steroids patients and particularly parents re often frightened at the prospect of using any of the currently available systemic options. They are uncertain if they will work and fearful of long term damage. They see

	it as a Hobson's choice between attempting to cope with a long term life limiting condition and starting a treatment of uncertain efficacy with the potential for significant long term harm
8. Is there an unmet need for patients with this condition?	Yes, there is a significant un met need for patients with moderate to severe eczema. Currently for those whose eczema is unresponsive to topical treatments topical steroids and topical calcineurin inhibitors) the options are quite limited. Phototherapy might be an option but requires frequent hospital visits, is not always accessible (there are variations in access across the UK), typically has long waiting lists, it is also reported as being a painful/uncomfortable treatment by patient contacts. More typically patients whose eczema is not responding to topical treatment will be offered systemic therapy. Despite the high prevalence of moderate to severe eczema the systemic treatments are quite limited. Only one, ciclosporin is licensed and then only for short courses (up to 8 weeks) but others methotrexate, azathioprine are commonly prescribed. All of these immunosuppress which Dupilumab does not. The current systemic treatment options also all have potential severe adverse events profiles including kidney damage (ciclosporin), liver damage (methotrexate) and increased risk of skin malignancy (azathioprine). This is of understandable significant concern to patients and parents of children with eczema. The reported adverse effects profile for Dupilumab is significantly less worrying and the data suggests that it is at least as effective if not more so than the current systemics.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Better adverse effects profile and that it is not an immunosuppressant. Patients also largely report more favourable outcomes than when using the current immunosupressants.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We have heard no patients reporting a disadvantage
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with moderate to severe eczema who do not respond to topical treatments and either • Are unsuitable for treatment with any of azathioprine, ciclosporin and methotrexate e.g. due to co – morbidity/ at high risk from adverse effects of those treatments as they have no other currently available options : or • Have tried treatment on one of azathioprine, ciclosporin and methotrexate without response. We do not think, given the adverse events profile of these immunosuppressant treatments it is reasonable to ask patients to try more than one of them while continuing to live with uncontrolled eczema now an alternative is available
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	
Topic-specific questions	
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- For those who have moderate to severe eczema the condition is a serious long term debilitating condition and needs treatment that differ to that for mild eczema.
- Moderate to severe eczema can be life limiting and have a huge negative impact on quality of life
- Current treatment options for moderate to severe eczema available on the NHS are limited, mostly used off licence and under researched as to efficacy
- The current options referred to immediately above all supress the immune system. This can have a deleterious impact on your health if you have to take them long term
- These current treatment options all have worrying potential adverse effects. Patients should not be asked to try more than one of them before being given the option of Dupilumab
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Dupilumab for treating adults with moderate to severe atopic dermatitis [ID1048]

Personal Statement [redacted]

I have suffered Severe Atopic Eczema, with asthma & allergies for 48 years. It has caused me a lifetime of disability & frequent hospitalizations, I missed much education. Excluded & isolated, I remain unmarried & childless from Premature Ovarian failure.

The only treatment has been increasing strengths of topical, inhaled & oral steroids, frequent antibiotics, & 10 years of Immunosuppressants, including cyclosporine & azathioprine. Neither controlled my eczema, whilst weakening my immune system, causing Adrenal Insufficiency, Stage 3 Kidney Damage, Hypertension, Osteoporosis, Bi-polar Disorder, I was at high risk of Kidney failure, Stroke, Cardiovascular disease & Cancer. I was not prescribed Methotrexate due to risk of renal failure & NHS advised I write my Advanced Directive. I attempted suicide twice & applied to Dignitas for Euthanasia.

A year ago, I was given early access to Dupilumab under the compassionate use scheme & my renal function is now normal & my skin clear. My IgE has halved 14K to 7K, I have hair, I sleep, I have increased mobility & greatly improved Quality of life. I couldn't stand or walk & I was told I needed all my toe nails removed, but infection risk was too high. Now my feet are near normal.

My medications have decreased from 20 plus tablets a day & bandages, topical treatments, now down to 10 tabs pd . I needed 3 weekly medical appointments that have dropped to 3 monthly. I have been discharged from Psychiatry & Nephrology.

[redacted]

NICE National Institute for Health and Care Excellence

Clinical expert statement

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

Thank you for agreeing to give us your 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 expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Michael Ardern-Jones**
2. Name of organisation	**Nominated by the British Association of Dermatologists (the BAD)**

3. Job title or position	**Academic Consultant Dermatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition 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)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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.)	**x** yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. 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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• 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?	
11. 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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. 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?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
14. 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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. 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?	
17. 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?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. 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?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

Thank you for agreeing to give us your 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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Catherine Smith**
2. Name of organisation	**Nominated by the British Association of Dermatologists (the BAD)**

3. Job title or position	**Professor of Dermatology & Therapeutics**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition 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)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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.)	**x** yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
8. 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.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• 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?	
11. 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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
12. 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?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
16. 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?	
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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?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	

19. 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?	
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not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • • • • •	

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Richard Weller**
2. Name of organisation	**Nominated by the British Association of Dermatologists (BAD)**

3. Job title or position	**Reader and Honorary Consultant**
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 this condition? ☐ a specialist in the clinical evidence base for this condition 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 didn't submit one, I don't 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

The aim of treatment for this condition	
7. 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 reduce the severity of disease, and ideally abolish all symptoms and signs of eczema. Symptoms of pruritus are most troubling to patients.
8. 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.)	I concur with the BAD submission. A reduction of 6 points, or a 50% fall in the EASI score at 16 weeks.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a significant unmet need. In my 2ry/3ry hospital based practice, the majority of patients have at least moderately severe eczema. Some can be controlled with optimum use of topical corticosteroids and emollients, but most patients with this degree of disease will need phototherapy (probably repeatedly) or systemic treatments. Only ciclosporin is licensed for this, but it is little used as the license is only for 8 weeks, which is of little use in patients with a chronic condition. All currently used systemic treatments have significant side effect profiles and are non specific immune suppressants. There has been no advance in treatment for patients with this spectrum of disease for many decades.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	This is outlined in the BAD document.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	
• 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?	Not all patients improve on current systemic agents, and some develop adverse effects limiting/preventing the use of current systemic agents. Dupilumab could be of benefit in both these patient groups.
11. Will the technology be used (or is it already used) in	Psoriasis is an analogous inflammatory skin disease which until the advent of biologics was treated with systemic drugs in a similar manner to eczema. I anticipate that Dupilumab will fit into care pathways for eczema in a similar way to the early biologics with psoriasis.

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Current phototherapy and systemic agent use both require fairly frequent monitoring and follow up visits. This will be reduced with Dupilumab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist dermatology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of prescribing doctors and pharmacists.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase	Yes, but these changes will probably be small.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some types of eczema may be more responsive to dupilumab, but disease stratification data is not yet robust enough to predict this.
The use of the technology	
14. 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	It should be easier. Starting patients on current systemic agents in particular needs fairly intensive monitoring and hospital/GP visits, and this will be reduced.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not all patients respond to dupilumab and those not responding (measured by An absent reduction in EASI for example) will need to have treatment stopped.
16. 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?	Undoubtedly more biologics will follow on from Dupilumab and these may act on other pathways such as IL22. Understanding of subtypes of eczema will be helped by looking at response to Dupilumab. This will add to the current studies attempting to stratify eczema.
17. Do you consider the technology to be innovative in	Yes.

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?	Yes, absolutely. A very very welcome new form of therapy for this distressing disease.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Patients with bad eczema not responding to current treatments.
18. 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 appear to be less side effects than existing systemic treatments, but registry based follow up will be required to confirm this.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
• 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?	EASI and POEM.
• 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?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in	

the NHS for treating [condition Y]?"] **if not delete highlighted rows and renumber below**	
Key messages	
25. In up to 5 bullet points, please summarise the key messages of your statement. • Eczema is a common distressing condition, with no new treatments for decades • Existing treatments do not improve all patients, or cause side effects that prevent their use. • Dupilumab is the first of a new class of targeted immunological treatments for eczema- a genuine step change. • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Dupilumab for treating adults with moderate to severe atopic dermatitis

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to declare.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Rodolfo Hernández, Maria Dimitrova and Graham Scotland acted as health economists: critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model, and carried out further sensitivity analyses. Moira Cruickshank and Michal Shimonovich acted as the systematic reviewers: critiqued the company's definition of the decision problem and the clinical effectiveness evidence. David Cooper and Lorna Aucott acted as statisticians: critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence. Cynthia Fraser acted as information scientist: critiqued the methods used for identifying relevant studies and conducted additional searches. Anthony Ormerod acted as clinical expert: provided clinical advice and general guidance. Miriam Brazzelli acted as project lead for this

appraisal: contributed to the critique and review of the clinical effectiveness methods, checked the final report and supervised the work throughout the project.

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List of abbreviations

AD	Atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse event
AESI	Adverse event of special interest
CCL	CHRONOS-CAFÉ-like
CG	Clinical Guideline
CS	Company submission
DALY	Disability-adjusted life year
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analysis
EAMS	Early Access to Medicines Scheme
EASI	Eczema Area Severity Index
EASI-50	Eczema Area Severity Index ≥50% response
EASI-75	Eczema Area Severity Index ≥75% response
EASI-90	Eczema Area Severity Index ≥90% response
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
FAS	Full analysis set
FDA	(United States) Food and Drug Administration
HRQoL	Health-Related Quality of Life
HADS	Hospital Anxiety and Depression Scale
HTA	Health technology assessment
ICER	Incremental Cost-Effectiveness Ratio
IEC	International Eczema Council
IGA	Investigators' Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IL-4	Interleukin-4
IL-13	Interleukin-13
IL-4 Rα	Interleukin-4 receptor α
ISR	Injection site reaction
ITT	Intention-to-treat
MAIC	Matching-adjusted indirect comparison
mg	Milligram
NHS	(UK) National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis

NRS	Numeric Rating Scale
OLE	Open-label extension
ONS	Office for National Statistics
OS	Overall Survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PASI	Psoriasis Area Severity Index
PASLU	Patient Access Scheme Liaison Unit
POEM	Patient-Oriented Eczema Measure
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QW	Every week
Q2W	Every two weeks
Q4W	Every four weeks
Q8W	Every eight weeks
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SCORAD	Severity Scoring of Atopic Dermatitis
SD	Standard deviation
SE	Standard error
SLR	Systematic Literature Review
TEAE	Treatment-emergent adverse event
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
UK	United Kingdom
US	United States

1 Summary

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory dermatitis that is remitting-relapsing in nature. It is characterised by chronic or relapsing red and inflamed skin (erythema), thickened and leathery skin (lichenification), dry skin (xerosis) and an intense itch (pruritus). The terms 'atopic dermatitis' and 'atopic eczema' are synonymous and tend to be used interchangeably in the literature.

Incidence or lifetime prevalence of atopic eczema symptoms in the UK increased by more than 10% between 1990 and 2010 and prevalence of AD in adults in the UK has been reported as 2.5%. In the UK, the reported proportion of people with AD classed as moderate-to-severe ranges from 53% to 67%, depending on the instrument used. In contrast, the company reports that 7% of people with AD have moderate-to-severe disease.

Dupilumab (Dupixent®, Sanofi and Regeneron Pharmaceuticals, Inc.) is a fully human monoclonal antibody to the interleukin(IL)-4 receptor α subunit that inhibits the signalling of two key inflammatory cytokines thought to be important drivers of atopic diseases, such as AD, i.e. IL-4 and IL-13.

1.1 Critique of the decision problem in the company submission

The company's submission considered dupilumab for adults with moderate-to-severe atopic dermatitis (AD) with a history of intolerance, inadequate response or contradiction to topical therapies (emollients, topical corticosteroids, topical calcineurin inhibitors) and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. The company also included a scenario analysis for dupilumab in the full licence population, i.e. adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

The decision problem addressed in the company's submission was broadly consistent with the NICE final scope. The company did not consider phototherapy to be a valid comparator as it is only suitable as a short-term treatment option. The ERG's clinical

expert agrees that phototherapy is not a long-term treatment but is of the opinion that in UK clinical practice it can be a constituent of BSC, as it can be used in the short-term to induce remission and can have lasting effects.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company consisted of four RCTs from the LIBERTY AD clinical trial programme; two trials compared dupilumab with placebo (SOLO 1 [16 weeks] and SOLO 2 [16 weeks]) and two compared dupilumab plus concomitant topical corticosteroids (TCS) with TCS plus placebo (CHRONOS [52 weeks] and CAFÉ [16 weeks]). All four trials included two dupilumab arms, with dupilumab administered either every week (QW) or every two weeks (Q2W). The co-primary outcomes in CHRONOS, SOLO 1 and SOLO 2 were proportion of patients with IGA score 0 or 1 and reduction from baseline of ≥2 points at week 16, and proportion of patients with ≥75% improvement in EASI score (EASI-75) from baseline to week 16. In CAFÉ, the sole primary endpoint was proportion of patients with EASI-75 from baseline to week 16. The primary analyses included patients considered non-responders after rescue at 16 weeks. Across all four trials, a greater proportion of participants in the dupilumab groups than the placebo groups achieved the primary endpoints. Proportion of patients who reached IGA score of 0 or 1 and reduction of ≥2 points from baseline ranged from 37.3% to 40.6% for Q2W dupilumab, from 38.1% to 42.0% for QW dupilumab and from 10.6% to 15.6% for placebo. The proportion of participants who achieved EASI-75 ranged from 11.9% to 29.6% of the placebo groups and 44.2% to 68.9% of the dupilumab groups. There was no difference in the primary outcomes between the QW and Q2W dupilumab groups.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG agrees with the company's assertion that the primary and secondary outcomes show a beneficial effect of dupilumab compared with placebo. The reduction in the instances of atopic dermatitis in comparison to placebo also suggest a beneficial effect. There are similar rates for many of the side effects between the placebo and dupilumab arms and in the case of the increased likelihood of allergic site reaction and allergic conjunctivitis, the additional investigation suggest that these were not serious problems.

The ERG agrees that a matched adjusted indirect comparison was an appropriate method to use for the comparison of dupilumab with ciclosporin. The small sample sizes, which result after mapping, are of concern and the ERG is in agreement with the company on not using superiority of dupilumab in the cost-effectiveness analysis and instead assuming equivalence with ciclosporin.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's main economic case considered the cost-effectiveness of dupilumab compared with best supported care (BSC) for a subgroup of the full licence population: adult patients with moderate-to-severe AD who are contraindicated to, intolerant of, had an inadequate response to or for whom it is medically inadvisable to receive treatment with systemic immunosuppressant therapies. Two different analyses were reported for this base case population; one assessing dupilumab with concomitant TCS, and the other assessing dupilumab as monotherapy. Model inputs for the former analysis were derived mainly from a pooled dataset consisting of patients from the CAFÉ trial and a subgroup of patients from the CHRONOS trial who also met the definition of the base case population (referred to as CAFÉ + CHRONOS CAFÉ-like [CCL]). Parameters for the monotherapy analysis were derived from a pooled dataset consisting of subgroups from the two SOLO trials who met the base case population definition – referred to as SOLO CAFÉ-like. The company also provided a scenario comparing dupilumab with ciclosporin in the broader licence population; patients who are eligible for immunosuppressant therapies.

The company submitted an economic model consisting of a decision tree component to model costs and outcomes to 52 weeks, and a simple three state Markov component to extrapolate long-term costs and effects. Based on observed trial data, the decision tree divides the cohorts into responders and non-responders at week16. Dupilumab non-responders then stop treatment and move to BSC from week 16, and dupilumab responders remain on treatment and are assessed again at week 52. Dupilumab patients who maintaining their week 16 response to week 52 then enter a dupilumab *maintenance treatment* state in the Markov model. All other patients (apart from those who die) enter the *BSC treatment* state in the Markov model. Trial data on

discontinuation rates are used to inform annual transition probabilities from dupilumab *maintenance treatment* to *BSC treatment*.

In the decision tree phase on the model (to week 52), health state utility data relevant to each arm and branch are derived from EQ-5D data collected from patients enrolled in the relevant clinical trials. Further assumptions, based on expert opinion, are used to extrapolate the trial based health state utility estimates over the lifetime of patients. Using quality of life maintenance proportions elicited form experts, the company base case assumes that the trial based estimates of utility gain in BSC patients diminish rapidly over time; by year four in the model, all those on BSC are assigned baseline utility for the remaining time horizon. It is further assumed, based on expert onion, that 8% of patients on dupilumab *maintenance treatment* lose their response over the first 5 years, stop treatment and move to BSC where they attract the modelled BSC utility weight.

Costs related to active treatment, administration, flare medication, adverse events, and other medical costs (e.g. clinical visits, use of background medications) are incorporated in the model. The 'other medical costs' are calculated by response status, whist the other costs elements are incorporated by treatment status. For the extrapolation of costs, it is assumed that the responder proportion on BSC declines to zero by year 4 in the model, such that all BSC patients attract non-responder 'other medical costs' from year 4 onwards. It is assumed that all patients who remain on dupilumab maintenance treatment are continuously responding. An option exists to add indirect costs in scenario analyses.

In the company base case for the CAFÉ + CCL population, the deterministic ICER for dupilumab versus BSC came to £28,874 per QALY gained, based on an incremental cost of [redacted] and a QALY gain of [redacted]. For the SOLO CAFÉ-like analysis, the ICER for dupilumab was £24,703, based on an incremental cost of [redacted] and a QALY gain of [redacted].

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG have some concerns that that the model structure lacks the flexibility to capture the waxing and waning nature of AD. It assumes that patients remaining on

dupilumab treatment are constantly responding, and that treatment stops immediately from the point in time that response is lost. It does not allow for continuing treatment through a fluctuating response. Related to the above, the response criteria applied in the model, whilst quite inclusive do not seem to be a particularly good predictors of gains in health state utility. That is, the utility gain from baseline in non-responders remains sizable. Thus the ERG wonder how feasible it will be to implement the stopping rules so efficiently in routine practice.

The ERG also have concerns regarding the extrapolation assumptions applied to patients on BSC in the company base case. A substantial proportion of patients randomised to BSC (placebo) in the trials informing the model achieved the modelled response criteria at 16 weeks (0.278 in CAFÉ+CCL, 0.239 in SOLO CAFÉ-like). Average EQ-5D scores also improved substantially by week 16 (by more than 0.15 from baseline). Whilst these gains are applied in the decision tree component of the model (year 1), they are assumed to wane to zero over three cycles in the Markov model (based on expert opinion). This substantially increases the difference in health state utility above that observed between dupilumab responders and BSC (placebo) patients in the relevant LIBERTY AD trials. The company argue that at least some of the gains observed for BSC patients in the trials are likely driven by improvements in adherence to topical treatments that would not continue outside the trial setting. They further assume that this effect may not be applicable to the dupilumab arm based on expert opinion. The ERG believe that these extrapolation assumptions are controversial given a lack of observed comparative data to verify them. For example, an alternative explanation for response in the placebo arm could be natural waxing and waning. In this case, the improvements observed in the placebo arm may be equally applicable to the dupilumab arm. Whist the above is speculative, the point is that RCTs are appropriately controlled to enable determination of the gain in benefit that can be attributed to a new active treatment. Therefore, the ERG believe there is a case for retaining the observed utility and response gains for BSC patients over the extrapolation phase of the model.

Further concerns noted by the ERG included the additive approach that that the company used to age adjust health state utility values in the model, when NICE DSU guidance appears to favour a multiplicative approach (i.e. a proportional rather than

additive decrement for increasing age). This issue, as well as the omission of a probability distribution on baseline utility (for probabilistic analysis), were queried by the ERG at the clarification stage. The company provided a revised model implementing these changes. The ERG also had some concern that distributions were not assigned to the resource use event rates and resource use multiplies in the company's probabilistic sensitivity analyses.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

- The submission was generally coherent and clear and appropriate methods were used fort the review of clinical evidence.
- The company have submitted a simple and well described economic model, which is based on high quality randomised evidence to inform differences in costs and effects in the short-term (to one year).

1.6.2 Weaknesses and areas of uncertainty

- While accepting that a matched adjusted indirect comparison (MAIC) was an acceptable method to use, the ERG have concerns with both the small sample sizes after adjusting and the heterogeneity of the studies being compared.
- The nature of the condition, combined with a lack of long-term data, meant that assumptions were required to extrapolate short-term differences in costs and effects over a life-time horizon. The company have not been able to present any observed longitudinal data to externally validate the extrapolation assumptions.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

In response to clarification the company provided alternative analyses for the base case populations using the multiplicative approach to age adjust utility. For this specification of the company model, the deterministic ICERs increased to £30,419 and £25,749 for the CAFÉ + CCL pool and the SOLO CAFÉ-like pool, respectively. Given that the NICE DSU guidance seems to favour the multiplicative approach, the ERG also reproduced the company's tables of deterministic sensitivity analyses

applying this method. This resulted in modest gains in all the ICERs compared with the additive approach. The ERG then explored the impact of several further changes to the company base case, whilst retaining the multiplicative approach to age adjusting utility:

- The ERG assessed the impact of switching off the waning assumptions applied in the model, and carrying forward the response and utility gains observed in the respective arms of the trials over the extrapolation phase. With this change, the ICER for dupilumab increased substantially to £70,684 and £49,596 in the CAFÉ+CCL and SOLO CAFÉ-like populations respectively.
- Recalculating the company's resource use event rates, using all the available data from the company's preferred data source, also resulted in modest increases in the ICER; to £34,355 and £28,851 in the CAFÉ+CCL and SOLO CAFÉ-Like cohorts respectively.
- Incorporating probability distributions on the resource use event rates and multipliers, resulted in very little change in the PSA results.
- To approximate the impact of removing the stopping rule for dupilumab, the ERG set the response rate to one in the dupilumab arm of the model and assigned the trial based utility estimate for all dupilumab patients to all those remaining on treatment. 'Other medical costs' (by response status) for those on dupilumab maintenance treatment were also weighted by the week 16 response rate in this analysis. These changes resulted in modest increases in the ICERs, to £33,279 and £29,468 for the CAFÉ+CCL and SOLO CAFÉ-Like cohorts respectively. Whilst the ERG appreciate that removal of a stopping rule for lack of response is unrealistic, this analysis was conducted to understand the impact of the stopping criteria on the cost-effectiveness of dupilumab.

While all the further exploratory analyses conducted by the ERG increased the ICER for dupilumab, the model results were most sensitive to changes in the quality of life (and response) waning assumptions applied to BSC patients over the extrapolation phase.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of atopic dermatitis (AD) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. Atopic dermatitis is a chronic, pruritic, inflammatory dermatitis that is remitting-relapsing in nature.[1] It is characterised by chronic or relapsing red and inflamed skin (erythema), thickened and leathery skin (lichenification), dry skin (xerosis) and an intense itch (pruritus).[2] Atopic dermatitis can be a major burden for patients due to sleep loss, psychosocial challenges and missed work.[3] The terms 'atopic dermatitis' and 'atopic eczema' are synonymous and tend to be used interchangeably in the literature.

Incidence or lifetime prevalence of atopic eczema symptoms in the UK increased by more than 10% between 1990 and 2010 .[4] Atopic dermatitis is more common in children and the majority of children with AD no longer have symptoms by adulthood .[5] Prevalence of AD in adults in the UK has been reported as 2.5% with 53% to 77% of those having moderate to severe disease (depending upon the instrument of assessment of severity).[6] In contrast, the company reports that 7% of people diagnosed and treated for AD have moderate-to-severe AD, based on data which was not available to the ERG.

Hospital Episode Statistics for Admitted Patient Care in England from 2016-2017 show that there were 1,258 finished consultant episodes and 1,135 admissions for "AD, unspecified" and "other AD" (codes L20.8 and L20.9).[7] The mean age of "other AD" patients was 16 years and the 227 finished consultant episodes and 197 admissions resulted in 41 day cases. The mean length of stay was 3 days. Patients who were categorised with "AD, unspecified" were older, with a mean age of 29 years, and stayed for a mean of 4 days. For these patients, there were 1,031 finished consultant episodes, 938 admissions and 568 day cases. Of all patients who had outpatient appointments, 2,353 of attendances were classified "other AD" (code L20.8) and 5,521 were "AD, unspecified" (code L20.9). It should be noted that, according to NHS Digital, primary diagnosis is not a mandated field in the outpatient dataset, and,

therefore, coverage within this field is poor. The ERG's clinical expert notes that many patients are managed with day care or drugs due to lack of availability of inpatient facilities, as a result of closure of a number of dermatology beds.
The severity of AD is the foundation on which treatment decisions are based and various instruments are used to assess the impact of AD. For example, SCORAD was used in 49% of trials in a systematic review of 295 RCTs. The next most commonly used instruments were modified Eczema Area and Severity Index (mEASI) (2.4%), Patient-Oriented Eczema Measure (POEM) (1.7%) and Atopic Dermatitis Severity Index (ADSI) (1.4%). According to a systematic review providing recommendations for usage of each instrument based on its quality, no instrument met all the requirements to be recommended in Category A, the highest level of recommendation.[8] Five instruments met the requirement for a Category B recommendation and have the potential to be recommended for future clinical trials: the paediatric Itch Severity Scale (ISS), POEM, Patient-Oriented SCOring Atopic Dermatitis (PO-SCORAD), self-administered Eczema Area and Severity Index (SA-EASI) and adapted SA-EASI. These outcomes are all included in the company's systematic review, in which the key measures of clinical signs and symptoms of AD are the EASI for impact on clinical severity and pruritus Numeric Rating Scale (NRS) and POEM scores for impact on disease symptoms. The improvement of these signs and symptoms is measured by the Dermatology Life Quality Index (DLQI) for impact on quality of life and mental health.

As noted in the company's submission, the NICE clinical guideline for the diagnosis and management of atopic eczema is only available for children under 12,[9] but there are currently no NICE guidelines or quality standards on the diagnosis, treatment and management of moderate-to-severe AD in adults.

Mild disease involves areas of dry skin, infrequent itching and possibly small areas of redness, with little impact on quality of life. The company states that mild disease is commonly managed in primary care with a combination of emollients and TCS (NICE TA81, CG57). Moderate disease involves frequent itching and redness, with or without excoriation and localised skin thickening; associated impact on quality of life is moderate. For moderate disease, NICE CG57 recommends emollients as first line treatment, followed by moderate potency TCS, TCIs and bandages. NICE TA82 also

recommends tacrolimus (a TCI) for second line treatment of adults with moderate to severe AD that is not controlled by TCS. Severe disease is typified by widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation). The effect on quality of life is severe. Severe AD is treated initially with emollients, potent TCS, TCIs and bandages. People whose disease does not respond to these treatments may then be treated with phototherapy or systemic therapy, of which only ciclosporin is approved for treating severe AD. Other systemic immunosuppressants, such as azathioprine and methotrexate, are used in UK clinical practice off-label if ciclosporin treatment fails.

According to the NICE Clinical Knowledge Summaries[10] on atopic eczema, patients who suffer from moderate eczema should be prescribed emollients and should apply them frequently and liberally. If the skin is inflamed, patients should be prescribed a moderately potent topical corticosteroid. Topical corticosteroids should be continued for 48 hours after the flare has been managed and for sensitive areas of the skin, such as the face, topical corticosteroids should be used for no more than 5 days. Severe itch should be treated with antihistamines (scenario 2). Patients who suffer from severe eczema should similarly be prescribed topical corticosteroid for inflamed areas and antihistamine for itching. If the eczema is causing psychological distress, an oral corticosteroid for one week may help treat the symptoms (scenario 3). The NICE Clinical Knowledge Summaries do not mention phototherapy or systemic immunosuppressants to treat patients with severe AD. The company submission states that phototherapy is not commonly used in the UK and only one systemic immunosuppressant therapy is licensed in the EU (i.e., ciclosporin).

2.2 Critique of company's overview of current service provision

The company's submission states that "*dupilumab is not expected to change the current treatment pathway in the UK, but is expected to provide an additional step for those patients in whom all other lines of treatment were not successful*". The company states that AD therapy routinely includes use of emollients to protect the skin barrier and, if symptoms persist despite this, anti-inflammatory topical corticosteroids (TCS) or topical calcineurin inhibitors can be used to treat active disease or prevent a relapse of symptoms. However, the company's submission states that TCS should not be used

on a long-term basis because of the risk of adverse effects on the skin and risk of secondary infections. The company states that phototherapy is an efficacious treatment for AD after the failure of topical therapies, but that it is not widely used in the UK due to cost, lack of clinical availability, lack of clinical experience and lack of evidence regarding long-term efficacy and safety. However, the ERG's clinical expert is of the opinion that phototherapy is widely available to clinicians in the UK and that most would use it. The company's submission also states that systemic immunosuppressants are used after the failure of topical therapies, including ciclosporin, which has dose-related adverse events and its use is limited to less than 12 months. In addition, other systemic immunosuppressants, such as azathioprine and methotrexate, are currently used off-label after the failure of ciclosporin.

Marketing authorisation for dupilumab (Dupixent®, Sanofi and Regeneron Pharmaceuticals, Inc.) was issued by the European Medicines Agency (EMA) on 28-09-2017 and is for treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy.[11] Dupilumab was granted Early Access to Medicines Scheme (EAMS) status in the UK on 13-03-2017, allowing patients to access the drug before it was granted marketing authorisation in the UK.[12] The EAMS status was subsequently withdrawn when dupilumab received marketing authorisation from the EMA. On 28-03-2017, the U.S. Food and Drug Administration (FDA) approved dupilumab for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without topical corticosteroids. [13]

Dupilumab is a fully human monoclonal antibody against interleukin (IL)-4 receptor alpha that specifically binds to the shared alpha chain subunit of the receptors for IL-4 and IL-13, inhibiting IL-4 and IL-13 signalling. IL-4 and IL-13 are key inflammatory cytokines thought to be important drivers of atopic diseases, such as AD. These cytokines are produced by T-helper type 2 (Th2) lymphocytes and are elevated in patients with moderate-to-severe AD. The lymphocytes (Th2) and the cytokines (IL-4 and IL-13) that they produce activate proinflammatory pathways, leading to chronic cutaneous inflammation.

