NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Sanofi – comments on the ACD
   - Sanofi – appendices
   - Allergy UK
   - National Eczema Society
   - British Association of Dermatologists
   - Centre of Evidence Based Dermatology

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Critique of the additional information submitted by the company from the Evidence Review Group**

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

Dupilumab for treating moderate to severe atopic dermatitis [ID1048]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	British Association of Dermatologists (the BAD)	From a clinical perspective, following experience of limited use in trials and during the EAMS phase, the BAD would like to highlight the life-transforming nature of dupilumab treatment in many patients. People with severe atopic eczema are a high-need population who have few treatment options (most of which are unlicensed and have very little or no evidence base) [Roekevisch, J Allergy Clin Immunol 2014,133: 429-38]. As dermatologists, we are exposed to NICE-approved, high-cost drugs for dermatological disease and have gained experience of the appropriate ratio for cost effectiveness in clinical practice. We strongly believe that the benefit accrued by dupilumab to patients with (severe) atopic dermatitis should be supported by the NHS and disagree with the decision to reject funding for this treatment.	Comments noted. The final appraisal document (sections 3.1, 3.12 and 3.24) recognises the limited treatment options available to people with atopic dermatitis, the clinical effectiveness and innovation of dupilumab.
2	Consultee	British Association of Dermatologists (the BAD)	Based on expert opinion, the BAD considers that best supportive care is not well represented by the placebo arm of these trials. The reduction of topical corticosteroids usage amongst those on the dupilumab arm (despite failure to achieve 100% clearance) as shown in the CAFÉ trial, but continued use in the placebo arm, suggests that the observed positive effects of dupilumab vs. placebo would have been greater if topical corticosteroids usage had been continued. We predict that the placebo response would regress towards baseline if followed for a longer time period as patients gradually give up on the intensive topical therapy required to maintain the placebo response. This is supported by the NICE analysis which shows that *with* best supportive care, EASI50 & DLQI $\geq$ 4 responders drop off much more significantly in the placebo/best supportive care groups (25% loss) than in the dupilumab groups (4-5% loss) between 16 and 52 weeks across all studies. Loss of placebo effect should be incorporated into the model.	Comments noted. In response to the appraisal consultation document, the company amended its definition of 'best supportive care' (see section 3.5 of the final appraisal document).
3	Consultee	British Association of Dermatologists (the BAD)	The health economic model needs to reflect the fact that patients with severe disease are likely to benefit more in terms of QALY change than those with moderate disease. Bearing in mind that disease severity data was captured for all patients, it would be relatively straightforward for Sanofi to provide a subgroup health economic analysis for the cohort of patients with severe disease.	Comments noted. The company did not provide separate evidence based on disease severity.
4	Consultee	British Association of	Patients with severe disease are highly unlikely to remain on best supportive care as this is not tolerable for them (as described in the trial) as they require systemic	Comments noted. The company did not provide separate evidence based on disease severity.

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		Dermatologists (the BAD)	therapy. Therefore, this group will generate increased costs from other areas not currently included in the model. These may include the cost of increased visits to GPs and dermatologists, admissions, complications from inappropriate use of prednisolone and toxicities from high dose systemic immunosuppression (for example nephrotoxicity with ciclosporin, skin cancer with azathioprine)	
5	Consultee	British Association of Dermatologists (the BAD)	We suggest that 'severe' disease (as opposed to moderate) should be defined clinically by atopic dermatitis requiring systemic therapy because of its profound impact on patients' quality of life [Simpson, J Am Acad Dermatol 2017, 77: 623-33] For the purposes of the health economic evaluation, 'severe' atopic dermatitis corresponds to an EASI score of ≥ 21.1 [Leshem, Br J Dermatol 2015,172: 1353-7], mirroring the severity inclusion criterion for the CAFÉ trial (EASI score ≥ 20 at screening and baseline).	Comments noted. The company did not provide separate evidence based on disease severity.
6	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	**Dupilumab is a real innovation** in a field that has been devoid of much progress for 30 years. I welcome such efforts very much. The studies have also been well reported. Dupilumab may be life transforming for those with severe disease, but I can see no data on just severe disease.	Comments noted. The final appraisal document (section 3.24) recognises that dupilumab is innovative.
7	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	I strongly disagree with the idea of applying for a marketing authority for moderate atopic eczema. Some moderate cases are challenging, but the real problem in atopic dermatitis is severe disease. **We do not have a problem in treating moderate disease** with good education and adequate and safe use of topical corticosteroids including proactive (weekend therapy) control. We do not often need to resort to systemics or UV light for such moderate cases. **The problem is the very small proportion with severe disease.** These are the poor folk who we try with UVB and systemics, with mixed success. The company probably realise that the population in need (ie those with severe disease) are too small to offer adequate financial returns for their investment, and therefore are understandably targeting and including the much larger moderate severity atopic eczema population where it is questionable if new drugs are needed. I have yet to see the vital data that shows evidence of effectiveness in just the severe atopic eczema population. Please see: Thomson J, Wernham AGH, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. Br J Dermatol. 2018 Jan 6. doi: 10.1111/bjd.16317. [Epub ahead of print] PubMed PMID: 29315479	Comments noted. NICE normally only appraises a technology within its marketing authorisation (see section 6.1.12 of NICE's Guide to the methods of technology appraisal). The company also did not provide separate evidence based on disease severity.
8	Commentator	Centre of Evidence-Based Dermatology at the University of	There is, as is so often the case, a **complete absence of active comparator trials** eg against standard systemic treatments such as ciclosporin or methotrexate or azathioprine, nor can I see any evidence of any plans to conduct further randomised trials against active comparators ie the most relevant comparison group in order to best understand the role of dupilumab in the treatment pathway.	Comments noted. In the treatment pathway, the company positioned dupilumab after systemic therapies, when best supportive care is the only available option; therefore comparisons with other active treatments were not considered relevant (see section 3.4 of the final appraisal document).

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		Nottingham	Very few doctors use placebos these days. I would have thought that NICE would at least have done a simple network meta-analysis using available data from existing RCTs on existing comparator systemics in your STA background document – this was a bit casual since the data is there. Thankfully, Cochrane Skin are doing one this year, so that should help you.	
9	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	The concept of randomising people with atopic eczema who according to the Lancet abstract had 'an inadequate response to topical corticosteroids' to be randomized to a control group of yet more topical corticosteroid plus placebo for a whole year seems rather **unethical**.	Comments noted.
10	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	Dupilumab used **every 2 weeks is probably just as good as weekly** in terms of trade-off between effectiveness and adverse events in the Liberty and CHRONOS trials, but the study report was strangely silent on making any recommendations on this issue	Comments noted. NICE normally only appraises a technology within its marketing authorisation (see section 6.1.12 of NICE's Guide to the methods of technology appraisal).
11	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	**The concept of treatment failure in existing studies and the post-hoc subgroup analysis is unconvincing**. I appreciate they only refer to ciclosporin (which is the only other licensed systemic), but in reality, it can only be used for around 4 months due to potential kidney damage. We use methotrexate for severe cases with good results and it can be used for years not "short periods" as implied on page 7 of the appraisal. The company should be encouraged to now evaluate dupilumab in those severe cases that have failed on ciclo, methotrexate, azathioprine or MMF as they encourage key dermatologists around the world to try out dupilumab for free.	Comments noted. Dupilumab has been recommended only if '*the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated*'.
12	Commentator	Centre of Evidence-Based Dermatology at the University of Nottingham	It is completely **unclear from the evidence presented how long dupilumab should be** continued – for 6 months to induce remission in order to return to topical therapy for the rest of a person's life?	Comments noted. The final appraisal document recommends to "*Stop dupilumab at 16 weeks if the atopic dermatitis has not responded adequately*". See section 1 of the final appraisal document.
13	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the side effects of current systemic treatment options for severe eczema, which is not responsive to topical management. People are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, and/or starting systemic treatments of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. Only one systemic treatment, ciclosporin, is licenced and with a usual maximum duration of 8 weeks. Dupilumab offers the potential of safer therapy and the opportunity for significantly reduced topical steroid treatment, which people with severe eczema so desperately want and deserve.	Comments noted. The final appraisal document (sections 3.1) recognises the importance of effective treatment options with manageable side effects to people with atopic dermatitis.

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14	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the overall impact of severe eczema, and is not demonstrating parity with other severe chronic conditions like psoriasis, urticaria, asthma and arthritis, all of which have had life-changing biologic treatments approved by NICE that have been life-transforming for patients. It seems especially harsh to withhold funding from the first game-changing new drug treatment for severe eczema in many years. The trial data results are impressive, both for symptom improvement and reduction in topical steroid use, which for the first time in decades gives people with severe eczema the prospect of an effective treatment.	Comments noted. The final appraisal document (sections 3.12 and 3.24) recognises the clinical effectiveness and innovation of dupilumab. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.
15	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the opportunities for greater treatment accessibility provided by dupilumab. It can be incredibly difficult and painful for people with severe eczema to travel to medical appointments in specialist dermatology centres. Dupilumab offers the potential for people to self-administer their treatment injections at home under supervision, and for the treatment to be supervised through all hospitals and not just specialist centres.	Comments noted. The final appraisal document (section 3.1) recognises the limited treatment options available to people with atopic dermatitis. The impact of the disease has also been considered in the patient and professional group submissions.
16	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the variable availability of systemic treatments and local clinical preferences in prescribing. There is no NICE quality standard or clinical guideline for the treatment of atopic eczema in adults, and people with eczema tell us about the varying ways they are treated. Phototherapy, for example, is not universally available and patients often find it extremely difficult to travel for frequent therapy sessions. Hence National Eczema Society believes it is only fair that the eligibility for dupilumab must be that patients have tried and failed on one systemic treatment only.	Comments noted. The final appraisal document (section 3.1) recognises the limited treatment options available to people with atopic dermatitis. Dupilumab has been recommended only if '*the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated*'.
17	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the impact on people's ability to study in further and higher education, as well as people's inability to maintain paid employment, because of the pain, constant discomfort and disrupted sleep caused by severe eczema. It is cruel that people's life chances are so negatively affected by this condition as a result of the limitations of current systemic treatments that offer only temporary respite from symptoms and topical treatments that for people with severe eczema are ineffective.	Comments noted. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, and therefore the effect on employment is not explicitly incorporated in economic modelling. However, the committee recognised the financial implications of having atopic dermatitis (see section 3.1 of the final appraisal document). The impact of the disease has also been considered in the patient and professional group submissions.
18	Consultee	National Eczema Society	We are concerned that NICE has not considered fully the negative impact of severe eczema on relationships and family life. Severe eczema ruins relationships and often prevents individuals from entering into relationships. Those in a relationship tell us they can't bear their partner to see their body or touch their rough, scaly inflamed skin. Teenagers fear never getting married or never having the chance to experience sex.	Comments noted. The committee recognised the social and psychological impact of having atopic dermatitis (see section 3.1 of the final appraisal document). The impact of the disease has also been considered in the patient and professional group submissions.
19	Consultee	National Eczema Society	We are concerned that NICE has not considered the social impact of living with severe eczema. People with severe eczema usually cannot hide their disease - facial and hand eczema in particular are on show to the public. People tell us they are often very self-conscious about their skin, and sadly eczema is still often perceived as infectious and a result of poor personal hygiene. Many people with severe eczema are	Comments noted. The committee recognised the social and psychological impact of having atopic dermatitis (see section 3.1 of the final appraisal document). The impact of the disease has also been considered in the patient and professional group

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			subject to cruel comments about their skin condition and will isolate themselves socially for fear of rejection.	submissions.
20	Consultee	Sanofi Genzyme	Sanofi Genzyme welcomes the opportunity to respond to the Appraisal Committee Document (ACD) for the above appraisal and are pleased to provide the Committee with additional data from the open-label extension study that are now available. We support the Committee's conclusion that dupilumab is innovative and a step change in managing atopic dermatitis. The success of the Early Access to Medicine Scheme (EAMS) for dupilumab for atopic dermatitis, which enrolled 244 patients over 6 months, indicates the scale of the unmet need for an effective treatment in this disease area. Sanofi Genzyme understands the reasons behind the initial Committee decision not to recommend dupilumab: they were not able to assess the product against all their preferred assumptions in the economic modelling. Therefore in our response we have incorporated all the Committee's preferred assumptions, provided additional data, analyses and adjusted the Patient Access Scheme, see Table 1. As noted above, the company has fully implemented the majority of the eight points from section 3.25 of the ACD. Two points are explored in more detail as these have a more sigificant impact on the ICER. These changes both marginally increase and marginally decrease the ICER estimates. With the revised PAS the updated analysis using section 3.25 preferred assumptions gives an ICER for dupilumab compared with best supportive care of £28,495. We believe the information provided in this document will increase certainty and confidence for the committee, that, in addition to being clinically effective, dupilumab is also a good use of NHS resources for patients with moderate to severe atopic dermatitis previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. There are two additional factors to consider. The first is employment and productivity. The company has received many reports of cases of patients returning to regular work and demonstrating less absenteeism whilst being treatment with dupilumab. The second is improved personal relationships. Clinicians report patients are describing new or improved intimate relationships following initiation on dupilumab treatment. Both employment and relationships should be an additional consideration by the appraisal committee. In line with feedback from clinicians Sanofi Genzyme expect dupilumab to be used in the post-immunosuppressant (IM) patient population. If patients can be effectively and sustainably managed with either TCS or systemic IMs, then they are not candidates for dupilumab. Dupilumab should be used for patients who have been previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. We heard from the clinical experts at the Committee Meeting that dupilumab can transform lives. Given the revised PAS and in the light of the information provided below, we hope that the Committee will reconsider their initial recommendation and	Comments noted. The committee reviewed the new evidence and analyses submitted by the company and revised the recommendation to "*Dupilumab, in combination with topical corticosteroids, is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if:* *• the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated* *• the company provides dupilumab according to the commercial arrangement (see section 2)*". See section 1 of the final appraisal document for all the recommendations. In line with NICE reference case, costs are considered from the NHS and Personal Social Services perspective, and therefore the effect on employment is not explicitly incorporated in economic modelling. However, the committee recognised the financial implications of having atopic dermatitis (see section 3.1 of the final appraisal document). The committee recognised the social and psychological impact of having atopic dermatitis (see section 3.1 of the final appraisal document). The impact of the disease has also been considered in the patient and professional group submissions.

