Dupilumab for treating adults with moderate to severe atopic dermatitis

Produced by Aberdeen HTA Group

Authors

Rodolfo Hernández[1]
Moira Cruickshank[2]
Maria Dimitrova[1]
David Cooper[2]
Lorna Aucott[2]
Cynthia Fraser[2]
Michal Shimonovich[2]
Anthony Ormerod[3]
Graham Scotland[1, 2]
Miriam Brazzelli[2]

1 Health Economics Research Unit, University of Aberdeen
2 Health Services Research Unit, University of Aberdeen
3 NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK

Correspondence to

Clinical effectiveness
Miriam Brazzelli
Senior Research Fellow
University of Aberdeen
Health Services Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: m.brazzelli@abdn.ac.uk

Cost-effectiveness
Graham Scotland
Senior Research Fellow
University of Aberdeen
Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

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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]

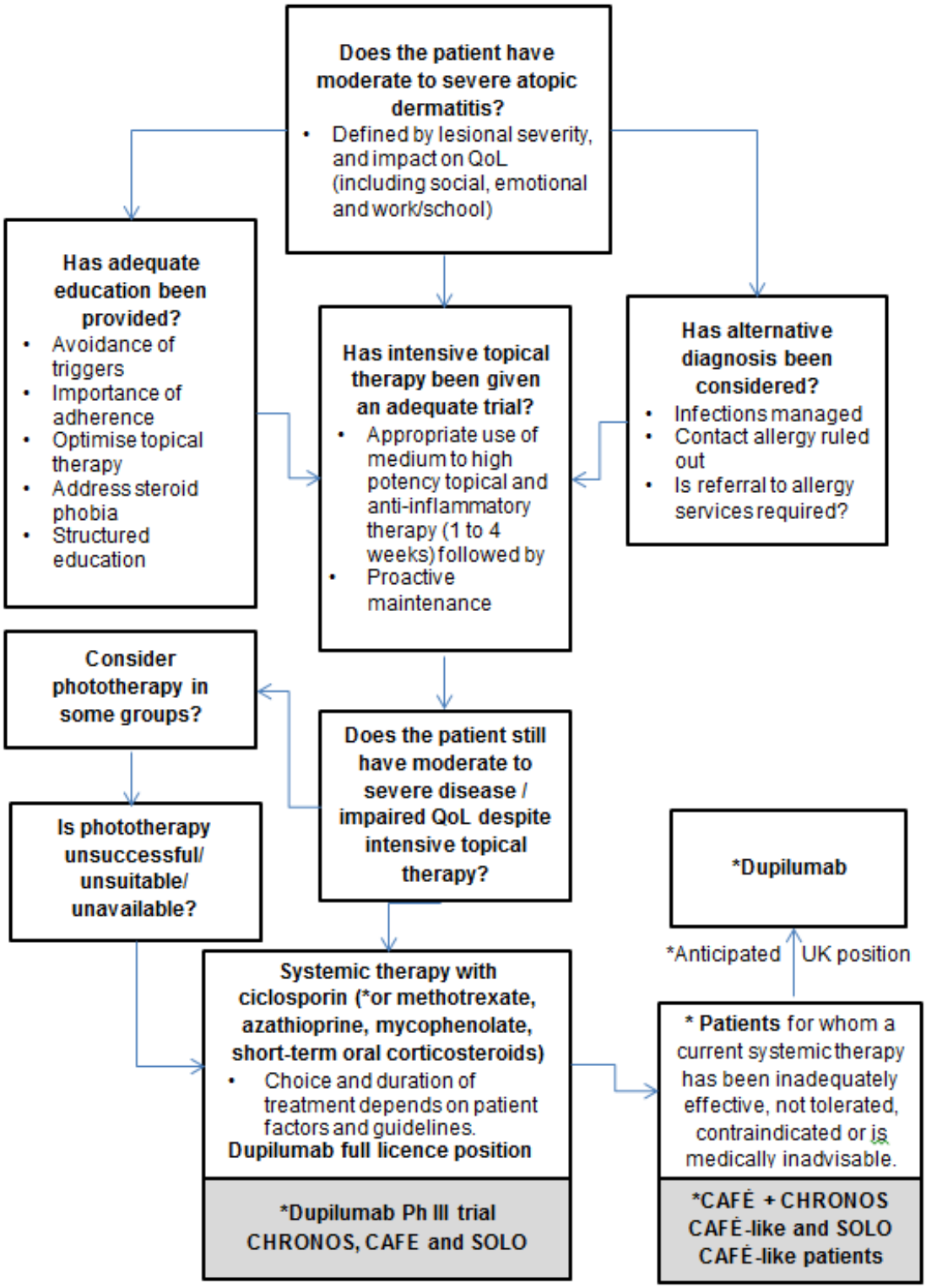


Figure 1 Company's anticipated positioning of dupilumab in clinical practice (adapted from the IEC algorithm) (reproduced from Figure 1.6 of the company's submission)

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 $\geq$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.

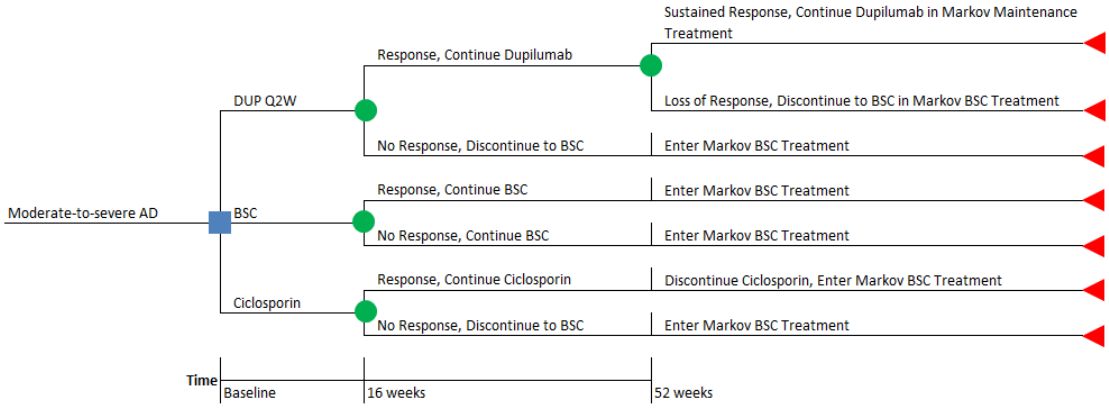


Figure 2 Short-term decision tree (Source: Company submission, Document B, Figure 3.3,)

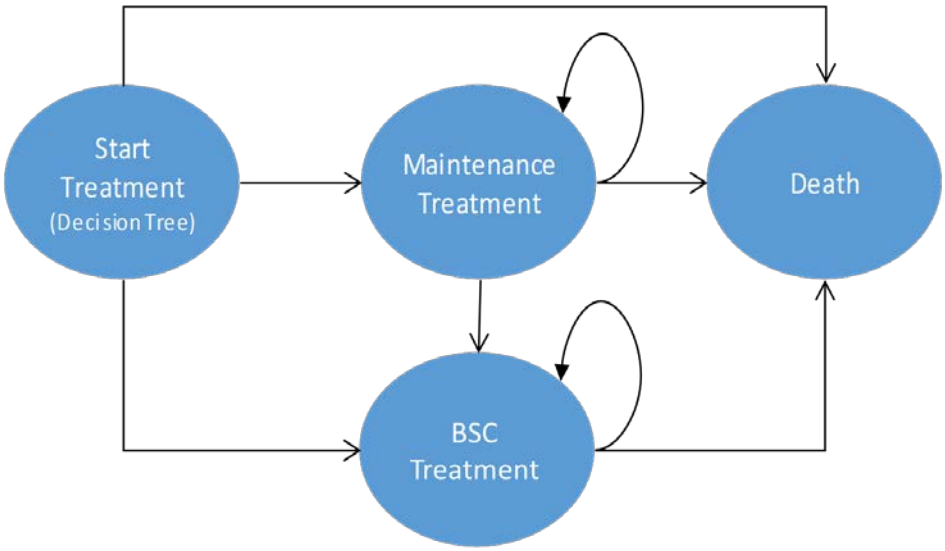


Figure 3 Long-term Markov model (Source: Company submission, Document B, Figure 3.4,)