Figure 1 presents the company's anticipated positioning of dupilumab in clinical practice, which is an adaptation of an algorithm based on recommendations from an expert panel of the International Eczema Council (IEC).[14] The company appropriately refers to the recommendations from other clinical guidelines and national policies. According to this, patients with moderate-to-severe AD should be prescribed medium-to-high potency topical anti-inflammatory therapy for one to four weeks followed by proactive therapy for maintenance. Proactive treatment concept is defined as a combination of predefined, long-term, low dose, anti-inflammatory treatment applied to previously affected areas of skin in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical control examinations .[15]

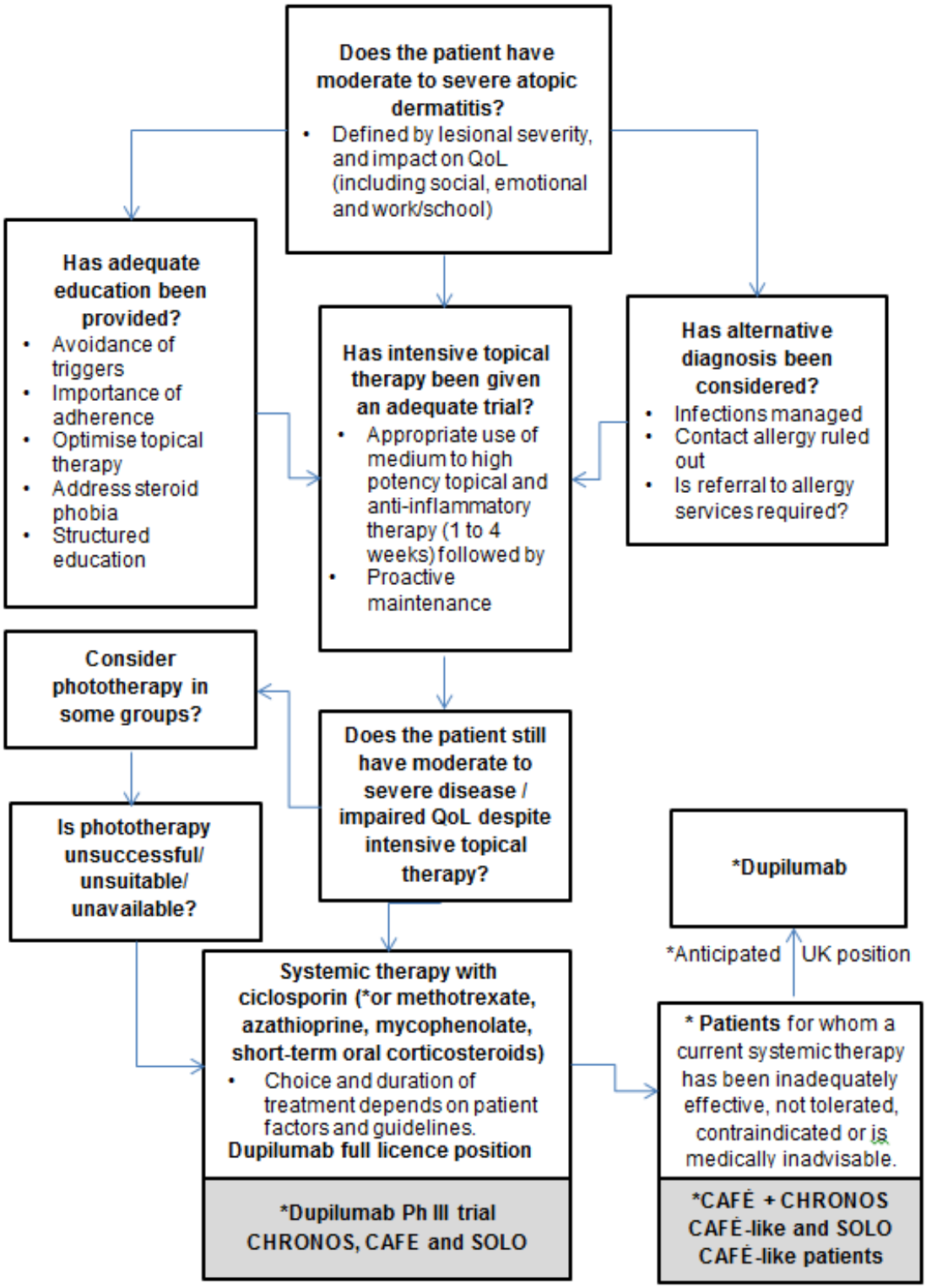


Figure 1 Company's anticipated positioning of dupilumab in clinical practice (adapted from the IEC algorithm) (reproduced from Figure 1.6 of the company's submission)

According to IEC recommendations, consideration should also be given to wet wrap therapy (i.e., where a topical agent on a significant flare-up is covered by a layer of wet bandages, gauze or cotton suit, followed by a second, dry layer, providing a barrier against itching and attenuates water loss;[16, 17] and soak and seal (i.e., application of emollient to the skin which is then bathed in lukewarm water to retain the moisture).[18]

Phototherapy should be considered if the patient still has moderate-to-severe disease or impaired quality of life following topical treatment, The IEC recommend phototherapy as a second-line or adjuvant therapy, especially in adults or older children with moderate-to-severe AD. Phototherapy requires a prolonged course of treatment and adherence is a challenge with the long-term risks, especially in fair-skinned patients, not fully understood. The decision to begin systemic immunosuppressant therapy depends on the patient's age, comorbidities and clinical experience with immunosuppressant therapy. The IEC identifies dupilumab as a common systemic therapy with the common or serious side effects of injection site reactions and conjunctivitis.

3 Critique of company's definition of decision problem

3.1 Population

The NICE final scope for this appraisal specified the population as "*adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy*". The decision problem addressed by the company specified the ("*base case*") population as "*adults with moderate-to-severe atopic dermatitis with a history of intolerance, inadequate response or contradiction to topical therapies (emollients, topical corticosteroids, topical calcineurin inhibitors) and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable*". The company also included a scenario analysis involving the "*full licence population for adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy*". The company acknowledges that its "base case" population is a subgroup of the full licence population and that the licence indication is broader than the expected position and usage of dupilumab in the real world. The company reported that the base case population was the opinion of a panel of clinical experts during an advisory board conducted by the company in September 2017. The company's justification of its specification of the population is that it is considered the most likely place in therapy for dupilumab as it reflects the highest unmet need in UK clinical practice.

The company further states that it expects clinicians in the NHS to use dupilumab after considering a systemic immunosuppressant agent and that this position reflects where dupilumab provides the most clinical benefit for patients in England and Wales.

In addition, the position is in line with use within the EAMS and the International Eczema Council's treatment algorithm.[14]

The ERG's clinical expert noted that azathioprine or methotrexate may be tried if ciclosporin fails, despite the fact that they are not licenced for this condition. In general, the ERG's clinical expert agrees that the base case population specified in the company's submission is appropriate to the decision problem.

3.2 Intervention

The NICE final scope specified the intervention as dupilumab. Atopic dermatitis is typified by type 2 helper T (Th2) cell-driven inflammation, and IL-4 and IL-13 are key cytokines in Th2-mediated pathways.[19-21] Interleukin-4 and IL-13 increase immunoglobin E production, stimulating further differentiation of Th2 and epidermal barrier disruption in people with AD.[22, 23] Dupilumab is a fully human monoclonal antibody to the IL-4 receptor α subunit that inhibits interleukin-4 and interleukin-13 signalling .[21, 24-26]

Dupilumab (Dupixent®, Sanofi and Regeneron Pharmaceuticals, Inc.) is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. Dupixent® is formulated as a solution for injection in pre-filled syringe. Each pre-filled syringe contains 300mg of dupilumab in 2ml solution. Dupixent® is administered by subcutaneous injection into the thigh or abdomen, except for the 5cm around the navel. The upper arm can also be used, if somebody else administers the injection. Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis. The recommended dose for adults is 600mg (administered in two 300mg injections consecutively in different injection sites), followed by 300mg every other week administered as subcutaneous injection. Dupixent® can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.[27]

A tabulated list of adverse reactions to Dupixent® is presented in Table 1. Adverse reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000). Within each frequency group, adverse reactions are presented in order of decreasing seriousness. [27]

Table 1 Adverse reactions to dupilumab (reproduced from Table 1 of Summary of Product Characteristics)

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Conjunctivitis Oral herpes
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Very rare	Serum sickness/serum sickness-like reactions
Nervous system disorders	Common	Headache
Eye disorders	Common	Conjunctivitis allergic Eye pruritus Blepharitis
General disorders and administration site conditions	Very common	Injection site reactions

3.3 Comparators

The final NICE scope specifies the comparators as: phototherapy, including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA); immunosuppressive therapies (azathioprine, ciclosporin, methotrexate); oral steroids; best supportive care (combination of emollients, low to mid potency topical corticosteroids, and rescue therapy, including higher potency topical or oral corticosteroids or topical calcineurin inhibitors); alitretinoin (in people with atopic dermatitis affecting the hands). In contrast, the decision problem addressed by the company specified the comparator as: *best supportive care (combination of emollients, low- to mid-potency topical corticosteroids, and rescue therapy, including higher potency topical or oral corticosteroids or topical calcineurin inhibitors. In the real world, BSC also includes systemic immunosuppressant therapies).* The ERG's clinical expert agrees that BSC in UK clinical practice includes immunosuppressant therapies. The company stated: *the evidence is sparse for comparison with the current systemic immunosuppressant therapies and we believe that dupilumab would be positioned after them. We do*

present a comparison with ciclosporin using a mixed adjusted indirect comparison (MAIC) in scenario analysis.

The company's justification for not including phototherapy or oral steroids as comparators was that they are short-term treatment options only and not for chronic, long-term continuous treatment of AD. In addition, the company points out that the recent International Eczema Council treatment algorithm places phototherapy after intensive topical therapy has failed and before systemic therapy. The ERG's clinical expert agrees that phototherapy is not a long-term treatment option but is of the opinion that phototherapy can be a constituent of BSC in clinical practice in the UK, as it can be used in the short-term to induce remission and can have lasting effects.

The ERG's clinical expert agrees that alitretinoin is not a valid comparator as it is licensed for hand eczema only, which is a distinct condition in its own right. The company did not include ciclosporin as a comparator, with the justification that the evidence base of dupilumab compared to ciclosporin is sparse and that the treatments would not, in any case, occupy the same place in the treatment pathway. The company compared ciclosporin with dupilumab in a scenario analysis using a MAIC. The ERG considers the company's approach to be appropriate. Ciclosporin is currently the only licenced therapy for AD. Other immunosuppressive therapies (azathioprine and methotrexate) are currently used in UK clinical practice if ciclosporin fails.

3.4 Outcomes

The outcomes specified in the NICE final scope were: measures of disease severity; measures of symptom control; disease-free period/maintenance of remission; time to relapse/prevention of relapse; adverse effect of treatment; health-related quality of life. The company stated: *clinical outcomes supported by evidence from the LIBERTY AD trial programme are reported addressing all the points raised in the scope.* The trials in the LIBERTY AD programme reported time to first rescue treatment as opposed to disease-free period/maintenance of remission or time to relapse/prevention of relapse; the ERG's clinical expert considers these outcomes to be equivalent. The outcomes used by the company in the economic model were stated as: measures of disease severity (for example, according to absolute EASI or IGA scores); measures of symptom control according to relative EASI scores (reduction in absolute score);

adverse effects of treatment; health-related quality of life. The ERG considers the company's approach to be appropriate to the decision problem.

3.5 Other relevant factors

The company's economic analysis was consistent with the NICE final scope, thus, expressing cost effectiveness in terms of incremental cost per quality-adjusted life year, considering a time horizon of sufficient length to reflect any differences in costs between the technologies being compared and considering costs from an NHS perspective. The company did not consider costs from a Personal Social Services perspective, as specified in the NICE final scope, as such costs were not considered relevant by the company. The ERG agrees that this approach is appropriate.

The NICE final scope specified the following subgroups to be considered: people with atopic dermatitis affecting the hands; people for whom therapies have been inadequately effective, not tolerated or contraindicated; and skin colour subgroups.

The company's base case addresses the subgroup of people for whom therapies have been inadequately effective, not tolerated or contraindicated. The company's submission does not address people with hand eczema or skin colour subgroups. The ERG's clinical expert considers this strategy to be appropriate as hand eczema is a distinct condition in its own right and skin colour is not considered to be pertinent in the treatment of atopic dermatitis.

Table 2 presents the NICE final scope and the decision problem addressed by the company and includes both the company's and the ERG's comments.

Table 2 Comparison of NICE final scope and decision problem addressed by the company

	Final scope issued by NICE	Decision problem addressed in the submission	Summary of comments from the company	Comments from the ERG
Population	Adults with moderate-to-severe AD who are candidates for systemic therapy	Base case: adults with moderate-to-severe AD with a history of intolerance, inadequate response or contraindication to topical therapies (emollients, TCS, TCI) and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable; Scenario analysis: full licence population for adults with moderate-to-severe AD who are candidates for systemic therapy	The base case population is considered the most likely place in therapy for dupilumab as it reflects the highest unmet need in UK clinical practice. This patient population is a subgroup of the full licence population. A scenario analysis based on the full licence population, as defined in the NICE decision problem, is also presented. Hence, the licence indication is broader than the expected position and usage of dupilumab in the real world.	The ERG consider the company's approach to be justified
Intervention	Dupilumab	Dupilumab	None	None

	Final scope issued by NICE	Decision problem addressed in the submission	Summary of comments from the company	Comments from the ERG
Comparators	• Phototherapy, including with ultraviolet (UVB) radiation or psoralen-ultraviolet A (PUVA) • Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate) • Best supportive care (combination of emollients, low-to-mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors) • Alitretinoin (in people with AD affecting the hands)	Best supportive care (combination of emollients, low-to-mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors. In the real world, BSC also includes systemic immunosuppressant therapies)	Phototherapy and oral steroids are not valid comparators as they are short-term treatment options and would not be used as chronic/ long term/ continuous treatment of AD. Alitretinoin is also not a valid comparator based on its licenced indication and place in therapy of severe chronic hand eczema. The evidence is sparse for comparison with the current systemic immunosuppressant therapies and we believe that dupilumab would be positioned after them. We present a comparison with ciclosporin using a mixed adjusted indirect comparison (MAIC) in scenario analysis	The ERG broadly agree with the company's approach but is of the opinion that phototherapy can be a part of BSC in UK clinical practice
Outcomes	• Measures of disease severity • Measures of symptom control	• Clinical outcome measures: o EASI o SCORAD o IGA	Clinical outcomes supported by evidence from the LIBERTY trial programme are reported addressing all the points raised in the	The four LIBERTY phase III trials included in the review of clinical effectiveness evidence report time to first rescue treatment as opposed to

	Final scope issued by NICE	Decision problem addressed in the submission	Summary of comments from the company	Comments from the ERG
	• Disease-free period/ maintenance of remission • Time to relapse/ prevention of relapse • Adverse effects of treatment • Health-related quality of life	• Time to first rescue treatment • Adverse events • Patient-reported outcomes: o DLQI o POEM o HADS o NRS	scope. Outcomes used in the economic modelling are: • Measures of disease severity (e.g. absolute EASI or IGA scores) • Measures of symptom control (reduction in absolute EASI scores) • Adverse effects of treatment • Health-related quality of life	disease-free period/ maintenance of remission or time to relapse/ prevention of relapse. The ERG are satisfied that these outcomes are comparable
Economic analysis	• Cost-effectiveness should be expressed in terms of incremental cost per QALY • Time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	• Cost-effectiveness expressed in terms of incremental cost per QALY • Lifetime horizon considered	• None • Phase III outcomes from LIBERTY are limited to 1 year. These are extrapolated to a lifetime horizon in accordance with NICE methods guide • None	• None • None

	Final scope issued by NICE	Decision problem addressed in the submission	Summary of comments from the company	Comments from the ERG
	• Costs from an NHS and Personal Social Services perspective should be considered	• Costs from an NHS perspective considered		• The ERG noted that Personal Social Services costs were not considered by the company. This approach was deemed appropriate
Subgroups	• People with AD affecting the hands • People for whom therapies have been inadequately effective, not tolerated or contraindicated • Skin colour subgroups	Base case: People for whom therapies have been inadequately effective, not tolerated or contraindicated	The clinical trial programme was not designed to measure the effect on localized areas, such as hand eczema. Although it is likely that dupilumab would have an effect on hand eczema, there were no associated outcomes in the study against which this could be measured. There is no evidence in the trial programme to suggest that outcomes for people with various skin colour groups are different	The ERG agree with the company's comments

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases were searched: MEDLINE, EMBASE, Cochrane CENTRAL Register of Controlled Trial and the Cochrane Database for Systematic Reviews (CDSR). In addition, recent key conferences from 2014 were searched as well as checking the bibliographies of recent reviews and meta-analyses. The searches were undertaken on 19th July 2016 and updated on 11th April 2017. Searches were restricted to literature published from 1980 onwards without language restrictions.

The search strategies are documented in full in Appendix D although the platform used is not stated.

The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: atopic dermatitis; dupilumab or any of the comparators (as detailed in Table 2.1); and randomised controlled trials. The relevant MeSH and Emtree terms were included in the search along with a comprehensive list of text terms. The ERG considered that the searches were appropriate.

Four publications, identified after the searches were carried out, were also included in the review. The company stated that these had been identified by internal processes (clarified by the Manufacturer as routine current awareness searches which were not as comprehensive as the strategies developed for the review and omitted specific comparator terms).

There were no separate searches for adverse events. Relevant data was obtained from the included trials.

4.1.2 Inclusion criteria

The company conducted a systematic review to assess the current clinical evidence on the effectiveness and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults who are candidates for systematic therapy. The company's inclusion criteria are shown in Table 3 below.

Table 3 Inclusion criteria for the company's systematic review of clinical effectiveness (reproduced from Table 2.1, Document B of company's submission)

Clinical Effectiveness	Inclusion criteria stated in the company submission
Population	• Adults or young adults (i.e., 15 years or older) with AD
Interventions	• At least one of the following treatments for AD: 1. Dupilumab monotherapy 2. Dupilumab in combination with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) 3. Biologic drugs (with or without TCS or TCIs) 4. Systemic immunosuppressants (with or without TCS or TCIs) 5. Phototherapy (with or without TCS or TCIs) or extracorporeal photopheresis
Comparators	• Any
Outcomes	At least one of the following outcomes (change from baseline): • Efficacy Outcomes 1. EASI 2. IGA 3. SCORAD 4. BSA 5. GISS • PROs 1. POEM 2. DLQI 3. Pruritus NRS 4. HADS 5. EQ-5D overall or any of the 5 domains or the EQ-5D VAS score (EQ-VAS)

Clinical Effectiveness	Inclusion criteria stated in the company submission
	• Safety Outcomes 1. AEs 2. SAEs 3. Treatment discontinuation (e.g., due to lack of efficacy or due to safety)
Study design	• Randomised controlled clinical study • Phase I, II, III, or IV clinical trials

Note. AD, atopic dermatitis; AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Sign Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; PRO, patient-reported outcome; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; TCI, topical calcineurin inhibitors TCS, topical corticosteroids; VAS, visual analogue scale

The company stated that its decision to include patients aged 15 years or older was made after initial screening of the relevant publications. As many included publications included young adults (15-18 years old) the company, in order to avoid discarding clinically meaningful information, chose to include publications reporting results from people aged at least 15, if they also included results from people aged at least 18. The ERG agrees with the company's choice.

A total of 51 publications (47 from the original search and four from the update) met all the inclusion criteria and were ultimately included in the company's systematic review. Five publications (9.8%) presented results from more than one study, bringing the total number of studies included to 56. After exclusion of studies involving comparators considered inappropriate by the company, 28 studies remained. The company further included four studies which "*were published after the searches were complete and identified through the Sanofi Genzyme internal processes*". At clarification, the company described these internal processes as "*a weekly literature search that the Sanofi European Medical Affairs team run routinely*" and provided the relevant search terms. The ERG agrees that the four studies identified by this process[28-31] are relevant to the decision problem. However, the ERG questions the inclusion of these four publications on a somewhat ad-hoc basis, which violates the

principles of integrity and reproducibility underlying the systematic review process, as set out in commonly used guidance documents.[32]

4.1.3 Critique of data extraction

The company specifies that its systematic review of clinical effectiveness was conducted according to current NICE guidelines. Two reviewers independently screened all titles and abstracts identified by the literature searches. Two reviewers assessed full text papers for inclusion, but it is unclear if it is the same two who screened titles and abstracts. Studies were first selected using inclusion criteria that did not limit the type of outcome reported. During the second phase, an additional criterion for selecting publications reporting results on at least one outcome of interest was added. During the study selection and data extraction processes, any discrepancies between the two reviewers were resolved through consensus or by involving a third reviewer. The ERG considers the methods used by the company to be appropriate.

For assessing the clinical effectiveness of dupilumab for the treatment of atopic dermatitis (AD) the company considered the comprehensive LIBERTY AD clinical trial programme, which consists of 20 studies (phase I, phase II, phase III and phase III extension studies). In particular, four phase III RCTs were considered relevant to the decision problem addressed by the company submission. These were SOLO 1,[31, 33] SOLO 2,[31, 33] CHRONOS[28] and CAFÉ.[29] SOLO 1 and SOLO 2 compared dupilumab with placebo whilst CHRONOS and CAFÉ compared dupilumab plus concomitant TCS with placebo plus concomitant TCS. The company in the safety section of the submission and in the Appendices Document described also a pivotal dose ranging Phase IIb study[34] and two open label extension studies (SOLO-CONTINUE – unpublished data - and MAINTAIN),[30] which were included in the LIBERTY AD clinical trial programme and provide evidence to support dosing and long-term safety of dupilumab

4.1.4 Quality assessment

The risk of bias of the four main RCTs was assessed by the company using the Cochrane Risk of Bias tool.[32] Two independent reviewers assessed each study. The methods used by the company are considered to be appropriate.

All four RCTs were randomised appropriately. The concealment of treatment allocation was adequate and groups were similar at the outset of studies in terms of prognostic factors. Care providers, participants and outcomes assessors were blind to treatment allocation and there were no unexpected imbalances in dropouts between groups. Baseline disease characteristics were similar between both groups with respect to the extent and severity of AD. There were no unexpected imbalances in drop-outs between groups. However, the proportion of patients who withdrew from study treatment was higher in the placebo groups of SOLO 1 (35/224; 15.6%) and SOLO 2 (46/236; 19.5%) than in the dupilumab groups (SOLO 1, combined dupilumab groups: 40/447 [8.9%]; SOLO 2: dupilumab Q2W: 13/233 [5.6%]; dupilumab QW: 18/239 [7.5%]).[31, 33]

The full analysis set (FAS) included all randomised patients. Efficacy analyses were based on the treatment allocated by the interactive voice response system (IVRS)/interactive web response system (IWRS) at randomisation, which was the primary analysis population for efficacy analysis. In CHRONOS,[28] patients who temporarily or permanently discontinued from study drug and who did not withdraw from the study were asked to return to the clinic for all remaining study visits and complete all study assessments per the study schedule. All four trials were supported by Sanofi and Regeneron Pharmaceuticals, Inc.

The company also used the Cochrane Risk of Bias tool to assess the risk of bias of the 56 publications initially identified by the literature searches. The ERG noted some discrepancies in the risk of bias assessment reported in Table D-10 of the company's Appendices Document and that reported in Tables 2.17 of company's Document B and again in the risk of bias assessment reported in Table D-10 and the complete risk of bias assessment reported in Tables D-37 and D-38 of the company's Appendices Document. For example, the majority of the assessment of SOLO 2 in Table D-10 differs from the assessments in Tables 2.17, D-37 and D-38; Table D-10 reports unclear risk of bias for selection, attrition, reporting and other biases whilst the other three tables report low risk of bias for all domains. In addition, Table D-10 reports SOLO 1 as having unclear risk of bias for selective reporting, but Tables 2.17, D-37 and D-38 state that all outcomes measured were pre-defined within the studies' protocols.

The ERG is of the opinion that the risk of bias assessments in Tables 2.17, D-37 and D-38 are the correct versions, for SOLO 1 and SOLO 2.[31, 33]

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 4.

Table 4 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The company provided evidence on the effectiveness of dupilumab from four main RCTs: two RCTs assessing dupilumab versus placebo (SOLO 1, SOLO 2) and two RCTs assessing dupilumab plus concomitant TCS versus placebo plus concomitant TCS (CHRONOS and CAFÉ). The company conducted a Matching-Adjusted Indirect Comparison (MAIC) to carry out a scenario analysis for a comparison of dupilumab versus ciclosporin, the only immunosuppressant with a licence for the treatment of AD.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Characteristics and critique of four included trials

The characteristics of the four main RCTs - SOLO1, SOLO 2, CHRONOS, CAFÉ -[14, 28, 29, 33] are described in details in the company submission.

SOLO 1 and SOLO 2[31, 33] were identical Phase II, double-blind, placebo-controlled, parallel-group studies to assess the efficacy, safety and tolerability of dupilumab monotherapy. In **SOLO 1**, 671 patients were randomised in a 1:1:1 ratio to receive, for 16 weeks, either weekly subcutaneous injections of dupilumab 300mg (n=223), subcutaneous injections of dupilumab 300mg every two weeks (n=224), or placebo (n=224). Participants also received a loading dose of dupilumab 600mg or matching placebo, according to randomisation group, on day one.

In **SOLO 2**, 708 participants were randomised in a 1:1:1 ratio to the three groups as described above for SOLO 1, with n=239, n=233 and n=236 in the groups, respectively. Participants were adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable.

Approximately 20% (288) of patients in **SOLO 1 and SOLO 2** had exposure or intolerance to ciclosporin. The company refers to these as **'SOLO CAFÉ- like'** patients.

CAFÉ[29] was a Phase III, double-blind, randomised, placebo-controlled, parallel-group study in which 325 participants were randomised in a 1:1:1 ratio to receive dupilumab 300 mg QW plus TCS for 16 weeks following a 600 mg loading dose on day 1 (n=110); placebo QW plus TCS (n=108); or dupilumab 300 mg Q2W plus TCS following a 600 mg loading dose on day1, alternating with placebo for 16 weeks (n=107). It worth noting that in CAFÉ patients had prior exposure or intolerance to ciclosporin whilst concomitant use of TCS was permitted along with any rescue therapy as required.

CHRONOS[28] was a Phase III, multicentre, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of dupilumab administered concomitantly with TCS. A total of 740 Participants were randomised in a 3:1:3 ratio to receive dupilumab 300mg QW plus TCS for 52 weeks following a 600 mg loading dose on day 1 (n=319); placebo QW plus TCS (n=315); or dupilumab 300 mg Q2W plus TCS following a 600 mg loading dose on day 1, alternating with placebo SC for 52 weeks (n=106). Participants were adults patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS. In CHRONOS

approximately 30% (137) of patients had prior exposure or intolerance to ciclosporin. The company refers to these as **'CHRONOS CAFÉ-like'** patients.

Table 5 presents a summary of the characteristics of the four RCTs included in the company's synthesis of clinical effectiveness evidence.

Table 5 Summary characteristics of the trials included in the company's review of clinical effectiveness evidence (reproduced from Table 4, Document A of company's submission)

Study title	**SOLO 1 & SOLO 2**[31, 33]	**CHRONOS**[28]	**CAFÉ**[29]
Study design	16- or 28-week (depending on entry to CONTINUE), Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study (n = 671 and 708, respectively)	64-week (52 weeks on treatment), Phase III, multicentre, randomised, double-blind, placebo-controlled study (n=740)	32-week (16 weeks on treatment), Phase III, double-blind, randomised, placebo-controlled, parallel-group (n = 325)
Population	Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable	Adults patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS	Adult patients with severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable
Intervention	• 600 mg loading dose dupilumab SC on Day 1, followed by 300 mg dupilumab SC QW or Q2W from Week 1–15 • Matching	• 600 mg loading dose dupilumab SC on Day 1, followed by 300 mg dupilumab SC QW or Q2W from Weeks 1–51 + TCS	• 600 mg loading dose dupilumab SC on Day 1, followed by 300 mg dupilumab SC QW or Q2W from Weeks 1–16 + TCS

	placebo injections, including loading dose on Day 1, followed by QW injections of placebo from Week 1–15	• Matching placebo injections, including a loading dose on Day 1, followed by QW injections of placebo from Weeks 1–51 + TCS	• Matching placebo injections, including a loading dose on Day 1, followed by QW injections of placebo from Weeks 1–16 + TCS
Comparator	Dupilumab vs. placebo	Dupilumab + TCS vs. placebo + TCS (Medium potency TCS to areas of active lesions stepped down after 7 days to low potency once daily)	
Outcomes specified in the decision problem	• Clinical severity/disease activity/symptom control • Proportion of patients with IGA 0/1 • Proportion of patients with EASI-75, EASI-50 • Change in pruritus NRS, BSA, SCORAD • Health-related quality of life • Change in EQ-5D, DLQI, POEM, HADS • Prevention of relapse/flares • Use of rescue medication	• Clinical severity/disease activity/symptom control • Proportion of patients with IGA 0/1 • Proportion of patients with EASI-75, EASI-50 at 16 weeks • Change in pruritus NRS, BSA, SCORAD • Maintenance of remission • EASI-75, EASI-50 at 52 weeks • Health-related quality of life • Change in EQ-5D, DLQI, POEM, HADS at 52 weeks • Prevention of relapse/flares	• Clinical severity/disease activity/symptom control • Proportion of patients with IGA 0/1 • Proportion of patients with EASI-75, EASI-50 at 16 weeks • Change in pruritus NRS, BSA, SCORAD • Health-related quality of life • Change in EQ-5D, DLQI, POEM, HADS • Prevention of relapse/flares • Use of rescue medication • Adverse effects of treatment at 16 weeks

	• Adverse effects of treatment	• Use of rescue medication • Adverse effects of treatment to 52 weeks	

Note. AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index score; EASI-50/75/90, 50%/75%/90% reduction in Eczema Area and Severity Index score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SAE, serious adverse events; SCORAD, Scoring atopic dermatitis; TCS, topical corticosteroid

Table 6 presents baseline demographics and disease characteristics of participants from the four RCTs included in the company's clinical effectiveness evidence. In general, participant and disease characteristics were fairly well balanced within and across trials.

Table 7 presents a summary of the primary endpoints of the four included RCTs for patients considered a non-responder after rescue treatment use.