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			enable access to this transformational medicine. [1]	
21	Consultee	Sanofi Genzyme	**Supporting data from the Open Label Extension study** One of the points in section 3.25 relates to the maintenance of clinical efficacy and quality of life benefit with dupilumab in the longer-term. Data now available from the open-label extension (OLE) study demonstrate dupilumab used over the longer term is associated with maintained or increased benefit over time in all of the endpoints required for the economic model, all of the clinical endpoints and all of the patient reported endpoints, see Appendix A. **Supporting data from EAMS** The company were able to collect follow up data on a cohort from EAMS. Thirty-five patients had baseline and follow up data, at a mean follow up 86 days (12.3 weeks). Median EASI scores at baseline were 24.9 (range 4.3 to 72.0) vs 7.5 (range 0.0 to 35.0) at 12 weeks (Wilcoxon $p<0.001$). There was a significant improvement in EASI score. (Appendix B) Dupilumab efficacy (as demonstrated by EASI-50), from EAMS, appears to be comparable with clinical trial data from CHRONOS / CAFÉ (Table 2). 52% of patients in EAMS were on an immunosuppressant at the point of severity scoring, making the EASI-50 score more difficult to achieve than in the clinical trials. The composite end-point, EASI-50 & DLQI 4 was met by 65.6% of patients in EAMS. Our economic model used 16 weeks as the time-point for assessment of response; these data suggest that response are seen earlier at 12 weeks. These emerging data from EAMS provide further support of dupilumab sustained benefit. What is more impressive is that EAMS are real world patients who are more likely to have complicating issues and difficult-to-treat disease.[1]	Comments noted. The committee noted that the evidence from the extension study in particular would help in the understanding of dupilumab's long-term clinical effectiveness and to inform the assumptions in the economic model (see section 3.7 of the final appraisal document).
22	Consultee	Sanofi Genzyme	**Economic analysis amendments** The company has implemented the majority of points in section 3.25 as accurately as possible in the revised model. It should be noted that most of them have only a marginal impact on the ICER estimates and that they work in both directions i.e., the ICER estimates both increase and decrease. For two points: • (The company) applied a constant annual stopping rate of 3.7%, which appeared low (see section 3.17) • (The company) applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms (see sections 3.19, 3.20 and 3.21) the Company is providing additional data and presenting scenarios that we believe will provide the Committee with increased certainty that the assumptions in the Company's original base case were plausible and consistent estimates of the cost per QALY gained for dupilumab compared with best supportive care in usual UK clinical practice.	Comments noted. The committee considered the additional analyses that used a range of stopping rates for dupilumab and noted that the different rates had minimal impact on the cost-effectiveness estimates. It agreed that the company's original stopping rate of 3.7% is plausible (see section 3.15 of the final appraisal document). The committee considered analyses that included assumptions in which patients maintained benefit from year 5 and beyond were more plausible than no patients maintaining benefit (see section 3.17 of the final appraisal document). The committee reviewed the new evidence and analyses submitted by the company and revised the recommendation to "*Dupilumab, in combination with topical corticosteroids, is recommended as an option*

[1] Additional information is available in full in committee papers.

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			The revised most plausible ICER estimates according to the committee's preferred assumptions are provided in Table 3 below. ICERs are tabulated at the original PAS discount and the updated discount for comparative purposes. In response to point 6, relating to the decline in clinical an utility benefit of best supportive care in the BSC and dupilumab arms, we considered Analysis 5 from the committee papers, the linear decline in utility from 75%, 50%, 25%, to 0% at year 5 to be the most appropriate. This was considered the most clinically plausible approach. Waning in the dupilumab arm is as per the company's original base case. Data from OLE suggest this is a conservative approach. This is therefore used in the updated analyses below. The revised assumptions in the updated anlaysis, as reflect the points in section 3.25 of the ACD are presented in Table 3. Thereafter key assumptions in the model are varied in each of the following tables, to test the impact these assumptions have. **Key sensitivity analyses** Sensitivity analyses around the key drivers are provided the tables below. As assumptions around the decline in utility for BSC are less certain, we tested different approaches to BSC waning, including the committee's suggestion using TCS. These analyses indicate that the majority of the ICERs incorporating the Committee's preferred assumptions fall below the £30,000 threshold which may be considered appropriate for an innovative product. We believe the most plausible, conservative scenario provides an ICER of £28,495. We hope the information provided in this document will increase certainty and confidence for the Committee, that, in addition to being clinically effective, dupilumab is also a good use of NHS resources for patients with moderate to severe atopic dermatitis previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable. The range of ICERs, with the revised PAS, is in line with the acceptability threshold for an innovative product. The data gaps in this assessment relate to the long-term treatment effectiveness. Emerging data from the OLE reduce uncertainty on the dupilumab arm, regarding maintenance of benefit. While there are data gaps on the BSC arm, the level of unmet need for an effective treatment in this disease area, as demonstrated by the number of patients on the EAMS and worldwide clinical consensus, highlights that BSC, including topcial corticosteroids, is not sufficient for the long-term management of this complex disease.[1]	*for treating moderate to severe atopic dermatitis in adults, only if:* *• the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated* *• the company provides dupilumab according to the commercial arrangement (see section 2)*". See section 1 of the final appraisal document for all the recommendations.
23	Public	Patient 1	I am an [redacted] who lived in Europe for nine years, up until 2017. I suffered from increasingly severe eczema beginning in 2010, and by the time I returned to the US, I was in such bad condition that I often couldn't sleep and I had to cancel my teaching at times after a bad flare up. During the years from 2012-2017, I spent a lot of time at the dermatologist, who monitored my condition, prescribed increasingly powerful steroid creams and pills, and provided UV treatments three times a week. I can't even guess how much I cost the Austrian national health service from what must have been over a hundred office visits.	Comments noted. The final appraisal document (sections 3.1, 3.12 and 3.24) recognises the limited treatment options available to people with atopic dermatitis, the clinical effectiveness and innovation of dupilumab. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and

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			I started with a new dermatologist upon arriving in the US who saw my condition, listened to my history, and immediately suggested Dupixent. I got insurance approval and I've been on it for the past six months. It has reduced my symptoms by about 80%, and returned me to what I could finally describe as a normal life. Severe eczema means living your life in extreme discomfort, with little chance for relief. This includes at night when you try to sleep, at work, taking a shower - it affects everything in your life, and for many people it never goes away on its own. Eczema is a condition that is not yet well-understood, and dermatologists have been limited in the tools they have to treat it. Steroids are generally very effective at tamping down flare-ups temporarily, but they are clearly not a long-term solution. Other forms of treatment are much less effective at addressing symptoms, and also don't address the underlying cause of the condition. Dupixent is the first sign that this condition might be controllable in a sustainable way, allowing people like me to return to normal, productive lives. It has brought about a complete turning point in my life, to give a single data point. I understand that your recommendation to reject Dupixent isn't based on its efficacy, but rather its cost to benefit ratio. I completely agree that the $37k sticker price is ridiculous, and I'm sure that whatever price the UHS is negotiating with Sanofi is just as unreasonable. I just hope that this initial recommendation to reject the drug is a negotiating tactic, and that the message is well-understood, that this medicine is about as valuable to sufferers of severe eczema as a drug could be. For someone who can't even sleep through the night without waking up constantly to intensely itchy skin, Dupixent is a life-changer, and I think you should weigh the "value" side of the equation very highly.	therefore dupilumab has been recommended.
24	Public	Patient 2	My name is [redacted] and I've suffered from eczema for almost my entire life. The past thirty years have been spent using steroid creams that has left my already damaged skin thin and fragile, taking oral steroids that only ever bring temporary relief, and taking immunosuppressants that leave me open to infections and possibly even cancer further down the line. And not one of these treatments has ever worked to the extent where I can live a normal life, with the exception of Cyclosporin, which unfortunately I couldn't continue to take due to the fact it rose my blood pressure to extremely dangerous levels. My eczema is very severe. Covering over 80% of my body severe. I'm in constant pain from my sore and open skin, and I feel extremely self conscious going out in public; I'm a young woman who should be making the most of her youth, and instead I'm hiding my skin and staying out of social situations because I feel like a monster. I had to miss my best friend's wedding because I was in the middle of an incredibly debilitating flare, not only could I not travel, I didn't want to ruin her wedding with my disgusting appearance. Holidays have been ruined because my skin was so bad, while my friends were having fun, I had to keep out of the sun and douse myself in	Comments noted. The final appraisal document (sections 3.1, 3.12 and 3.24) recognises the limited treatment options available to people with atopic dermatitis, the clinical effectiveness and innovation of dupilumab. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.

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			moisturiser and take pain killers just to cope. I have to take painkillers every day to cope with the pain, and even then that doesn't always help. I have no job prospects outside of my low-level retail job because of my skin, I have no chance of meeting anyone when I look so hideous, and I have no future while my skin is so bad. I'm overweight because eating is the one thing I can do when I'm stuck inside alone because my skin is so bad. I'm lonely, I'm depressed, and sometimes I hate myself so much because of my awful skin. I won't lie, I've entertained suicide. The only things keeping me here are my family and my dog. Without them, I dread to think of where I would be. All because of the pain, emotional and physical, that I'm in almost every single day. I started Dupilumab/Dupixent just two days ago. And I've already seen an improvement in my skin. I couldn't believe it, I thought it was to good to be true, but there's already signs of improvement when it was so painfully bad before. The redness is receding, I can see patches of my unblemished skin appear. My eczema has become dry and peeling, but the painful sores are gone already. I think this is the first day in a very long time where I could move my arms without pain, I've not even taken any painkillers. It's early days, but Dupilumab has already given me so much hope for the future. I can finally see a future, one where I can function like anyone else. I don't have any grand dreams, but I would love to find a job that isn't restricted by my skin, I'd love to meet someone, I'd love to be able to travel and not have to spend my days frozen up because of how much pain I'm in. I'm looking forward to when I can just jump in the shower and not have to worry about the pain that comes with it. Please consider making Dupilumab available on the NHS. It's the biggest breakthrough in eczema treatment for a long time, and there are countless success stories out there where people like me are finally able to do things that normal people take for granted. I've been in such a dark place for such a long time, and now I can finally see light at the end of the tunnel. I know there are others out there who are still suffering, and they should get the chance to live a normal life. My name is [redacted] and I've suffered from eczema for almost my entire life. I have posted my comment here before after being on Dupilumab for just two days, but I feel that I must update my situation now that I've been on it for over two weeks. My skin is around 70% healed. My hands and wrists are still very sore, but they were very bad before I started Dupilumab, but they're starting to finally heal. What sore skin I have left is peeling and growing soft and healthy. I have absolutely no pain at all	

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			now, asides from the odd twinge from a sore on my shin. I can actually see my skin again, my actual skin, and not layers of rashes and sores. I've also learnt that my fingers and wrists were actually swollen from the severity of my eczema now that they've gone down to a normal size. Dupilumab has changed my life. I can do so much more than I used to be able to. I can jump in the shower without having to worry about pain or an extensive moisturising routine afterwards. I can do housework without having to take painkillers just to cope with moving around the house. I can sleep peacefully at night, and when I wake up it's not in pain, it's in amazement that my skin is only getting better and better with each passing day. I feel like a new person. People have commented, not just on my skin, but on how positive I am lately. My nephew expressed amazement that I wasn't 'in a bad mood' like usual, and my customers have told me that I'm happier. I feel happier. I feel so happy right now, because I'm pain free. My skin not only looks good, it feels good, and I feel good because of that. I just can't get over not being in any pain, after I've been in so much pain for so long. I can't recommend Dupilumab enough. It truly is a life changer.	
25	Public	Patient 3	I am a university student in Scotland, and would like to input my experience with atopic dermatitis and why I am very saddened at the potential of this ground breaking drug not being approved by the NHS. I have suffered with atopic dermatitis (AD) all my life, and it was in my early teens when it got completely out of control. From that point on my entire youth had a damper put on it and affected me both physically and mentally. At certain points it was too painful to wake up in the morning, and my high school attendance suffered as a result. Furthermore, my friend circle had shrunk due to my lack of being able to feel confident enough to engage with people outside school due to being in pain, or feeling unconfident about how I looked. AD has been the toughest hurdle in my life and I feel like I am far from over coming it. When I heard of news that Dupilumab would potentially be available to AD sufferers in the UK I finally felt that I may see a day where I wont have to plan my entire schedule and life around the condition of my skin at that time... I sincerely hope that this decision is considered thoroughly, through the input of other sufferers and those that have experienced this life destroying condition.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.
26	Public	Patient 4	I have severe atopic eczema. It's a painful and debilitating condition that means I'm not able to concentrate on work and spend a lot of my life in pain or with severe irritation. My condition also leads to a weak immune system which means that I am usually in a state of permanent illness. These factors also have a big impact on my mental health, further inhibiting the activities I can take part in and the work I can do.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and

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			Being in my final year of university, my condition has had a big impact on my grades and has lead to me submitting work late and under extenuating circumstances. A treatment such as Dupilumab would go a long way to helping me regain control of my life and realise my full potential as a software engineer.	therefore dupilumab has been recommended.
27	Public	Patient 5	As a sufferer of Severe Atopic Dermatitis I believe you should reconsider this drug. At the moment the treatments available as immunosuppressant or the other don't work and the quality of life of people like me is so poor that you cannot even imagine. If there is another option available it should be approved for the severe cases. Thank you for your understanding. Kind Regards	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.
28	Public	Patient 6	Pre-face: I am an adult with severe eczema currently prescribed 4th line systemic treatments (methotrexate) which has been met with a positive response, and blood tests have revealed that I have adequate tolerance to the drug to use as a long-term treatment. I now endure more manageable eczema ranging from mild to moderate for most of my days, but further treatment methods including regular application of moisturising ointments and occasional corticosteroid ointments. Despite the effort and risk of my treatments, I still live a life plagued by past mental damage and poor skin generally. The document, which I have read in its entirety, is a breath of fresh air regarding the appreciation of atopic eczema symptoms, physical and mental, in adults, where we are otherwise ignored or misunderstood. It has taken 21 years of NHS care with countless physicians and treatments tested to finally have my condition taken seriously. This is not an attack on the NHS as an institution, but rather of the perceptions of atopic eczema until recently being fundamentally flawed. Immune system treatment is pivotal to many patients who feel they have tried everything to no avail, and if it wasn't for extensive research, I wouldn't even know of their availability, much less has it been even mentioned by GPs. If not for dermatologists at the [redacted] treating me for my 4th bout of infected eczema last summer, I would have certainly killed myself should the 5th have shown itself. Systemic treatment is a necessity for me to have skin in a condition where infections are not nearly as high a concern, i.e. less areas of damaged skin, but despite this I now forever live in fear of infections happening again. If 4th line treatments were not effective for me, then I would have no other options, and suicide would be entirely a plausible release from the suffering this condition has caused to my life. I hope that whether Dupilumab is accepted or not in its current state, it will lead to a shift in awareness for the underlying causes of the debilitating, life consuming illness. As a 5th line treatment the idea of cost effectiveness should be more critically evaluated as a last resort for people with no other options than to suffer tremendously or brave the side effects of systemic treatments. Would it be fair in this case to consider that cost effectiveness for eczema treatment is based on generations of poor	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended only if '*the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated*'.