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

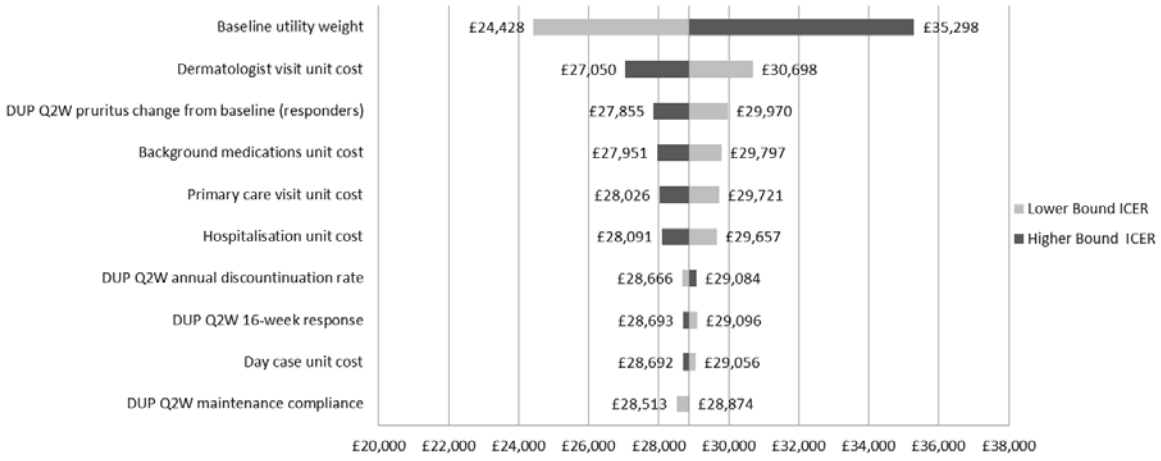
The probabilistic sensitivity analysis for the base case populations were based on 10,000 probabilistic iterations of the model. For the base case CAFÉ +CCL cohort, dupilumab was associated with an expected incremental cost of [redacted] for a mean incremental QALY gain was [redacted]. The corresponding 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

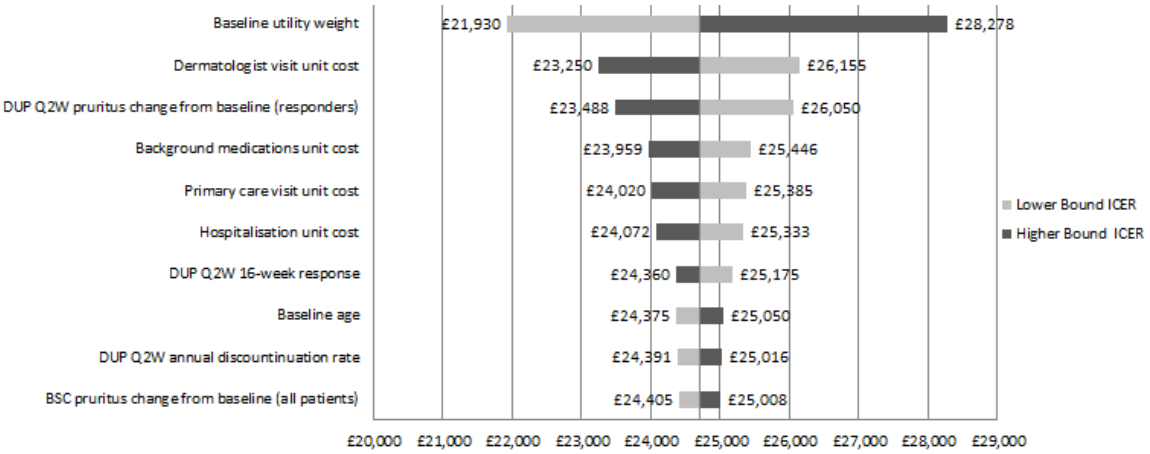
The company present also deterministic one-way sensitivity analyses on the 10 parameters to which the model results were found to be most sensitive. The results are reproduced in the form of tornado diagrams in Figures 4 and 5 below. The vertical line in the diagrams represents the base case ICER for 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