Table 6 Baseline demographic and disease characteristics of the participants of the four RCTs included in the company's review of clinical effectiveness evidence

	SOLO 1 (n=671)[31, 33]			SOLO 2 (n=708)[31, 33]			CHRONOS (n=740)[28]			CAFÉ (n=325)[29]		
	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS
	n=224	n=224	n=223	n=236	n=233	n=239	n=315	n=106	n=319	n=108	n=107	n=110
PARTICIPANT CHARACTERISTICS												
Mean age, years (SD)	39.5 (13.91)	39.8 (14.68)	39.3 (14.39)	37.4 (14.09)	36.9 (13.96)	37.1 (14.51)	36.6 (13.01)	39.6 (13.98)	36.9 (13.67)	38.9 (13.35)	37.5 (12.89)	38.7 (13.21)
Gender (male), n (%)	118 (52.7)	130 (58.0)	142 (63.7)	132 (55.9)	137 (58.8)	139 (58.2)	193 (61.3)	62 (58.5)	191 (59.9)	68 (63.0)	65 (60.7)	66 (60.0)
Weight (kg), mean (SD)	75.3 (18.36)	76.1 (17.06)	78.5 (18.45)	77.1 (18.14)	77.6 (19.51)	76.8 (19.25)	75.0 (18.61)	73.1 (17.73)	74.4 (17.63)	78.3 (18.45)	74.5 (15.41)	74.7 (16.78)
BMI, mean (SD)	26.4 (5.82)	26.3 (4.82)	26.7 (6.07)	26.6 (5.71)	26.4 (5.82)	26.4 (6.04)	25.8 (5.69)	25.5 (5.80)	25.6 (5.12)	26.1 (5.19)	24.7 (3.97)	25.2 (4.57)
Race, n (%)												
White	146 (65.2)	155 (69.2)	149 (66.8)	156 (66.1)	165 (70.8)	168 (70.3)	208 (66.0)	74 (69.8)	208 (65.2)	104 (96.3)	104 (97.2)	105 (95.5)
Black	16 (7.1)	10 (4.5)	20 (9.0)	20 (8.5)	13 (5.6)	15 (6.3)	19 (6.0)	2 (1.9)	13 (4.1)	0	0	2 (1.8)
Asian	56 (25.0)	54 (24.1)	51 (22.9)	50 (21.2)	44 (18.9)	45 (18.8)	83 (26.3)	29 (27.4)	89 (27.9)	2 (1.9)	2 (1.9)	2 (1.8)
Other or missing data	6 (2.7)	5 (2.2)	3 (1.3)	7 (3.0)	6 (2.6)	4 (1.7)	5 (1.6)	1 (0.9)	9 (2.8)	2 (1.9)	1 (0.9)	1 (0.9)
DISEASE CHARACTERISTICS												
Duration of AD, mean years (SD)	29.5 (14.46)	28.5 (16.12)	27.9 (15.79)	28.2 (14.41)	27.2 (14.24)	27.4 (15.01)	27.5 (14.34)	30.1 (15.53)	27.9 (14.46)	29.2 (14.72)	29.6 (15.61)	32.3 (14.00)

	SOLO 1 (n=671)[31, 33]			SOLO 2 (n=708)[31, 33]			CHRONOS (n=740)[28]			CAFÉ (n=325)[29]		
	Placebo	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo**	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo QW + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**	**Placebo QW + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**
	n=224	**n=224**	**n=223**	**n=236**	**n=233**	**n=239**	**n=315**	**n=106**	**n=319**	**n=108**	**n=107**	**n=110**
% body surface area with AD, mean (SD)	57.5 (23.38)	54.7 (23.19)	56.1 (22.96)	54.3 (23.06)	52.7 (21.23)	52.2 (21.51)	56.9 (21.69)	59.5 (20.84)	54.1 (21.76)	55.0 (20.51)	56.1 (17.83)	56.0 (19.26)
EASI (0-72, >20=severe), mean (SD)	34.5 (14.47)	33.0 (13.57)	33.2 (13.98)	33.6 (14.31)	31.8 (13.08)	31.9 (12.70)	32.6 (12.93)	33.6 (13.30)	32.1 (12.76)	32.9 (10.80)	33.3 (9.93)	33.1 (11.02)
IGA score (0-4, 4=severe), mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)
Number of patients with IGA score 4, n (%)	110 (49.1)	108 (48.2)	106 (47.5)	115 (48.7)	115 (49.4)	112 (46.9)	147 (46.7)	53 (50.0)	147 (46.1)	52 (48.1)	50 (46.7)	52 (47.3)
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	7.4 (1.77)	7.2 (1.89)	7.2 (2.06)	7.5 (1.85)	7.6 (1.60)	7.5 (1.81)	7.3 (1.84)	7.4 (1.66)	7.1 (1.90)	6.4 (2.23)	6.6 (2.10)	6.2 (2.01)
SCORAD score (0-103, >50=severe), mean (SD)	68.3 (13.96)	66.9 (13.97)	67.5 (13.61)	69.2 (14.91)	67.2 (13.48)	67.5 (13.10)	66.0 (13.53)	69.3 (15.24)	65.9 (13.63)	67.0 (12.20)	68.6 (11.91)	66.0 (12.70)
POEM score (0-28, >24=severe), mean (SD)	20.3 (5.90)	19.8 (6.37)	20.4 (6.25)	21.0 (5.94)	20.8 (5.49)	20.9 (5.59)	20.0 (5.99)	20.3 (5.68)	20.1 (6.05)	19.1 (5.99)	19.3 (6.21)	18.6 (6.97)
DLQI score (0-30, >10=very large effect), mean (SD)	14.8 (7.23)	13.9 (7.37)	14.1 (7.51)	15.4 (7.69)	15.4 (7.07)	16.0 (7.33)	14.7 (7.37)	14.5 (7.31)	14.4 (7.17)	13.2 (7.60)	14.5 (7.63)	13.8 (8.03)
Total HADS score (0-42, 11 overt depression/anxiety), mean (SD)	12.6 (8.33)	12.2 (7.26)	12.6 (7.95)	13.7 (8.32)	13.7 (7.52)	14.6 (8.24)	12.6 (8.06)	12.9 (7.73)	12.8 (8.01)	13.0 (7.85)	12.8 (8.01)	13.3 (8.15)

	SOLO 1 (n=671)[31, 33]			SOLO 2 (n=708)[31, 33]			CHRONOS (n=740)[28]			CAFÉ (n=325)[29]		
	Placebo	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo**	**Dupilumab 300 mg Q2W**	**Dupilumab 300 mg QW**	**Placebo QW + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**	**Placebo QW + TCS**	**Dupilumab 300 mg Q2W + TCS**	**Dupilumab 300 mg QW + TCS**
	n=224	**n=224**	**n=223**	**n=236**	**n=233**	**n=239**	**n=315**	**n=106**	**n=319**	**n=108**	**n=107**	**n=110**
GISS (0-12) score, mean (SD)	9.0 (1.85)	8.9 (1.81)	8.9 (1.74)	9.2 (1.78)	9.0 (1.80)	9.0 (1.75)	8.7 (1.84)	8.9 (2.04)	8.9 (1.80)	9.4 (1.63)	9.3 (1.64)	9.1 (1.63)
EQ-5D VAS (0-100), mean (SD)	54.7 (24.83)	56.8 (23.34)	56.0 (24.83)	57.0 (24.38)	55.4 (22.96)	53.6 (23.82)	56.5 (23.70)	57.9 (22.63)	56.0 (22.77)	53.4 (24.53)	55.5 (22.77)	55.9 (20.77)
EQ-5D (0-1) utility, mean (SD)	0.603 (0.3413)	0.649 (0.3178)	0.640 (0.3205)	0.606 (0.3465)	0.607 (0.3212)	0.572 (0.3555)	0.630 (0.3212)	0.648 (0.2768)	0.641 (0.2902)	0.681 (0.2870)	0.717 (0.2590)	0.694 (0.2477)

AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, European Quality of Life-5 Dimensions; GISS, Global Individual Signs Score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; QW, once a week; Q2W, every two weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue scale

Table 7 Summary of primary outcomes reported by the four included RCTs; patients considered non-responders after rescue treatment use at 16 weeks

Outcome *p−values vs placebo all <0.0001 unless otherwise stated	CHRONOS[28]			CAFÉ[29]			SOLO 1[31, 33]			SOLO 2[31, 33]		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab		Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS		Q2W	QW		Q2W	QW
	n=315	n=106	n=319	n=108	n=107	n=110	n=224	n=224	n=223	n=236	n=233	n=239
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: n (%)	39 (12.4)	41 (38.7)	125 (39.2)	15 (13.9)	43 (40.2)	43 (39.1)	23 (10.3)	85 (37.9)	83 (37.2)	20 (8.5)	84 (36.1)	87 (36.4)
Difference: % (95% CI)		26.3 (16.34, 36.26)	26.8 (20.33, 33.28)		26.3 (14.95, 37.65)*	25.2 (13.99, 36.41)*		27.7 (20.18, 35.17)*	27.0 (19.47, 34.44)*		27.6 (20.46, 34.69)*	27.9 (20.87, 34.99)*
Proportion of patients	74 (23.5)	73 (68.9)	203 (63.6)	32 (29.6)	67 (62.6)	65 (59.1)	33 (14.7)	115 (51.3)	117 (52.5)	28 (11.9)	103 (44.2)	115 (48.1)

Outcome *p−values vs placebo all <0.0001 unless otherwise stated	CHRONOS[28]			CAFÉ[29]			SOLO 1[31, 33]			SOLO 2[31, 33]		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab		Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS		Q2W	QW		Q2W	QW
	n=315	n=106	n=319	n=108	n=107	n=110	n=224	n=224	n=223	n=236	n=233	n=239
who achieved EASI−75: n (%)												
Difference: % (95% CI)		45.4 (35.39, 55.36)	40.1 (33.09, 47.20)		33.0 (20.41, 45.57)*	29.5 (16.87, 42.05)*		36.6 (28.58, 44.63)*	37.7 (29.70, 45.77)*		32.3 (24.75, 39.94)*	36.3 (28.69, 43.81)*

Note. Difference refers to dupilumab minus placebo. Values for CHRONOS reproduced from Table 2.18, Document B of company's submission. QW: every week; Q2W: every 2 weeks; TCS: topical corticosteroids; CI: confidence interval

In the primary analysis of patients considered non-responders after rescue treatment use, there was not a difference between the dupilumab QW and dupilumab Q2W groups in the proportion of patients who achieved IGA score of 0 or 1 and a reduction of ≥2 points from baseline. The patients who received dupilumab QW and achieved the IGA score and the reduction ranged from 36.4-39.2%. The patients who received dupilumab Q2W and achieved the IGA score and the reduction ranged from 36.1-40.2%. The patients who received placebo and achieved the IGA score and reduction ranged from 8.5-13.9%.

The proportion of patients in this analysis who achieved EASI-75 was higher in CHRONOS and CAFÉ than SOLO 1 and SOLO 2, for the intervention groups and control group. The proportion of patients who received placebo and achieved EASI-75 was 23.5% for CHRONOS and 29.6% for CAFÉ, as compared to 14.7% for SOLO 1 and 11.9% for SOLO 2. For all trials, the proportions of patients who achieved EASI-75 were similar between patients who received dupilumab QW and those who received dupilumab Q2W.

Table 8 presents a summary of the primary endpoints of the four included RCTs for all observed values regardless of rescue treatment use.

Table 8 Summary of primary outcomes reported by the four included RCTs; all observed regardless of rescue treatment at 16 weeks

Outcome *p−values vs placebo all <0.0001 unless otherwise stated	CHRONOS[28]			CAFÉ[29]			SOLO 1[31, 33]			SOLO 2[31, 33]		
	Placebo QW+TCS	Dupilumab		Placebo QW+TCS	Dupilumab		Placebo QW	Dupilumab		Placebo QW	Dupilumab	
		Q2W + TCS	QW + TCS		Q2W + TCS	QW + TCS		Q2W	QW		Q2W	QW
	n=315	n=106	n=319	n=108	n=107	n=110	n=224	n=224	n=223	n=236	n=233	n=239
Proportion of patients who achieved IGA score of 0 or 1 and reduction of ≥2 points from baseline: n (%)	49 (15.6)	41 (38.7)	134 (42.0)	16 (14.8)	43 (40.2)	44 (40.0)	29 (12.9)	91 (40.6)	85 (38.1)	25 (10.6)	87 (37.3)	91 (38.1)

Difference: % (95% CI)		23.1 (13.03, 33.22)	26.5 (19.72, 33.19)		25.4 (13.92, 36.83)*	25.2 (13.84, 36.53)*		27.7 (19.89, 35.47)*	25.2 (17.43, 32.91)*		26.7 (19.40, 34.09)*	27.5 (20.18, 34.78)*
Proportion of patients who achieved EASI−75: n (%)	102 (32.4)	78 (73.6)	226 (70.8)	35 (32.4)	69 (64.5)	67 (60.9)	50 (22.3)	133 (59.4)	136 (61.0)	37 (15.7)	116 (49.8)	138 (57.7)
Difference: % (95% CI)		41.2 (31.35, 51.06)	38.5 (31.28, 45.65)		32.1 (19.42, 44.73)*	28.5 (15.81, 41.19)*		37.1 (28.62, 45.49)*	38.7 (30.26, 47.07)*		34.1 (26.19, 42.03)*	42.1 (34.27, 49.86)*

Note. Difference refers to dupilumab minus placebo. Values for CHRONOS reproduced from Table 2.18, Document B of company's submission. QW: every week; Q2W: every 2 weeks; TCS: topical corticosteroids; CI: confidence interval

Table 9 Summary of TEAEs with incidence ≥5% for any TEAE in any treatment group during the 16 week study period

Event, n (%)	CHRONOS (16 weeks) (n=740)[28]			CAFÉ (n=325)[29]			SOLO 1 (n=669)[31, 33]			SOLO 2 (n=707)[31, 33]		
	Placebo + TCS (n=315)	Dupilumab Q2W + TCS (n= 110)	Dupilumab QW + TCS (n= 315)	Placebo + TCS (n=108)	Dupilumab Q2W +TCS (n=107)	Dupilumab QW + TCS (n=110)	Placebo (n=222)	Dupilumab Q2W (n=229)	Dupilumab QW (n=218)	Placebo (n=234)	Dupilumab Q2W (n=236)	Dupilumab QW (n=237)
At least 1 TEAE	215 (68.3)	81 (73.6)	228 (72.4)	75 (69.4)	77 (72.0)	76 (69.1)	148 (66.7)	171 (74.7)	151 (69.3)	172 (73.5)	156 (66.1)	159 (67.1)
At least 1 AE	NR	NR	NR	NR	NR	NR	145 (65.3)[a]	167 (72.9)[a]	150 (68.8)[a]	168 (71.8)[a]	154 (65.3)[a]	157 (66.2)[a]
At least 1 TESAE	6 (1.9)	3 (2.7)	4 (1.3)	2 (1.9)	2 (1.9)	2 (1.8)	12 (5.4)	7 (3.1)	2 (0.9)	16 (6.8)	6 (2.5)	9 (3.8)
At least 1 SAE	NR	NR	NR	NR	NR	NR	11 (5.0)[a]	7 (3.1)[a]	2 (0.9)[a]	13 (5.6)[a]	4 (1.7)[a]	8 (3.4)[a]
Death	0	0	0	0	0	0	0	0	0	0	1	1
Injection site reaction	18 (5.7)	11 (10.0)	51 (16.2)	0	1 (0.9)	4 (3.6)	13 (5.9)	19 (8.3)	41 (18.8)	15 (6.4)	32 (13.6)	31 (13.1)
Exacerbation of atopic dermatitis	86 (27.3)	12 (10.9)	25 (7.9)	16 (14.8)[a]	8 (7.5)[a]	9 (8.2)[a]	67 (30.2)	30 (13.1)	21 (9.6)	81 (34.6)	32 (13.6)	38 (16.0)
Headache	15 (4.8)	4 (3.6)	20 (6.3)	9 (8.3)	10 (9.3)	10 (9.1)	13 (5.9)	21 (9.2)	11 (5.0)	11 (4.7)	19 (8.1)	22 (9.3)
Infections and infestations	111 (35.2)	39 (35.5)	109 (34.6)	44 (40.7)	49 (45.8)	47 (42.7)	63 (28.4)	80 (34.9)	74 (33.9)	76 (32.5)	65 (27.5)	68 (28.7)
Nasopharyngitis	33 (10.5)	15 (13.6)	37 (11.7)	18 (16.7)	22 (20.6)	17 (15.5)	17 (7.7)	22 (9.6)	25 (11.5)	22 (9.4)	20 (8.5)	20 (8.4)
Upper respiratory tract infection	20 (6.3)	7 (6.4)	21 (6.7)	1 (0.9)	1 (0.9)	3 (2.7)	5 (2.3)	6 (2.6)	11 (5.0)	5 (2.1)	7 (3.0)	9 (43.8)
Allergic conjunctivitis	9 (2.9)	7 (6.4)	19 (6.0)	7 (6.5)	16 (15.0)	10 (9.1)	2 (0.9)	12 (5.2)	7 (3.2)	2 (10.9)	2 (10.8)	3 (1.3)
Conjunctivitis	2 (0.6)	0	3 (1.40)	3 (2.8)	12 (11.2)	8 (7.3)	2 (0.9)	11 (4.8)	7 (3.2)	1 (0.4)	9 (3.8)	9 (3.8)

Note. The figures in this table are based on the safety analysis sets of the studies, which include all randomised patients who received any study drug and is based on the treatment received. The values for CHRONOS are reproduced from the company's submission. [a]Data reproduced from the company's submission. TEAE: treatment-emergent adverse event; AE: adverse event; TESAE: treatment-emergent serious adverse event; SAE: serious adverse event; QW: every week; Q2W: every 2 weeks

Similarly, in the analysis of all observed regardless of rescue treatment, the proportion of patients who achieved IGA score of 0 or 1 and a reduction of ≥2 points from baseline was comparable for the dupilumab QW and Q2W groups. The patients who received dupilumab QW and achieved the IGA score and the reduction ranged from 38.1-42.0%. The patients who received dupilumab Q2W and achieved the IGA score and the reduction ranged from 37.3 to 40.6%. The patients who received placebo and achieved the IGA score and reduction ranged from 10.6 to 15.6%.

The proportion of patients who achieved EASI-75 was higher in CHRONOS and CAFÉ than SOLO 1 and SOLO 2, for the intervention and control groups. The proportion of patients who received placebo and achieved EASI-75 was 32.4% for both CHRONOS and CAFÉ, as compared to 22.3% for SOLO 1 and 15.7% for SOLO 2. For the majority of trials, the proportions of patients who achieved EASI-75 between patients who received dupilumab QW and those who received dupilumab Q2W were similar. However, in SOLO 2, the proportion of patients who achieved EASI-75 was 49.8% in the group that received dupilumab Q2W and 57.7% in the group that received dupilumab QW.

In all of the studies, dupilumab reduced the use of rescue treatments which include topical calcineurin inhibitor, oral corticosteroids and systemic immunosuppressants. In CHRONOS, 53% of patients who received the placebo required a rescue treatment compared with 16% of those treated with dupilumab Q2W. In CAFÉ, 17.6% of the placebo participants received rescue treatment compared to 3.7% of the dupilumab Q2W. In SOLO 1, the proportion of patients who required a rescue treatment in the placebo and dupilumab groups were 51.3% and 21%, respectively, whilst in SOLO 2 were 52.1% and 15%, respectively.

Table 9 presents a summary of TEAEs with an incidence of at least 5% in any treatment group during the 16-week study period.

Across all four studies, there were two deaths, with one in each of the dupilumab groups of the SOLO 2 study. Both deaths were classed as treatment emergent; a man (in the QW group) with a history of depression committed suicide (8 days after dose

of dupilumab) and a woman (in the Q2W group) with asthma died of an asthma attack (84 days after study completion).

The number of TEAEs was generally low across studies, although higher in the placebo groups of SOLO 1 (5.4% as compared to 3.1% and 0.9% of the dupilumab Q2W and QW groups, respectively) and SOLO 2 (6.8% as compared to 2.5% and 3.8% of the dupilumab Q2W and QW groups, respectively).

The most frequently experienced TEAEs were exacerbation of AD, infections and infestations and nasopharyngitis. Exacerbation of AD was more common in the placebo groups (27.3%, 14.8%, 30.2%. 34.6% for CHRONOS, CAFÉ, SOLO 1 and SOLO 2, respectively) than the Q2W or QW dupilumab groups (10.9%/7.9%, 7.5%/8.2%, 13.1%/9.6%, 13.6%/16% for CHRONOS, CAFÉ, SOLO 1 and SOLO 2, respectively) of all four studies. Infections and infestations and nasopharyngitis were more balanced across the groups, albeit higher for all three groups in CAFÉ (40.7%, 45.8%, 42.7% for placebo, dupilumab Q2W and dupilumab QW, respectively) than the other three RCTs, where values ranged from 27.5% (dupilumab Q2W group, SOLO 2) to 35.5% (dupilumab Q2W group, CHRONOS).

The company's submission also reported pooled safety data for the SOLO 1 and SOLO 2 trials and the pivotal phase IIb trial, which assessed different doses of dupilumab (see Table 2.47, section B 2.10.2, page 139 of the submission). There is an obvious overlap between the primary safety pool data reported in Table 2.47 and the safety data reported in the two SOLO trials. There is, however, some additional information presented in Table 2.47, which shows a greater reduction in skin and subcutaneous tissue disorders for participants receiving dupilumab compared with those receiving placebo (20.2% and 36.2%, respectively). Nervous system disorders and headache are more frequent among those receiving dupilumab than those receiving placebo (11.9% and 8.2%, versus 9.5% and 5%, respectively).

The long-term safety data from the extension studies SOLO-CONTINUE and MAINTAIN from the LIBERTY AD clinical trial programme, supported those reported from SOLO 1, SOLO 2, CHRONOS and CAFÉ with no new safety issues identified.

4.2.2 Critique of statistical techniques used in trials

The ERG accepts the reasons provided by the company for not undertaking any meta-analysis. As the most relevant comparator is best supportive care, the selection of trials comparing dupilumab to placebo is appropriate. Comparing the placebo arm to the intervention arms and presenting the effect sizes and associated confidence intervals is the approach the ERG would have expected to see used. The ERG is also happy with the method of presentation of the safety data as the adverse events experienced by participants in all of the trials are presented clearly. The matching adjusted indirect comparison (MAIC) approach used to compare dupilumab to ciclosporin is discussed in section 4.4 below.

The trials included by the company all compare dupilumab to placebo and are three arm trials with weekly and fortnightly doses of dupilumab being compared to placebo. There is consistency of outcomes used in the four trials with all trials reporting change in the EASI score as a primary outcome and CHRONOS and SOLO 1 and SOLO 2 also reporting the IGA score as a primary outcome. All four trials show significantly higher proportions of participants achieving the EASI-75 score with effect sizes ranging up to 45.4% of participants. The CHRONOS, SOLO1 and SOLO2 studies also show a significantly higher proportion of participations achieving an IGA score of 0 or 1 indicating that they were clear or almost clear of the condition.

There are a number of measures reported as secondary outcomes including Patient-oriented Eczema Measure, Dermatology Quality of Life Index, change in the EASI score, change in the Severity Scoring of Atopic Dermatitis, change in the pruritus numerical rating scale are among the secondary outcomes reported in the trials. The list below shows the secondary outcomes reported in each study:

- Percentage change in EASI score from baseline
- Proportion who achieved EASI-50
- Percentage change from baseline in SCORAD
- Percentage change in pruritus NRS from baseline
- Proportion achieving at least a 4 point reduction in pruritus NRS from baseline
- Change from baseline in POEM
- Proportion achieving at least a 4 point change in POEM

For these secondary outcomes, the reported significant large treatment effects indicate benefit from dupilumab compared to placebo. There are also a series of quality of life and mental health outcomes reported in each study. These also show benefits from dupilumab compared to placebo.

All studies provide a complete list of adverse events experienced by participants. A number of these events are extremely rare and Table 10 below reports the more common adverse events and how they differ between the placebo and dupilumab arms.

The summary of adverse events show increases in the dupilumab arms for events such as injection site reactions and allergic conjunctivitis but there are several events where there is no difference between the placebo and intervention arms. The rate of exacerbation of atopic dermatitis is more than halved for participants receiving either dose of dupilumab.

Table 10 More common adverse events (≥10%) for included studies and how they differ between the placebo and dupilumab arms at 16 weeks

	CHRONOS			CAFE			SOLO1			SOLO2			Effect
	P	D Q2W	D QW	P	D Q2W	D QW	P	D Q2W	D QW	P	D Q2W	D QW	
Injection site reaction	5.7	10.0	16.2	0	0.9	3.6	5.9	8.3	18.8	6.4	13.6	13.1	More common in the dupilumab arm (CHRONOS and SOLO studies only)
Exacerbation of atopic dermatitis	27.3	10.9	7.9	14.8	7.5	8.2	30.2	13.1	9.6	34.6	13.6	16.0	Reduced proportion in the dupilumab arms
Allergic conjunctivitis	2.9	6.4	6.0	6.5	15.0	9.1	0.9	5.2	3.2	10.9	10.8	1.3	Higher proportions in the dupilumab arms.

P, Placebo; D Q2W Dupilumab every other week; D QW Dupilumab every week

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

The company did not conduct a network meta-analysis because of the '*considerable heterogeneity in methodologies within the studies identified from the literature searches (e.g. the same treatment administered in different doses or assessed at*

different time-to-endpoints, a small number of studies per treatment, and a lack of common comparators - see Appendix D)'.

The company conducted a Matching-Adjusted Indirect Comparison (MAIC) using patient-level data from CHRONOS to carry out a scenario analysis for the comparison of dupilumab with ciclosporin, the only immunosuppressant with a licence for the treatment of AD. The ERG agree that in the absence of any trials comparing dupilumab with ciclosporin this is an appropriate means of comparison.

The MAIC approach was applied separately for the comparison of dupilumab Q2W plus TCS versus ciclosporin from the Haeck et al., study[36] and ciclosporin from the Jim et al., study.[35] From what is presented in Tables 2.39 and 2.40 the ERG are reasonably confident that the MAIC has been conducted correctly. There is a concern with the ciclosporin before weighting figures from the Jin et al., study[35] (section 2.9, Table 2.40 page128 of the submission) as these appear identical to the before weighting figures presented for ciclosporin in the Haeck et al., study[36] (section 2.9, Table 2.39, page 127 of the submission). The ERG is of the opinion that this is simply a table entry error and that the correct data has been used and the after weighting column for ciclosporin, which is compared to the weighted dupilumab data from CHRONOS should also appear as the before weighting column for ciclosporin. As often happens with the MAIC approach, the after weighting sample sizes are very low and the validity of the comparison becomes questionable. The ERG agree with the company's decision not to place too much emphasis on these results and while the MAIC shows dupilumab to be superior to ciclosporin the company have only assumed dupilumab to be equivalent to ciclosporin in the cost-effectiveness modelling.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG has not undertaken any additional work.

4.6 Conclusions of the clinical effectiveness section

The ERG are happy with the methods of analysis used in the various studies and agree that there is a beneficial effect from dupilumab compared to placebo. There are large effect sizes on the primary outcome(s) and the differences between intervention and

control are significant. The secondary outcomes also provide evidence of a beneficial effects from dupilumab.

There are a large number of treatment emergent adverse events both infectious and non-infectious. Many of these are very rare and in the case of the more common events there is little difference between the placebo arms and dupilumab arms in occurrence rates. Across all studies the rate of exacerbation of atopic dermatitis is more than halved in the dupilumab arms. In the dupilumab arms there is an increased rate of reactions at the injection site and allergic conjunctivitis is more common.
The ERG are satisfied with the reasons provided by the company for not undertaking any meta-analysis. While accepting that a matched adjusted indirect comparison is an acceptable method to use in the circumstances the ERG have concerns with both the small sample sizes after adjusting and also the heterogeneity of the studies being compared. The ERG therefore agree with the company's decision not to place much emphasis on the result of the MAIC and would recommend interpreting the result with caution.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company submission includes separate systematic literature reviews to identify: economic evaluations of dupilumab or other AD therapies, health related quality of life (utilities) and resources used for individuals with AD or atopic eczema due to AD.

Reports of cost effectiveness were sought by the company by searching MEDLINE, EMBASE and EconLit (via OvidSP); NHS Economics Evaluation Database (NHS EED), HTA Database, CENTRAL, CDSR and DARE (via The Cochrane Library); and the CEA Registry. Searches were conducted 22-23 May 2017 and were restricted to publications reported in English. Relevant conference abstracts were also searched from 2015.

The search strategies are documented in full in Appendix G and are reproducible. The search strategies for MEDLINE, EMBASE and the databases in the Cochrane Library combined two search facets using the Boolean operator AND: atopic dermatitis and economic evaluations. These searches were run separately for each database. The search strategies for NHS EED, Econlit and the conference proceedings included only dermatitis terms which was appropriate.

Reports of quality of life studies were sought by the company by searching MEDLINE, EMBASE, PsycINFO and EconLit (via OvidSP); NHS Economics Evaluation Database (NHS EED) and HTA Database (via The Cochrane Library); and the CEA Registry, ScHARRHud and the NICE website. Searches were conducted 15-17 August 2017.

The search strategies are documented in full in Appendix H and are reproducible.

The search strategies for MEDLINE, EMBASE and PsycINFO combined two search facets using the Boolean operator AND: atopic dermatitis and quality of life. These searches were run separately for each database. The search strategies for the remaining databases only included dermatitis terms which was appropriate.

For both reviews, appropriate and extensive controlled vocabulary and text terms were used in the search strategies and as such were considered by the ERG to be appropriate

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

The company inclusion and exclusion criteria for identifying relevant economic evaluation studies are summarized in Table 3.1 of the company submission (Document B) and a full description is provided in Appendix G. The SLR included full economic evaluations for adult AD populations (aged 18 and over) of any severity, including eczema and atopic eczema. However, studies reporting patients with hand eczema were excluded. Outcomes of interest were quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICER), and total costs. Study designs included economic evaluations, published economic models, HTA reports investigating cost-effectiveness, studies published as abstracts or conference presentations (published from 2015 onward). Case reports, case studies, news, comments, editorials and letters were excluded. Non-English language studies were also excluded. The ERG believes that the inclusion-exclusion criteria for the SLR of existing economic evaluations are adequate and reflect the focus of the submission.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies

The company submission reported on the results of the search using a PRISMA diagram (Figure 3.1, Document B, page 168). A total of 3093 records were initially identified. Thirty five full text documents were assessed and 14 studies were deemed eligible: One study reporting a dupilumab economic evaluation[37, 38] and 13 studies reporting on other interventions (i.e., pimecrolimus [5 studies]; tacrolimus [7 studies], emollient cream [4 studies], corticosteroids [7 studies], phototherapy [1 study] and

barrier strengthening cream [2 studies]). One study evaluated intermittent ciclosporin therapy versus UVAB phototherapy (see company submission appendix G for further details).[39]

The economic evaluation of dupilumab was published by the Institute for Clinical and Economic Review (ICER) in June 2017 [37] and subsequently published as a peer reviewed manuscript.[38]. The authors used to Markov model to estimate the cost-effectiveness of dupilumab compared to usual care (emollients) in 38 year-old patients in the US over a lifetime horizon. The study reported a base case ICER of $124,541 which was reduced to $101,830 when net price instead of list price for dupilumab was used in the analysis. The total reported QALYs were 16.28 for dupilumab and 14.37 for emollients. This equates to a lifetime QALY gain of 1.91 for dupilumab versus emollients alone.