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			perceptions and factually flawed opinion? I believe that at least having it available as a last resort to a very select group of people should be a necessity in a 5th line context, considering NICE has already identified so many reasons why adults with severe atopic eczema need treatments.	
29	Public	Patient 7	Having this disease is extremely debilitating physically and psychologically. So much so that I have considered suicide. Existing treatments don't work properly and if there is a glimmer of a chance that Dupixent will help patients it should be given without hesitation.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.
30	Public	Patient 8	As someone who has tried all available therapies for atopic dermatitis and found no relief, it is deeply disappointing and shocking to find the initial NICE guidance is to reject Dupilumab as a treatment for eczema. For many eczema sufferers the current therapies (which are cost effective) are sufficient, but in my personal case my life has been torn apart by eczema for over 20 years with no light at the end of the tunnel. This treatment must be made available for severe eczema sufferers who have no other sustainable alternatives. Dupilumab for the first time in a long time has provided hope for those without sufficient treatment. Whilst i understand the cost is high for Dupilumab, it would not be needed for every single eczema patient in the UK, and i implore the committee to understand that life sufferers of eczema are individuals that are regularly suffering from mental illness. This includes depression, severe sleep loss, anxiety, self loathing and suicide to name a few. These can be alleviated to an extent with the control of an individuals eczema. Surely these mental illnesses also provide a cost to the NHS? Certainly in terms of hours of treatment/ counselling and medication. The use of Dupilumab could help severe sufferers like myself come out of the darkness and control mental illnesses with the improvement of ones eczema. This opportunity cost must be considered The real life of eczema is hard to understand for a non sufferer, it is a highly visible and painful underserving condition which can debilitate a person physically and mentally. Personally speaking and from what i can gauge from fellow sufferers is that once the eczema is sub dued individuals can start to rebuild their life and feel a sense of normality and crucially build momentum towards life goals. However with eczema flares which in severe sufferers are prolonged and regular, this halts any progress you have made in your personal and professional life, inhibiting any success you had been working towards. It is this constant 'one step forward, two steps back' approach which can drive a eczema sufferer towards severe mental illness, something i can speak for personally. The current eczema treatments are unsustainable which really provides no hope for ones life. Personally i have reacted badly to topical steroids with peri-oral and orbital dermatitis and been recommended by a NHS dermatologist to cease use.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.

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			Immunosuppressants such as ciclosporin and methotrexate have cause strong painful side effects and do not present a long term solution for myself without incurring other painful side effects a 'catch 22 situtation'. UVB treatment has provided n relief and after 2 separate periods of maximum treatment with UVB (in 2008 and 2017). I have also tried Elidel and protopic multiple times to no avail with a painful burning sensation side effect. So my question is for someone in my position...What do i do? What NHS resources are dedicated to helping me? What does the NHS recommend i do? Before Dupilumab, I had NHS dermatologists simply say their was nothing more they could offer me and they 'wish and hope for a turn in my fortunes in the furture'. This is completely unacceptable, especially when there is a treatment option available in existence. UK's Medicines and Healthcare Products Regulatory Agency (MHRA) granted dupilumab, an investigational treatment for atopic dermatitis (AD), a positive scientific opinion through the Early Access to Medicines Scheme (EAMS). The aim of EAMS is to provide early availability of innovative new unlicensed medicines to UK patients that have a high degree of unmet clinical need. Crucially from my understanding Dupilumab was added to EAMS to help patients with a high degree of unmet clinical need. Hypothetically speaking if Dupilumab is rejected as a treatment for atopic dermatitis by the NHS, how would this unmet clinical need have been met? I find it difficult to understand how a medicine which was added to EAMS because of an 'unmet clinical need' is now being rejected. Essentially demonstrating the NHS/NICE is neglecting severe eczema sufferers with no options moving forward into the future.	
31	Public	Patient 9	Thank you for giving me this opportunity to comment on NICE's draft guidance on dupilumab, published in March 2018. Please allow me to convey some of my personal experience with Atopic Dermatitis (AD) and dupilumab from the perspective of a patient. I am 39 years old and have been affected by severe AD for most of my life. As you know, AD covers a broad spectrum and can manifest itself in a wide range of clinical presentations, with the vast majority of patients affected by a mild form of the disease which is more easily managed. As a result, the rarer, severe form of AD is often misunderstood or underappreciated. Your draft guidance repeats a common misconception about severe AD, by implicitly tying the burden experienced by the patient to the 'stigma' associated with the disease. My quality of life was severely impacted, not because of embarrassment about my physical appearance, but because of the incessant and intolerable physical discomfort. It is difficult to describe the intense itch which I would experience and the persistent chronic pain from my oozing, cracked and bleeding skin, which was often infected. The itch and pain caused chronic sleep deprivation, which condemned me to live a zombie-like	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended only if '*the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated*'.

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			existence during my formative years and beyond, contributing to deep depression, despair and a profound sense of helplessness. Effective relief from the itch was only temporarily available through short-term courses of systemic cortisone and immunosuppressants (ciclosporin and off-label mycophenolate mofetil), but always in the uncomfortable knowledge that these therapies posed a serious risk of severe adverse effects in the long term and that their discontinuation would immediately trigger a violent relapse. Having long since exhausted the arsenal of therapies available to me through current 'Best Supportive Care', I was excited to learn that dupilumab was being tested as the first new AD drug to directly target the inflammatory pathway, rather than merely suppress the immune system indiscriminately. The AD patient community had been hoping for this development for some time, given that similar biologics had already proven to be extremely effective in the treatment of psoriasis for many years. Although fully aware of the potential risks inherent in using an experimental drug, I decided to enrol in a Phase 2 study for dupilumab, and eventually a Phase 3 open-label extension study at [redacted] (principal investigator: [redacted]). The experience was transformational, causing my quality of life to improve radically and sustainably. Rapid onset of action occurred within the first two weeks of therapy, the itch abated substantially and my skin soon cleared completely. Furthermore, I have been able to maintain this radical improvement through monotherapy, alone, without the need to resort to topical corticosteroids. It is no exaggeration to credit dupilumab with giving me a new lease on life. I was therefore shocked and surprised when I learned that NICE's draft guidance recommended against providing access to dupilumab through the NHS on the grounds of cost effectiveness. Clearly, dupilumab is not appropriate as first-line therapy, and every attempt should be made to control the disease through traditional therapies first. But to force patients with severe AD to continue to rely on ciclosporin for episodic management of symptoms, when dupilumab has been shown to be a far safer, more effective and better tolerated long-term treatment option for this chronic relapsing condition, is surely unconscionable. It seems to me that there's a significant risk of underestimating both, dupilumab's radical improvement to patients' quality of life, and the substantial costs associated with current Best Supportive Care, which, in my personal experience, includes frequent visits to the GP and dermatologist, the use of topical and systemic corticosteroids, topical and systemic immunosuppressives, phototherapy sessions, regular treatment of infections (antibiotics, antivirals, antifungals, antiseptics), as well as the use of sleeping pills; all of these costs have fallen away, now that I'm being treated with dupilumab as monotherapy. And that's before taking into account the increase in productivity from this patient population (I was unemployed, and frankly unemployable, for 3 years prior to my treatment with dupilumab) and the benefit that accrues to society in general as a result of this whole population no longer being marginalized.	

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			I am reassured by the committee's acknowledgement that dupilumab 'is innovative and a step change in managing atopic dermatitis', and I remain optimistic that a way will be found to secure access through the NHS to this revolutionary treatment that is so vital to improving the quality of life of patients with severe AD. As a participant in the clinical trial, I have been assured that I would be guaranteed access to dupilumab for at least the next 12 months, but I'd like to advocate on behalf of the many other AD patients who are not so fortunate and risk being denied access to dupilumab and, by extension, the entire new class of biologics currently being developed.	
32	Public	Patient 10	As a 40-year-old atopic dermatitis (AD) patient, I have lived with my condition for around 30 years. In recent years, my condition has become increasingly difficult to manage: I am now on fourth-line treatment, having rapidly progressed through topical corticosteroids, a topical calcineurin inhibitor, and phototherapy, to no avail. Having kept a close eye on research into dupilumab throughout its clinical development (see disclosure comment), I had high hopes it would one day be a drug I could access through the NHS. Having read the project documents, I believe the impact on the individual AD patient has been described well, and I can identify with all of the experiences documented within them. But in my view, a fundamental missing piece in the analysis is alluded to in slide 39 of the public committee slides, titled 'Innovation', namely the statement: 'Benefit to society, carers and family not included in quality-adjusted life year'. Why is this the case? When I was a child and teenager with AD, it could have been argued that the impact of my AD did not extend far beyond myself. However, as an adult with AD, the situation is markedly different. There are many times when I simply cannot interact with family members in a normal way. In addition, at work, I am increasingly challenged in meeting the expectations of those to whom I have professional responsibilities, including: the people I manage; my company's management team, of which I am a member; and the clients our business serves. I propose that a broader review be conducted, taking into account the impacts of AD not only on patients but also on these numerous other parties. It might lead to a more favourable conclusion about the cost-effectiveness of dupilumab.	Comments noted. The final appraisal document recognises the effect of moderate to severe atopic dermatitis on the quality of life of families and carers but had not seen any evidence to support this. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.
33	Public	Carer	I am writing with reference to the recent recommendation not to back use of Dupixent as treatment for severe atopic dermatitis (AD). My son has suffered from this disease since his birth in 1978. Its effect is often underestimated, since it is seen as 'only' a skin problem. However, I can testify that it is excruciatingly painful and profoundly debilitating, leading to acute infections, sleep deprivation, inability to concentrate, impaired capacity for social interaction and chronic depression which, coupled with the perpetual agony, can turn suicidal.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.

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			With discipline and strength of character, my son managed to complete his degree in [redacted] at the [redacted] and get a [redacted] from [redacted]. He is neither a complainer nor a quitter, but it was clear that his life and opportunities were critically diminished. Awake all night, in a daze all day, he would spend hours applying creams merely to keep the worst at bay. He visited countless specialists and tried every treatment on offer - each new option raising hopes only to be dashed, and all at great expense to the NHS, ultimately to no effect. The advent of Dupixent has completely changed, one might even say: saved his life. In his late thirties, he is finally able to get a healthy night's sleep, concentrate with success on a demanding job, pursue sports and generally enjoy being alive. He shares this transformative experience with many other former sufferers. Dupixent is an expensive drug, but from what I hear, it was also very expensive to develop, so Sanofi is not being greedy. And the financial cost is offset by the fact that people like my son can now work full-time, pay taxes and contribute to society, rather than suffer chronic pain and frustration that leave them a burden to society, their families and most tragically: themselves. Given the price tag, nobody expects the NHS to resort to Dupixent as the first port of call when treating AD. It is perfectly legitimate to try other treatments and medications first. But in cases like my son's, where nothing else has worked, Dupixent should please be available as a last resort. Please reconsider this decision!	
34	Public	Health care professional	As a skin specialist caring for patients with severe eczema, I was very disappointed to hear that NICE approval for dupilimumab has not been granted. There is a pressing need to find more effective systemic therapies for our patients and this drug has shown to be effective both in clinical trials and the early access scheme. This drug should be made available to patients who have failed to respond to conventional treatments and it is concerning that NICE has not granted patients access to it. I hope the decision will be reconsidered.	Comments noted. Following the appraisal consultation document, the company revised its model and patient access scheme. The revised cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources and therefore dupilumab has been recommended.

The following consultees/commentators indicated that they had no comments on the Appraisal Consultation Document

Department of Health and Social Care

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

24th April 2018.

Dear Elisabeth,

Re: Dupilumab for the treatment of dermatitis (atopic, moderate, severe), after topical treatment [ID1048]

Sanofi Genzyme welcomes the opportunity to respond to the Appraisal Committee Document (ACD) for the above appraisal and are pleased to provide the Committee with additional data from the open-label extension study that are now available.

We support the Committee's conclusion that dupilumab is innovative and a step change in managing atopic dermatitis. The success of the Early Access to Medicine Scheme (EAMS) for dupilumab for atopic dermatitis, which enrolled 244 patients over 6 months, indicates the scale of the unmet need for an effective treatment in this disease area.

Sanofi Genzyme understands the reasons behind the initial Committee decision not to recommend dupilumab: they were not able to assess the product against all their preferred assumptions in the economic modelling. Therefore in our response we have incorporated all the Committee's preferred assumptions, provided additional data, analyses and adjusted the Patient Access Scheme, see Table 1.

Table 1. Annual list price and updated Patient Access Scheme (PAS)

List price						£16,500													

*An additional loading dose is required on initiation. This is factored into the modelling as an extra single injection cost.

As noted above, the Company has fully implemented the majority of the eight points from section 3.25 of the ACD. Two points are explored in more detail as these have a more sigificant impact on the ICER. These changes both marginally increase and marginally decrease the ICER estimates. With

the revised PAS the updated analysis using section 3.25 preferred assumptions gives an ICER for dupilumab compared with best supportive care of £28,495.

Our response is structured as follows:

- **Summary**

  This provides a summary of the impact on the ICER estimates of the revised PAS and the committee's preferred assumptions, as described in section 3.25 of the ACD.

- **Detailed response**

  We detail our response to the committee's preferred assumptions listed in section 3.25. More detail is given below but, to summarise, these amendments work in both directions, i.e., some increase the ICER and some reduce it. Together, all the Committee's preferred assumptions plus the revised PAS result in the majority of plausible ICERs being below the £30,000 threshold for an innovative product and so demonstrate that dupilumab is a good use of NHS resources.

- **Results and Scenario Analyses**

  We report the ICER estimates in detail and run a series of scenario analyses testing the plausibility and stability of the different assumptions from section 3.25. The estimated ICERs that result from these analyses, with the revised PAS, range from dupilumab being dominant to £35, 303. The lowest ICER estimates are driven by resource use assumptions about hospital admissions required to maintain the best supportive care treatment effect over the long-term.

- **Technical appendix**

  Further data and details of analyses are given in a technical appendix, again relating to the points listed in section 3.25 of the ACD.

We believe the information provided in this document will increase certainty and confidence for the committee, that, in addition to being clinically effective, dupilumab is also a good use of NHS resources for patients with moderate to severe atopic dermatitis previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.

There are two additional factors to consider. The first is employment and productivity. The company has received many reports of cases of patients returning to regular work and demonstrating less absenteeism whilst being treatment with dupilumab. The second is improved personal relationships. Clinicians report patients are describing new or improved intimate relationships following initiation on dupilumab treatment. Both employment and relationships should be an additional consideration by the apprailsa committee.

In line with feedback from clinicians Sanofi Genzyme expect dupilumab to be used in the post-immunosuppressant (IM) patient population. If patients can be effectively and sustainably managed with either TCS or systemic IMs, then they are not candidates for dupilumab. Dupilumab should be used for patients who have been previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.

We heard from the clinical experts at the Committee Meeting that dupilumab can transform lives. Given the revised PAS and in the light of the information provided below, we hope that the Committee will reconsider their initial recommendation and enable access to this transformational medicine.

Yours sincerely,

Claire Grant
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UK & Ireland
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Appendices

Appendix A. Evidence from the Open Label Extension (OLE) study
Appendix B. Evidence from EAMS
Appendix C. Calculation of updated resource use estimates
Appendix D: A&E tariff.
Appendix E. Comparison of aggregate and split utilities in the BSC arm of the model
Appendix F: Calculations for the maintenance of treatment effect using a factor derived from the use of TCS
Appendix G: Model fits with time to first rescue treatment or withdrawal from CHRONOS for BSC treated patients.
Appendix H. Settings for simplistic testing of extreme resource use

1. Summary

We have addressed each of the eight points raised in section 3.25 of the ACD to accommodate the committee's preferred assumptions. (See Section 2 below for more details).

Supporting data from the Open Label Extension study

One of the points in section 3.25 relates to the maintenance of clinical efficacy and quality of life benefit with dupilumab in the longer-term. Data now available from the open-label extension (OLE) study demonstrate dupilumab used over the longer term is associated with maintained or increased benefit over time in all of the endpoints required for the economic model, all of the clinical endpoints and all of the patient reported endpoints, see Appendix A. Taking one example: the proportion of the OLE trial population that meet the composite response measure (EASI 50 and DLQI of 4 points or more). At week 48 (for which there are data for 295 patients) 92.5% of patients met this response threshold. At week 76 (data available for 208 patients), 93.8% of patients met this response threshold. At week 100 (data are available for 41 patients), 97.6% of patients met this response threshold.

Supporting data from EAMS

The company were able to collect follow up data on a cohort from EAMS. Thirty-five patients had baseline and follow up data, at a mean follow up 86 days (12.3 weeks). Median scores at baseline were 24.9 (range 4.3 to 72.0) vs 7.5 (range 0.0 to 35.0) at 12 weeks (Wilcoxon $p<0.001$). There was a significant improvement in EASI score. (Appendix B)

Dupilumab efficacy (as demonstrated by EASI-50), from EAMS, appears to be comparable with clinical trial data from CHRONOS / CAFÉ (table x). 52% of patients in EAMS were on an immunosuppressant at the point of severity scoring, making the EASI-50 score more difficult to achieve than in the clinical trials.

Table 2. Patients meeting EASI-50 response criteria in RCTS compared to real-world EAMS study

Clinical setting	Q2W dosing (n)	EASI 50 at 12 weeks
CHRONOS trial	106	79.2
CAFÉ trial	107	87.9
EAMS	35	72.7

The composite end-point, EASI-50 & DLQI 4 was met by 65.6% of patients in EAMS. Our economic model used 16 weeks as the time-point for assessment of response; these data suggest that response are seen earlier at 12 weeks.

Physicians were also asked to rate patient response to treatment (Much worse; worse; about the same; somewhat better; much better)

- At mean follow up of 24 days, 92% of patients were deemed to be somewhat better or much better.
- At mean follow up of 63 days, 89% of patients were deemed to be somewhat better or much better.

These emerging data from EAMS provide further support of dupilumab sustained benefit. What is more impressive is that EAMS are real world patients who are more likely to have complicating issues and difficult-to-treat disease.

Economic analysis amendments

The company has implemented the majority of points in section 3.25 as accurately as possible in the revised model. It should be noted that most of them have only a marginal impact on the ICER estimates and that the request work in both directions i.e., the ICER estimates both increase and decrease.

For two points:

- (The company) applied a constant annual stopping rate of 3.7%, which appeared low (see section 3.17)

- (The company) applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms (see sections 3.19, 3.20 and 3.21)

the Company is providing additional data and presenting scenarios that we believe will provide the Committee with increased certainty that the assumptions in the Company's original base case were plausible and consistent estimates of the cost per QALY gained for dupilumab compared with best supportive care in usual UK clinical practice.

The revised most plausible ICER estimates according to the committee's preferred assumptions are provided in Table 3 below. ICERs are tabulated at the original PAS discount and the updated discount for comparative purposes.

In response to point 6, relating to the decline in clinical an utility benefit of best supportive care in the BSC and dupilumab arms, we considered Analysis 5 from the committee papers, the linear

decline in utility from 75%, 50%, 25%, to 0% at year 5 to be the most appropriate. This was considered the most clinically plausible approach. Data from OLE suggest this is a conservative approach. This is therefore used in the updated analyses below.

The revised assumptions in the updated anlaysis, as reflect the points in sction 3.25 of the ACD are presented in Table 3. Thereafter key assumptions in the model are varied in each of the following tables, to test the impact these assumptions have.

Table 3. Comparison of the original base case and most plausible revised analysis according to committee preferences.

Analysis	Settings	ICER (original PAS)	ICER (Revised PAS)
Original company base case	As original submission	£28,874	[redacted]
Updated analysis to accommodate section 3.25 revised assumptions	• Updated PAS • Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear decline of 75%, 50%, 25% and 0% • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm: @ 16 weeks to average of BSC and dupilumab non-responder utility; @ 52 weeks to BSC non-responder utility, after 52 weeks, to BSC non-responder utility • Utility split by response in the BSC arm • Updated resource use estimates from the completed case-notes review • Annual injection site cost applied • All costs updated to reflect latest HRG and PSSRU costs	[redacted]	£28,495

Key sensitivity analyses

Sensitivity analyses around the key drivers are provided the tables below. As assumptions around the decline in utility for BSC are less certain, we have tested a number of different approaches to waning effect of BSC, including the Committee suggestion using TCS.

Table 4 Different approaches to the waning effect

Sensitivity analysis around the waning effect			
No dupilumab waning	• Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • **No waning in the dupilumab arm** • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.	[redacted]	£27,742
BSC waning estimator according Weibull fit to time to event analysis for BSC from CHRONOS	• Discontinuation rate for dupilumab 3.7% • **Waning in the BSC arm using curve fit estimator of maintenance of response 18.2%, 10.3%, 6.2% and 3.7%** • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.	[redacted]	£27,410
BSC waning estimator according to BSC annual rate for rescue or discontinuation in CHRONOS	• Discontinuation rate for dupilumab 3.7% • **Waning in the BSC arm using annual rate of 57%** • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.	[redacted]	£27,756
Dupilumab waning estimator according to TCS use in CAFE	• Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • **Waning in the dupilumab arm according proportional difference according to TCS decline in CAFÉ (38.4%)** • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.	[redacted]	£35,303

Table 5 Discontinuation rates varied in line with OLE data

Sensitivity analysis around the discontinuation rate			
Dupilumab discontinuation in the OLE according to proportion of patients	• **Discontinuation rate for dupilumab 2.1%** • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end	[redacted]	£27,623

with EASI-50 and DLQI ≥4points in the parent trial at 24 weeks.	• Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.		
Dupilumab discontinuation in the OLE according to overall proportion of patients with treatment discontinuation	• **Discontinuation rate for dupilumab 6.4%** • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter.	[redacted]	£30,126

Table 6 Other critical assumptions varied

Sensitivity analysis around other drivers			
Non-responder utility for dupilumab patients	• Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • Waning in the dupilumab arm according to clinician survey as original submission • **Non-responder utility in the dupilumab arm is set to BSC non-responder utility at 16 weeks and thereafter**	[redacted]	£28,690
Resource use for dermatology appointments increased to 4 appointments for responders in all years	• Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter. • **Dermatology appointments set to 4 for non-responders**	[redacted]	£29,963
Increased hospitalisation to provide respite care	• Discontinuation rate for dupilumab 3.7% • **No waning in BSC arm** • **No waning in the dupilumab arm** • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter. • **Hospitalisation set to 2 for 'non-responders and non-responder utility increased to responder utility to reflect additional**	[redacted]	£17,190

	benefit (BSC and dupilumab arms)		
Utility benefit for carers and families	• Discontinuation rate for dupilumab 3.7% • Waning in the BSC arm using a linear maintenance of effect at 75%, 50%, 25% and 0% over 4 years post trial end • Waning in the dupilumab arm according to clinician survey as original submission • Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility @16 weeks and @ BSC non-responder utility thereafter. • **Utility benefit for carers whilst on treatment (0.01)**	[redacted]	£27,257

*Key settings are included in the table as a reminder of varied parameters. Settings in **bold** have been changed. Where there are no variations from Table 3 at all the settings in Table 3 are assumed to be constant.

These analyses indicate that the majority of the ICERs incorporating the Committee's preferred assumptions fall below the £30,000 threshold which may be considered appropriate for an innovative product. Therefore we believe the plausible, conservative scenario provides an ICER of £28.495. We hope the information provided in this document will increase certainty and confidence for the Committee, that, in addition to being clinically effective, dupilumab is also a good use of NHS resources for patients with moderate to severe atopic dermatitis previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.

The range of ICERs, with the revised PAS, is in line with the acceptability threshold for an innovative product. The data gaps in this assessment relate to the long-term treatment effectiveness. Emerging data from the OLE reduce uncertainty on the dupilumab arm. While there are data gaps on the BSC arm, the level of unmet need for an effective treatment in this disease area, as demonstrated by the number of patients on the EAMS and worldwide clinical consensus, highlights that BSC, inclduing topcial corticosteroids, is not sufficient for the long-term management of this complex disease.

2. Detailed response to each of the key points raised in the ACD document.

Below we provide a summary of Sanofi Genzyme's response to each of the eight points raised in section 3.25: the Committee's preferred assumptions. The Company accepts the majority of points as reasonable and plausible. These are implemented as accurately as possible in the revised model. It should be noted that most of them have only a marginal impact on the ICER estimates and that the request work in both directions i.e., the ICER estimates both increase and decrease.

For two points:

- (The company) applied a constant annual stopping rate of 3.7%, which appeared low (see section 3.17)

- (The company) applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms (see sections 3.19, 3.20 and 3.21)

the Company is providing additional data and presenting scenarios that we believe will provide the Committee with increased certainty that the assumptions in the Company's original base case were plausible and consistent estimates of the cost per QALY gained for dupilumab compared with best supportive care in usual UK clinical practice.

1. The company) included only part of the best supportive care likely to be offered in NHS practice (see sections 3.4 and 3.6)

Sanofi would like to give the Committee reassurance that the appropriate components of best supportive care are included in the model. Some elements were thought to be omitted in the base case: phototherapy, education, psychological support, bandages and hospitalisation.

- *Phototherapy:* this is now included at a rate of 6% per year based on data from the updated case note review, previously this was not included (see Appendix C).

- *Education:* We were unable to find a reasonable estimate for the nature or costs of an atopic dermatitis educational programme, therefore this has not been included. While this has not been included, it would only increase costs for BSC which would reduce the ICER estimate.

- *Psychological support:* This is now included at a rate of 7% per year based on the updated case note review.

- *Bandages*: these were captured in the Company's original base case under 'day case' treatment. We have not disaggregated bandaging as it accounted for only 9% of the total day case admissions. The updated case note review changes the original base case rate of 0.17 day case admissions per patient per year to 0.21 day case admissions per patient per year.

- *Hospitalisation:* the rate of hospitalisation has been updated in line with the updated case note review from 0.23 to 0.12 episodes per patient per year.

We test the hospitaliation rate discussed in the committee meeting relating to patients being admitted for 1 or 2 weeks at a time for respite and disease management in scenario analysis.

Assumptions relating to resource use impact the ICER. However, even when increased to a frequency of dermatologist visits that is not likely in a patient population who have a significant improvement in disease, the ICER is in the range of £29,000-£30,000. At the other end of the ICER estimates, the ICER range is less than £20,000 if frequency of hospital admissions discussed in the committee meeting is used.