The model reported in ICER report (2017) is very similar in structure to the one used for the current submission, with a decision tree model linked to a Markov model to reflect the short and long terms costs and consequences. Only dupilumab and standard care (emollients) were considered, and use of topical corticosteroids were not permitted in the patient population. Thus, clinical and utility parameters in the model were derived from the SOLO trials, which assessed the clinical effectiveness of dupilumab as monotherapy. The model used for the current submission is an adaptation of the ICER model used to assess cost effectiveness in the US.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details

The company submission concludes that the models identified in the SLR were for topical treatments that examined short term or episodic therapy and not long term treatments. The company did not use these models to develop the dupilumab model as the models did not assess chronic treatment satisfactorily, correspond to a different treatment pathway and they relied extensively on assumptions due to evidence gaps. The company note that they based their model structure on a model developed for the assessment of a biologic treatment for psoriasis. The company chose the model that was most cited (i.e., the York model).[40]

The ERG agree that the economic evaluations identified by the SLR cannot be used for the assessment of dupilumab for the UK and that the adaptation of the model used for the ICER assessment is a reasonable strategy. A detailed critique of the submitted model and economic evaluation follows below.

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

Table 11 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Phototherapy (including UVB and PUVA) Immunosupressive therapies (azathioprine, ciclosporin and methotrexate) Best supportive care (combination of emollients, low-to-mid potency topical corticosteroids and rescue therapy including higher potency topical or oral corticosteroids or topical calcineurin inhibitors) Alitretinoin	No. The chosen comparator, best supportive care (BSC), is generally appropriate given the company's proposed positioning for dupilumab in the care pathway (see below). However, the ERG are uncertain about the extent to which phototherapy might also be used in the selected population. An indirect comparison with ciclosporin, as a representative of immunosuppressant therapies, was also presented in a scenario analysis to assess cost-effectiveness in the broader licensed population. This was informed by evidence from a mixed adjusted indirect comparison (MAIC).
Patient group	Adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy	Partly. The base case analysis in the company submission focuses on adults with moderate-to-severe AD

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		for whom topical therapies have failed and have had either an unsuccessful treatment with immunosupressants (contraindication, intolerance, etc.) or they are medically inadvisable. However, the company submission does consider the full license population in a scenario analysis.
Perspective costs	Costs from an NHS and Personal Social Services (PSS) perspective	Partly, the submission has adopted the NHS England perspective only. The company claims that the PSS costs "are not expected to be a significant cost element in this disease area" (CS section B 3.2)
Perspective benefits	All direct health effects, whether for patients or, where relevant, carers	Yes. All health effects for patients, measured directly using EQ-5D and converted into QALYs, are presented in the company submission. Health effects for carers are not considered.
Form of economic evaluation	Cost-effectiveness analysis expressed in terms of incremental cost per quality-adjusted life year	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being assessed	Yes. A life-time horizon (up to 100 years of age) is modelled from a starting age of 38 in the base case analysis.
Synthesis of evidence on outcomes	Evidence synthesis should be based on a systematic review	Yes, systematic reviews were undertaken to inform clinical effectiveness, cost and utility parameters.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Outcome measure	Quality-adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, the health status of patients was directly measured using EQ-5D in the clinical trials used in the company submission.
Benefit valuation	Time-trade off or standard gamble	The UK time trade-off tariff was used to value health status.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes, representative sample of the UK population
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes, most relevant parameters were included in the PSA. The company did not initially assign a distribution to the baseline utility parameter in the model, but did so in an additional analysis at the clarification stage. The ERG not that no distributions were assigned to resource use parameters in the model, which result in some underestimation of the decision uncertainty.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Sensitivity analysis		Yes, the company presented results of one way sensitivity analysis and further deterministic analyses where assumptions and data sources were varied.

5.2.1 Models structure

The company submission describes an economic model with two components: a decision tree for the first year (Figure 2) and a Markov model for extrapolation thereafter (Figure 3). Three strategies are included in the decision tree: dupilumab, Best Supportive Care (BSC) and ciclosporin. However, the CS considers only two-way comparisons (i.e., either dupilumab vs. BSC or dupilumab vs. ciclosporin depending on the population being considered [see 5.2.3 below]). All the strategies in the decision tree divide individuals between responders and non-responders at 16 weeks. Using clinical trial evidence, dupilumab responders are further divided between those who continue to respond to dupilumab at 52 weeks and those who lose their response at 52 weeks.

Three Markov states are defined in the long-term Markov model (Figure 3): "*Maintenance treatment"*, "*BSC treatment"* and "*Death"*. Those individuals who retain their response to dupilumab at 52 weeks enter the *Maintenance Treatment* state whilst those who never respond or lose their response enter the *BSC treatment* state. All individuals in the BSC and ciclosporin decision tree arms enter the *BSC treatment* Markov state at 52 weeks. Therefore, in scenarios that compare dupilumab to ciclosporin, it is assumed that ciclosporin treatment is discontinued at week 52 and patients are revert immediately to the BSC profile of costs and utility.

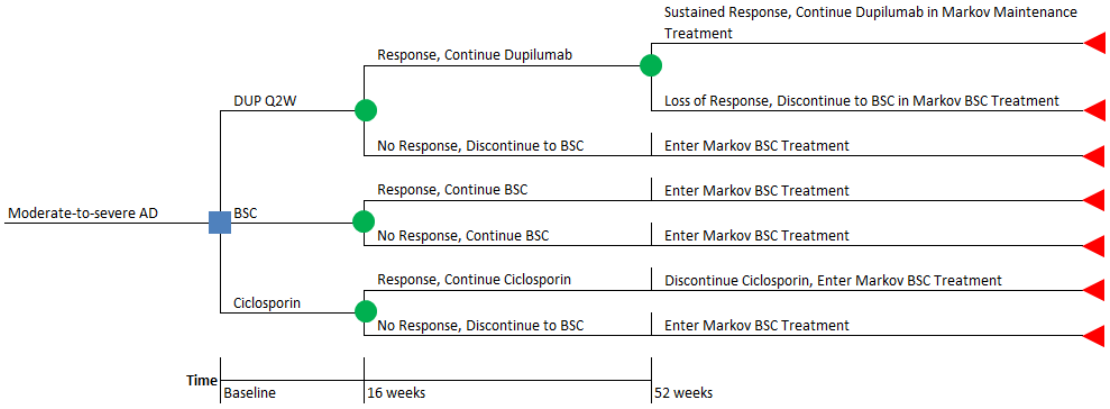


Figure 2 Short-term decision tree (Source: Company submission, Document B, Figure 3.3,)

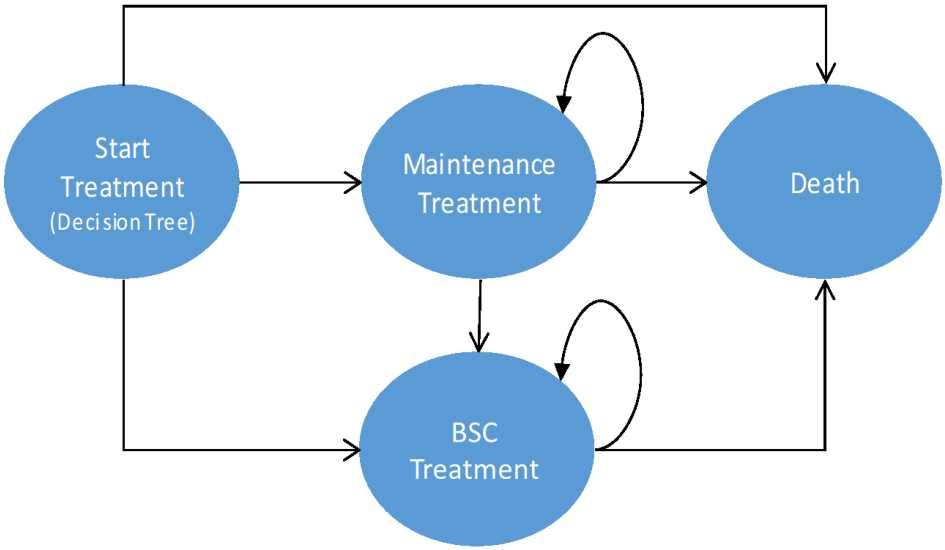


Figure 3 Long-term Markov model (Source: Company submission, Document B, Figure 3.4,)

Costs and health state utilities are applied in the decision tree and the Markov components of the model according to the assumptions of the different model branches or health states respectively. In the dipilumab arm of the decision tree, all patients incur the costs of treatment up to week 16. Thereafter, only responders remain on treatment for the rest of the year (to 52 weeks), with non-responders reverting to the BSC cost profile.

In terms of health state utility, all patients commence the decision tree at baseline utility, and transition to the estimated 16 week utility (for the specified arms of the model). The transition from baseline utility to week 16 utility is assumed to occur at 8 weeks for QALY calculations and the company model includes a switch that contains the option to incur week 16 utilities at week 4. Those who respond to dupilumab treatment at 16 weeks then attract the utility of dupilumab responders between 16 and 52 weeks, whilst those who don't respond receive the average utility observed for all BSC patients. All patients in the BSC branches of the decision tree attract the average utility of BSC patients. Dupilumab patients who retain their response to treatment between at 52 weeks then enter the dupilumab *Maintenance treatment* state of the Markov model, and retain the utility of dupilumab responders. Dupilumab responders who lose their response 1t 52 weeks enter the BSC treatment state of the Markov model, and attract BSC utility values. All patients in the BSC (or ciclosporin) arms of the model, enter the *BSC treatment* state for the Markov phase, and attract BSC utilities.

In the Markov component of the model, patients who continue to respond to dupilumab treatment remain in the "*maintenance treatment*" state and continue to attract the costs and health state utility of responders. A proportion of patients who lose their response over time in the Markov model, stop treatment and thereafter attract the costs and utility values assumed for BSC patients.

All the health state utility weights in the model are derived from EQ-5D data collected prospectively in the clinical trials underpinning the company's evidence for clinical effectiveness. No further utility decrements are applied for adverse events in the model, although these do attract further costs. The rationale for this is that quality of life data in the clinical trials were collected every two weeks (every 4 weeks in CHRONOS) and are assumed to capture any disutility arising due to adverse events. Costs incorporated in the model include the active treatment costs, administration costs, flare medication costs, adverse event costs, and other medical costs. An option also exists to incorporate indirect costs, but these are appropriately omitted from the base case.

A yearly cycle is used in the Markov component of the model, and costs and QALYs are discounted at 3.5% per year beyond the first year. The model is run over a lifetime horizon with the risk of death is based on that of the UK general population adjusted for age and sex. No increments for AD-related mortality have been incorporated. These assumptions are consistent with the NICE reference case.[41]

The ERG note that the Markov states in the company model are not defined by disease severity or staging, but are instead based on treatment received, with only responders assumed to remain on dupilumab treatment. Furthermore, the utility gain associated with dupilumab response is held stable over the time in the model, whilst observed short term gains in utility (from baseline) in the BSC patients are assumed to diminish rapidly over time – creating a greater gap in utility between dupilumab responders and BSC patients during the extrapolation phase than that observed during the clinical trials. The ERG have some concerns that the chosen model structure and assumptions lack the flexibility to capture the sometimes relapsing and remitting nature of AD described in the CS (section B 1.3.2 and B 1.3.3). Further, the observed intra-patient variability in response over time, illustrated in Figure 2.28 of the CS (Document B), would suggest that the response status of both BSC patients and dupilumab treated responders may be expected to fluctuate over time. This was queried by the ERG at the clarification stage. The company acknowledged that the model may lack the sensitivity afforded by a more complex structure but given the available data the company believe that the (decision) uncertainty is minimised and that their approach is robust. The ERG remain concerned that the company's modelling approach may underestimate the ICER and underestimate the decision uncertainty.

5.2.2 Population

The company base case analysis considers the population as "patients with moderate-to-severe AD who are contra-indicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant". Two main analyses are conducted for this base case population. The first assesses the cost-effectiveness of dupilumab used concomitantly with topical corticosteroids compared to BSC. The second considers dupilumab used as monotherapy versus BSC.

The first of these analyses is based on pooled data from all patients recruited to the CAFÉ trial[29] (all of whom met the definition of the base case population) and a subgroup of patients from CHRONOS[28] who also met the definition of the base case population (CHRONOS CAFÉ-like - CCL). Use of concomitant TCS was allowed in both studies. The second base case analysis relies on pooled data from subgroups of patients from SOLO1 and SOLO2 (SOLO CAFÉ-like) who met the base case population definition. Use of concomitant TCS was not permitted in the SOLO trials.[31, 33]

Table 12 illustrates the baseline characteristics of the two pooled populations (CAFÉ+CCL and SOLO+CAFÉ-like). For both the pooled populations, the mean EASI and pruritus scores are slightly higher than the respective values in the individual trials and the mean DLQI and EQ-5D scores are slightly lower. This appears consistent with the fact that these are patients with a prior history of contra-indication to, intolerance of, or inadequate response to systemic immunosuppressive therapies.

Table 12 Patient characteristics at baseline for the base case, CAFÉ+CHRONOS CAFÉ-like and SOLO CAFÉ-like populations (Source: Company submission, Document B, Table 3.3)

	CAFÉ + CHRONOS CAFÉ-like	SOLO CAFÉ- like
	N=462	N=288
Mean age – years (SD)	38.1 (12.9)	38.1 (13.0)
Gender (male) n (%)	277 (60.0%)	186 (64.6%)
Weight (kg), mean (SD)	74.8 (17.1)	75.0 (17.0)
EASI score, mean (SD)	34.2 (11.5)	36.1 (14.5)
Weekly average of peak daily Pruritus NRS, mean (SD)	6.8 (2.1)	7.6 (1.6)
EQ-5D utility, mean (SD)	0.663 (0.290)	0.547 (0.357)

As acknowledged in the CS, the base case population reflects a subgroup of the full license population and the population defined in the NICE final scope. However, the CS also includes two scenario analyses for the broader licensed population, defined in the summary of product characteristics (SmPC) as adults with moderate-to-severe

atopic dermatitis who are candidates for systemic therapy.[27] The first of these compares dupilumab to BSC and the second compares it to ciclosporin.

5.2.3 Interventions and comparators

Intervention

The company submission describes dupilumab as a "*fully human monoclonal antibody that specifically binds to the shared alpha chain subunit of the receptors for interleukin (IL)-4 and IL-13, inhibiting IL-4 and IL-13 signalling. IL-4 and IL-13 are key inflammatory cytokines thought to be important drivers of atopic diseases, such as atopic dermatitis (AD)"*(Company submission, Document B, Table 1.2). It is provided as 300mg solution in single use prefilled syringes for subcutaneous injection into the thigh or abdomen. As stated in the SmPC an initial dose of 600mg (two 300 mg injections) should be administered, followed by 300 mg (one injection) once every two weeks.[27] The SmPC state that "Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of atopic dermatitis". It also notes that a patient may self-administer (or have a caregiver administer) dupilumab if deemed appropriate by their health professional and proper training is provided. The company model assumes self-administration by all patients following once of training provided by a nurse.[27]

Comparators

Given the proposed positioning of dupilumab in the company base case analysis, the appropriate comparator is best supportive care (BSC), which includes emollients, low-to-mid potency topical corticosteroids, and rescue therapy which may include higher potency topical corticosteroids, oral corticosteroids or topical calcineurin inhibitors. In a scenario analysis for the broader licensed population, the company also compare dupilumab with ciclosporin (the only licensed systemic immunosuppressant for AD). Whilst this may be the case, the company acknowledge, based on a survey of 61 consultant dermatologists (CS section B 3.7.3.2), that other immunosuppressive therapies are often used in clinical practice, including azathioprine, oral corticosteroids, and methotrexate.

The chosen comparators are only partly in line with the NICE final scope which also lists phototherapy (ultraviolet (UVB) and psoralen-ultraviolet (PUVA)), other

immunosuppressive therapies (azathioprine, methotrexate), oral steroids and alitretinoin (in people with AD affecting the hands) as relevant comparators. The company argue that phototherapy and oral steroids are not appropriate comparators as they are short term treatments that would not be used for the continuous chronic treatment of AD. They also note that phototherapy is typically recommended earlier in the treatment pathway, after the failure of topical treatments and prior to the use of immunosuppressants. The ERG would note that oral corticosteroids are already included as rescue therapies in both arms of the model (based on their observed use in the relevant trials), but phototherapy is not. The company justify the exclusion of alitretinoin as a relevant comparator on the basis that it is only licensed for the treatment of hand eczema, an umbrella term which is not synonymous with AD affecting the hands. They also reference studies that report low percentages of hand eczema cases being attributable to AD.[42, 43]

5.2.4 Perspective, time horizon and discounting

Direct health effects in the company model are assessed in terms of quality adjusted life years based on EQ-5D-3L data collected from patients enrolled in the LIBERTY AD clinical trial programme. The health state values were appropriately derived using the UK population time trade-off (TTO) tariff. The perspective on costs is that of the NHS in England, as the company consider personal social services costs not to be relevant to the decision problem. The ERG believe this to be appropriate.

According to NICE guidelines the time horizon of a model should be sufficiently long to adequately capture differences in costs and outcomes between the technologies being assessed. The company's model adopts a life-time horizon (up to a maximum age of 100 years), since AD is a chronic condition and treatment with dupilumab is assumed to continue indefinitely and continue delivering long-term benefits in those who remain in the *maintenance treatment* state of the model. However, it should be noted that the model relies on observed data collected out to a maximum of 52 weeks in the CHRONOS trial. The remainder of the modelled time horizon relies on extrapolation assumptions. Both costs and health effects are discounted at 3.5% per annum, in line with the NICE methods guide.[41]

5.2.5 Treatment effectiveness and ***extrapolation***

The decision tree component of company's model divides the cohort from week 16, by the proportion of patients in each arm who achieve the defined response and those who do not. In the economic model, response is defined in the base case as those patients achieving EASI-50 and a DLQI improvement of 4 points or more - to reflect significant improvement in quality of life as well as a reduction in extent and severity. The impact of adopting alternative response criteria was also assessed by the company in scenario analyses. The response rates in the base case are taken from the CAFÉ+CCL and the SOLO CAFÉ-like pooled populations at week 16; for analyses permitting the use of and not permitting the use of TCS respectively (Table 13). The company note that in each of the trials feeding into the pooled populations, the primary efficacy analysis excluded patients who had rescue treatment even if they had met the definition of response. As this is unlikely to reflect clinical practice, the company utilised parameter estimates from an 'All observed' data analysis which does not exclude patients who received rescue treatment. The ERG are satisfied with this approach to data analysis.

From week 16, patients who do not respond to dupilumab treatment are modelled to stop taking the drug and incur the costs and utilities of BSC for the remainder of the year. For responders at week 16, the proportion retaining their response at week 52 was estimated, by treatment arm, based on data from the CHRONOS trial (Table 14), and applied to the week 16 response rates in the pooled populations to estimate the percentages of the cohorts expected to remain on response at 52 weeks (Table 13). Dupilumab patients who lose their response at week 52 are modelled to stop taking the drug and enter the *BSC treatment* state of the Markov model. Only those dupilumab patients who are responders at week 16 and retain their response at week 52 enter the maintenance treatment state of the Markov model. It should be noted that whilst the BSC arm of the decision tree is dichotomised by responder status at 16 weeks, based on the data observed in the clinical trials, the average utility weight for BSC is applied to responders and non-responders. However, the response status is used to adjust health service costs in BSC patients, and the week 52 BSC response rate is also used to adjust health state utilities and certain costs in the Markov component on the model.

The decision tree model includes a half-period correction, based on the assumption that, on average, responders at 16 weeks will have responded by week 8. This seems reasonable. In addition, the company submission states that clinical trial data for dupilumab suggests that a significant response was achieved before week 8, and so a sensitivity analysis was conducted by the company to assess the impact of assuming the response occurs at week 4. A similar half period correction does not appear to have been implemented in the model for those who lose response between week 16 and week 52. However, this is unlikely to have significant impact on results, as only 6% of dupilumab week 16 responders are modelled to lose response by week 52.

Table 13 Response data used in the model to support UK base case (all observed) (Source: Company submission, Document B, Table 3.4)

			CAFÉ+CHRONOS-CAFÉ-LIKE		SOLO-CAFÉ LIKE	
Time point	**Criteria**	**Analysis method**	**DUP Q2W %**	**BSC %**	**DUP Q2W %**	**BSC %**
Base case						
Week 16	**EASI 50+DLQI≥4**	**All observed**	**73.1**	**27.8**	**58.7**	**23.9**
Week 52*	**EASI 50+ DLQI≥4**	**All observed**	**68.6**	**21.3**	**55.1**	**18.3**
Sensitivity analysis						
Week 16	EASI 50+ DLQI≥4	Primary	68.5	20.7	51.9	11.4
Week 52	EASI 50+ DLQI≥4	Primary	64.3	15.9	48.8	8.7
Week 16	EASI 50	All observed	88.5	48.5	67.3	34.1
Week 52	EASI 50	All observed	83.6	39.4	63.6	27.7
Week 16	EASI 50	Primary	83.1	37.9	60.6	19.3
Week 52	EASI 50	Primary	78.5	30.8	57.2	15.7
Week 16	EASI 75	All observed	66.9	30.2	45.2	17.0
Week 52	EASI 75	All observed	54.9	21.3	37.1	12.0
Week 16	EASI 75	Primary	63.8	25.4	40.4	11.4
Week 52	EASI 75	Primary	52.4	18.0	33.1	8.0

BSC, best supportive care; DLQI, Dermatology Quality of Life Index; DLQI>4, DLQI score at least 4 point change from baseline; DUP Q2W, dupilumab 300mg every 2 weeks; EASI, Eczema Area and Severity Index; EASI-50, EASI, ≥50% response; IGA , Investigator Global Assessment; N/A , not applicable; Source: Sanofi, 2017, unpublished data.
*The ERG note that the week 52 response proportions are not directly observed estimates, but are predicted based on probabilities of week 16 responses being retined to week 52. They represent pecentages of patients responding at 16 weeks and 52 weeks, not just total percentaees responding at 52 weeks.

Table 14 Conditional probability of response at 52 weeks on 16-week response in CHRONOS (all observed data). (Source: Company submission, Document B, Table. 3.5)

Efficacy Response	52-week Conditional Response Probability	SE
DUP Q2W		
EASI-50 AND DLQI ≥4	0.939	0.028
EASI-50	0.945	0.025
EASI-75	0.821	0.053
BSC		
EASI-50 AND DLQI ≥4	0.767	0.048
EASI-50	0.813	0.035
EASI-75	0.706	0.064

In the Markov component of the model, an annual probability of discontinuation is applied to the dupilumab *treatment maintenance* state. Reasons cited by the company for applying this include "lack of long-term efficacy, adverse events, patient preference, or physician preference". For the analysis based on the CAFÉ-CCL population (allowing concomitant TCS), the annual discontinuation probability (0.037 in the base case) was based on the observed probability of week 16 responders discontinuing treatment by week 52 in the CHRONOS study. For the analyses based on the SOLO trials (concomitant TCS not permitted), the discontinuation probability was based on the number of patients who discontinued from the SOLO CONTINUE study (Table 15). Patients that discontinue dupilumab from the *maintenance treatment* state transit to the *BSC treatment* state of the Markov model.

Table 15 Annual probability of discontinuation. (Source: Company submission, Document B, Table 3.6)

Trial response	Annual Probability of discontinuation	alpha	beta
SOLO (all levels of response)	0.063	24	357
CHRONOS			
EASI 50 AND DLQI ≥4	0.037	24	357
EASI 50	0.055	5	86
EASI 75	0.051	4	74

Extrapolation assumptions

It should be noted that whilst the model uses observed data to dichotomise the dupilumab and BSC cohorts by response status out to 52 weeks in the decision tree model, the remainder of modelled time horizon requires assumptions regarding maintenance of response in the *maintenance treatment* and *BSC treatment* states of the Markov model. It is important to note here that different assumptions are applied in the two states. First of all, the predicted week 52 response for BSC patients is assumed to be short lived and diminish rapidly over time, based on probabilities of quality of life maintenance elicited from five clinical experts who were PIs in the dupilumab studies (Table 16). These elicited probabilities of retained quality of life response are used to adjust down the week 52 response rate and health state utility gain in BSC patients over time in the Markov model, such that the assumed responder rate and utility gain from baseline is 0 by year 4. Thus for all living patients in the BSC arm, and all patients who discontinue to BSC in the dupilumab arm of the model, the responder proportion is assumed to be zero and utility is set to the baseline value from this point onwards in the model. The rationale provided for this assumption is outlined in B 3.3.6 of the CS, and is centred on the argument that quality of life benefits observed in the BSC (placebo) arms of the relevant trials, were likely protocol driven effects related to improved adherence to topical treatments, which would not be observed outside the trial setting.

For those patients responding at 52 weeks in the dupilmab arm of the model, who then enter the dupilumab *maintenance treatment* state of the Markov model, different assumptions are made about loss of response (Table 16). Here, based on the responses of the five clinical experts consulted, it is assumed that the response is more stable, diminishing to a minimum of 92% of the week 52 response rate by year 5. The percentage of patients who lose response in the *maintenance treatment* state of Markov model are assumed to stop treatment and revert to the BSC utility and cost assumptions. It is not entirely clear to the ERG why these further discontinuations are applied on top of the observed discontinuation rates reported in Table 15 above.

Those losing response in the *BSC treatment* state of the model revert to baseline utility and a non-responder cost profile. Thus, form cycle 4 onwards in the model, all patients in the BSC arm receive baseline utility and non-responder medical care costs.

Table 16 Probability of sustained response for years 2-5+ (Source: Company submission, Document B, Table 3.16)

	Probability of Sustained Quality of Life (%)	
Year	**Dupilumab Q2W**	**BSC**
Year 2	98.0	37.0
Year 3	95.0	9.0
Year 4	93.0	0.0
Years 5+	92.0	0.0

The ERG believe that stripping out the observed utility gain and responder proportion from the BSC arm, during the extrapolation phase, is a controversial assumption which cannot be validated by observed longitudinal data. It appears to be based on the assumption that all improvement (from baseline) observed in patients on BSC in the relevant trials was down to protocol driven improvements in adherence to topical treatment, which would not be obtained in the clinical practice. An alternative explanation for some of the observed benefit could be the waxing and waning clinical course of AD. The ERG acknowledge that the company have explored less extreme extrapolation assumptions in sensitivity analysis, but these all assume a total or substantial loss of quality of life gain in the BSC arm. Given a lack of observed longitudinal data to inform the extrapolation of the BSC data, the ERG believe it is also appropriate to explore the impact of maintaining the observed response and utility gains in both arms of the model over the entire time horizon.

Adverse events

Adverse events are also considered in the company model to allow for the costs associated with them to be incorporated. The adverse events included are injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes, based on the observed event rates per 100 person years' in the CHRONOS, CAFÉ and SOLO trials. The ERG understand that the reported rates are generally in keeping with the adverse event data reported elsewhere in the CS for the primary safety pool, and that the main adverse events of interest are incorporated in the economic model.

The event rates are reported for the CHRONOS and CAFÉ trials separately in the CS (see Table 3.7 of the CS), but appear to be estimated for the pooled CAFÉ+CCL

population for incorporation in the economic model. Conversely, adverse event rates for the SOLO CAFÉ-like population appear to follow the event rates for the SOLO population as whole, rather than the CAFÉ-like subgroups.

The adverse events are generally converted for application in the model to numbers of events per patient year, and applied cycle-on-cycle. However, the company note that injection site reaction is assumed to be one-time event, with costs occurring only in the first cycle for dupilumab. Little justification is offered for this assumption, and the ERG believe it may have been more appropriate to apply the rate for this adverse event on cycle-by-cycle basis in the dupilumab *maintenance treatment* state.

Utility decrements are not applied for adverse events in the model. The company claims that this is necessary to avoid double-counting their utility impact, since the EQ-5D was measured every 2 weeks in the CAFÉ, SOLO1 and SOLO2 trials and every 4 weeks in the CHRONOS trials up to week 16. Therefore, the company claims that the observed utility data will already incorporate the impact of adverse events. However, with its focus on the patient's health status on the day of completion, the two week schedule may have missed the full impact of short lived adverse events.

Mortality

Finally, general population mortality adjusted by age and gender is applied in the model with no adjustment for AD response. The ERG understands that there is very little evidence on the impact of moderate to severe AD on mortality and that any increase in the risk of death attributable to AD related complications is likely to be very small. This supports the omission of any mortality benefit from model.

5.2.6 Health related quality of life

Health state utility data applied in the model were based on EQ-5D data collected from participants enrolled in the relevant LIBERTY AD trials. The exact source of utility data varies by modelled population, with the CAFÉ data being the primary source for derivation of the utility weights for the CAFÉ + CCL population, and the overall SOLO population being the source for the SOLO CAFÉ-like population. The company describe a process whereby they: 1) fit mixed multiple regression models to the observed utility data in each trial separately; 2) use these regression models to

predict utility values for the pooled base case populations; and 3) dichotomise the fitted values by responder status (in the dupilumab arm). As an alternative approach, the company apply the observed rather than regression fitted values as a sensitivity analysis.

Sources of health-related quality of life data

Table 3.9 in Document B of the CS summarises and compares the results of a systematic literature review (SLR) to identify relevant HRQoL data. These include published dupilumab studies[31, 33] as well as previous technology appraisals which report utility data for adults with various severities of AD.

Simpson[33] *"reports findings from a Phase IIb trial for dupilumab across seven countries; 380 patients with moderate-to-severe AD provided EQ-5D-3L data. Baseline utilities ranged from 0.578 to 0.658 and mean utility increments at 16 weeks were reported for placebo (0.028) and for the intervention (range: 0.106 to 0.240)."*

Simpson[31] conducted a pooled analysis of EQ-5D response data from 1,379 patients enrolled in the SOLO 1 and SOLO 2 trials. Baseline utilities ranged from 0.607 to 0.629 and mean utility increments at 16 weeks were reported for placebo (0.031), dupilumab 300 mg once weekly (0.207) and dupilumab 300 mg every two weeks (0.210).