2. ***(The company) used data that included patients who had rescue therapy ('all observed' analyses; see section 3.11)***

Sanofi have re-run all the analyses using the 'primary analysis' method, in line with the Committee's preferred assumption. This is also in line with the LIBERTY clinical trial programme method of analysis of trial primary endpoints. In the base case, the Company used the 'all observed' method as it considered it better estimated usual UK clinical practice in which patients would not permanently discontinue dupilumab if they needed rescue treatment with more potent topical corticosteroids (than their background treatment), topical calcineurin inhibitors or oral corticosteroids. Clinical practice varies across the UK with regards to continuing or discontinuing systemic immunosuppressants (IMs) when patients need rescue treatment. Holistic assessment of each patient's response is taken into account and the risk benefit of treatment versus toxicity is considered.

It is important to note that using either analysis method (primary or all observed) the ICER estimates change by less than £1000 and remain below the £30,000 threshold for an innovative treatment.

3. ***(The company) pooled 'responders' and 'non-responders' in best supportive care (see section 3.16)***

In the original model utility was pooled for responders and non-responders while resource use was handled separately. In response to the ACD we have amended the model to handle non-responder and responder utilities separately, in line with the approach used with resource use.

This structural adjustment has a minimal impact on the ICER estimates. In the first 52 weeks (decision tree component of the model) the difference is 0.0074 QALYs. In the post 52 week (Markov component) of the model the total difference is 0.0267 discounted QALYs and there was a 0.0342 difference on the total QALY over a 64 years (See Table 21 in Appendix E). Across the entirety of the model (both decision tree and Markov model), the total difference this made was to increase the incremental QALY gain associated with dupilumab compared with best supportive care from 1.498 to 1.526. This leads to a marginal reduction in the ICER estimate, less than £500 on the total cost per QALY gained.

4. ***(The company) applied a constant annual stopping rate of 3.7%, which appeared low (see section 3.17)***

Patients discontinue treatment with dupilumab at different points in the economic model. The first assessment point is at week 16. If a patient does not meet the responder threshold of EASI 50 and DLQI 4 or more points, then they stop dupilumab and move to best supportive care. Using the efficacy response threshold of EASI-50 and DLQI 4 or more points change 31.5% of patients stop dupilumab at this point. More patients stop dupilumab treatment at week 52, bringing the total proportion of patients that have stopped dupilumab treatment in the first 52 weeks to 36.9%. The 3.7% used in the Company's original base case referred only to patients that were responders at both weeks 16 and 52 in the CHRONOS clinical trial, and so reflects treatment discontinuation for dupilumab responder patients only. We are not sure that the treatment stopping in weeks 16 and 52 had been well understood. As such, we consider the stopping rate plausible in this effective and well-tolerated treatment.

Discontinuation rate data for patients that met the composite endpoint (EASI 50 and DLQI4) are now available from the open-label extension (OLE) study and are shown in Table 7. These range from 1.5% to 3.0%. These are lower discontinuation rates than in the Company's original base case.

Table 7. Discontinuation rate from treatment for patients having met the composite end point of EASI-50 and DLQI 4+ in the parent studies at 24 or 12 weeks in the OLE*

Achieving DLQI Score Reduction	Dupilumab naïve	Total with exposure to dupilumab	Trt. Blinded in Parent Study	Total

>=4 and EASI50 from Baseline of Parent Study (n/N(%))	(N=606)	(N=850)	(N=35)	(N=1491)
at Week 12	6/288 (2.1)	14/470 (3.0%)	0/4	20/762 (2.6)
at Week 24	2/135 (1.5)	7/295 (2.4%)	0/0	9/430 (2.1)

*Evaluation of DLQI at 16 weeks was not available for these analyses.

In the analysis with the assumptions updated in line with section 3.25 the discontinuation rate is maintained at 3.7% which is a a conservative estimate given that the data above lending credibility to the original assumption. Different discontinuation rates (see Table 8) are tested in the scenario analyses (including those in Table 7Table 7).

Table 8 Discontinuation rate from the OLE study that are tested in sensitivity analyses

	Dupilumab Naive	Re-treatment	Interrupted treatment	Continuous treatment	Trt. Blinded in Parent Study	Total
n/N1 (%)	**(N=606)**	**(N=381)**	**(N=409)**	**(N=60)**	**(N=35)**	**(N=1491)**
Overall discontinuation rate at 52 weeks	20/606 (3.3)	36/381 (9.4)	19/409 (4.6)	0/60 (0)	1/35 (2.9)	76/1491 **(5.1)**
Discontinuation rate from treatment at week 52 in the OLE by response at week 16.	31/606 (5.1)	30/381 (7.9)	30/409 (7.3)	2/60 (3.3)	2/35 (5.7)	95/1491 **(6.4)**
Patients with TEAEs resulting in permanent study drug discontinuation: n (%)	6 (1.0%)	11 (2.9%)	9 (2.2%)	0 (0)	1 (2.9%)	27 **(1.8%)**
Patients with at least one rescue therapy in the OLE (Safety analysis set)	19 (3.1%)	15 (3.9%)	19 (4.6%)	2 (3.3%)	0	55 **(3.7%)**

The likelihood that this is a realistic/conservative estimate is further supported by emerging EAMS data. Based on communication from the majority of EAMS sites we understand that overall seven patients have stopped treatment from a total of 221 patients initiated on dupilumab, equivalent to 3.17%. This again supports the low discontinuation rate data used in the economic model base case in the Company's submission.

5. ***(The company) generalised the utility value for 'responders' and 'non-responders' in the best supportive care arm to dupilumab 'non-responders' (see section 3.18)***

Data from week 16 in the LIBERTY trial programme indicate a considerable quality of life benefit is conferred to dupilumab patients even if they did not reach the threshold definition of response at EASI 50 and DLQI4 or more. See Table 9 for the week 16 utility values for BSC and dupilumab responders and non-responders. Note the measure of utility for BSC *responders* is lower than that of dupilumab *non-responders*, indicating a benefit even for patients who do not reach threshold.

Table 9. EQ-5D utilities for responder and non-responder BSC patients

	EASI-50 and DLQI 4+	
Parameter	**BSC**	**Dupilumab**
Week 16 generalised responder and non-responder utility	0.7974	0.8907
Week 16 responders	0.8479	0.8979
Week 16 non-responders	0.7732	0.8679

In the original economic model, dupilumab non-responders were sent immediately to the BSC treatmentm state where they accrued the generalised BSC utility value. As commented previously, the model had a generalised utility value for responders and non-responders. The Committee suggested, in section 3.18, that it was more appropriate to use the utility value specific to people whose condition had not responded to dupilumab plus topical corticosteroids at 16 weeks than the utility value from everyone having best supportive care. We consider implementing this suggestion fully would not have recognised that the dupilumab treatment effect is likely to reduce once dupilumab treatment is discontinued. Therefore the company incorporated the following:

- Week 16 - dupilumab non-responders accrue the average of the dupilumab and the BSC non-responder utility value (0.8205)
- From Week 52 onwards - dupilumab non-responders accrue the BSC non-responder utility value (0.7732)

The impact of these assumptions is minimal given the short period of time in the model that this encompasses (8 months in the decision tree) and the relatively small proportion of responders in the best supportive care arm, increasing the ICER estimate by around £1000 per QALY gained.

6. ***(The company) applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms (see sections 3.19, 3.20 and 3.21)***

We believe the decline, or maintenance, of clinical and utility benefit used in the model needs to be considered separately for both dupilumab and BSC arms because of availability of data. There are emerging data for dupilumab in the longer-term (up to 76 weeks with over 200 patients; up to 100 weeks approximately 40 patients). Data are not available beyond the original trials for placebo/best support care. For the dupilumab arm OLE trial data can inform the long-term data. For BSC, in the absence of data, we ran a number of scenarios.

Dupilumab maintenance of clinical and utility benefits over time

The data available for dupilumab from OLE demonstrate that dupilumab maintained clinical and utility benefit over time with TCS used variably as background therapy and increased potency TCS as rescue therapy. For the endpoints required for the economic model, and all other clinical endpoints and patients reported outcomes, the treatment effect of dupilumab is maintained or increases over time indicating that there is no loss of efficacy out to 76 weeks, with data for over 200 patients (these are included in Appendix A).

See Table 10 for the proportion of patients that achieve the composite endpoint across the time points for which data are available. Note, patient numbers do not reflect discontinuation data but available data. As the trial is ongoing, patients continue to accrue time on treatment (ie, they are censored).

Table 10. Proportion of patients achieving EASI50 and DLQI score reduction >=4 from baseline of parent study (Safety analysis set)

	Dupilumab Naïve	Re-treatment	Interrupted treatment	Continuous treatment	Trt. Blinded in Parent Study	Total
Visit n/N (%)	**(N=606)**	**(N=381)**	**(N=409)**	**(N=60)**	**(N=35)**	**(N=1491)**
Baseline	85/443 (19.2%)	131/302 (43.4%)	120/327 (36.7%)	17/47 (36.2%)	27/33 (81.8%)	380/1152 (33.0%)
Week 12	288/365 (78.9%)	212/250 (84.8%)	221/290 (76.2%)	37/44 (84.1%)	4/5 (80.0%)	762/954 (79.9%)
Week 24	135/153 (88.2%)	202/226 (89.4%)	73/89 (82.0%)	20/23 (87.0%)	0/0	430/491 (87.6%)
Week 36	65/72 (90.3%)	206/222 (92.8%)	23/27 (85.2%)	3/3 (100.0%)	0/0	297/324 (91.7%)

Week 48	56/59 (94.9%)	196/215 (91.2%)	20/20 (100.0%)	1/1 (100.0%)	0/0	273/295 (92.5%)
Week 76	28/31 (90.3%)	153/161 (95.0%)	13/15 (86.7%)	1/1 (100.0%)	0/0	195/208 (93.8%)
Week 100	6/6 (100.0%)	26/27 (96.3%)	7/7 (100.0%)	1/1 (100.0%)	0/0	40/41 (97.6%)

*Note: **dupilumab-naïve patients** (patients who did not receive any dupilumab doses in the parent study), **re-treated patients** (patients who came from the dupilumab arm of parent studies and had a gap of >13 weeks between the last injection in the parent study and the first injection in the current study), **interrupted-treatment patients** (patients who came from the dupilumab arm of parent studies and had a gap of ≥6 weeks but ≤13 weeks between the last injection in the parent study and the first injection in the current study), and **continuously-treated** patients (patients who came from the dupilumab arm of parent studies and had a gap of <6 weeks between the last injection in the parent study and the first injection in the current study).*

The data are striking: for patients for whom there are data available beyond 24 weeks, the proportion of patients meeting the EASI 50 and DLQI 4 composite endpoint is above 85%. There is no indication in the trial data that dupilumab clinical or utility benefit wanes in the way proposed by the Committee.

In OLE, best supportive care is used in line with the licence and how we understand dupilumab is being used in UK clinical practice: patients were allowed topical concomitant treatments including topical calcineurin inhibitors (TCI), and TCS. No systemic or oral concomitant medication was permitted. The concomitant medication data from the OLE demonstrate that patients on dupilumab are able to reduce use of topical concomitant medication, see Table 11 and Table 12. Concomitant medication use decreases from 92.9% at OLE baseline to 47.4% for all patients with available data at the most recent data cut off.

Table 11. Topic concomitant Medication in the OLE (Safety Analysis Set)

Dupilumab Naïve	Re-treatment	Interrupted treatment	Continuous treatment	Total exposed	Trt. Blinded in parent study	Total
(N=606)	(N=381)	(N=409)	(N=60)	(N=850)	(N=35)	(N=1491)
562 (92.7%)	360 (94.5%)	377 (92.2%)	55 (91.7%)	792 (93.2%)	31 (88.6%)	1385 (92.9%)

Table 12. Topical concomitant medication at data cut off in the OLE (Safety Analysis Set)

Dupilumab Naïve	Re-treatment	Interrupted treatment	Continuous treatment	Total exposed	Trt. Blinded in parent study	Total
(N=606)	(N=381)	(N=409)	(N=60)	(N=850)	(N=35)	(N=1491)
283 (46.7%)	193 (50.7%)	196 (47.9%)	27 (45.0%)	416 (48.9%)	7 (20.0%)	706 (47.4%)

Taken together these data suggest that a reduction in topical concomitant corticosteroid use is concurrent with maintained treatment effect. This is in the opposite direction to the relationship proposed by the Committee: that without trial effect and TCS, some portion of the dupilumab treatment effect will rapidly wane.

This also doesn't align with insight from EAMS sites. In the 10 out of 12 EAMS sites that we were able to confirm this data with, clinicians that have experience in treating 177 patients with dupilumab in routine clinical practice, report that there is a clear trend towards significant reduction, up to and including complete cessation of TCS as background treatment. Given clinicians will only reduce TCS if the signs of AD are managed this strongly suggests a maintenance of dupilumab treatment effect concurrent with a significant reduction in topical concomitant medication.

It is also critical to note that Sanofi Genzyme, in line with feedback from clinicians, expect dupilumab to be used in the post-IM patient population. If patients can be effectively and sustainably managed with either TCS or systemic IMs, then they are not candidates for dupilumab in terms of our target patient population. We believe dupilumab should be used for patients who have been previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.

Best supportive care maintenance of clinical and utility benefits over time

There are no long-term data available for best supportive care maintenance of clinical and utility benefits over time. In the ACD the Committee concludes that the effect of best supportive was likely to wane fairly rapidly but how rapidly was uncertain.

The company has used Analysis 5, as presented in the Committee Briefing notes, as the most appropriate baseline waning assumption for BSC. Therefore, the company's updated analysis uses the assumption from the company's original base case to wane the dupilumab treatment effect (98%, 95%, 93% and 92% in years 2 to 5) over and above any annual rate of decline. This was chosen as it seemed plausible. The OLE data suggest this is a conservative estimate.

Given criticality of this assumption, a number of different approaches to test the waning effect of BSC have been performed as sensitivity analyses. For each, we discuss the plausibility below.

Time to first rescue treatment or withdrawal using CHRONOS BSC study arm

We appreciate that the Committee put forward a suggestion which considered the decline in TCS use however, in reflecting on what the Committee was looking for, we consider the OLE data the most appropriate information for the dupilumab arm, and time to first rescue or treatment

discontinuation from CHRONOS to be a good proxy of maintenance of BSC efficacy and utility benefit over time, especially given the information regarding the days on rescue treatment. (See Table 13 below).

The additional benefit of a time to event analysis is that it allows for extrapolation and curve fitting, which we undertook for the BSC arm. The Kaplan Meier data for time to first rescue treatment or withdrawal from study (CHRONOS) were fitted with the usual parametric curves. There are minimal differences between the AIC, AICC, BIC and Loglikelihood criteria for these estimators. (Appendix G). Because of the structure of the model, the 'curve' data are implemented as an annual proportion of patients that had not required rescue or withdrawn from the trial, which we consider to be an appropriate proxy for maintenance of effect on the BSC arm.

We suggest this is a better approach in determining the relative treatment effect on both arms due to BSC, if one must be taken. The output from the curve fitting exercise is used to wane the BSC treatment effect. Compared with the company's original submission, keeping all other assumptions the same, this approach increases the ICER estimate by approximately £200 (with the revised PAS), with an ICER estimate of approximately £27,000 per QALY gained.

Using TCS proportional decrease to estimate the 'trial effect'

The committee's suggested proxy for the relative effect of best supportive care on clinical benefit and health-related quality of life in each arm would be a reasonable approach if (1) both treatments are subject to the same study protocols with respect to frequency of contact (2) BSC is the same on both arm (3) rescue treatment is the same on both treatment arms and (4) there were no long-term data to validate the clinical benefit seen in the trial.

Underlying this suggestion appears to be the suggestions that TCS acts in the same way when used as treatment mainstay and when used as an adjuvant to a treatment with a different mechanism of action. Data are not available here. However, it is clinically plausible that there is a different effect when TCS is used as an adjuvant, with TCS and biologic treatment working synergistically together, as opposed to a topical steroid being required to fully control this complex disease.

We know that both study arms had the same level of mandated clinical contact, so this effect is likely true 'trial effect'. BSC consisted of emollients/moisturisers and low-medium potency TCS. Rescue treatment included stronger potency TCS, and systemic treatment. However, trial protocol allowed

for adjustment of both topical corticosteroids and for rescue treatment dependent upon the severity of the patient's disease. As a result, the extent of BSC use and rescue treatment are not identical in both study arms. Had TCS use on both arms been identical, it would have been less contentious to allocate treatment effect on the placebo or dupilumab arms to TCS or 'trial effect'. However, TCS use varied between arms in response to the patients' disease severity. As such the relationship with TCS, disease state and trial effect is very difficult to unpick.

Similarly, data on days on rescue therapy for both arms provides information regarding what drives the placebo response. Days on rescue treatment data should have informed this discussion more: in CHRONOS patients in the BSC arm report substantively different days on rescue therapy compared with dupilumab patients. In CHRONOS, patients on the BSC arm spent almost a third of the year on rescue treatment (108.3 days) compared to less than 3 weeks (19.3 days) for patients treated with dupilumab Q2W. (Table 13)

Table 13. Analysis of Cumulative Number of Days on Rescue Medication at week 52 in CHRONOS (Full analysis set)

	Placebo QW + TCS (N=315)	**Dupilumab 300 mg Q2W + TCS (N=106)**	**Dupilumab 300 mg QW + TCS (N=319)**
Occurrence rate per Patient-year (SE)	108.321 (0.617)	19.287 (0.442)	29.563 (0.314)
95% CI of Rate	(107.109, 109.532)	(18.419, 20.154)	(28.946, 30.180)
Rate Difference (SE)		-89.034 (0.759)	-78.757 (0.693)
95% CI of Rate Difference		(-90.524, -87.544)	(-80.117, -77.398)
P-Value		<0.0001	<0.0001

We consider it unlikely that this difference in days on rescue therapy does not contribute to the placebo arm treatment effect. Again, had dupilumab patients received the identical days on rescue therapy, it would have been easier to disaggregate treatment effect due to dupilumab, treatment effect due to improved TCS adherence, treatment effect due to time on recue treatment. However, because of the substantial difference it is not possible to disaggregate the contribution of these elements.

Furthermore, this approach leads to rates of patients remaining on treatment at 5 years that are implausibly low, given data insights and clinician feedback. Given 37% of patients stop treatment in the model at week 16 and week 52 due to not hitting the responder threshold, this approach would

leave fewer than 40% of the patients initiated on dupilumab at the end of year 5. This this seems an implausibly high rate of treatment stopping for dupilumab patients and potentially not representative of the treatment effect.

Lastly, as shown above, long term data are available to support the clinical benefit seen with dupilumab in the CHRONOS study, supporting a maintenance of effect with dupilumab irrespective of concomitant TCS.

This trend of maintained benefit is also reflected in EAMS where there has been a low rate of discontinuation (3.17%) since dupilumab was made available in May 2017. There have been seven patients' discontinue treatment out of the 221 patients on dupilumab at 12 EAMS sites, that the company has been made aware of.

Therefore the company does not accept the premise that a proportion of the dupilumab arm treatment effect should be waned in the same way as the placebo arm but have produced scenarios at the committee's request.

7. ***(The company) overestimated the long-term costs of best supportive care (see sections 3.22 and 3.23)***

The committee's concern regarding long term costs for BSC arise from two related concerns.

The first concern relates to the application of costs on the BSC arm for responders and non-responders: the Committee was concerned that the higher costs for non-responders were used in the BSC arm for all patients once they had 'waned' to baseline. The Committee suggested the responder and non-responder costs be pooled. We believe this is not appropriate for two reasons.

- Data to support the submission was collected specifically in the case notes of patients that meet the same definition as the dupilumab target patient population: patients for whom an immunosuppressant has failed or is contraindicated and who are considered by their clinicians to be uncontrolled on current therapy. These patients would be considered to be the non-responder group in the model. Therefore it is appropriate to use these non-responder costs for non-responder BSC patients.

- Having now amended the model to split utility estimates by responder and non-responder, it is appropriate to apply the same rule to resource use.

The impact of this assumption on the ICER estimate is minimal.

The concern regarding long term costs of BSC also relate to the assumptions made for in the company submission for waning effect of BSC. We have addressed this point above.

8. ***(The company) underestimated the cost of injection site reactions, and accident and emergency visits (see section 3.24).***

The model has now been updated to provide annual injection site reactions. Injection site reactions occurred at a very low rate in the dupilumab arm. For example, in the CAFÉ + CHRONOS CAFÉ-like base case the rate is 0.091. Because rates are low, this amendment has only had a minimal impact upon the ICER estimates.

We are unable to provide a specific cost for an accident and emergency visits for atopic dermatitis as this is not captured in the databases we have available to us. However, we have updated the cost from £137.82 used in the company submission to reflect the latest A&E tariff. The average of VB01Z:VB09Z for type 1 and 2 departments has been used. This amounts to £159.78. (See Appendix D for the A&E tariff).

According to the case notes review frequency for A&E attendances is low, this low frequency is used in the model and therefore this update makes minimal difference to ICER estimates, with a range of between £26,000-£30,000 per QALY gained.

2.1 Summary of the impact of the eight committee preferred assumptions

The majority of the committee's preferred assumptions have only a minimal impact on the cost per QALY gained for dupilumab compared with best supportive care in patients with moderate to severe atopic dermatitis and for whom systemic immunosuppressants have failed because of inadequate control, contraindication, intolerance or they were otherwise medically inadvisable. Assumptions that have a more significant impact on the ICER estimates are point 1 (composition of best supportive care and the associated costs); point 4 (annual discontinuation rate for dupilumab responders after year 1) and point 6 (waning of treatment effect for both dupilumab and best supportive care in the context of the contribution of the 'trial effect' to the overall treatment effect).

Varying plausible assumptions that relate to the eight points leads to an ICER range of £17,190 to £35,303, with nine out of twelve of those ICER estimates in the high £20,000s and a most plausivle

ICER estimate of £28,495. This is a narrow range, indicating a stable model and a consistency in results below the £30,000 threshold to support committee decision making.

In line with feedback from clinicians Sanofi Genzyme expect dupilumab to be used in the post-immunosuppressant (IM) patient population. If patients can be effectively and sustainably managed with either TCS or systemic IMs, then they are not candidates for dupilumab. Dupilumab should be used for patients who have been previously optimised on topical treatments and for whom current systemic immunosuppressants have failed because of inadequate control due to contraindication, intolerance or they were otherwise medically inadvisable.

A summary of the revised model inputs and key scenario/sensitivity analyses is provided in Table 14. These settings are used in the revised economic model.

Table 14. Revised base case settings and scenarios tested.

<table>
<tr><th>Variable</th><th>Value</th><th>Scenario analysis*</th><th>Justification</th></tr>
<tr><td colspan="4">Key settings carried over from the original model</td></tr>
<tr><td>Population</td><td>CAFÉ + CHRONOS CAFÉ-like</td><td>Not varied</td><td>As original submission</td></tr>
<tr><td>Continuation criterion</td><td>EASI-50 and DLQI≥4 points change</td><td>Not varied</td><td>As original submission</td></tr>
<tr><td>Time horizon</td><td>Lifetime</td><td>Not varied</td><td>As original submission</td></tr>
<tr><td colspan="4">Updated structural settings</td></tr>
<tr><td>Utility for BSC patients. Split by responder and non-responder.</td><td>Using response criterion EASI50 and DLQI≥4 at 16 weeks:
Non-responder: 0.7732
Responder: 0.8479</td><td>Response criterion not varied so utility values do not vary.</td><td>To address ACD Section 3.25. Point 3</td></tr>
<tr><td>Utility for dupilumab non-responders</td><td>At 16 weeks: Return to average of dupilumab and BSC non-responder utility : 0.8205
At annual cycle: return to BSC non-responder: 0.7732</td><td>16 week utility tested at BSC non-responder value</td><td>To address ACD Section 3.25. Point 5</td></tr>
<tr><td>Injection site reaction rate applied in each cycle</td><td>Annual rate: 9.1%.</td><td>Not varied</td><td>To address ACD Section 3.25. Point 8</td></tr>
<tr><td colspan="4">Updated model inputs</td></tr>
<tr><td>Dupilumab price</td><td>[redacted]</td><td>Not varied</td><td>Updated PAS to provide certainty in the cost-effectiveness estimates</td></tr>
<tr><td>Dupilumab discontinuation rate</td><td>3.7%</td><td>Varied between 2.1% 6.4% for the rate of treatment discontinuation for all patients in the OLE regardless of efficacy in parent study.</td><td>To address ACD Section 3.25. Point 4.</td></tr>
<tr><td>Resource use count estimates</td><td><table><tr><th></th><th colspan="2">Annual count</th></tr><tr><th>Resource</th><th>Responder</th><th>Non-responder</th></tr><tr><td>Dermatologist</td><td>6.09</td><td>4 in first year, 2</td></tr></table></td><td>1. Number of dermatologist visits examined at 3 and 4 in years 2+.
2. Additional hospitalisation and</td><td>Updated to include all the data from the case notes review (59 patients) and used as per patient</td></tr>
</table>

	visits		thereafter
	Hospitalisation	0.12	0.02
	Day case	0.21	0
	A&E visit	0.09	0.02
	Phototherapy	0.06	0
	Psychology	0.07	0
		day case to maintain utility	per year. 1. To address comments made in committee 2. Extra hospital visits tested with Waning assumption switched off and utility for responder and non-responders set equal
Resource use costs	Updated to the latest values in the Unit Costs of Health and Social Care 2017 and the NHS Reference Costs 2016-17	Not varied	Latest costs available.
A&E cost	£159.78 Average of unit cost for emergency medicine with treatment (VB01Z-VB09Z; Type 01 Non-Admitted) for type 1 and 2 departments	Varied between £83 (VB09Z) and £246 (VB01Z)	To address ACD Section 3.25. Point 8
Carer perspective	Not included in the updated base case	Care giver utility benefit for responders 0.01	To illustrate the wider impact of dupilumab treatment
Societal perspective	Not included in the updated base case	Indirect costs applied for days missed. Responder : 0.36 days per month. Non-responder : 1.08 days per month missed	As per original submission
Updated assumptions			
BSC waning estimator	Linear decline 75%, 50%, 25% and 0% thereafter.	• BSC waning fitted to Kaplan Meier data from CHRONOS for time to first rescue or discontinuation. 18,2%, 10.3%, 6.2% and 3.9% thereafter • Linear decline 75%, 50%, 25% and 0% • Base case setting 39%, 9%, 0% and 0%	To address ACD Section 3.25. Point 6
Dupilumab waning estimator	According to clinical opinion presented in the original base case : 98%, 95%, 93% and 92% thereafter.	• NICE suggested factor derived from TCS. Also time to rescue and treatment discontinuation.	To address ACD Section 3.25. Point 6 Evidence from the OLE and

			EAMS sites suggests that whilst a responder there is unlikely to be decline in QoL and so no waning is an appropriate setting in the base case
Analysis method	Primary	Not varied	To address ACD Section 3.25. Point 2

3. Results

3.1. Updated most plausible ICER according to committee preferred assumptions.

The economic model has been updated to accommodate the concerns of the committee.

- Updated PAS
- Discontinuation rate for dupilumab 3.7%
- Waning in the BSC arm using a linear decline of 75%, 50%, 25% and 0%
- Waning in the dupilumab arm
- Non-responder utility in the dupilumab arm is set to the average of BSC and dupilumab non-responder utility
- Utility split by response in the BSC arm
- Updated resource use estimates from the completed case-notes review
- Annual injection site cost applied
- All costs updated to reflect latest HRG and PSSRU costs

The most plausible ICER according to these settings is presented in Table 15 below.