Whilst the company's systematic literature review did not identify any published studies focusing specifically on the analysis of EQ-5D data from the CAFÉ or CHRONOS trials, the company have presented further analyses of these data in their submission. The company note that the utility data in the LIBERTY AD trials were collected using the EQ-5D-3L instrument and valued using the UK general population tariff. Apart from the published dupilumab studies, few other studies identified in the company's literature review used the EQ-5D instrument directly to measure HRQoL in patients with moderate to severe AD. The ERG agree that the LIVERTY AD trial data represents the best available source of utility data for the current appraisal.

Derivation of Health-related quality of life data for use in the modelling

Utility weights used in the model were derived directly from the four clinical trials (CAFÉ, CHRONOS, and pooled SOLO1 and SOLO2)[28-31, 33] underpinning in the clinical effectiveness evidence for dupilumab. Utilities were analysed using mixed (repeated measures) regression models controlling for baseline age, gender, and EQ-5D, and included the following predictors: total EASI score, total weekly average of peak daily pruritus, the interaction between total EASI and pruritus scores, and an indicator variable for treatment allocation. Goodness-of-fit was assessed using the two diagnostic plots, the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) statistics. The ERG note that in section B3.3.3 of the CS, it states that it was the mean changes in the EASI and pruritus scores from baseline that were included in the mixed regression models, but this is not the ERGs understanding from the way the estimated coefficients are presented and applied in the model.

The ERG note that both the total EASI score and pruritus NRS (numerical rating scale) increase with increasing severity of symptoms. However, in all three regressions the main effect for the EASI score has a positive coefficient (significant in CAFÉ and SOLO1/2, but insignificant in CHRONOS) and the coefficient for the main effect for pruritus NRS has a negative sign. In all three regressions, the EASI-Pruritus interaction is also significant and negative. The positive sign for the main effect of the EASI score may raise some concerns about its relative importance as a driver of quality of life when compared with pruritus. For example, it may prove difficult implementing the proposed stopping rule if patients who do not achieve EASI50 + DLQI>4 were to experience a significant quality of life improvement mediated through a reduction in daily pruritus.

The company go on to generate utility weights for application in the model by multiplying the coefficients from the mixed regression models by the mean baseline characteristics and mean EASI and pruritus NRS scores (estimated by adding mean changes from baseline scores) of the base case populations. The treatment indicator is also applied, generating treatment arm specific utility weights. For the base case analysis in the CAFÉ+CCL population, the company use the regression coefficients from the CAFÉ trial to estimate utility weights based on the characteristics and

changes in EASI and pruritus scores of the CAFÉ+CCL pooled population. For the pooled SOLO CAFÉ-like population, the company use the coefficients from the regression analysis of all SOLO patients to generate the utility weights.

In the dupilumab, ciclosporin and BSC arms of the model, mean estimated changes (from baseline) in EASI and pruritus scores at week 16 are used to estimate the average utility weight for each treatment arm at week 16. As indicated earlier, a mid-point correction is applied in the decision tree component of the model, so that the estimated week 16 values are applied from week 8. Beyond week 16 in the dupilumab and ciclosporin arms of the model, the estimated utility of dupilumab responders is applied to the fraction of the cohorts that achieve the modelled response.

This utility value is estimated based on the dupilumab responder specific reductions in EASI and pruritus scores at 16 weeks. The same responder utility value is carried through to the utility calculations in the *Maintenance Treatment* state of the Markov model. The dupilumab/ciclosporin responder utility value changes based on the response definition selected in the model.

Beyond week 16 in the BSC arm of the model, and beyond week 16 for non-responders to dipulimab, all patients share the same overall utility value; i.e. that estimated for all patients in the BSC arm at week 16.

Table 17 (columns 3 and 5) below summarises the base case utility values for application in the model, as presented in the Document B of the company submission. The ERG has noticed a slight discrepancy between the values reported in the submission and the values actually used in the model (Table 17, columns 4 and 6). Although the absolute values are slightly lower in the model, the incremental differences between dupilumab and BSC are very similar subject to rounding.

Table 17 Base case utility weights reported in the CS and applied in the model (all observed) – (Source: Adapted from Company submission Document B, Table 3.14)

Patient population (baseline utility)	Parameter	DUP Q2W (company submission)	DUP Q2W (model)	BSC (company submission)	BSC (model)
CAFÉ + CCL	All patients week 16	0.898	0.891	0.811	0.797
(0.66)	Week 16 responder	0.904	0.898	*	*
SOLO – CL	All patients week 16	0.830	0.817	0.718	0.6986
(0.55)	Week 16 responder	0.855	0.845	*	*

Utility adjustment for age

In the initial model submitted by the company, age-adjusted utility decrements were derived using general population UK data from Ara et.al.,[44] and applied additively per cycle. However, since a constant decrement (-0.004) has been simultaneously applied to both arms of the study, the QALY increment remains unchanged and the age-adjustment has no impact on the ICER. At the clarification stage, the ERG requested that the company explore the impact of applying the multiplicative method for age adjustment as per NICE DSU guideance.[45]

In their response, the company provided an updated Markov model with an option to use the multiplicative approach as requested. This further sensitivity analysis is reproduced in the results section below.

Extrapolation of HRQoL over time

The temporal extrapolation of health state utilities in the model required a number of assumptions. Data are not available from the LIBERTY AD clinical trial programme to illustrate how utility values change beyond the follow-up period of the available trials. However, the company argue that it is improbable that the response observed in

a significant proportion of patients receiving BSC would be maintained outside the trial setting, where behaviours around adherence to topical treatments are no longer mandated. To support this claim, the company highlight the results from a time trade-off study which they conducted to assess the impact of topical treatment on patients' quality of life. The survey was conducted on a UK representative sample of 484 individuals over the age of 18 years. The task involved trading-off time in life years on one of seven skincare regimens to live life in full health. The results illustrate the increasing disutility associated with increasingly burdensome regimens (Table 18). The company claim that the burden associated with some regimens may be one factor that will prevent a sustained quality of life benefit with BSC. They also note that adherence to burdensome skin care regimens may not affect maintenance of response with dupilumab, since clinical experts in an advisory board suggested that patients with a good response are likely to reduce their use of steroids to a minimum and use 50% to 80% less emollient as required.

Table 18 Average utility values for each skincare regimen (Source: Company submission, Appendix Document, Table R-4)

No.	Skincare regimen	N	Mean (SD)
1	Steroid twice daily and emollient four times daily	473	0.7968 (0.2159)
2	Steroid twice daily and emollient twice daily	466	0.8471 (0.1744)
3	Steroid once daily and emollient twice daily	446	0.8835 (0.1469)
4	Light emollient twice daily	404	0.9862 (0.0340)
5	Light emollient once daily	396	0.9906 (0.0267)
6	Light emollient once every other day	370	0.9997 (0.0021)
7	Light emollient on occasion, as needed	371	0.9999 (0.0012)

Based on the above rational, the company apply a "Profiles" approach to utility extrapolation. This method utilises expert elicited probabilities of maintaining a quality of life response in each arm beyond the trial period (see Table 16 above). The

questionnaire on which the maintenance of quality of life percentages was based, was reproduced in Appendix T.5 of the CS. In the introduction the authors explain that the aim of the questionnaire was to elicit clinical judgement about how the quality of life for patients from the trial might evolve if they continued their allocated treatment in usual clinical practice. The questionnaire has two parts, one for each arm of the study (dupilumab and BSC), and each consisting of two questions. The first question asks whether the patient will sustain the quality of life gained by the end of the study indefinitely if they continue their treatment. Depending on their answer, the expert is prompted to either end the questionnaire (if "Yes") or proceed to the second question (if "No").

The second question requires experts to state "what percentage of the quality of life gained by the end of the trial would be lost" by the end of one, two, three and four years if patients continued their treatment in usual clinical practice. An assumption is made that the probability of sustained response is constant beyond the end of year four in usual clinical practice.

The elicited quality of life maintenance percentages for BSC are used to adjust down the utility weight applied over time in the *BSC treatment* state of the Markov model - calculated as a weighted average of the utility value for all BSC patients during the trial period, and the baseline utility. Therefore, by the end of year four in the model, all patients in the *BSC treatment* state receive baseline utility.

In the duplimab arm of the model, the quality of life maintenance percentages are used to adjust down the percentage of patients in the duplimab *maintenance treatment* state. The patients losing their respose are assumed to stop treatment and transit to the *BSC treatment* state where they receive the BSC utility (and cost) profile thereafter. As noted above, the ERG assess the impact of switching off the quality of life waning assumptions so that the unadjusted week 16 utility values for BSC patients and dupilumab responders are held constant over the duration of the model.

Deterministic sensitivity analysis of utility data

As a result of the health state utility extrapolation assumptions in the BSC arm of the model, the baseline utility value is the one of the parameters to which the company

ICER is most sensitive. However, the company varied this parameter through +- 10% in deterministic sensitivity analysis without providing justification for the chosen range, and no distribution was attached to it in the PSA. Therefore, the ERG requested further deterministic and probabilistic sensitivity analyses, with this parameter varied according to its 95% confidence limits.

5.2.7 Resources and costs

The CS reports four main activities to identify resource use and costs for the economic model; 1) a systematic literature review of published and unpublished cost and resource use studies in adults with AD; 2) a secondary care case note review exercise; 3) an integrated records review using the Salford Integrated Record (SIR); and 4) Market research to evaluate UK clinicians perceptions of health care resource use.

Firstly, the systematic literature review identified twelve studies that met the inclusion criteria, seven of these were economic evaluations. No relevant UK data were identified for use in the economic model.

The review of secondary care case notes was reported as ongoing with a target sample size of 50 to 80 adults with uncontrolled moderate-to-severe AD and history of immunosuppressant use or immunosuppressant contraindication. The aim of the study is to assess the current treatment pathways and associated NHS resource use for this group of patients. The review is described as an "observational, multicentre retrospective descriptive research study conducted in five secondary/tertiary NHS Hospital Trusts selected to provide an even geographical spread across the UK". The CS presents data form an interim analysis, based on 30 patients, on the number of clinician visits, number of nurse visits, number of day case admissions, and number of admissions to A&E and hospital (see Tables 3.18 and 3.19 of the CS, document B).

The CS notes that this data is tabulated for year 3 of the study, which provides the most complete and up to date estimates. The ERG are uncertain about how representative of wider target population this sample of 30 patients is. Further, the ERG are unsure why the reported events per patient year were based only on data from year three of the study, rather than all the data observed over the three years. It is

also worth noting that the seven reported hospital admissions used to calculate the rate of admission applied in the model (i.e. 7/30 = 0.23), appear to correspond to a single patient who was admitted seven times. Given a the limited justification for the approach, the ERG also explore the impact of re-estimating the relevant event rates applied in the model using all the data reported from the case notes review.

To complement the data obtained from the case notes review, the company undertook and an evaluation of the current treatment pathways and associated NHS resources use using the Salford Integrated Record (SIR). Salford is a metropolitan borough of Greater Manchester with a relatively static population and served by a single hospital (Salford Royal Foundation Hospital (SRFH)). The SIR is an electronic patient health record that combines primary care records from all GP practices in Salford into a single database that can be linked to secondary care data from SRFT stored electronically in the hospital's own database. A search was conducted for individuals with moderate to severe AD and a history of immunosuppressant use. From 27,026 records, data for 37 individuals were finally included for the analysis. The mean number of primary care encounters, dermatology clinic outpatient visits, dermatology related hospital admissions, and A&E dermatology related visits are reported in Table 3.20 of the CS (document B).

The fourth source of resource use data the company refer to comes from a series of interviews with clinical dermatologists (and dermatology nurses). A total of 51 dermatologists (48 consultants, three SpR 4+) and 19 dermatology specialist nurses were interviewed in February and March 2017. The respondents were asked to give their opinions on resource use for candidates responding to systemic immunosuppressant therapy (assumed to represent 'responders' in the modelling for dupilumab) and candidates not responding to systemic immunosuppressant therapy or who are intolerant of or contraindicated to them (representing 'non-responders' in the modelling for dupilumab). Whilst these elicited resource use estimates are not applied directly in the model base case, they were used to derive multiplying factors for responders versus non-responders. Where necessary these are then applied to the directly collected data for uncontrolled patients that are included in the model, to the generate resource use estimates for patients who are responding to treatment.

Table 19 Mean number of visits per patient per year (Dermatologist responses) (Source: Company submission, Document B, Table 3.21, page 192)

	Responding to SI	Not responding to SI/ intolerant/ contraindicated	Multiplier
Total number of patients	**560**	**290**	
OP visits to dermatologist (total pt visits/yr)	3.53	4.92	0.72
OP visits to dermatology nurse (total pt visits/yr)	1.84	2.39	0.77
Visits to the GP (total pt visits/year)	2.30	4.78	0.48
A&E attendance (total pt visits/ year)	0.43	1.74	0.25
Hospital admissions (total pt admissions/year)	0.15	1.16	0.13

The company note that the secondary care case not review is their preferred source of resource use data for the base case analysis, as these data come from patients who were selected by their clinicians because they were uncontrolled on current systemic therapies and so would be candidates for dupilumab treatment. The company supplement this secondary care resource use data with the primary care data derived from the SIR analysis. Each resource use variable is entered in the model as the number of events per patient year, and multiplied by the relevant unit cost (per event) to generate annual costs for responders and non-responders.

The final resource use data incorporated in the company base case analyses are reported in Table 20 below. The company states that the number of dermatology and specialist nurse visits were discussed in an advisory board, and further validated with two UK specialists with experience of dupilumab. With the exception of the average number of primary care visits per year, all resource used data were considered to be conservative by the advisory panel.

The ERG note that there appears to be a discrepancy between the 0.25 A&E visits per year reported for non-responders in Table 20 (and applied in the model), and the

average number of 0.1 reported for patients in the case note review (the stated source). The ERG are unsure which of the values are correct but note that switching the values has a very small impact on the results.

Finally, the ERG note that no probability distributions are attached to any of the resource use estimates applied in the model (mean values or multipliers). This may lead to underestimation of the decision uncertainty. Therefore, the ERG explore the impact on the PSA results of applying distributions to these parameters in the model.

Table 20 Resource use data used in the economic model (Source: Company submission, Document B, Table 3.22)

Resource	Dupilumab		BSC		Source and justification as reported in the Company Submission
	Year 1	Years 2+	Year 1	Years 2+	
Dermatologist outpatient consultation (per patient per year)					
Responder	4	2	2	2	Advisory board. Expert opinion stated that dupilumab patients would be seen every three months for the first year and if well controlled every 6 months thereafter. For patients responding well on BSC a conservative assumption of 2 visits per year is implemented in line with the dupilumab estimate. This is in line with the value implemented in TA82 of 2.7[46]
Non-responder	7.03	7.03	7.03	7.03	B 3.4.2 The number of dermatologist visits is similar between B 3.4.2 and the retrospective database review described in B 3.4.3 (7.53) respectively. This is also consistent with the value implemented in TA82 of 6.5 although the latter was in a moderate population.
Dermatology related GP consultation (per patient per year)					
Responder	2	2	2	2	Assumption. During validation it was suggested that no attendances to the GP were made by patients responding to dupilumab. In the absence of any other data a figure of 2 attendances per year over and above attendance for other reasons (See below) was suggested by the expert. This is in line with the estimate provided by the clinicians collected during the market research. B 3.4.4
Non-responder	12.81	12.81	12.81	12.81	GP visits are not in the secondary care record (B 3.4.2) and so they are taken from the next most robust source, the retrospective database review. B 3.4.3 The number of visits recorded was 17.72. The reason for consultations is not given and so this number represents all visits. The average number of contacts per registered patient per year has been estimated recently to range from 3.64 to 9.88 with a mean of 4.91. In the absence of other data, we have reduced the number of GP consultations observed in the database review by 4.91 to 12.81 in order to avoid over counting. The number of visits accepted in TA82 was 11.7, which is slightly lower but TA82 examined a less severe population

Dermatology Nurse visit (per patient per year)					
Responder	1	0.44	0.44	0.44	Advisory board. A nurse visit at 4 weeks after initiation would be expected for dupilumab. Thereafter the number of visits observed in B 3.4.2. is reduced by the multiplier (0.77) derived from the market research. B 3.4.4 Likely to be underestimated.
Non-responder	1	0.57	0.57	0.57	Number of visits per person observed in the case notes review. B 3.4.2 . Likely to be underestimated.
Accident and emergency visit (per patient per year)					
Responder	0.06	0.06	0.06	0.06	The number of visits observed in B 3.4.2 is reduced by the multiplier (0.25) derived from the market research B 3.4.4. Likely to be overestimated.
Non-responder	0.25	0.25	0.25	0.25	Number of visits per person observed in the care notes review B 3.4.2.
Hospitalisation					
Responder	0.03	0.03	0.03	0.03	The number of hospitalisations observed in B 3.4.2 is reduced by the multiplier (0.13) derived from the market research B 3.4.4. Likely to be overestimated.
Non-responder	0.23	0.23	0.23	0.23	Number of hospitalisations per person observed in the care notes review B 3.4.2.
Tests and investigations (per patient per year)					
Responder	0	0	4	4	The SmPC for dupilumab states that no tests are required (see Appendix C). During validation expert opinion stated that testing for patients on current therapies would be carried out on a quarterly basis. Conservative estimate (See Table 3.21).
Non-responder	4	4	4	4	During validation expert opinion stated that testing for patients on current therapies would be carried out on a quarterly basis. Conservative estimate (See Table 3.21).
Day case					
Responder	0.00	0.00	0.00	0.00	Assumption based on feedback obtained from UK clinicians at an advisory board
Non-responder	0.17	0.17	0.17	0.17	The number of day-cases observed in B 3.4.2

Dupilumab acquisition and administration costs

The recommended dose for adult patients, as stated in the SmPC,[27] is reflected in the model. This includes an initial dose of 600 mg (two 300 mg injections), followed by 300 mg once every 2 weeks (Q2W). This equates to 26 doses per year during the maintenance phase with an additional loading dose at start of treatment (year 1).

The annual cost for dupilumab is £16,500. [redacted] The annual PAS adjusted cost and cost per dose are reproduced in Table 21 below.

Table 21 Cost per dupilumab dose (Source: Company submission, Document B, Table 3.23)

Treatment	Annual PAS adjusted cost	PAS adjusted cost per dose	Source
[redacted]	[redacted]	[redacted]	Sanofi Genzyme
[redacted]	[redacted]	[redacted]	

PAS, patient access scheme

The company assume that all patients will self-administer dupilumab, once they have received a half-hour training session delivered by a band 6 nurse (£54).[47] Patients are assumed to be 100% compliant with treatment and costs for all scheduled doses are incurred in the model.

Background treatment costs (concomitant medications)

The model incorporates the costs of moisturisers, emollients and background medications taken by patients with AD. These are applied under the following sub-categories: Bathing products; Emollients; background TCS; and background TCIs.

The average weekly cost of bathing products was calculated as the weighted average cost of the five most commonly prescribed preparations, based on an analysis of 2016 prescribing data.[48] Treatment was implemented according to package labelling and assumed one application per day. Expert opinion was used to support the assumption of a 50% reduction in use for responders (Table 3.24 of the company submission). A similar approach was taken to costing emollients (Table 3.25 of the company

submission). Published guidelines for emollient dosage[5] were discussed with experts who supported a dose of 500g per week for patients unresponsive to treatment, and also supported a 50% to 80% reduction for responders to dupilumab. The company apply a 50% reduction in their base case.

For TCS the company apply costs based on the most usually prescribed mid-potency preparation in the UK; mometasone 0.1%. Costs are estimated based on the body surface area involvement (BSA) recorded at baseline for patients enrolled in the CAFÉ trial (55.7%) and the BNF dose recommendations for mometasone 0.1%. The calculations generate an estimated use of 32g per day, assuming twice daily application. The company also highlight a 49% reduction in the use of TCS observed in the dupilumab Q2W arm of the CAFÉ trial; from a weekly dose of TCS active ingredient of 34.18mg to 17.3mg at study end. This percentage reduction is used to estimate the weekly cost of mometasone 0.1% ointment for treatment responders in the company model.

A similar approach has been taken to cost background topical calcineurin inhibitors (TCIs). The clinical experts directed that for facial involvement TCIs are more appropriate than steroid treatments and that protopic 0.1% ointment (Tacrolimus) is preferred. They also noted that the use of TCIs would stop for responders to treatment. Based on the product label advice and methodology applied for TCS, the company estimate that 1.75g per week are sufficient for maintenance treatment.

Treatment of flares

The cost of treating flares is based on data from the CHRONOS study to 52 weeks. Flare was not a study end point and therefore the company used a proxy as suggested in the literature: ‘escalation of treatment’ or ‘use of topical anti-inflammatory medications’.[49] The proportions of participants requiring potent or very potent topical corticosteroids, systemic steroids and topical calcineurin inhibitors in the placebo and dupilumab Q2W arms of CHRONOS, were used to calculate the cost of treating a flare in the respective arms of the model. Based on data from the CHRONOS study at 52 weeks, the annualised rate of flares was estimated for BSC (0.78 per patient year) and dupilumab Q2W (0.18 per patient year). The cost of flares per year is therefore

calculated as the product of the treatment arm specific cost per flare and the treatment arm specific rate of flare.

The company assert that it is very likely that these calculations underestimate the cost of flares in the real world. The company sites data reported by Simpson [33] supporting exacerbation rates of 15.5 and 2.8 per patient year for patients treated with placebo and dupilumab respectively. The company apply these higher rates in sensitivity analysis.

Test and investigations

The company maintain that full blood counts (FBC) are routinely ordered for patients with AD under currently available treatment regimens. The cost for a FBC is estimated at £3.10.[50] At the clarification stage, the ERG queried the company assumption that no monitoring tests would be required for dupilumab responders. The company responded that no monitoring of hepatic or renal function, drug levels or blood testing is recommended in the SmPC during treatment with dupilumab. They further noted that "as a therapeutic protein, dupilumab is not expected to undergo significant hepatic or renal elimination (or to interact directly with cytochrome P450)" (company response to clarification, Jan 11, 2018). However, the ERG remain uncertain about the company assumption that patients responding in BSC would require four FBC tests per year, whist responders to dupilumab would require none.

Unit cost of physician appointments

The unit costs for a consultant appointment is derived from the National Schedule of Reference Costs (Year 2015-16) for consultant led appointments (i.e. weighted average for currency codes WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C).[50] The CS remarks that 12% of respondents in the dermatologist market research interviews stated that their centre had a multi-disciplinary team (MDT). The CS also references an example of a locally negotiated tariff for an eczema MDT first and follow-up visit, which is fixed at [redacted]. The unit cost for a clinical appointment in the model is therefore calculated as a weighted average at [redacted]. The ERG are unable to comment on the suitability of the weighted estimate since no details were provided to explain why the locally negotiated MDT visit cost is [redacted] the NHS

reference costs for the WF02 currency codes which relate to multiprofessional first and follow-up (face-to-face) dermatology visits (£157 and £147 respectively). However, the company also assess the impact of omitting the higher locally negotiated tariff from the weighted cost in sensitivity analysis.

Unit costs for a GP consultation (9.22 minutes) and a GP practice nurse visit (15 minutes) are taken from the Unit Costs of Health and Social Care 2016:[47] £36 and £10.75, respectively. The cost of a day case admission (£492.19) is obtained from the National Schedule of Reference Costs (2015-16) based on the weighted average of the currency codes related to skin disorders: JD07A, JD07B, JD07C, JD07D, JD07F, JD07G, JD07H, JD07J and JD07K.[50] The unit cost for a visit to A&E is calculated at £137.82 based on the weighted average of currency codes VB01Z-VB09Z - National Schedule of Reference Costs (2015 to 2016).[50] The ERG are satisfied that the unit costs applied for these services are appropriate.

Hospital unit costs

The company describe a search of Hospital Episode Statistics (HES)[7] data to identify non-elective admissions between 01/4/2016 and 31/3/2017 in England with a primary or secondary diagnosis of atopic dermatitis (ICD L20). Using data on 265 admissions, a weighted average unit cost of £1,795 is computed. The ERG do not have access to the data and therefore are not in the position to verify the estimate. However, as a cross check, the ERG calculated the weighted average NHS reference cost for non-elective in-patient admissions for skin disorders (JD07A to JD07K), and note that the resulting cost is similar (£1,569) to the company estimate based on HES data.

Adverse events

The model assumes the unit cost for injection site reaction to be equal to the unit cost of a dermatologist visit (£104). The cost for allergic conjunctivitis or oral herpes is equated with the unit costs of a GP visit (£36). The unit cost for infectious conjunctivitis is computed as the weighted average between the cost of a GP visit (90%) and a visit to an ophthalmologist (10%). In addition, the cost of prednisolone (£3.66) is added. It should be noted that the visit to the ophthalmologist in this calculation is incorporated as a substitute for visiting the GP, and not in addition to a

GP or optometrist visit prior to referral. However, the small additional cost of a pre-referral visit to a GP would unlikely have a significant impact on results.

Indirect costs

The model includes an option to consider indirect costs as a sensitivity analysis. The company submission indicates that indirect costs are based on estimates of absenteeism for the UK, and a reported three-fold increase in the rate of absenteeism for people with moderate-to-severe AD in the 2013 National Health and Wellness survey. The average number of days lost to work in the UK for 2016 was 4.3.[51] Therefore, the company submission states that 4.3 and 12.9 days of lost productivity per year have been implemented in the model for responders and non-responders, respectively. The ERG identified a mismatch between these reported days of lost productivity and those implemented in the model. The number of days lost to work in the Excel model correspond to estimates from the AWARE study (Sanofi Genzyme, unpublished data, 2017) and are higher than those referred to in the company submission (i.e., 11.7 and 53.7 for responders and non-responders, respectively).

The weighted average of full and part-time employment wages (per hour) from the ONS,[52] were used in conjunction with the percentage of individuals employed in the AWARE study, and the weighted average of full and part-time employment hours per work day [52], to obtain a unit cost per day of work lost in the model.

5.2.8 Cost effectiveness results

All the final data inputs and assumptions applied in company base case analyses are summarised in Table 3.38 and Table 3.39 of the company submission (Document B, pages 206-212).

Company base case results

The company base case results are reproduced below for the CAFÉ + CHRONOS CAFÉ-like population and the SOLO CAFÉ-like populations. These results relate to the base case population of "*patients who have been optimised on topical therapies and an immunosuppressant but for whom these therapies have failed, are contraindicated or are not tolerated*" (company submission, section B 3.6.1). The presented results include the confidential patient access scheme.

CAFÉ+CHRONOS CAFÉ-like pool analysis

Dupilumab and BSC produced the same number of life-years gained ([redacted]) as it was assumed that dumilumab infers no mortality benefit over BSC. Dupilumab generated [redacted] additional QALYs at an additional cost of [redacted], resulting in an incremental cost per QALY of £28,874 (Table 22).

Table 22 Base case results for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients (Source: Company submission, Document B, Table 3.41)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,874

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The company submission provide further disaggregation of the base case analysis results within the appendices. Tables 23 and 24 below reproduce details of these. This information was complemented by a response to an ERG clarification question asking for further disaggregation of costs under the 'Other Medical Cost' category. The incremental QALY gain associated with dupilumab is [redacted] (Table 23). Table 24 indicates [redacted] The greatest saving for dupilumab arises [redacted].

Table 23 Summary of QALY gain by health state for the comparison of CAFE FAS + CHRONOS CAFE-like pool including dupilumab Q2W patients with BSC (Source: Company submission, Appendix J, Table J-4,)

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Decision Tree Health State	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Treatment Health State	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC Treatment Health State	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutilities					
Decision Tree Health State	0.00	0.00	0.00	0.00	0%
Maintenance Treatment Health State	0.00	0.00	0.00	0.00	0%
BSC Treatment Health State	0.00	0.00	0.00	0.00	0%
Total	[redacted]	[redacted]	[redacted]	[redacted]	**100%**

BSC=Best Supportive Care; FAS= full set analysis; QALY= Quality Adjusted Life Year; Q2W = once every two weeks

Table 24 Disaggregated costs by health state for the comparison of CAFE FAS + CHRONOS CAFE-like pool including dupilumab Q2W patients with BSC (Source: Company submission, Appendix J, Table J-5,)

	Dupilumab	BSC	Increment	Absolute increment	% absolute increment
Decision Tree					
Active Treatment Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Medication Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indirect Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance Treatment Health State					
Active Treatment Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Medication Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indirect Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SC Health State					
Active Treatment Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant Medication Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Medical Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indirect Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	**100%**

BSC=Best Supportive Care; FAS= full set analysis; QALY= Quality Adjusted Life Year; Q2W = once every two weeks

SOLO CAFÉ-like pool analysis

Similarly for the SOLO CAFÉ-like analysis, the number of life years gained for dupilumab and BSC are the same at [redacted] (Table 25). Dupilumab produces [redacted] extra QALYs compared with BSC for an additional cost of [redacted]. The incremental cost per additional QALY is £24,703 (about £4,000 lower than the ICER for the CAFÉ CHRONOS CAFÉ-like analysis).

Table 25 Base case results for the SOLO CAFÉ-like pool including dupilumab Q2W patients (Source: Company submission, Document B, Table 3.42)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]				
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,703

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The company reported disaggregated results for the SOLO CAFÉ-like pooled population and provided further details as a response to the ERG clarification questions. This identified the same drivers of the incremental cost and QALY as indicated for the CAFÉ + CCL population.

5.2.9 Sensitivity analyses

The company submission reports the results for probabilistic sensitivity analyses, one-way sensitivity analyses and two further scenario analyses considering the full license population; one comparing dupilumab to BSC and the other comparing it to ciclosporin.