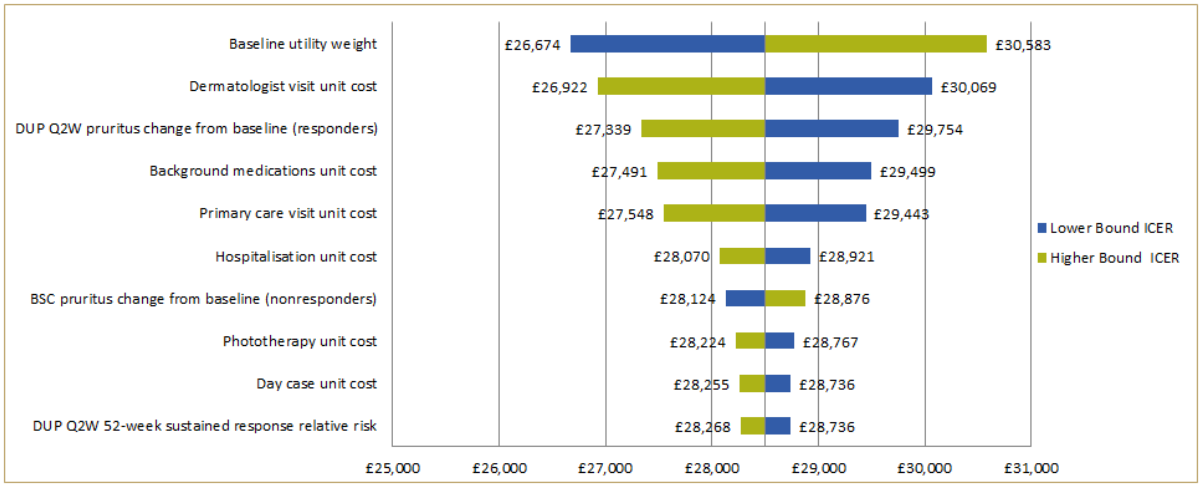
Table 15. Updated base case results for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,495

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

One way sensitivity analysis is presented in Figure 1 overleaf.

Figure 1. Updated tornado diagram for one-way sensitivity analyses.



BSC, Best Supportive Care; FAS, full analysis set; ICER, incremental cost-effectiveness ratio; DUP Q2W, dupilumab 300 mg

The probabilistic results for the comparison of the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients vs. BSC are presented in Figure 2 and Figure 3.

Figure 2. Updated Cost-Effectiveness Acceptability Curve (CEAC) (10,000 iterations)

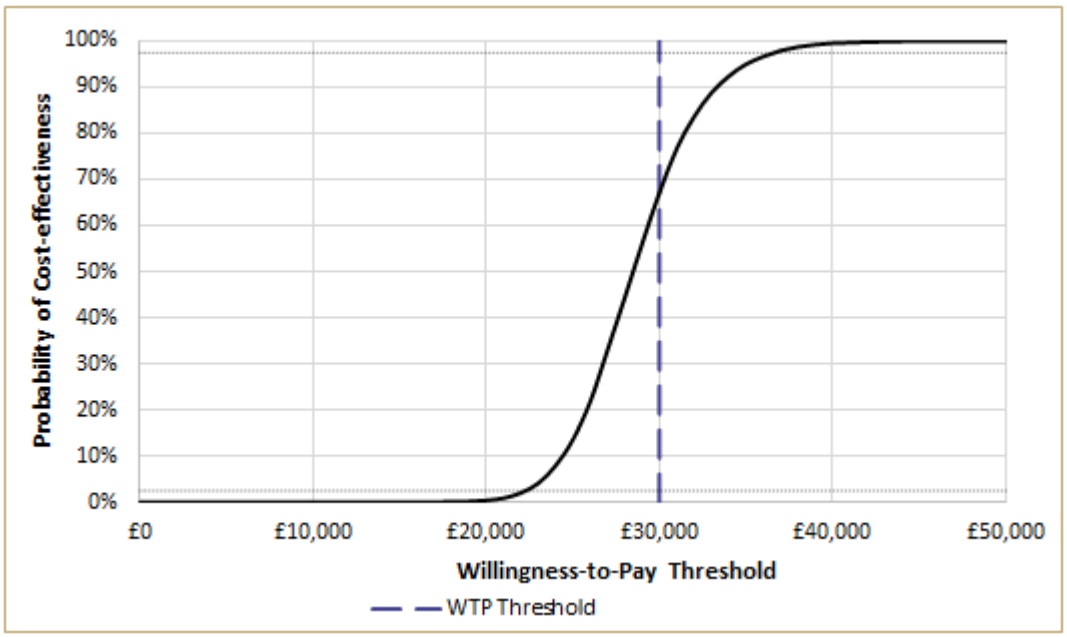
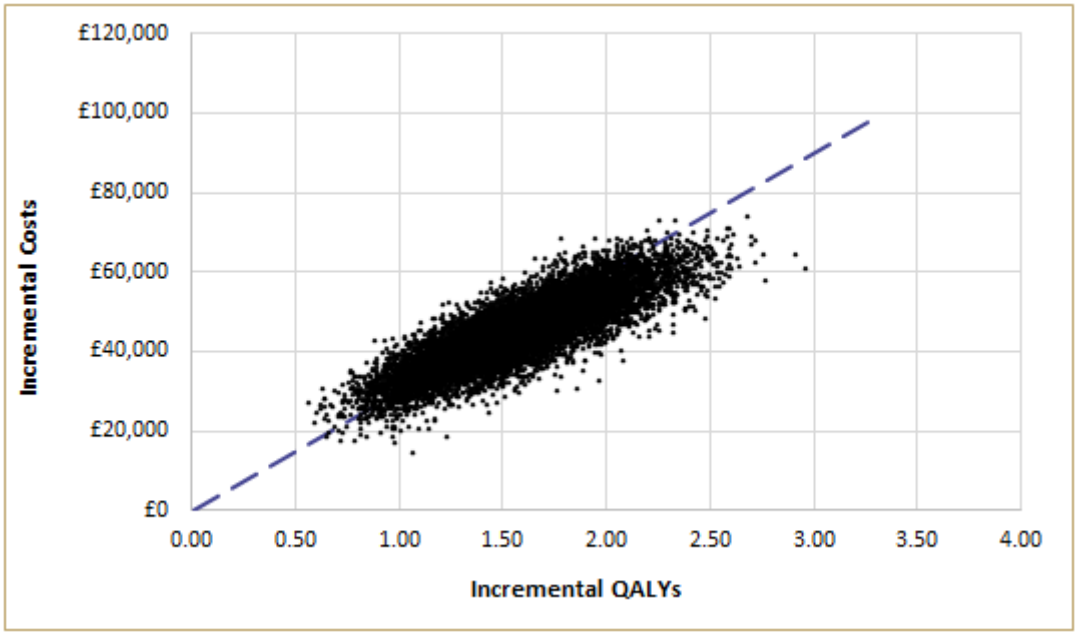


Figure 3. Updated scatter plot (10,000 iterations)



The probabilistic results are presented in Table 16 overleaf.

Table 16. Updated probabilistic base case results for the CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab Q2W patients

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC (placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, Best Supportive Care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

3.2 Scenario and sensitivity analyses

3.2.1. Impact of dupilumab discontinuation rate and BSC waning estimator

Sensitivity analysis for the impact of the dupilumab discontinuation rate and the BSC waning estimator are cross tabulated in Table 17 (including dupilumab patients returning to the average of dupilumab and BSC non-responder utility at 16 weeks followed by annual decline to BSC non-responder utility) and Table 18 (including dupilumab patients returning to BSC non-responder utility at all time points).

Table 17. Impact of dupilumab discontinuation rate on the ICER (dupilumab non-responders return to combination of BSc and dupilumab non-responder utility at 16 weeks).

BSC waning estimator		Dupilumab discontinuation rate				
		Discontinuation from treatment In OLE With EASI50 + DLQI4 at week 24 in parent study	Discontinuation from treatment In OLE With EASI50 + DLQI4 at week 12 in parent study	Discontinuation in CHRONOS with EASI50 + DLGQI4 in parent study OR rate of use of systemic rescue therapy	Discontinuation from study in OLE	Discontinuation from treatment in OLE
		2.1%	2.6%	3.7%	5.1%	6.4%
With waning in the dupilumab arm according to survey of clinicians						
Company base case	37%, 9%, 0% 0%	£26,546	£26,742	£27,199	£27,820	£28,429
Weibull fit to Kaplan Meier disc and/or rescue	18.2%, 10.3%, 6.2%, 3.9%	£26,805	£26,986	£27,410	£27,987	£28,553
Linear return to base line	75%, 50%, 25%, 0%	£27,623	£27,886	£28,495	£29,320	£30,126
Rate for BSC patients with rescue or withdrawal	57% annually	£27,074	£27,279	£27,756	£28,405	£29,040

in CHRONOS at 52 weeks.						
With no additional waning in the dupilumab arm.						
Company base case	37%, 9%, 0% 0%	£26,035	£26,208	£26,619	£27,194	£27,768
Weibull fit to Kaplan Meier disc and/or rescue	18.2%, 10.3%, 6.2%, 3.9%	£26,331	£26,490	£26,870	£27,403	£27,937
Linear return to base line	75%, 50%, 25%, 0%	£26,952	£27,188	£27,742	£28,510	£29,273
Rate for BSC patients with rescue or withdrawal in CHRONOS at 52 weeks.	57% annually	£26,541	£26,722	£27,152	£27,754	£28,354

Table 18. Impact of dupilumab discontinuation rate on the ICER (dupilumab non-responders return to BSC non-responder utility).

BSC waning estimator		**Dupilumab discontinuation rate**				
		Discontinuation from treatment In OLE With EASI50 + DLQI4 at week 24 in parent study	**Discontinuation from treatment In OLE With EASI50 + DLQI4 at week 12 in parent study**	**Discontinuation in CHRONOS with EASI50 + DLGQI4 in parent study OR rate of use of systemic rescue therapy**	**Discontinuation from study in OLE**	**Discontinuation from treatment in OLE**
		2.1%	**2.6%**	**3.7%**	**5.1%**	**6.4%**
With additional waning in the dupilumab arm according to survey of clinicians						
Company base case	37%, 9%, 0% 0%	£26,692	£26,898	£27,377	£28,029	£28,668
Weibull fit to Kaplan Meier disc and/or rescue	18.2%, 10.3%, 6.2%, 3.9%	£26,953	£27,145	£27,590	£28,199	£28,794
Linear return to base line	75%, 50%, 25%, 0%	£27,780	£28,055	£28,690	£29,552	£30,394
Rate for BSC patients with rescue or withdrawal	57% annually	£27,225	£27,440	£27,941	£28,623	£29,290

in CHRONOS at 52 weeks.						
With no additional waning in the dupilumab arm.						
Company base case	37%, 9%, 0% 0%	£26,156	£26,338	£26,769	£27,373	£27,975
Weibull fit to Kaplan Meier disc and/or rescue	18.2%, 10.3%, 6.2%, 3.9%	£26,454	£26,622	£27,023	£27,584	£28,146
Linear return to base line	75%, 50%, 25%, 0%	£27,081	£27,327	£27,905	£28,706	£29,503
Rate for BSC patients with rescue or withdrawal in CHRONOS at 52 weeks.	57% annually	£26,666	£26,856	£27,309	£27,940	£28,569

3.2.2. Scenarios testing NICE suggested methodology for dupilumab waning

As discussed above in line with the suggestion of the committee to consider the magnitude of reduction in TCS use as a proxy for the trial effect in both arms we implement this methodology (See Appendix F for an explanation of the calculations) and settings) to the TCS used 'factor' for the magnitude of the trial effect (Table 19). The two BSC waning estimators are provided: The fitted curve to the Kaplan Meier data (Appendix G) and the linear drop (75%, 50%, 25% and 0%. The dupilumab non-responder utility at the 16 week assessment point is examined between these tables. Discontinuation rate for dupilumab = 3.7%.

Table 19. ICERs using factors derived from various rates for rescue and discontinuation (dupilumab non-responders return to combination of BSc and dupilumab non-responder utility followed by BSC non-responder utility or all return to BSC non-responder utility).

Source	Dupilumab treated patients (OLE)	BSC treated patients (CHRONOS)	Factor	ICER: Curve fit for BSC	ICER: BSC: Linear decline
Proportional reduction in TCS in CAFE	19.30%	50.30%	38.40%	£29,444	£35,839
Proportional reduction in TCS in CAFE	19.30%	50.30%	38.40%	£29,169	£35,303

3.2.3. Sensitivity analysis testing cost of A&E appointment

The cost of an A&E appointment was queried in the ACD and because it has been very difficult to determine an accurate cost for an AD episode we have tested the range of costs for the HRG codes for A&E visits. These are tabulated in

Table **20** considering the plausible range of discontinuation rates dupilumab discontinuation and the key BSC waning estimators.

Table 20. Sensitivity analysis for the cost of an A&E appointment.

Code	HRG	Cost	ICER	
			Weibull fit to Kaplan Meier disc and/or rescue	Linear return to base line
Base case (average of VB01Z-VB09Z; Type 01 Non-Admitted) for type 1 and 2 departments) (dupilumab discontinuation = 3.7%)		**£159.78**	**£27,410**	**£28,495**
Discontinuation in the OLE for patients who were responders in the parent studies according to EASI-50 and DLQI ≥4 points change (2.1%).				
VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	£83	£26,830	£27,649
VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	£246	£26,777	£27,595
Discontinuation according to overall rate of treatment discontinuation in the OLE (6.4%)				

VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	£83	£28,577	£30,151
VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	£246	£28,525	£30,097

As there are so few events in this category the cost of an A&E visit has minimal impact in the ICER

3.2.4. Sensitivity analysis testing additional annual visits to dermatologist for responders

All the dermatologists we have spoken to have confirmed that 2 visits a year for dupilumab responders would be sufficient given the lack of a testing requirement. The committee heard that for a new biologic there may be caution and that for a while additional annual visits may be requested. We think that once clinicians are familiar with the drug, this will reduce in line with other biologic treatments in other therapy areas, however, we have modelled 3 and 4 visits for responders accordingly. The results are presented in Table 21 below.

Table 21. Additional annual visits to dermatologist for responders (both arms).