Probabilistic SA analyses

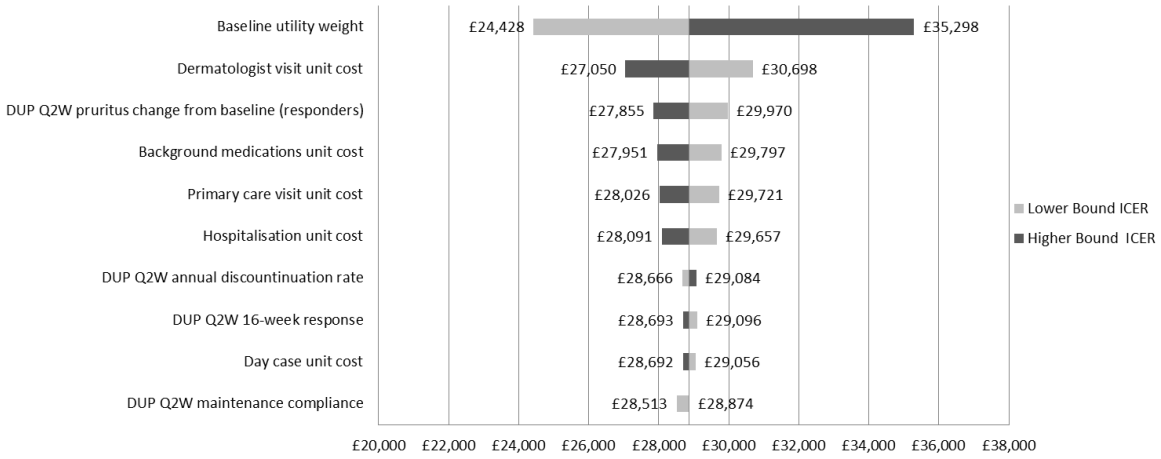
The probabilistic sensitivity analysis for the base case populations were based on 10,000 probabilistic iterations of the model. For the base case CAFÉ +CCL cohort, dupilumab was associated with an expected incremental cost of [redacted] for a mean incremental QALY gain was [redacted]. The corresponding ICER (£28,686) is similar to the equivalent deterministic ICER (£28,874). Similarly in the SOLO-CAFÉ like cohort, the reported probabilistic ICER was similar to the deterministic ICER; £24,640 per QALY gained versus £24,703 per QALY gained. The ERG note that the model structure and assumptions generate a high degree of positive correlation between expected incremental costs and expected incremental QALY gains (see Figures 3.10 and 3.12 of the company submission, Document B). This results in a steep cost-effectiveness acceptability curve (CEACs) for dupilumab in both of the

base case populations (see Figures 3.9 and 3.11 of the company submission, Document B). In the CAFÉ + CCL analysis, the probability of cost-effectiveness increases from zero at a willingness-to-pay (WTP) threshold of £20,000 per QALY to approximately 70% at a WTP threshold of £30,000 per QALY. In the SOLO CAFÉ-like pool, the curve is even steeper, increasing from zero at the threshold of £20,000 to 100% at the threshold of £30,000.

Deterministic SA analyses

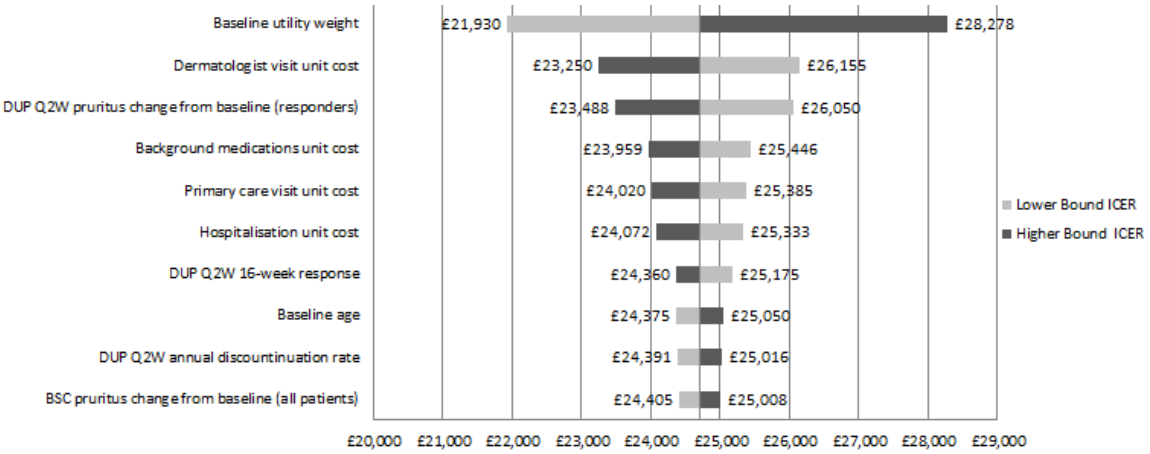
The company present also deterministic one-way sensitivity analyses on the 10 parameters to which the model results were found to be most sensitive. The results are reproduced in the form of tornado diagrams in Figures 4 and 5 below. The vertical line in the diagrams represents the base case ICER for the respective cohorts. The horizontal bars represent the range of variation in the ICER when each parameter is varied individually through its tested range or confidence interval.

The results indicate that the ICER is most sensitive to the baseline utility value. The observed sensitivity to this parameter is likely influenced by the assumption that all best standard care patients are returned to baseline utility from year four in the model. Therefore, it is a key driver of the incremental QALY gain associated with dupilumab.



BSC, Best Supportive Care; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; DUP Q2W, dupilumba 300 mg every two weeks

Figure 4 Tornado diagram for one-way sensitivity analyses for the comparison CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC (Source – Company submission, Document B, Figure 3.13)



BSC, Best Supportive Care; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; DUP Q2W, dupilumba 300 mg every two weeks

Figure 5 Tornado diagram for one-way sensitivity analyses for the comparison SOLO CAFÉ-like pool including dupilumab Q2W patients vs. BSC (Source – Company submission, Document B, Figure 3.14)

The company also provided further tables of deterministic sensitivity analysis surrounding other parameter inputs and assumptions. These are reproduced in Table

26 (CAFÉ+CCL population) and Table 27 (SOLO CAFÉ-like population) below. The results highlight the important influence on the ICER of the extrapolation assumptions surrounding the maintenance of utility benefit for BSC patients, particularly in the CAFÉ + CCL population. The results are also sensitivity to adopting a short model time horizon (5 years). This is likely related to the retention of some utility benefit in BSC patients in the earlier cycles of the model. Thus the incremental QALY is smaller relative to the incremental costs over a short time horizon. Longer time horizons decrease the ICER because the difference in utility between patients on dupilumab maintenance treatment and patients on BSC is maximised from year 4 onwards. Note, based on the details described in the company submission, the ERG were unable to replicate scenarios 15 and 17 in the Tables below.

Table 26 One-way sensitivity analyses for the CAFÉ FAS+CCL population (Source: Company submission Document B, Table 3.45)

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Reproduced by the ERG?
1	Base case	[redacted]	[redacted]	[redacted]	**£28,874**	✓
	Utility					
2	Methodology: Obs change from baseline.	[redacted]	[redacted]	[redacted]	£26,436	✓
	Maintenance of utility benefit post trial period					
3	Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£36,378	✓
4	No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£28,127	✓
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£30,456	✓
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£29,313	£29,314
7	No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£39,567	✓
	Time horizon					
8	5 years	[redacted]	[redacted]	[redacted]	£40,823	✓
9	10 years	[redacted]	[redacted]	[redacted]	£33,110	✓
10	20 years	[redacted]	[redacted]	[redacted]	£29,993	✓
	Measure of response					
11	Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£30,903	✓
12	Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£30,445	✓
13	Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£28,730	✓
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£28,945	✓
15	Additional efficacy assessment at 24 weeks	[redacted]	[redacted]	[redacted]	£29,206	No
	Resource use					
16	TA82[46] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£30,157	✓
17	Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC)	[redacted]	[redacted]	[redacted]	£25,770	No

	GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92) A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)					
18	Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£30,316	✓
19	Number of flares increased in accordance with Simpson 2016 (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£28,052	✓
20	Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£29,797	✓
21	No nurse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£28,844	✓
	Societal costs,					
22	Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 (National Health and Wellness Survey, Whitely, 2016)[53]	[redacted]	[redacted]	[redacted]	£26,474	✓

Table 27 One-way sensitivity analyses for the SOLO-CAFÉ like population (Source: Company submission Document B, Table 3.46)

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Reproduced by the ERG?
1	Base case	[redacted]	[redacted]	[redacted]	**£24,703**	✓
	Utility					
2	Methodology: Obs change from baseline	[redacted]	[redacted]	[redacted]	£23,349	✓
	Maintenance of utility benefit post trial period					
3	Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£29,773	✓
4	No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£24,036	✓
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£26,153	✓
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£25,108	✓
7	No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£31,711	✓
	Time horizon					
8	5 years	[redacted]	[redacted]	[redacted]	£33,762	✓
9	10 years	[redacted]	[redacted]	[redacted]	£27,723	✓
10	20 years	[redacted]	[redacted]	[redacted]	£25,376	✓
	Measure of response					
11	Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£25,544	✓
12	Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£25,052	✓
13	Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£24,514	✓
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£26,092	✓
15	Additional efficacy assessment at 24 weeks	[redacted]	[redacted]	[redacted]	£25,544	No
	Resource use					
16	TA82[46] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£25,701	✓
17	Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC) GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92)	[redacted]	[redacted]	[redacted]	£22,164	No

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Reproduced by the ERG?
	A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)					
18	Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£25,851	✓
19	Number of flares increased in accordance with Simpson 2016[54] (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£24,025	£24,028
20	Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£25,446	✓
21	No nurse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£24,664	✓
	Societal costs,					
22	Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 NHWS, [53]	[redacted]	[redacted]	[redacted]	£22,690	✓

Further sensitivity analysis provided in response to clarification

At clarification, the ERG requested a number of further sensitivity analyses to explore the impact of certain assumptions. These included 1) an analyses exploring the impact of applying a multiplicative approach to the age adjustment of the utility parameters in the model, rather than the constant additive approach applied; and 2) deterministic and probabilistic analyses that varied the baseline utility parameter through its 95% confidence limits and an appropriately assigned distribution (the base case PSA assigned no distribution to the baseline utility).

The company provided all the requested analyses and a revised version of the model with a switch to enable either the multiplicative or the additive approach to utility age adjustment. Applying the multiplicative approach to the age adjustment of utility values, the deterministic base case ICER for the CAFÉ+CCL population increased from £28,874 to £30,419. For the SOLO CAFÉ-like cohort, the base case ICER changed from £24,703 to £25,749. For the requested sensitivity analysis surrounding

the baseline utility values, it appears that the standard error for this parameter in both base case analytical samples is small (0.013 in the CAFÉ + CCL pooled sample and 0.021 in the SOLO CAFÉ-like sample). Consequently, the confidence interval for the baseline utility value in both samples is tighter than the range of +- 10% applied in the company's original tornado diagrams (Figures 4 and 5 above). Applying the lower and upper bounds of the CIs therefore resulted in a tighter ICER range: between £26,912 and £31,145 in the CAFÉ + CCL cohort and between £22,544 and £27,318 in the SOLO CAFÉ-like cohort. These ranges retain the additive approach to age adjustment of utility, but the company also provided additional tornado diagrams using the multiplicative approach to utility adjustment. These showed the same pattern of results, and only shifted the upper limits of the ICER ranges up slightly (by approximately £1,600 in the CAFÉ +CCL cohort and approximately £1000 in the SOLO CAFÉ-like cohort). See company response to clarification for details.

Finally, the company also provided further probabilistic results incorporating a distribution for the baseline utility parameter, and applying both the additive and multiplicative approaches to age adjust utility. Incorporating the distribution on baseline utility (retaining the additive approach to age adjustment) resulted in no real change in the point estimates of the ICERs, but increased the decision uncertainty slightly in the in the CAFÉ + CCL cohort; reducing the probability of dupilumab being cost-effective at the £30,000 threshold from 70% to ~68%. Applying the multiplicative approach to utility age adjustment, the decision uncertainty increased further in the CAFÉ + CCL population, with the probability of cost-effectiveness dropping below 50% at the WTP threshold of £30,000 per QALY. Whilst the multiplicative approach also increased the ICER slightly in the SOLO CAFÉ-like cohort, the probability of cost-effectiveness remained very high at the £30,000 threshold (98%).

Scenario analyses

The company provided results from two further scenario analyses as part of their submission: 1) comparing dupilumab to BSC for the full license population (moderate to severe AD patients who are eligible for systemic therapy); and 2) comparing dupilumab with ciclosporin for the full licensed population. Neither of these analyses are restricted based on prior systemic therapy history

Scenario analysis 1 – full license population as defined in the dupilumab licence

The full licence population as defined by the dupilumab licence includes moderate-to-severe AD patients who are eligible for systemic therapy. These scenario analyses are based on data from full analytical samples of the CHRONOS trial and pooled SOLO trials. The SOLO analysis reflects dupilumab monotherapy whereas the CHRONOS analysis reflects dupilumab with concomitant use of TSC/TCI as required. The results are presented in Tables 28 and 29 below. Using the full CHRONOS sample, the ICER is somewhat lower (Table 28) compared to the base case analysis for the CAFÉ+CCL population. With the full SOLO analysis, the ICER is slightly higher than when the analysis is restricted based on systemic therapy history (i.e. to the SOLO CAFÉ-like cohort).

Table 28 Incremental cost-effectiveness results for CHRONOS FAS, including dupilumab Q2W patients (Source: Company submission, Document B Table 3.50)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]				
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,188

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; FAS, full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W, once every two weeks; QALYs, quality-adjusted life years

Table 29 Incremental cost-effectiveness results for SOLO FAS, including dupilumab Q2W patients (Source: Company submission. Document B Table 3.51)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]				
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,729

BSC, Best Supportive Care; EASI, Eczema Area Severity Index; FAS, full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W, once every two weeks; QALYs, quality-adjusted life years

Scenario analysis 2 – Cost-effectiveness compared to ciclosporin

In response to the final scope for the appraisal, which included immunosuppressive therapies as comparators, the company included a comparison with ciclosporin. The company note that a survey of 61 consultant dermatologists suggested commonly prescribed immunosuppressive agents include azothyoprine, used first line, followed by oral corticosteroids, ciclosporin and methotrexate.[55] The company justify the comparison with ciclosporin alone on the basis that it is the only licenced immunosuppressive therapy in severe AD. They further note that the majority of respondents reported using ciclosporin for a maximum of 7 to 12 months. The modelled comparison therefore assumes a maximum of 12 months treatment with ciclosporin.

The decision tree component of the model for ciclosporin follows the same structure to that of dupilumab, with response being assessed at 16 weeks and only responders continuing on treatment to 52 weeks. Thereafter, all ciclosporin responders are assumed to stop treatment and enter the BSC treatment state of the Markov model where they receive the cost and utility profile of BSC patients. This assumes that the utility gain for all ciclosporin responders wanes immediately to the utility of BSC patients after 12 months. The utility gain (from baseline) and the responder proportion in the *BSC treatment* state continue to wane to zero by year 4 as previously described. Thus, it is only the decision tree component of the model that is different for the ciclosporin strategy compared to the BSC arm.

Based on evidence from the matched adjusted indirect comparison (MAIC) described in the clinical effectiveness section of the company submission, critiqued in section 4.4 above, equivalent 16 week response rates and associated utility gains were assumed for ciclosporin and dupilumab in the decision tree component of the model (to 52 weeks). Treatment costs do differ during this time period, with the unit cost of ciclosporin based on the lowest package cost of 30 x 25-mg capsules taken from the BNF September 2017 update (Capimune £13.05) at £0.44 per 25mg tablet.[56] The dosing inputs for ciclosporin are based on doses reported in the ciclosporin study used in the MAIC [36]; 5 mg/kg daily for 6 weeks followed by 3 mg/kg daily (up to 52 weeks). An average weight of 75kg was assumed, resulting in a daily cost of £6.53 for the first 6 weeks and a daily cost of £3.92 thereafter.

Other elements of resource use for patients on ciclosporin were also generally considered equivalent to those for dupilumab expect for some different monitoring requirements, based on recommendations in the BNF September 2017 update [56] These differences were expressed in the model as:

- Two fewer dermatologist visits for responders on ciclosporin compared to responders on dupilumab in year one.
- 15 FBC tests per year for all patients on ciclosporin, compared with zero for dupilumab responders and 4 per year for dupilumab non responders - to reflect increased testing requirements with ciclosporin (including serum creatinine).
- 7.5 dermatology nurse visits per year for all patients on ciclosporin compared to one visit per year for patients on dupilumab - to reflect additional nurse visits required to administer FBC tests.

Results for the comparison of dupilumab with ciclosporin

The company's results for the comparison of one year of ciclosporin with dupilumab are presented in Tables 30 and 31 below, based on data from the full CHRONOS and full SOLO cohorts, respectively.

Table 30 Incremental cost-effectiveness results for CHRONOS FAS including dupilumab Q2W patients versus ciclosporin. (Source: Company submission, Document B, Table 3.55)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
Ciclosporin	[redacted]	[redacted]	[redacted]				
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,638

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

Table 31 Incremental cost-effectiveness results for SOLO FAS including dupilumab Q2W patients versus ciclosporin. (Source: Company submission, Document B, Table 3.56)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr.LYG	Incr. QALYs	ICER (£/QALY)
Ciclosporin	[redacted]	[redacted]	[redacted]				
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,092

BSC= Best Supportive Care; EASI= Eczema Area Severity Index; FAS= full set analysis; ICER, incremental cost-effectiveness ratio; LYG, life years gained; Q2W= once every two weeks; QALYs, quality-adjusted life years

As ciclosporin can be used for more than one cycle in some patients in the real world, and given that the average length of a course of treatment was estimated at 5.8 months,[55] the company state that the analysis above can be interpreted as equivalent to two courses of treatment. The ERG agree with this assertion by the company. However, the ERG believe that the above analysis should be treated with caution for a number of reasons:

1. It does not reflect the availability of multiple immunosuppressive therapies that patients and clinicians have access to.
2. The assumption surrounding the waning of response obtained with ciclosporin beyond year one does not appear to be well justified.
3. The model structure does not allow for future courses of immunosuppressive treatment to be considered for those who respond to the first course but then relapse over time, or for the trial of other agents in those who do not respond following a course of ciclosporin.

5.2.10 Model validation and face validity check

The company reported a number of steps undertaken to assess the internal validity of the model. The company submission states that model has been quality controlled by a different consultancy firm (York Health Economics Consortium – YHEC). They note that face validity was tested throughout model development with external health economic and clinical experts, and that internal validity was also checked by researchers not involved in the model development. In addition, the model was put through a number of diagnostic checks by the researchers conducting the quality control, to ensure the model react as expected.

The ERG checked the model calculations and carried out a number of diagnostic checks. Whilst no calculation errors were found, the ERG did identify a mismatch between the reported number of days of absenteeism in the company submission and the number actually applied in the model. This only applies in two sensitivity analyses that incorporate indirect costs. In addition, the company applied a value of 0.25 A&E admissions per patient year in the model (for non-responders), but the original data source suggests a value of 0.1. This has a negligible impact on results. The ERG also conducted a number of checks to ensure coherence of the QALY and life-year calculation. It was not possible to assess the external validity of the model due to a lack of available existing longitudinal data on the long-term quality and response status of moderate-to-severe AD patients. The biggest assumption of the model is the setting of health state utility to baseline in BSC patients during the extrapolation, rather than carrying forward the observed placebo arm utility gain, and this cannot be verified by observed longitudinal data.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Given that the NICE DSU guidance seems to favour a multiplicative approach to adjusting and combining health state utilities for age and comorbidities, the ERG first of all reproduced the company's tables of deterministic sensitivity analysis using this method. These results are presented in Table 32 for the CAFÉ + CCL cohort and Table 33 for the SOLO CAFÉ-like cohort. As noted previously, the ERG were unable to reproduce two of the scenarios based on the information provided in the company submission: i) Scenario 15, which assumed an additional efficacy assessment at 24 weeks for partial responders to dupilumab at 16 weeks; and ii) an analysis that incorporated costs based on market research (described in section B 3.4.4 of the submission) to elicit dermatologists' perceptions of the resource use requirements for responders and non-responders. The impact that these changes had when using the additive approach to utility adjustment, can be reviewed in Tables 26 and 27 above.

It can be noted that the ICERs in all assessed deterministic scenarios increase slightly with the multiplicative approach to age adjustment of utility (Tables 32 and 33) compared with the additive approach (Tables 26 and 27).

Table 32 Sensitivity analyses for the CAFÉ FAS+CCL population – Age adjusted using multiplicative approach

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	Base case	[redacted]	[redacted]	[redacted]	£30,419
	Utility				
2	Methodology: Observed change from baseline.	[redacted]	[redacted]	[redacted]	£27,387
	Maintenance of utility benefit post trial period	[redacted]	[redacted]	[redacted]	
3	Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£38,267
4	No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£29,792
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£32,154
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£30,901
7	No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£41,838
	Time horizon				
8	5 years	[redacted]	[redacted]	[redacted]	£41,283
9	10 years	[redacted]	[redacted]	[redacted]	£33,807
10	20 years	[redacted]	[redacted]	[redacted]	£31,118
	Measure of response				
11	Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£32,350
12	Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£31,843
13	Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£30,260
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£30,492
15	Additional efficacy assessment at 24 weeks	Unable to reproduce			
	Resource use				
16	TA82[46] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£31,771
17	Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC) GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92) A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)	Unable to reproduce			

18	Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£31,938
19	Number of flares increased in accordance with Simpson 2016[54] (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£29,556
20	Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£31,391
21	No burse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£30,387
	Societal costs,				
22	Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 (National Health and Wellness Survey, Whitely, 2016)[53]	[redacted]	[redacted]	[redacted]	£27,890

Table 33 Sensitivity analyses for the SOLO-CAFÉ like population – Age adjusted using multiplicative approach

		Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
1	Base case	[redacted]	[redacted]	[redacted]	£25,749
	Utility				
2	Methodology: Observed change from baseline	[redacted]	[redacted]	[redacted]	£24,340
	Maintenance of utility benefit post trial period				
3	Probability of sustained QoL response does not decline beyond anticipated year 2 level (37%)	[redacted]	[redacted]	[redacted]	£30,992
4	No decline in the Dupilumab treated patients	[redacted]	[redacted]	[redacted]	£25,148
5	Linear decline in utility for BSC patients to year 5 (75%, 50%, 25%, 0%)	[redacted]	[redacted]	[redacted]	£27,308
6	Linear decline in utility for BSC patients to year 5 (50%, 25%, 0%, 0%)	[redacted]	[redacted]	[redacted]	£26,184
7	No decline in the Dupilumab treated patients, 50% decline in BSC patients	[redacted]	[redacted]	[redacted]	£33,127
	Time horizon				
8	5 years	[redacted]	[redacted]	[redacted]	£34,126
9	10 years	[redacted]	[redacted]	[redacted]	£28,270
10	20 years	[redacted]	[redacted]	[redacted]	£26,221

	Measure of response				
11	Efficacy evaluation at 16 weeks: EASI75	[redacted]	[redacted]	[redacted]	£26,611
12	Efficacy evaluation at 16 weeks: EASI50	[redacted]	[redacted]	[redacted]	£26,117
13	Efficacy attribute applied at week 4	[redacted]	[redacted]	[redacted]	£25,546
14	Primary analysis method for response	[redacted]	[redacted]	[redacted]	£27,196
15	Additional efficacy assessment at 24 weeks	Unable to reproduce			
	Resource use				
16	TA82[46] inputs for Dermatologist (2.7 vs. 6.5) and GP visits (4.0 vs. 11.7)	[redacted]	[redacted]	[redacted]	£26,790
17	Market research: dermatologist perception (Annual visits (DUP Q2W vs. BSC) GP (2.3 vs.4.78) Dermatologist (3.53 vs 4.92) A&E attendance (0.43 vs. 1.74) Hospital admissions (t0.15 vs. 1.16) Dermatology nurse (1.84 vs. 2.39)	Unable to reproduce			
18	Cost of a dermatologist visit without MDT costs (@ £104.24)	[redacted]	[redacted]	[redacted]	£26,946
19	Number of flares increased in accordance with Simpson 2016[54] (2.8 vs. 15.5)	[redacted]	[redacted]	[redacted]	£25,046
20	Adherence to concomitant (background) topical medications reduced to 50%	[redacted]	[redacted]	[redacted]	£25,466
21	No burse initiation in secondary care (assume all initiated through home care)	[redacted]	[redacted]	[redacted]	£27,709
	Societal costs				
22	Absenteeism (days lost per month) 0.36 responder; 1.08 non-responder. Productivity loss per hour £15.13 Percentage employed: 78.5% Hours worked per day: 6.67 NHWS,[53]	[redacted]	[redacted]	[redacted]	£23,651

5.4 Further exploratory analysis undertaken by the ERG

The ERG have four main areas of concern in the modelling:

i) the waning assumption;

ii) the selective use of third year data form the case note review to estimate rates of resource use for responders and non-responders;

iii) the feasibility of the assumptions regarding the stopping of dupilumab treatment in non-responders; and
iv) the omission of probability distributions on the resource use estimates in the PSA, and the potential underestimation of decision uncertainty.

The ERG have therefore undertaken a number of exploratory analyses to illustrate the impact of these four issues on the company model results. The starting point for the further analysis is the model provided by the company in their response to clarification, with the multiplicative approach for age adjusting utilities switched on. The base case ICERs for this specification of the company revised model are £30,419 and £25,749 for the CAFÉ + CCL pool and the SOLO CAFÉ-like pool, respectively.

The waning assumptions
The Excel model provided by the company contains a switch where the user can exclude the base case quality life (and EASI/DLQI response) waning assumptions. Given the uncertainty regarding the extrapolation assumptions, the ERG assessed the impact of implementing this. This analysis carries forward the estimated utility gains in BSC patients, derived from the observed data in the placebo arms of the respective trials, through the extrapolation phase of the model. It also assumes no waning of the utility gain in dupilumab responders but retains an annual discontinuation rate based on observed data. In addition, the ERG implemented three further analysis assuming that 25%, 50% or 75% of the utility gain in BSC patients is maintained over the lifetime horizon, whilst retaining the base case waning assumptions for dupilumab responders. The results for these analyses are reported as scenarios 1 to 4 in Tables 34 and 35 below, for the CAFÉ + CCL pooled and the SOLO CAFÉ-like pooled cohorts respectively.

Removing or reducing the quality of life (responder) waning assumption in BSC patients has a substantial effect on the ICER, due primarily to reductions in the QALY difference between the dupilumab and BSC arms. The incremental cost associated with dupilumab also increases since the BSC waning assumption is also used to adjust down the responder proportion for the estimation of certain costs in the BSC treatment state.

Selective use of data form the case notes review

The company base case analysis used data from a case note review to calculate rates (per patient year) of dermatologist outpatient consultations, dermatologist nurse consultations, A&E attendances, hospital admissions, and daycase admissions in non-responders. The company stated that this is an ongoing study, and further noted that their rates were calculated based on data from 30 patients collected in year three of the study. They justify this with the statement that these data are the most recent and most complete. On inspection of the Table I-15 in the Appendices, the ERG note that data are also reported for 30 patient in year 2 and 25 patients in year 1. It is not clear why the company did not utilise this data. Therefore, the ERG explored the impact of using all the available data to recalculate the resource use event rates, assuming each patient in each year of the study contributes one year at risk. These estimated rates are reported in Appendix 1. The data used in the company base case are reported in Table 20 (section 5.2.8 above).

The results of this change are presented as scenario 5 in Tables 34 and 35, for the CAFÉ + CCL cohort and the SOLO CAFÉ-like cohort, respectively. The ICER increased from £30,419 to £34,355 for the CAFÉ +CCL pool and from £25,749 to £28,851 for the SOLO CAFÉ like pool. Further scenarios six to nine in Tables 34 and 35 illustrate the upward uncertainty in the ICER arising from the combined application of the different waning assumptions with the recalculated resource use event rates.

Impact of the stopping rule

To approximate the impact of removing the stopping rule within the confines of the company's model structure, the ERG assessed the impact of setting the response rate (at weeks 16 and week 52) to one in the dupilumab arm, and then applying the utility weight for all dupilumab patients at 16 weeks as the utility weight for responders. For these analysis, we also applied a weighted average of responder and non-responder 'other medical costs' to patients in the dupilumab *maintenance treatment* state, using the relevant observed 16 week response rate. The results are shown as scenario 10 in Tables 34 and 35 below. They show only a modest impact on the ICER, since the 16 week utility gain for all dupilumab patients is only slightly lower than the utility gain for dupilumab responders.

Table 34 ERG further analysis – age adjustment using the multiplicative approach conducted by the ERG – CAFÉ + CCL pool

Number	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	Base Case	[redacted]	[redacted]	[redacted]	30,419
Varying waning effect assumptions (Base case: 37% year 2, 9% year 3, 0% year 4)					
1	Assuming 25% of responders in BSC will sustain the QoL beyond 52 weeks. Waning assumption for dupilumab as for base case	[redacted]	[redacted]	[redacted]	35,022
2	Assuming 50% of responders in BSC will sustain the QoL beyond 52 weeks. Waning assumption for dupilumab as for base case	[redacted]	[redacted]	[redacted]	42,460
3	Assuming 75% of responders in BSC will sustain the QoL beyond 52 weeks. Waning assumption for dupilumab as for base case	[redacted]	[redacted]	[redacted]	53,451
4	No waning assumptions. Probability of sustained quality of life does not decline in either arm after the trial ends.	[redacted]	[redacted]	[redacted]	70,684
Varying resource use calculations (using all available data from case notes review) Base case value in Table 3.22 company submission document B)					
5	ERG resource use calculations (using three years data from case notes review)	[redacted]	[redacted]	[redacted]	34,355
Combination of waning effect and resource use calculation					
6	1&5	[redacted]	[redacted]	[redacted]	39,293
7	2&5	[redacted]	[redacted]	[redacted]	47,274
8	3&5	[redacted]	[redacted]	[redacted]	59,069
9	4&5	[redacted]	[redacted]	[redacted]	77,701
10	Exploring removal of the stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	33,279

Table 35 ERG further analysis – age adjustment using the multiplicative approach conducted by the ERG – SOLO CAFÉ like pool

Number	Scenario	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
0	Base Case	[redacted]	[redacted]	[redacted]	25,749
Varying waning effect assumptions					
1	Assuming 25% of responders in BSC will sustain the QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	28,807
2	Assuming 50% of responders in BSC will sustain the QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	33,729
3	Assuming 75% of responders in BSC will sustain the QoL beyond 52 weeks	[redacted]	[redacted]	[redacted]	40,467
4	No waning assumptions. Probability of sustained quality of life does not decline in either arm after the trial ends.	[redacted]	[redacted]	[redacted]	49,596
Varying resource use calculations (using all available data from case notes review) Base case value in Table 3.22 company submission document B)					
5	ERG resource use calculations (using three years data from case notes review)	[redacted]	[redacted]	[redacted]	28,851
Combination of waning effect and resource use calculation					
6	1&5	[redacted]	[redacted]	[redacted]	32,118
7	2&5	[redacted]	[redacted]	[redacted]	37,378
8	3&5	[redacted]	[redacted]	[redacted]	44,579
9	4&5	[redacted]	[redacted]	[redacted]	54,438
10	Exploring removal of stopping rule for dupilumab	[redacted]	[redacted]	[redacted]	29,468

Assigning probability distributions to the resource use data

The company probabilistic analysis did not vary any of the resource use event data (obtained from the case note review or integrated record review) or the resource use multipliers used to calculate resource use for treatment responders (derived from views elicited from 51 dermatologists). The company state that uncertainty was assessed by attaching probability distributions to unit cost variables. However, the ERG believe that the company approach may only partially characterise the uncertainty surrounding the model based estimates of incremental cost.

Therefore, the ERG implemented further exploratory PSAs attaching probability distributions to the company's resource use estimates and the ERG's alternative estimates. Gamma and beta distributions were used, with standard deviations estimated as 10% of the mean parameter value, or using counts of events where these were available (details are reported in Tables 38 and 39 in Appendix 1).

Results are reported in Table 36 for the CAFÉ+CCL pool and in Table 37 for the SOLO CAFÉ like pool. For comparison, the results are presented in a stepwise manner, starting with the company's original results. The original PSA presented in the company submission for the CAFÉ+CCL cohort, showed dupilumab to have a 70% probability of being cost-effective at £30,000 per QALY. Adding a probability distribution to the baseline utility (0.66) parameter marginally reduced this probability to 67%, while using a multiplicative approach to adjust utilities by age further reduced the probability of cost-effectiveness to 43% at a WTP threshold of £30,000. Attaching probability distributions to the resource use parameter values assumed by the company further reduced the probability cost-effectiveness but by only 1%. Finally, applying the ERG alternative estimates for the resource use parameters, and assigning distributions to these, the probability of dupilumab being cost effective falls to 9% in the CAFÉ+CCL cohort. This larger reduction is due to the upward shift in the ICER from just over £30,000 to over £34,000. These results illustrate that it is the structural changes -applying the multiplicative approach to age adjust utilities and sourcing resource use event rates from all the available data – that have the larger impacts on the probability of cost-effectiveness. The assignment of probability distributions to the baseline utility weight and the resource use parameters has little impact.

Table 36 Further probabilistic sensitivity analysis – CAFÉ + CCL pool

Number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Probability of being cost effective at		
					£20,000	£30,000	£50,000
1	Original CS base case analysis	[redacted]	[redacted]	28,670	0%	70%	100%
2	Adding probability distribution to baseline utility	[redacted]	[redacted]	28,663	0%	67%	100%
3	2 + multiplicative approach for age adjustment	[redacted]	[redacted]	30,290	0%	43%	100%
4	3 + probability distributions attached to CS resource use parameters	[redacted]	[redacted]	30,318	0%	42%	100%
5	3 + probability distributions attached to ERG alternative resource use parameters	[redacted]	[redacted]	34,239	0%	9%	100%

Table 37 reports the stepwise PSA runs for the SOLO CAFÉ like pool. Dupilumab retains a high probability of being cost effective (98% or over) for most of the scenarios. Only when the ERG alternative estimates of resource use are applied does the probability of dupilumab being cost-effective at the £30,000 threshold drop substantially, to 63%.

Table 37 Further probabilistic sensitivity analysis – SOLO CAFÉ like pool

Number	Scenario	Incremental costs (£)	Incremental QALYs	ICER	Probability of being cost effective		
					£20,000	£30,000	£50,000
1	Original CS base case analysis	[redacted]	[redacted]	24,648	0%	100%	100%
2	Adding probability distribution to baseline utility	[redacted]	[redacted]	24,641	0%	99%	100%
3	2 + multiplicative approach for utility age adjustment	[redacted]	[redacted]	25,695	0%	97%	100%
4	3 + probability distributions attached to CS resource use parameters	[redacted]	[redacted]	25,703	0%	98%	100%
5	3 + probability distributions attached to ERG alternative resource use parameters	[redacted]	[redacted]	28,753	1%	63%	100%

5.5 Conclusions of the cost effectiveness section

The original company base case ICER for the CAFÉ + CCL population (allowing for background TCS), came to £28,874 per QALY gained. For the analysis assessing the cost-effectiveness of dupilumab as monotherapy, based on SOLO CAFÉ-like patients, the company's original ICER was £24,703.

In response to clarification the company provided alternative analyses for the base case populations using a multiplicative approach to age adjust utility. For this specification of the company model, the deterministic ICERs increased to £30,419 and £25,749 for the CAFÉ + CCL pool and the SOLO CAFÉ-like pool, respectively. The ICERs for all the deterministic sensitivity analyses also increase similarly when the multiplicative approach to utility adjustment was applied instead of the additive approach. In addition, the probabilities of cost-effectiveness declined when the multiplicative approach to age adjustment was applied and a distribution was included for baseline utility: to 43% and 97% at the £30,000 per QALY threshold for the CAFE+CCL and the SOLO CAFÉ-like cohorts respectively.

Based on deterministic sensitivity analysis conducted by the company and further exploratory analyses conducted by the ERG, the company's base case results were found to be particularly sensitivity to the health state utility and response extrapolation assumptions applied in the in the model. When the ERG assessed the impact of switching off the waning assumptions, and carrying forward the response and utility gains observed in the respective arms of the trials over the extrapolation phase, the ICERs for dupilumab increased substantially to £70,684 and £49,596 in the CAFÉ+CCL and SOLO CAFÉ-like populations respectively. Intermediate extrapolation assumptions generated ICERs between these highest estimates and the company base case estimates.

The impact of further exploratory analyses conducted by the ERG are summarised below (all are applied with the multiplicative approach to utility age adjustment).

- Recalculating the company's resource use event rates, using all the available data from the company's preferred data source, also resulted in modest increases in the ICER; to £34,355 and £28,851 in the CAFÉ+CCL and SOLO CAFÉ-Like cohorts respectively.

- Incorporating probability distributions on the resource use event rates and multipliers, resulted in very little change in the PSA results.
- To approximate the impact of removing the stopping rule for dupilumab, the ERG set the response rate to one in the dupilumab arm of the model and assigned the trial based utility estimate for all dupilumab patients to all those remaining on treatment. 'Other medical costs' (by response status) for those on dupilumab maintenance treatment were also weighted by the week 16 response rate in this analysis. These changes resulted in modest increases in the ICERs, to £33,279 and £29,468 for the CAFÉ+CCL and SOLO CAFÉ-Like cohorts respectively. Whilst the ERG appreciate that removal of a stopping rule for lack of response is unrealistic, this analysis was conducted to understand the impact of the stopping criteria on the cost-effectiveness of dupilumab.

Whilst the company also provided as scenario analysis comparing dupilumab with cilcosporin in the broader licensed population, the ERG believes that this additional analysis may not adequately reflect the availability and sequencing of immunosuppressant therapies in routine clinical practice.

6 Overall conclusions

The company's submission considered dupilumab for adults with moderate-to-severe atopic dermatitis (AD) with a history of intolerance, inadequate response or contradiction to topical therapies and for whom current systemic immunosuppressants have failed. The company also included a scenario analysis for dupilumab in the full licence population (i.e., adults with moderate-to-severe atopic dermatitis who are candidates for systemic therapy).

6.1 Clinical effectiveness evidence

The NICE final scope specified the comparators as phototherapy, immunosuppressive therapies, oral steroids, best supportive care and alitretinoin. The company's systematic review identified a number of studies involving all the specified comparators (with the exception of alitretinoin) but ultimately considered only studies with best supportive care as comparator. The ERG agrees with the omission of immunosuppressive therapies, oral steroids, and alitretinoin as comparators but is of the opinion that phototherapy can be a constituent of BSC in clinical practice in the UK and was, therefore, a relevant comparator.

Four trials comparing dupilumab with placebo were included in the company's clinical effectiveness evidence; SOLO 1 and SOLO 2 compared dupilumab monotherapy with placebo. CHRONOS and CAFÉ compared dupilumab administered concomitantly with topical corticosteroids (TCS) with TCS + placebo. In all four studies, randomisation was to dupilumab 300mg every week (QW), dupilumab 300mg every two weeks (Q2W) or placebo.

The primary endpoints were proportion of patients who reached IGA score of 0 or 1 and reduction of ≥2 points from baseline and proportion of patients who achieved EASI-75. In all four trials, the proportion of participants who achieved the primary outcomes was greater in both dupilumab groups than the corresponding placebo groups. The proportions of participants who achieved the primary outcomes was similar across the dupilumab QW and dupilumab Q2W groups within each trial.

There were two deaths across all four studies; both were classed as treatment emergent. The number of treatment-emergent serious adverse events was low. The most frequently experienced treatment-emergent adverse events were exacerbation of AD, infections and infestations, and nasopharyngitis. Exacerbation of AD was more common in the placebo groups than the dupilumab groups.

The ERG is in agreement with the company about the nature, conduct and interpretation of the clinical effectiveness analysis. The included studies suggest a benefit from dupilumab with similar effects for both the weekly and fortnightly treatments. The safety profile of dupilumab does not raise concerns. The company acknowledge the increased incidence of allergic site reaction and allergic conjunctivitis in the dupilumab arms and describe the additional investigations carried out regarding adverse events.

The company used a matched adjusted indirect comparison (MAIC) to compare dupilumab with the only immunosuppressant with a licence for AD, ciclosporin. The ERG considers the company's choice correct in this context, but finds the MAIC results unsatisfactory due to the resulting small sample sizes. The company's decision to ignore the results of the MAIC and instead assume equivalence with ciclosporin for the cost-effectiveness modelling is supported by the ERG.

6.2 Cost-effectiveness evidence

The company's main economic case considered the cost-effectiveness of dupilumab compared with best supported care (BSC) for a subgroup of the full licence population: "adult patients with moderate-to-severe AD who are contraindicated to, intolerant of, had an inadequate response to or for whom it is medically inadvisable to receive treatment with systemic immunosuppressant therapies". Two different analyses were reported for this base case population: 1) assessing dupilumab with concomitant TCS based on data from the CAFÉ + CHRONOS CAFÉ-like pool; 2) assessing dupilumab as monotherapy based on data from the SOLO CAFÉ-like pool. The company also provided a scenario comparing dupilumab with ciclosporin in the broader licence population; patients who are eligible for immunosuppressant therapies.

The company submitted an economic model consisting of a decision tree component to model costs and outcomes to 52 weeks, and a simple three state Markov component to extrapolate long-term costs and effects. Patients on dupilumab are assessed for response at 16 weeks in the model, with those not responding stopping treatment and reverting to BSC costs and utilities. Those who respond at week 16 continue on dupilumab for the remainder of the first year, and response is assessed again at week 52. Those retaining their response continue in the Markov model on *maintenance treatment* and attract the utility and cost profile of dupilumab responders. Those who lose response by week 52, and all other patients, move to the *BSC treatment* state of the Markov model where and attract the BSC cost and utility profile.

Whilst the company model is based on observed data from high quality randomised controlled trials out to 52 weeks (one year), the nature of the condition, combined with a lack of long-term data, results in assumptions being required to extrapolate short-term differences in costs and effects over a life-time horizon. The company apply a set of assumptions, based on expert opinion, that reduce the response rate and utility gain observed in the BSC (placebo) arms of the trials to zero from year four onwards in the model. The ERG believe that these assumptions may exaggerate the magnitude of the benefit attributable to dupilumab, and note that the cost-effectiveness results are particularly sensitive to them. The assumptions cannot be verified by observed longitudinal data.

6.3 Implications for research

The ERG's clinical expert recommends for future studies to consider re-randomising participants to placebo and then re-treating exacerbations of AD, to more accurately reflect UK clinical practice. This strategy is commonly utilised in studies of people with psoriasis.

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Appendices

Appendix 1 Data used by ERG for further analyses

Table 38 Resource used data used for the ERG further analyses

Resource	Dupilumab		BSC		Source and justification	Probability distributions attached for probabilistic analysis
	Year 1	Years 2+	Year 1	Years 2+		
Dermatologist outpatient consultation (per patient per year)						
Responder	4.32	4.32	4.32	4.32	Responders resource use calculated using the multipliers (0.72) based on data from the company submission market research	No distribution attached. Varies as a results of probability distribution attached to responders and that assumed for the multiplier
Non-responder	6	6	6	6	A total of 510 visits were collected from case notes for the three year period (94+205+211) / 85 patient years = 6 visit per patient year clinician	Gamma, mean: 6; SD: 0.6
Dermatology related GP consultation (per patient per year)						
Responder	6.15	6.15	6.15	6.15	Calculated using the company submission market research multiplier (0.48)	No distribution attached. Varies as a results of probability distribution attached to responders and that assumed for the multiplier
Non-responder	12.81	12.81	12.81	12.81	As for the company submission	Gamma, mean: 12.81; SD: 1.281

Dermatology Nurse visit (per patient per year)						
Responder	1	0.35	0.35	0.35	Advisory board. A nurse visit at 4 weeks after initiation would be expected for dupilumab. Thereafter the number of visits observed in for non-responders is reduced by the multiplier (0.77) derived from the company market research.	No distribution attached. Varies as a results of probability distribution attached to responders and that assumed for the multiplier
Non-responder	1	0.46	0.46	0.46	First year for dupilumab as for the company submission. BSC and dupilumab further years calculated from Table I-15 of the compamny submission. A total of 39 nurse visits for 85 patient years (39/85 = 0.46)	Gamma, mean: 0.459; SD: 0.046
Accident and emergency visit (per patient per year)						
Responder	0.021	0.021	0.021	0.021	The number of visits par patient year is reduced by the multiplier (0.25) derived from the market research (company submission section B 3.4.4).	No distribution attached. Varies as a results of probability distribution attached to responders and that assumed for the multiplier
Non-responder	0.082	0.082	0.082	0.082	Seven A&E admissions for the three year period (7/85 patient years = 0.082 per patient year)	Beta, alpha: 7; beta: 78
Hospitalisation						
Responder	0.017	0.017	0.017	0.017	The number of hospitalisations calculated using all available data from case notes is reduced by the multiplier (0.13) derived from the market research (company submission section B 3.4.4)	No distribution attached. Varies as a results of probability distribution attached to responders and that assumed for the multiplier

Non-responder	0.13	0.13	0.13	0.13	Number of hospitalisations per person per year calculated from the care notes review data (11 admissions for 85 patient years = 0.13 admissions per patient year)	Beta, alpha: 11; beta: 74
Tests and investigations (per patient per year)						
Responder	0	0	4	4	As for the company submission	No distribution attached
Non-responder	4	4	4	4	As for the company submission	No distribution attached
Day case						
Responder	0	0	0	0	As for the company submission	No distribution attached
Non-responder	0.2	0.2	0.2	0.2	17 day cases reported in CS Table I-16 (17/85 = 0.2)	Beta, alpha: 17; beta: 68

Table 39 ERG data and assumption for further analyses: resource use multipliers for responders with respect to non-responders

Variable	Mean	SD	Assumed probability distribution for Probabilistic Sensitivity Analysis
OP visits to dermatologist (total pt visits/yr)	0.72	0.072	Log-normal
OP visits to dermatology nurse (total pt visits/yr)	0.77	0.077	Log-normal
Visits to the GP (total pt visits/year)	0.48	0.048	Log-normal
A&E attendance (total pt visits/ year)	0.25	0.025	Log-normal
Hospital admissions (total pt admissions/year)	0.13	0.013	Log-normal

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dupilumab for treating moderate to severe atopic dermatitis after topical treatments [ID1048]

You are asked to check the ERG report from Aberdeen HTA Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 14 February** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Use of the term placebo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The word 'placebo' occurs 106 times within the document. This might suggest that the comparator arm in the studies does not contain any active treatment.	We suggest that the following amendment is made… In all cases placebo is substituted for Best Supportive Care (BSC)	A placebo injection was given to patients not treated with dupilumab in addition to BSC during the studies. BSC is broadly defined in CAFÉ and CHRONOS as a combination of emollients, low-to-mid potency topical corticosteroids (TCS) and rescue therapy (such as higher potency topical or oral corticosteroids or topical calcineurin inhibitors (TCIs)). This is largely consistent with clinical practice although patients may also be treated with immunosuppressants. Immunosuppressants were permitted in the studies as rescue therapy but uptake was very low (See also Issue 3 below for a discussion of the monitoring effect). Hence BSC can be considered to be active management and is not placebo treatment.	The ERG is of the opinion that the use of the word 'placebo' when referring to the non-treatment arms in the ERG report is accurate. The report states in a number of places that BSC is included as part of the comparator. Moreover, the crucial clinical evidence is based on placebo controlled trials (e.g., Blauvelt A, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids [LIBERTY AD CHRONOS]: a 1-year, randomised, double-blinded, **placebo-controlled**, phase 3 trial. Lancet, 2017; 389(10086): 2287-303.) The ERG does not consider this to be a factual inaccuracy. No amendment required.

Issue 2 Prevalence of moderate to severe AD

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 1, Section 1, paragraph 2 Text in the report reads: *In the UK, the reported proportion of people with AD classed as moderate-to-severe ranges from 53% to 67%, depending on the instrument used. In contrast, the company reports that 7% of people with AD have moderate-to-severe disease.* We are keen that there is no confusion about the proportions quoted for the UK. See also page 8, section 2.1, paragraph 2	We suggest that the following addition is made… *In a study involving patient-self reporting, the proportion of people with AD from the UK cohort (256) classed as moderate-to-severe ranges from 53% to 67%, depending on the instrument used. In contrast, the company reports that 7% of people with AD have moderate-to-severe disease. This value was based on EASI scores observed in an externally syndicated data UK set used by the company.*	To calculate the proportion of patients with moderate to severe AD in the UK a methodology was used which focused on an externally produced dataset (Adelphi DSP 2015) which included perceptual impressions of severity and also patient record research. The perceptual and self-reported data seems to indicate a higher prevalence than that recorded in patient records. When EASI score was included in the calculation (moderate: 16-24, severe: (25+) it was found that the proportion with moderate to severe AD was 7%. Key features of the analysis were: • Externally produced syndicated dataset (Adelphi DSP 2015) • Patient record based dataset – sample of 52 PCPs and 84 specialists • Disconnect between perceptual assessment of patient severity (mild, moderate and severe) vs recognised medical classification (EASI) • Analysis of patient numbers based on EASI generates moderate/severe patient	The ERG does not consider this to be a factual inaccuracy. No amendment required.

		population of 7% The methodology used to arrive at this estimate differs from the study cited in the ERG report which included self-reporting of disease severity using the PRO-SCORAD, POEM and PGA tools sampled from a general population cohort.	

Issue 3 Phototherapy as a constituent of Best Supportive Care

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 1 - 2 Section 1.1, paragraph 2 Text in the report reads: *The company did not consider phototherapy to be a valid comparator as it is only suitable as a short-term treatment option. The ERG's clinical expert agrees that phototherapy is not a long-term treatment but is of the opinion that in UK clinical practice it can be a constituent of BSC, as it can be used in the short-term to induce remission and can have lasting effects* There is variability in the provision and accessibility of phototherapy around the country and it is our understanding that the effects of phototherapy are	We request that the following amendment is made… *The company did not consider phototherapy to be a valid comparator as it is only suitable as a short-term treatment option. The company also states that it is not a common constituent of BSC because it is placed before the expected position of dupilumab in the treatment algorithm and is not universally available. The ERG's clinical expert agrees that phototherapy is not a long-term treatment but is of the opinion that in UK clinical practice it can be a constituent of BSC, as it can be used in the short-term and may induce remission and can have lasting effects*	We agree with the ERG that phototherapy is not a direct comparator but argue that it is also not a common place constituent of BSC. **Use of phototherapy in NHS England** We recognise the benefits that phototherapy can bring to some patients. However it is not universally available or accessible across England. Where it is available there is a restriction on the number of courses of therapy a patient may have. 'UK clinical practice' is cited in the report. Our discussions with dermatologists in Scotland have indicated that phototherapy is probably used more widely within NHS Scotland than it is in NHS England suggesting a difference in access to the service	The ERG does not consider this to be a factual inaccuracy. No amendment required.

not necessarily long lasting in all patients. See also… Page 11 Section 2.2, paragraph 1 Page 18 Section 3.3, paragraph 1 Page 21 Table 2, Page 52 Table 11, Page 114 Section 6.1, paragraph 1		between countries. **Clinical evidence** There is some evidence in the literature to support the durability of response to phototherapy with reports of single remission periods up to 6 months. However RCTs are generally small and of heterogeneous quality with no longer-term data available. [British Journal of Dermatology (2014) 170, pp501–513]. When phototherapy is used, flares and recurrences are common events after finishing a treatment schedule [Advances in Experimental Medicine and Biology 996, https://doi.org/10.1007/978-3-319-56017-5_23. Springer International Publishing AG 2017 279]. Hence we believe that the statement that it can have lasting effects should be treated with caution. Maintenance therapy with long term exposure should always be avoided especially in younger patients due to an increased risk of photoaging and photocarcinogenesis [[Advances in Experimental Medicine and Biology 996, https://doi.org/10.1007/978-3-319-56017-5_23. Springer International Publishing AG 2017 279]. The use of topical calcineurin inhibitors can be a contraindication for phototherapy as is the concomitant use of immunosuppressants. For example	

		the international eczema council IEC state that '*Phototherapy should be discontinued if cyclosporine or other systemic treatments (eg, azathioprine or mycophenolate mofetil) are initiated to avoid the synergistic risk of inducing skin malignancy*' [J Am Acad Dermatol. 2017 Oct;77(4):623-633]. Similarly the German Guideline on Phototherapy states "*A concomitant or subsequent administration of CsA is contraindicated due to a higher risk of skin cancer*." [J Dtsch Dermatol Ges. 2016 Aug;14(8):e1-e25]. Experience from the EAMS for dupilumab indicates that patients were heavily pretreated with immunosuppressants and all had exposure to TCIs. Around a third of patients had tried phototherapy in the past. Similarly ~40% of CAFÉ patients had tried UV light therapy + Phototherapy + PUVA in the past, indicating that this is a therapy used ahead of immunosuppressants. **Patient burden** One of the biggest drawbacks of UV therapy is that the patient must travel between 3 and 5 times per week for up to 12 weeks to a site that offers the therapy. In addition, UV light does not effectively treat hairy areas such as scalp and skin folds. (JEADV 2016, 30,	

		729 – 747) Phototherapy places considerable burden on the patient making it a less attractive option for many patients. **Phototherapy as a constituent of BSC** Given the expected positioning for dupilumab after the use of an immunosuppressant, the position of phototherapy in the IEC algorithm as a second-line treatment and reserved for cases where behavioural measures and topical therapy have failed, along with the patient burden imposed by therapeutic use of phototherapy and the availability or accessibility of the service in England we do not believe that it can be considered to be a typical constituent of BSC. **Evidence from the study program** Only 5 patients in CHRONOS (3 in placebo and 2 in dupilumab groups over 52 weeks) used phototherapy as rescue treatment and so there is insufficient evidence to support a relative treatment effect on efficacy between dupilumab and BSC treated patients. Therefore a relative frequency of use for dupilumab treated patients vs. BSC cannot be derived from the study program. Nonetheless we believe that inclusion	

		of phototherapy as a constituent of BSC would reduce the ICER and hence our base case which does not include it, is conservative. The outpatient procedure tariff for the reference cost JC47Z (phototherapy), is £75 (2016/17 National Prices and National Tariff Workbook). Typically phototherapy is administered 3 to 5 times a week for up to 12 weeks. Therefore this could be a significant driver of BSC cost which is otherwise relatively inexpensive. The reduction in the number of exacerbations due to dupilumab treatment relative to BSC would be likely to result in less phototherapy treatment and so a relative reduction in cost in the dupilumab arm.	

Issue 4 Use of the term 'Stopping rule'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The term 'stopping rule' occurs in the following places in the ERG report: Page 5, paragraph 1 Page 7, bullet point 4 Page 69, paragraph 2	We request that as a reflection of the SmPC for dupilumab which refers to some patients achieving response beyond 16 weeks that the binary term '*stopping rule'* is replaced with the phrase '*treatment continuation decision'*.	We are concerned that the term stopping rule implies a binary patient response which may create a risk that the decision to continue or discontinue treatment is not described in way that is consistent with NICEs guidelines for children or within the context of the market authorisation.	The ERG notes that the company's model utilises precise criteria and a decision rule is applied to stop treatment in those not meeting the threshold for response applied in the model. This may be partly semantics, but the ERG understand this to be a binary rule for stopping/continuing

Page 104, point iii) Page 106, paragraph 3 Page 107, table 34 Page 108, table 35 Page 113, bullet point 2 Page 116, paragraph 1 We do not agree with the terminology 'stopping rule' as this can be interpreted to be a binary decision based on limited criteria.		The SmPC states that: *'Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.'* We have argued in the submission that the assessment of response in AD should be holistic and be guided by clinical judgement. This is consistent with the current NICE guideline for AD for children (GC57), which suggests that healthcare professionals should adopt a holistic approach when assessing a child's atopic dermatitis. It is important to recognize that a snapshot at a single point using an isolated measure such as EASI is not adequate to fully describe control. This is stated by the expert panel of the International Eczema Council (IEC) who recommend that severity-based scoring systems alone cannot determine the need for systemic therapy The term 'treatment continuation	treatment. The ERG does not consider this to be a factual inaccuracy.

		criteria' is more reflective of the need for holistic assessment consistent with CG57 taking into account progress towards control.	

Issue 5 The relevance of the 'Stopping rule'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Related to the wider point above on Page 69, paragraph 2 the text in the report reads: *The positive sign for the main effect of the EASI score may raise some concerns about its relative importance as a driver of quality of life when compared with pruritus. For example, it may prove difficult implementing the proposed stopping rule if patients who do not achieve EASI50 + DLQI>4 were to experience a significant quality of life improvement mediated through a reduction in daily pruritus.*	No amendment is proposed.	We believe that the most appropriate judgement to continue treatment should be made jointly between the clinician and the patient. For the purposes of the health economic model an objective measure was required. In line with the recommended holistic approach to AD care advocated above we use a composite measure of response in the model for the treatment continuation decision that incorporates improvement in signs (EASI 50) and QoL (DLQI). DLQI is a commonly used measure of QoL in dermatology and clinicians are familiar with it. The first question of the instrument asks: '*Over the last week, how itchy, sore, painful or stinging has your skin been?*' and so it does explicitly incorporate a measure of pruritus. However we recognise that this	No amendment required.

		constitutes only one part of the instrument (although itching is likely to impact on many of the other questions). There are other specific measures for itch such as the pruritus NRS scale (which was collected in the LIBERTY trial program). However it is not practicable to combine multiple measures into a workable treatment continuation decision to fully reflect a holistic approach. This further illustrates the need for a practical decision making framework in which the clinician can also use judgement as well as clinical and QoL measures to decide to continue treatment or not.	

Issue 6 Description of the timing associated with efficacy response assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5, Section 1.5, 1st paragraph Text in the report reads: *It assumes that patients remaining on dupilumab treatment are constantly responding, and that treatment stops immediately from the point in time that response is lost. It does not allow for continuing*	We request that the following amendment is made… *It assumes that patients remaining on dupilumab treatment after the 16 week assessment point continue to respond. Thereafter treatment stops according to discontinuation rates observed in the study program at the end of each annual cycle. The company recognise that such a binary outcome may not be appropriate in AD which is a disease with fluctuating signs and symptoms*	We recognise the spirit in which this statement is made which suggests that benefit for patients treated with dupilumab and judged to be 'responders' continues to accrue over time despite potential fluctuations in day-to-day disease symptom scores. We agree but would like to ensure that there is no potential for misinterpretation. We have made the point in the	The ERG does not consider this to be a factual inaccuracy but an augmentation of the text. No amendment required.

treatment through a fluctuating response. This statement could be misinterpreted to state that treatment is withdrawn at any time point in the model after initial response is 'lost'. This is not the case.	*and so test a second efficacy response assessment point at 24 weeks in scenario analysis for those patients with initial partial response who may subsequently improve with continued treatment beyond 16 weeks'*	company submission and above that reliance on scoring tools alone such as EASI to judge efficacy response is not optimal and that a holistic approach considering signs, symptoms and quality of life is required. We would also like to emphasise that the binary nature of an efficacy response decision at a single point in time may not be optimal for some patients. Hence we have tested the inclusion of a second assessment point in scenario analysis in the spirit of the wording in the SmPC: '*…for patients with initial partial response who may subsequently improve with continued treatment beyond 16 weeks'* Assessment at 24 weeks was shown to have minimal impact on the ICER.	

Issue 7 Alternative explanation for the treatment effect in the BSC arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5, Section 1.5, paragraph 2 BY way of explanation for the treatment effect in the BSC arm the ERG offers the following explanation:	No amendment is proposed	We acknowledge the ERG speculation about alternative explanations for the response in the BSC arm. However we strongly dispute that natural waxing and waning could be an explanation for	The ERG does not consider this to be a factual inaccuracy. No amendment required.

For example, an alternative explanation for response in the placebo arm could be natural waxing and waning See also Page 66, paragraph 1		the benefit seen in either arm of the study. It is not credible to assume that in a large cohort of patients a sudden natural sustained waxing in patient response would be observed. Any natural fluctuations in disease would be more likely 'cancelled out' allowing for the treatment effect to be observed. As the ERG note this is one of the key properties of an RCT. Inspection of of the key efficacy graphs from the trial program show that, for example, LS MEAN change from baseline in EASI and DLQI occurs rapidly in the first 2 to 4 weeks of the studies for both BSC and dupilumab treated patients. (For an example see Figures 2.9 and 2.11A from the CHRONOS study in the company submission). Although it is difficult to specify duration for waxing and waning, the observed rapid improvement in signs and quality of life in the studies occurs more quickly than the average duration of a flare (which may be several weeks). Assessment in the studies is likely to be more granular than the duration of fluctuations in the disease and so any such 'natural'	

		effect would be observable in the measure of variance around each time point. In all cases the small error bars indicate that the variance within the data sets is low and that improvements are consistent within the cohorts. (Figures 2.9 and 2.11A). Error bars would be larger if the effect were due to sudden waxing of patients as the natural course of the disease between patients will be different. Similarly if natural waxing is an explanation for the sudden improvement in all patients then conversely natural waning must also be invoked. This is not seen in the long term CHRONOS study where response is maintained over the 52 week period. Durable response is also seen in the other shorter term studies. See also the justification for issue 12 below which includes discussion of the treatment effect in the BSC arm.	

Issue 8 Missing HADS instrument description

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9, Section 2.1, paragraph 1 The report states that:	We request that the following amendment is made…	This more fully reflects the instruments used.	The ERG does not consider this to be a factual inaccuracy but an augmentation of the

The improvement of these signs and symptoms is measured by the Dermatology Life Quality Index (DLQI) for impact on quality of life and mental health. The HADS instrument is missing from this description	*The improvement of these signs and symptoms is measured by the Dermatology Life Quality Index (DLQI) for impact on quality of life and by the Hospital Anxiety and Depression Scale (HADS) for impact on mental health.*		existing text. No revision required.

Issue 9 Missing FDA breakthrough therapy designation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, Section 2.2, paragraph 2 The report states that: *On 28-03-2017, the U.S. Food and Drunk Administration (FDA) approved dupilumab for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.* The FDA breakthrough status is missing from this description	We request that the following amendment is made… *On 28-03-2017, the U.S. Food and Drug Administration (FDA) approved dupilumab for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The FDA granted Breakthrough Therapy Designation In November 2014.*	This section deals with the regulatory status of dupilumab and also refers to the EAMS designation in the UK. It is also important to note that the FDA has also acknowledged the importance of both the disease area and the innovative nature of dupilumab through the granting of breakthrough therapy designation.	The ERG does not consider this to be a factual inaccuracy but an augmentation of the existing text. No revision required.

Issue 10 Missing footer

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, Figure 1 The Sanofi additions to the IEC algorithm are marked with an asterisk*. This was intended to indicate where we had made an addition. The footnote related to this is missing	We request that the following footnote is included below the figure. *Sanofi adaptation	It is not clear why there is an asterisk in the diagram if the footnote is missing. We are keen to ensure that our adaptation of the IEC algorithm is clear in order to remove the possibility of confusion about where additional steps have been added.	The ERG agrees that the footnote is missing. Amendment made as requested.

Issue 11 Description of the comparison with ciclosporin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, Section 3.3, paragraph 3 The report states that: *The company compared ciclosporin with dupilumab in a scenario analysis using a MAIC.* This suggests that the results from the MAIC were used in the cost-effectiveness scenario analysis. This is inaccurate.	We suggest that the following addition is made… *The company carried out MAIC in order to examine the relative efficacy of dupilumab and ciclosporin. The results suggest that dupilumab is more efficacious than ciclosporin, however the analysis was associated with a high degree of uncertainty and therefore the MAIC was not used in the cost effectiveness analysis. For the scenario comparing dupilumab with ciclosporin equivalent efficacy was assumed.*	This is inaccurate because the results from the MAIC were not used in the scenario analysis comparing dupilumab vs. ciclosporin.	Thank you. Factual inaccuracy noted. We have replaced the offending sentence with the following…. "*The company compared ciclosporin with dupilumab in a scenario analysis assuming equivalent efficacy over the common treatment period".*

Issue 12 Uncertainty surrounding the resource use parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54, Table 11, 'Probabilistic modelling' The report states that: *The ERG note that no distributions were assigned to resource use parameters in the model, which result in some underestimation of the decision uncertainty.* This is correct but uncertainty is captured in these estimates by increased intervals applied around the costs for these parameters See also page 77, paragraph 2	We suggest that the following addition is made… *The ERG note that no distributions were assigned to resource use parameters in the model, which may result in some underestimation of the decision uncertainty. However the company did vary the costs for these parameters by ±50% in an attempt to capture uncertainty in both cost and use.*	We acknowledge that no distributions were assigned to the resource unit parameters and they were not varied separately in sensitivity analysis. However in an attempt to capture uncertainty in these estimates we tested a high variation in the costs of the resource parameters in sensitivity analysis. In order to reflect the uncertainty in both of these parameters the unit costs were varied by 50%. This large variation is likely to be a conservative estimate and decision uncertainty may be overestimated as a result.	The ERG acknowledge the company's approach to incorporating uncertainty in the unit cost variables on page 109 of our report. However, we felt this might underestimate the uncertainty as it is the applied difference in resource use that will drive the expected difference in costs between responders and non-responders. The ERG does not consider this to be a factual inaccuracy but an augmentation of the existing text. No amendment required.

Issue 13 Extrapolation of treatment effect applied to patients on BSC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65, paragraph 1. The report states: *The rationale provided for this assumption is outlined in B 3.3.6 of the CS, and is centred on the*	We suggest the following text amendment: *The rationale provided for this assumption is outlined in B 3.3.6 of the CS, and is centred on the argument that quality of life benefits observed in the BSC arms of the relevant trials, were likely protocol driven effects related to*	A proportion of patients in the BSC arm met the primary end points and so for BSC patients a significant utility benefit was observed in aggregate It is likely that the higher than	The ERG acknowledges the company's suggestion but considers it an augmentation of the existing text rather than an amendment of a factual inaccuracy. No revision

argument that quality of life benefits observed in the BSC (placebo) arms of the relevant trials, were likely protocol driven effects related to improved adherence to topical treatments, which would not be observed outside the trial setting. This represents only part of the argument we have used to support the effect. In addition it is important to note that BSC is not placebo as might be suggested by the 'juxtaposition of 'BSC' and '(placebo)'	*placebo effect, improved adherence to topical treatments (which were recorded in a patient diary) and increased psychological support which is an important factor in AD, derived from increased (biweekly) clinician meetings with the clinician when appropriate measures are taken to tackle worsening in symptoms. The company argues that these factors are likely to contribute to an improvement in signs, symptoms and QoL and may reduce or prevent exacerbations of AD. The company states that the influence of these factors would not be durable outside the trial setting.*	expected BSC utility response recorded in the studies (particularly in CAFÉ and CHRONOS where TCS was used in combination with dupilumab as required) is due to a number of factors: • Placebo effect • Poor compliance with topical medications in the real world • Trial protocol supported adherence to topical treatments leading to better outcomes for some patients • Protocol driven 'psychological support' (an important factor in AD) • Mandated patient diary • Biweekly meetings with the clinician when appropriate measures were taken to tackle worsening in symptoms. This is evidenced by the higher use of rescue therapy in the BSC arm (eg In CHRONOS 16% of dupilumab treated patients received rescue compared with 53% of patients in the BSC arm) It is unlikely that such a high rate of clinical visits and therefore prompt treatment of exacerbations would occur outside the trial setting. This means that on return to real world	required. Further, section 5.2.6 (pages 71-73) of our report expands further on the company's rationale for these assumptions with respect to extrapolation of utility gains.

		clinical practice patients may experience more and worse exacerbations. This is documented in the literature (See New Engl J Med 2016;375:2335-48 for an example). This effect is also likely to contribute to the return to base line levels of quality of life. All of these factors are likely to contribute to an improvement in the signs, symptoms and QoL for patients and to reduce or prevent exacerbations of AD. We tested these arguments with a number of clinicians who all agreed that the BSC response in the studies would not be durable in real world clinical practice. We have supported these arguments by reporting the considerable preference observed in a Time Trade Off exercise for reduction in topical treatment regimens. The literature also reports that patients in the real world are poorly compliant with topical dermatological preparations due to their burdensome nature and unpleasant cosmetic characteristics along with the widely accepted fear of steroids. The use of topical treatments is also likely to reduce in the real world setting in patients successfully	

		treated with dupilumab; however there is an important distinction. Clinical experts consulted by us and by the ERG have agreed that patients would be likely to reduce the use of the topical treatments by as much as 80% as their skin and symptoms clear and that the treatment effect due to dupilumab would persist. The studies also show a reduction in TCS use by ~50% for dupilumab treated patients. This is consistent with a preference for less topical treatment. Patients on BSC, for the reasons described above, may reduce the use of topical treatments (their only medication) after leaving the protocol driven trail setting and this is likely, in part, to contribute to a return to pre-trial levels of AD signs, symptoms and QoL impairment. We note that the ERG did not seek the opinion of the clinical expert on the likelihood of maintaining treatment effect in the BSC arm after the end of the studies.	

Issue 14 Discontinuation rate applied to dupilumab responders.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65, paragraph 1. The report states: *It is not entirely clear to the ERG why these further discontinuations are applied on top of the observed discontinuation rates reported in Table 15 above.* This does not acknowledge that sensitivity analysis that was carried out to examine the effect of no discontinuations in the dupilumab arm according to levels returned from the trial investigator questionnaire.	We suggest the following text amendment: *It is not entirely clear to the ERG why these further discontinuations are applied on top of the observed discontinuation rates reported in Table 15 above. However the company does explore the effect of not including the estimated discontinuation rates in the dupilumab arm of the model in sensitivity analysis.*	We acknowledge that the discontinuations in the dupilumab arm are included on top of the natural attrition rate for the first 5 years in the base case model however sensitivity analysis was carried out to examine the effect of removing the trial investigator estimates. This is reported in the one way sensitivity analysis tables as '*No decline in the Dupilumab treated patients'*. In these analyses the ICER is marginally reduced.	The ERG acknowledges the company's suggestion but considers it an augmentation of the existing text rather than an amendment of a factual inaccuracy. No revision required.

Issue 15 Frequency of injection site reactions applied in the modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67, paragraph 2 The report states that: *However, the company note that injection site reaction is assumed to be one-time event, with costs occurring only in the first cycle for dupilumab. Little justification is offered for this assumption, and the ERG believe it may have been*	We suggest the following text amendment: *The company note that an injection site reaction is assumed to be one-time event, with costs occurring only in the first cycle for dupilumab. In response to a clarification question the company provided justification for this assumption based on their use of the entire injection site reaction data set and the observed rate of injection site reactions for those patients*	We recognise that the inclusion of an injection site reaction (ISRs) solely in cycle 1 of the modelling may appear to underestimate the impact of this adverse event. However, in clarification we offered further evidence to support the assumption and suggested that in fact we took a conservative approach to assigning ISR	The ERG acknowledges the company's suggestion but considers it an augmentation of the existing text rather than an amendment of a factual inaccuracy. No revision required.

more appropriate to apply the rate for this adverse event on cycle-by-cycle basis in the dupilumab maintenance treatment state.	*who had a reaction in the CHRONOS study. However the ERG believe it may have been more appropriate to apply the rate for this adverse event on cycle-by-cycle basis in the dupilumab maintenance treatment state.*	frequency for use in the modelling. We acknowledge that the simplifying assumption may not reflect the natural pattern this event however the risk is applied to the overall cohort in cycle 1 as opposed to a sub-cohort which would be required if the event were made time dependent. This was done by including the total number of events observed in the studies and adjusting for patient years. In this way all ISRs were accounted for. We also provided a commentary of the number of ISRs for patients in whom an ISR was observed. The data from CHRONOS shows that the majority of ISRs occurred only once for those patients with any ISR over the course of 1 year and that ISRs become much rarer over time. This indicates that patients learn to self-inject more The inclusion of ISRs on a cycle-by-cycle basis is very unlikely to impact the ICER due to the low rate of reactions. Nonetheless we believe that we provided robust evidence to support the inclusion of ISRs in cycle 1 only.	

Issue 16 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, paragraph 5 *The ERG agree that the LIVERTY AD trial data represents the best available source of utility data for the current appraisal.*	We request the following text amendment: *The ERG agree that the LIBERTY AD trial data represents the best available source of utility data for the current appraisal.*	Minor typographic error in the trial programme name.	Inaccuracy acknowledged. Typographical error noted and erratum provided.

Issue 17 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69, paragraph 1 The report states the following: *The ERG note that in section B3.3.3 of the CS, it states that it was the mean changes in the EASI and pruritus scores from baseline that were included in the mixed regression models, but this is not the ERGs understanding from the way the estimated coefficients are presented and applied in the model.*	No amendment is proposed. We apologise that the text in Section B3.3.3 is misleading. The regressions were fitted using total EASI score and weekly average of peak daily pruritus, not change from baseline values.	For completeness the relevant text in Section B3.3.3 in the dossier should read: Mixed models were fitted for each trial using a forward selection process, controlling for baseline age, gender and EQ-5D utility score using the following variables: • Total EASI score • Total weekly average of peak daily pruritus NRS • Interaction between total EASI score and total weekly average of peak daily pruritus • Treatment (dupilumab Q2W, dupilumab every week, or	The ERG does not consider this to be a factual inaccuracy. No amendment required.

		BSC)	

Issue 18 Incomplete description of indirect costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84, paragraph 2 The report states the following: *Therefore, the company submission states that 4.3 and 12.9 days of lost productivity per year have been implemented in the model for responders and non-responders, respectively. The ERG identified a mismatch between these reported days of lost productivity and those implemented in the model. The number of days lost to work in the Excel model correspond to estimates from the AWARE study (Sanofi Genzyme, unpublished data, 2017) and are higher than those referred to in the company submission (i.e., 11.7 and 53.7 for responders and non-responders, respectively).* This was an oversight on our part. However, the correct numbers used in sensitivity analysis and the ICERs reported in the dossier	We request the following text addition: *Therefore, the company submission states that 4.3 and 12.9 days of lost productivity per year have been implemented in the model for responders and non-responders, respectively. The ERG identified a mismatch between these reported days of lost productivity and those implemented in the model. The number of days lost to work in the Excel model correspond to estimates from the AWARE study (Sanofi Genzyme, unpublished data, 2017) and are higher than those referred to in the company submission (i.e., 11.7 and 53.7 for responders and non-responders, respectively). However the ICERs reported in the company submission do derive from the stated 4.3 and 12.9 days of lost productivity per year.*	We apologise that the submitted model had the incorrect number of days lost to work implemented in it, this was an oversight on our part. We have checked the submission model and have noted that in the Excel spreadsheet the number of days per month is mistakenly entered as the AWARE data. We believe these data are likely to be an overestimate of productivity loss and so we used values from the literature to calculate more conservative estimates. (4.3 and 12.9 days as stated in the company submission). However in tables 3.45 and 3.46 in the company submission the ICER is correctly reported using 4.3 and 12.9 days of lost productivity per year for the calculation.	Factual inaccuracy acknowledged. Text has been replaced on page 84 and page 101: "*The ERG identified a mismatch between these reported days of lost productivity and those provided in the company model (11.7 and 53.7 for responders and non-responders), which were derived from the AWARE study (Sanofi Genzyme, unpublished data, 2017). However, upon closer inspection the ICERs reported by the company do derive from the stated 4.3 and 12.9 days of lost productivity per year.*"

are correct. See also Page 101, paragraph 1			

Issue 19 Replication of scenarios 15 and 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84, paragraph 2 The report states the following: *Note, based on the details described in the company submission, the ERG were unable to replicate scenarios 15 and 17 in the Tables below.* See also Page 101, paragraph 2	No amendment is proposed.	We apologise that the information required to replicate scenarios 15 and 17 was not clear or incorrect in the company submission (CS). **Scenario 15** is based on a simple adjustment made to the model engine which changes the decision point from 16 to 24 weeks. We can supply an amended model to support this scenario analysis if required. **Scenario 17** is based on the data provided in the one way sensitivity analysis tables. However there was a mistake in the number of primary care visits for non-responders implemented in the modelling. The value observed (and tabulated in the CS) was 4.78 but the value used to calculate the scenario analyses was 4.70. The original and corrected scenario ICERs are provided below:	No amendment required.

Population	Erroneous CS ICER	Corrected ICER
CAFÉ + CCL	£25,770	£25,757
SOLO CL	£22,164	£22,154

Issue 20 Selective use of data from the case note review

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106, paragraph 1 The report states the following: *The company stated that this is an ongoing study, and further noted that their rates were calculated based on data from 30 patients collected in year three of the study. They justify this with the statement that these data are the most recent and most complete. On inspection of the Table I-15 in the Appendices, the ERG note that data are also reported for 30 patient in year 2 and 25 patients in year 1. It is not clear why the company did not utilise this data. Therefore, the ERG explored the impact of using all the available data to recalculate the resource use event rates, assuming each patient in each year of the study contributes one year at risk*	No amendment is proposed. We have now received the full data set of 60 patients from the case notes review and can provide this evidence if required.	It is correct to state that the data used in the analysis was taken from the most recent year of the study and not the 'average' use recorded. It is important to note that in year 1 of the study not all patients had a full record for the year and so the number of events is probably underestimated for this year. Hence we do not support the use of all three years' worth of data in the analysis. The data in the CS were taken from an interim data cut of 30 patients. We have now received the full data set of 60 patients and can provide this evidence if required. Using the data from the last two years in this full data set the number of events is largely consistent with the ERG calculated resource use event rates. We note that the resource use for dupilumab responders in the ERG analysis has been calculated according to the multipliers taken from the market research. We used these multipliers in the CS where there was no other data or opinion for responder rates. However for	The ERG acknowledges the company's further clarification and data.

		events such as GP and consultant visits we had strong direction from clinicians about the number of events that would be expected for dupilumab. These are lower than the ERG adjustments. It is also worth noting that the clinical experts consulted by the ERG felt that resource use event rates were underestimated in the modelling. This means that the incremental cost benefit associated with dupilumab treatment is likely to be undervalued. Hence we believe that the ICERs associated with the updated ERG resource use estimates are overestimated/	

Aberdeen HTA Group

Dupilumab for treating moderate to severe atopic dermatitis

Erratum

Completed 23 February 2018

This report was commissioned by the NIHR HTA Programme as project number 16/168/08.

This document is intended to replace pages 8, 13, 18, 68, 84 and 101 of the original ERG assessment report for *Dupilumab for treating moderate to severe atopic dermatitis,* which contained a few inaccuracies. The main issues relate to changes in phrasing to avoid misunderstanding. The amended pages follow in order of page number below.

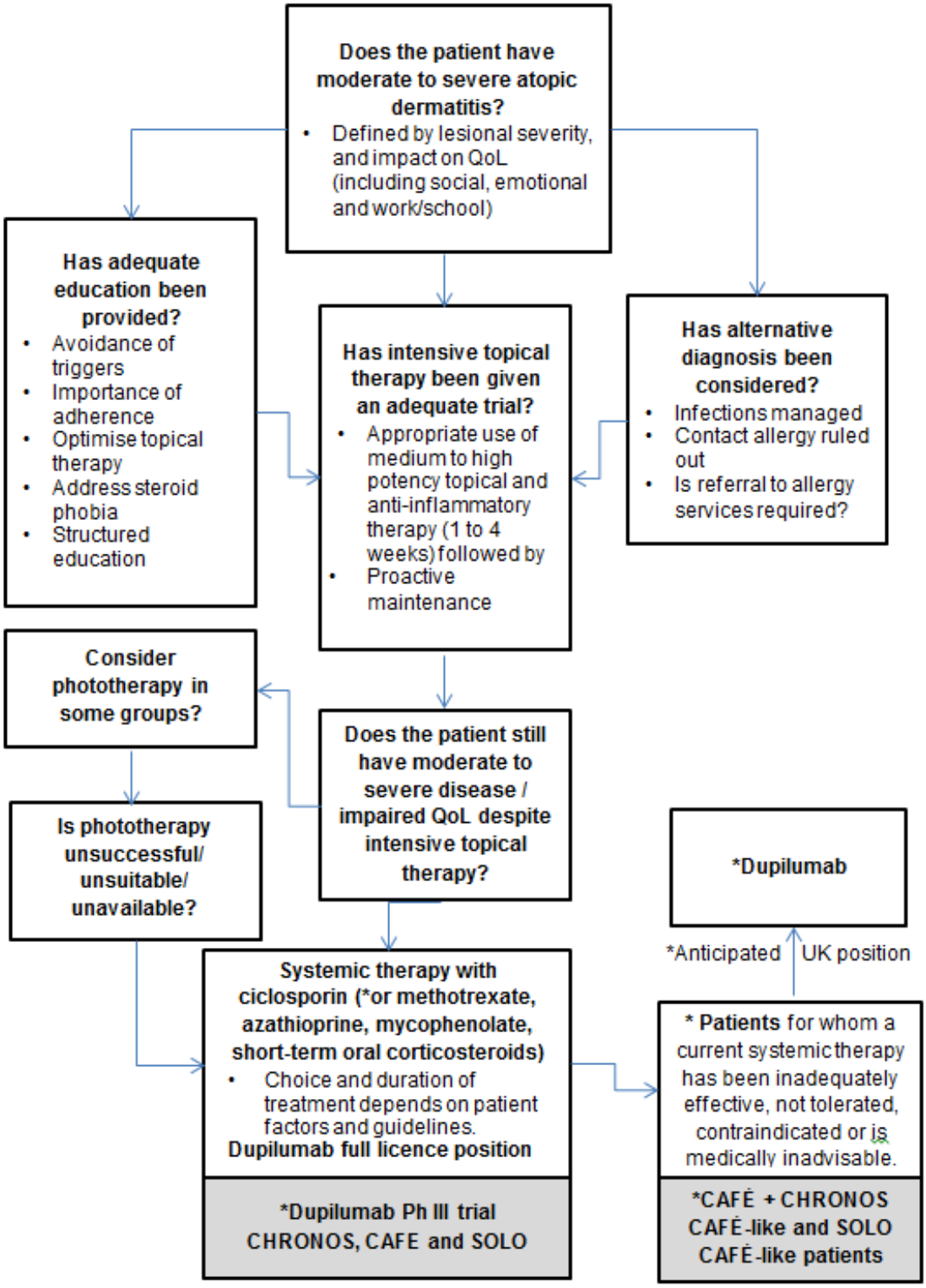
2 Background

2.1 Critique of company's description of underlying health problems

The company's description of atopic dermatitis (AD) in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem. Atopic dermatitis is a chronic, pruritic, inflammatory dermatitis that is remitting-relapsing in nature.[1] It is characterised by chronic or relapsing red and inflamed skin (erythema), thickened and leathery skin (lichenification), dry skin (xerosis) and an intense itch (pruritus).[2] Atopic dermatitis can be a major burden for patients due to sleep loss, psychosocial challenges and missed work.[3] The terms 'atopic dermatitis' and 'atopic eczema' are synonymous and tend to be used interchangeably in the literature.

Incidence or lifetime prevalence of atopic eczema symptoms in the UK increased by more than 10% between 1990 and 2010 .[4] Atopic dermatitis is more common in children and the majority of children with AD no longer have symptoms by adulthood .[5] Prevalence of AD in adults in the UK has been reported as 2.5% with 53% to 67% of those having moderate to severe disease (depending upon the instrument of assessment of severity).[6] In contrast, the company reports that 7% of people diagnosed and treated for AD have moderate-to-severe AD, based on data which was not available to the ERG.

Hospital Episode Statistics for Admitted Patient Care in England from 2016-2017 show that there were 1,258 finished consultant episodes and 1,135 admissions for "AD, unspecified" and "other AD" (codes L20.8 and L20.9).[7] The mean age of "other AD" patients was 16 years and the 227 finished consultant episodes and 197 admissions resulted in 41 day cases. The mean length of stay was 3 days. Patients who were categorised with "AD, unspecified" were older, with a mean age of 29 years, and stayed for a mean of 4 days. For these patients, there were 1,031 finished consultant episodes, 938 admissions and 568 day cases. Of all patients who had outpatient appointments, 2,353 of attendances were classified "other AD" (code L20.8) and 5,521 were "AD, unspecified" (code L20.9). It should be noted that, according to NHS Digital, primary diagnosis is not a mandated field in the outpatient dataset, and,



*Sanofi adaptation

Figure 1 Company's anticipated positioning of dupilumab in clinical practice (adapted from the IEC algorithm) (reproduced from Figure 1.6 of the company's submission)

present a comparison with indirect comparison (MAIC) in	13	*ciclosporin using a mixed adjusted scenario analysis*.

The company's justification for not including phototherapy or oral steroids as comparators was that they are short-term treatment options only and not for chronic, long-term continuous treatment of AD. In addition, the company points out that the recent International Eczema Council treatment algorithm places phototherapy after intensive topical therapy has failed and before systemic therapy. The ERG's clinical expert agrees that phototherapy is not a long-term treatment option but is of the opinion that phototherapy can be a constituent of BSC in clinical practice in the UK, as it can be used in the short-term to induce remission and can have lasting effects. The ERG's clinical expert agrees that alitretinoin is not a valid comparator as it is licensed for hand eczema only, which is a distinct condition in its own right. The company did not include ciclosporin as a comparator, with the justification that the evidence base of dupilumab compared to ciclosporin is sparse and that the treatments would not, in any case, occupy the same place in the treatment pathway. The company compared ciclosporin with dupilumab in a scenario analysis assuming equivalent efficacy over the common treatment period. Ciclosporin is currently the only licenced therapy for AD. Other immunosuppressive therapies (azathioprine and methotrexate) are currently used in UK clinical practice if ciclosporin fails.

3.4 Outcomes

The outcomes specified in the NICE final scope were: measures of disease severity; measures of symptom control; disease-free period/maintenance of remission; time to relapse/prevention of relapse; adverse effect of treatment; health-related quality of life. The company stated: *clinical outcomes supported by evidence from the LIBERTY AD trial programme are reported addressing all the points raised in the scope.* The trials in the LIBERTY AD programme reported time to first rescue treatment as

opposed to disease-free time to relapse/prevention of relapse;	18	period/maintenance of remission or the ERG's clinical expert considers

these outcomes to be equivalent. The outcomes used by the company in the economic model were stated as: measures of disease severity (for example, according to absolute EASI or IGA scores); measures of symptom control according to relative EASI scores (reduction in absolute score);

predict utility values for the pooled base case populations; and 3) dichotomise the fitted values by responder status (in the dupilumab arm). As an alternative approach, the company apply the observed rather than regression fitted values as a sensitivity analysis.

Sources of health-related quality of life data

Table 3.9 in Document B of the CS summarises and compares the results of a systematic literature review (SLR) to identify relevant HRQoL data. These include published dupilumab studies[31, 33] as well as previous technology appraisals which report utility data for adults with various severities of AD.

Simpson[33] *"reports findings from a Phase IIb trial for dupilumab across seven countries; 380 patients with moderate-to-severe AD provided EQ-5D-3L data. Baseline utilities ranged from 0.578 to 0.658 and mean utility increments at 16 weeks were reported for placebo (0.028) and for the intervention (range: 0.106 to 0.240)."*

Simpson[31] conducted a pooled analysis of EQ-5D response data from 1,379 patients enrolled in the SOLO 1 and SOLO 2 trials. Baseline utilities ranged from 0.607 to 0.629 and mean utility increments at 16 weeks were reported for placebo (0.031), dupilumab 300 mg once weekly (0.207) and dupilumab 300 mg every two weeks (0.210).

Whilst the company's systematic literature review did not identify any published studies focusing specifically on the analysis of EQ-5D data from the CAFÉ or CHRONOS trials, the company have presented further analyses of these data in their submission. The company note that the utility data in the LIBERTY AD trials were collected using the EQ-5D-3L instrument and valued using the UK general population tariff. Apart from the published dupilumab studies, few other studies identified in the company's literature review used the EQ-5D instrument directly to measure HRQoL in patients with moderate to severe AD. The ERG agree that the LIBERTY AD trial data represents the best available source of utility data for the current appraisal.

GP or optometrist visit prior to referral. However, the small additional cost of a pre-referral visit to a GP would unlikely have a significant impact on results.

Indirect costs

The model includes an option to consider indirect costs as a sensitivity analysis. The company submission indicates that indirect costs are based on estimates of absenteeism for the UK, and a reported three-fold increase in the rate of absenteeism for people with moderate-to-severe AD in the 2013 National Health and Wellness survey. The average number of days lost to work in the UK for 2016 was 4.3.[51] Therefore, the company submission states that 4.3 and 12.9 days of lost productivity per year have been implemented in the model for responders and non-responders, respectively. The ERG identified a mismatch between these reported days of lost productivity and those provided in the company model (11.7 and 53.7 for responders and non-responders), which were derived from the AWARE study (Sanofi Genzyme, unpublished data, 2017). However, upon closer inspection the ICERs reported by the company do derive from the stated 4.3 and 12.9 days of lost productivity per year.

The weighted average of full and part-time employment wages (per hour) from the ONS,[52] were used in conjunction with the percentage of individuals employed in the AWARE study, and the weighted average of full and part-time employment hours per work day,[52] to obtain a unit cost per day of work lost in the model.

5.2.8 Cost effectiveness results

All the final data inputs and assumptions applied in company base case analyses are summarised in Table 3.38 and Table 3.39 of the company submission (Document B, pages 206-212).

Company base case results

The company base case results are reproduced below for the CAFÉ + CHRONOS CAFÉ-like population and the SOLO CAFÉ-like populations. These results relate to the base case population of "*patients who have been optimised on topical therapies and an immunosuppressant but for whom these therapies have failed, are contraindicated or are not tolerated*" (company submission, section B 3.6.1). The presented results include the confidential patient access scheme.

The ERG checked the model calculations and carried out a number of diagnostic checks. Whilst no calculation errors were found, the ERG did identify a mismatch between the reported number of days of absenteeism in the company submission and the number actually applied in the model. However, the reported ICERs do derive from the input values stated in the company submission and only apply in two sensitivity analyses that incorporate indirect costs. In addition, the company applied a value of 0.25 A&E admissions per patient year in the model (for non-responders), but the original data source suggests a value of 0.1. This has a negligible impact on results. The ERG also conducted a number of checks to ensure coherence of the QALY and life-year calculation. It was not possible to assess the external validity of the model due to a lack of available existing longitudinal data on the long-term quality and response status of moderate-to-severe AD patients. The biggest assumption of the model is the setting of health state utility to baseline in BSC patients during the extrapolation, rather than carrying forward the observed placebo arm utility gain, and this cannot be verified by observed longitudinal data.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Given that the NICE DSU guidance seems to favour a multiplicative approach to adjusting and combining health state utilities for age and comorbidities, the ERG first of all reproduced the company's tables of deterministic sensitivity analysis using this method. These results are presented in Table 32 for the CAFÉ + CCL cohort and Table 33 for the SOLO CAFÉ-like cohort. As noted previously, the ERG were unable to reproduce two of the scenarios based on the information provided in the company submission: i) Scenario 15, which assumed an additional efficacy assessment at 24 weeks for partial responders to dupilumab at 16 weeks; and ii) an analysis that incorporated costs based on market research (described in section B 3.4.4 of the submission) to elicit dermatologists' perceptions of the resource use requirements for responders and non-responders. The impact that these changes had when using the additive approach to utility adjustment, can be reviewed in Tables 26 and 27 above.

It can be noted that the ICERs in all assessed deterministic scenarios increase slightly with the multiplicative approach to age adjustment of utility (Tables 32 and 33) compared with the additive approach (Tables 26 and 27).