Number of visits of dermatologist		ICER	
Year 1 responder	**Year 2+ responder**	**Weibull fit to Kaplan Meier disc and/or rescue**	**Linear return to base line**
Base case (4)	**Base case (2)**	**£27,410**	**£28,495**
4	3	£28,123	£29,229
4	4	£28,826	£29,963

3.2.5. Scenarios testing resource use estimates which may be required to maintain treatment effect in the BSC arm.

The committee heard that best supportive care may include hospitalisations for 1 week to 2 weeks to intensify treatment and provide respite for people having to apply topical medications. In order to examine this we provide a simplistic test which includes 1 and 2 hospitalisations per year for non-responders and test the ICERs under different BSC waning estimators including the extreme case of NO Waning. In this case the additional hospitalisations are assumed to provide 'responder' like utility (See Appendix H for an explanation of the calculations in the economic model). This is likely to be an over estimation of the benefit as 'non-responders' are likely to 'wane' significantly before respite care is offered.

Table 22. Additional hospital visits for non-responders (both arms). (Dupilumab discontinuation rate = 3.7%).

Number of hospital visits per year	ICER		
	Weibull fit to Kaplan Meier disc and/or rescue	**Linear return to base line**	**No waning**
1	£20,856	£22,142	£33,819
2	£12,808	£13,639	£17,190

3.2.6. Scenarios testing impact on family and care givers.

The NICE reference case(1) states that the perspective on outcomes should encompass all direct health effects, whether for patients or, when relevant, carers. This implies that the indirect impact of a disease or treatment on caregivers can be considered when assessing the cost effectiveness of therapies. A treatment that maintains or improves a caregivers' health related quality of life (HRQL) is therefore a relevant benefit that can be considered in an economic evaluation.(2)

There is limited literature on the spillover disutility of illness on family members or carers and none that we could find directly addressing atopic dermatitis. A recent review of the literature identified disutilities including −0.04 for parents of children with spina bifida, −0.08 for parents of children with activity limitations −0.09 for parents of children with gastroenteritis and −0.14 for caregivers of persons with multiple sclerosis and substantially burdened caregivers of stroke patients. (3) In TA373 (Juvenile Idiopathic Arthritis, 2015) values between 0.01 and 0.07 were included in scenario analysis.
Atopic dermatitis is known to have a substantial impact on families and carers(4) and so we have tested values for care giver disutilities between 0.01 and 0.1 in line with the estimates above for chronic conditions.

As for the other analyses above the range for the two key waning estimators are examined in this scenario analysis (Table 23).

Table 23 Analysis of disutility impact on families and carers

Carer utility benefit whilst patient is on treatment	ICER	
	Weibull fit to Kaplan Meier disc and/or rescue	Linear return to base line
0.01	£26,247	£27,251
0.1	£18,997	£19,562

C3.2.7. Societal impact

Patients with AD report lower work productivity compared to non-AD controls(5). The impact of productivity loss on the ICER is examined according to the parameters in Table 24 and Table 25 overleaf which were also implemented in the company base case in the original submission.

Table 24. Productivity loss inputs

Productivity loss	Responder (days per month)	Non-responder (days per month)	Source
UK population norm adjusted for moderate-to-severe AD using the National Health and Wellness Survey	0.36	1.08	ONS 2016, Whitely 2016 (5, 6)

Table 25. Employment Parameters

Employment Parameters	Input	Source
Value of productivity loss per hour	£15.13	Weighted average of full- and part-time employment wages per hour using data from the Office of National Statistics(7, 8)
Percentage employed	78.5%	Percentage of employed participants in the AWARE study(9). Like the percentages in SOLO1+2 (72.4%), CHRONOS (76.6%), and CAFÉ (76.6%).
Working hours per day	6.67	Weighted average of full- and part-time employment hours per work day using data from the Office of National Statistics(8)

As for the other analyses above the two key waning estimators are examined in this scenario analysis (Table 26).

Table 26. Simple analysis of productivity loss

ICER	
Weibull fit to Kaplan Meier disc and/or rescue	**Linear return to base line**
£24,587	£25,586

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Appendices

Contents

Appendix A. Evidence from the Open Label Extension (OLE) study

Description of the study

This study is an ongoing, multicenter, open-label extension study (NCT01949311) to evaluate the long-term use of dupilumab in adults who had previously participated in Phase 1, 2, and 3 dupilumab clinical trials of dupilumab in AD.

Patients were enrolled at 319 study sites in 23 North American, European, and Asia Pacific countries. Main exclusion criteria were dupilumab-related serious AEs (SAEs) and AEs leading to discontinuation from the previous (parent) study. The primary objective is to assess long-term safety of dupilumab in patients with AD with the primary endpoint of incidence and rate (events per patient-year) of AEs. Additionally, efficacy parameters (Eczema Area Severity Index (EASI), peak pruritus Numerical Rating Scale (NRS), Dermatology Life Quality Index (DLQI) and Patient-Oriented Eczema Measure (POEM)) and also immunogenicity are assessed.

In the study patients receive weekly (qw) subcutaneous doses of dupilumab and concomitant topical treatments are allowed without restriction or mandate. Rescue treatment with systemic medications (corticosteroids or nonsteroidal immunosuppressants) could be used at investigator's discretion.

Four patient subsets were identified in this study based on patients' prior experience with dupilumab in the parent studies. These subsets included dupilumab-naïve patients (patients who did not receive any dupilumab doses in the parent study), re-treated patients (patients who came from the dupilumab arm of parent studies and had a gap of >13 weeks between the last injection in the parent study and the first injection in the current study), interrupted-treatment patients (patients who came from the dupilumab arm of parent studies and had a gap of ≥6 weeks but ≤13 weeks between the last injection in the parent study and the first injection in the current study), and continuously-treated patients (patients who came from the dupilumab arm of parent studies and had a gap of <6 weeks between the last injection in the parent study and the first injection in the current study).

Patients in the dupilumab-naïve group came from the placebo groups of the phase 1, 2, or 3 studies and included patients screened but not randomized into the PhIII study. Patients in the re-treatment and interrupted-treatment groups generally came from the PhI or II studies. Most patients in the continuous treatment group came from the dupilumab groups in the PhIII studies (R668-AD-1334 and R668-AD-1416) who either did not qualify for the maintenance study (ie, IGA 0, 1 and EASI-75 non-responders) or who completed the maintenance study and received dupilumab during this study.

Table 1. Baseline characteristics of patients used in the economic modelling and OLE patients

	CAFÉ + CHRONOS-CAFÉ-like			OLE (MAINTAIN)
	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Dupilumab Total
	N=169	N=130	N=163	[redacted]
EASI (0-72, 20=severe), mean (SD)	34.8 (12.0)	33.6 (10.5)	34.2 (11.7)	[redacted]
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	6.9 (2.1)	6.9 (2.1)	6.6 (2.0)	[redacted]
DLQI score (0-30, >10=very large effect), mean (SD)	14.8 (7.7)	14.6 (7.5)	15.0 (8.0)	[redacted]
EQ-5D utility, mean (SD)	0.632 (0.324)	0.719 (0.249)	0.646 (0.282)	[redacted]

The baseline characteristics for the Company base case population and that of the OLE study is shown above. Although the numeric scores were lower in OLE, more than half the patients (59%) had previously been treated with dupilumab.

[redacted]

[redacted]							
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[redacted]							

Compliance in the OLE

Injection compliance was calculated as: (number of injections during the exposure period)/(number of planned injections during the exposure period) x 100%. The mean injection compliance for all patients during the OLE was 98.3% (±4.92%) (Table 2). Most patients had ≥80% injection compliance during the first 52-week treatment period and over the course of the entire study.

Table 2, Summary of Treatment Compliance – SAF

Mean (SD)	[redacted]
Median	[redacted]
Q1:Q3	[redacted]
Min:Max	[redacted]
≥80%	[redacted]
<80%	[redacted]

Proportion of Patients with EASI-75 and EASI-50 Relative to Baseline of Parent Study

The proportion of patients with EASI-75 (defined as a ≥75% reduction in EASI score from baseline EASI score of the parent study) at baseline of the OLE was 18.2%. Increases in the proportion of patients who achieved EASI-75 relative to baseline of the parent study were observed at as early as week 2 and a consistent high-level (>75%) response was observed from week 16 throughout the remaining relevant study time points

[redacted]

		Previously Treated with Dupilumab					
Visit	Dupilumab Naive (N=606) n/N1 (%)	Re-treatment (N=381) n/N1 (%)	Interrupted treatment (N=409) n/N1 (%)	Continuous treatment (N=60) n/N1 (%)	Total Exposed (N=850) n/N1 (%)	Trt. Blinded in Parent Study (N=35) n/N1 (%)	Total (N=1491) n/N1 (%)
Baseline of current study	58/577 (10.1%)	89/381 (23.4%)	86/408 (21.1%)	7/59 (11.9%)	182/848 (21.5%)	26/35 (74.3%)	266/1460 (18.2%)
Week 2	149/549 (27.1%)	145/367 (39.5%)	144/398 (36.2%)	16/57 (28.1%)	305/822 (37.1%)	26/29 (89.7%)	480/1400 (34.3%)
Week 4	259/537 (48.2%)	217/358 (60.6%)	199/397 (50.1%)	32/59 (54.2%)	448/814 (55.0%)	19/20 (95.0%)	726/1371 (53.0%)
Week 8	344/524 (65.6%)	242/347 (69.7%)	224/385 (58.2%)	37/56 (66.1%)	503/788 (63.8%)	6/6 (100%)	853/1318 (64.7%)
Week 12	369/498 (74.1%)	245/328 (74.7%)	242/367 (65.9%)	37/56 (66.1%)	524/751 (69.8%)	5/5 (100%)	898/1254 (71.6%)
Week 16	356/461 (77.2%)	247/313 (78.9%)	229/337 (68.0%)	43/55 (78.2%)	519/705 (73.6%)	0/0	875/1166 (75.0%)
Week 20	290/357 (81.2%)	247/309 (79.9%)	181/238 (76.1%)	36/49 (73.5%)	464/596 (77.9%)	0/0	754/953 (79.1%)
Week 24	216/267 (80.9%)	236/298 (79.2%)	126/158 (79.7%)	25/35 (71.4%)	387/491 (78.8%)	0/0	603/758 (79.6%)
Week 28	192/224 (85.7%)	236/293 (80.5%)	91/120 (75.8%)	19/25 (76.0%)	346/438 (79.0%)	0/0	538/662 (81.3%)
Week 32	170/191 (89.0%)	239/291 (82.1%)	72/91 (79.1%)	17/21 (81.0%)	328/403 (81.4%)	0/0	498/594 (83.8%)
Week 36	147/164 (89.6%)	250/286 (87.4%)	58/72 (80.6%)	9/14 (64.3%)	317/372 (85.2%)	0/0	464/536 (86.6%)
Week 40	130/143 (90.9%)	236/281 (84.0%)	48/57 (84.2%)	9/12 (75.0%)	293/350 (83.7%)	0/0	423/493 (85.8%)
Week 44	113/126 (89.7%)	241/280 (86.1%)	41/52 (78.8%)	5/6 (83.3%)	287/338 (84.9%)	0/0	400/464 (86.2%)
Week 48	99/113 (87.6%)	236/277 (85.2%)	36/41 (87.8%)	4/5 (80.0%)	276/323 (85.4%)	0/0	375/436 (86.0%)
Week 52	85/97 (87.6%)	238/272 (87.5%)	24/30 (80.0%)	3/3 (100%)	265/305 (86.9%)	0/0	350/402 (87.1%)
Week 60	72/82 (87.8%)	220/253 (87.0%)	15/21 (71.4%)	1/1 (100%)	236/275 (85.8%)	0/0	308/357 (86.3%)
Week 68	65/75 (86.7%)	218/245 (89.0%)	12/17 (70.6%)	1/1 (100%)	231/263 (87.8%)	0/0	296/338 (87.6%)
Week 76	42/47 (89.4%)	185/206 (89.8%)	14/17 (82.4%)	1/1 (100%)	200/224 (89.3%)	0/0	242/271 (89.3%)
Week 84	36/40 (90.0%)	156/173 (90.2%)	14/16 (87.5%)	1/1 (100%)	171/190 (90.0%)	0/0	207/230 (90.0%)
Week 92	29/30 (96.7%)	98/104 (94.2%)	15/16 (93.8%)	1/1 (100%)	114/121 (94.2%)	0/0	143/151 (94.7%)
Week 100	13/14 (92.9%)	34/36 (94.4%)	8/9 (88.9%)	1/1 (100%)	43/46 (93.5%)	0/0	56/60 (93.3%)
Week 108	6/6 (100%)	7/7 (100%)	0/0	0/0	7/7 (100%)	0/0	13/13 (100%)
Week 116	2/2 (100%)	0/0	0/0	0/0	0/0	0/0	2/2 (100%)
Week 124	1/1 (100%)	0/0	0/0	0/0	0/0	0/0	1/1 (100%)

The proportions of patients achieving EASI 50 from the baseline of the parent study at each visit are provided in [redacted] below. Total patient numbers reduce

at each time point mainly due to the recruitment of patients into the study which occurred over time as each of the parent studies completed. Data for over 100 patients is recorded for 92 weeks in the OLE.

At baseline of the OLE, [redacted] patients had achieved EASI-50 relative to baseline of the parent study. Further increases in the proportion of patients who achieved EASI-50 relative to baseline of the parent studies were observed from week 2, and a high level of response (>90%) was maintained from week 12 throughout the remainder of the study time points.

[redacted]

		Previously Treated with Dupilumab					
Visit	Dupilumab Naive (N=606) n/N1 (%)	Re-treatment (N=381) n/N1 (%)	Interrupted treatment (N=409) n/N1 (%)	Continuous treatment (N=60) n/N1 (%)	Total Exposed (N=850) n/N1 (%)	Trt. Blinded in Parent Study (N=35) n/N1 (%)	Total (N=1491) n/N1 (%)
Baseline of current study	178/577 (30.8%)	193/381 (50.7%)	206/408 (50.5%)	26/59 (44.1%)	425/848 (50.1%)	31/35 (88.6%)	634/1460 (43.4%)
Week 2	303/549 (55.2%)	254/367 (69.2%)	287/398 (72.1%)	36/57 (63.2%)	577/822 (70.2%)	28/29 (96.6%)	908/1400 (64.9%)
Week 4	403/537 (75.0%)	300/358 (83.8%)	314/397 (79.1%)	51/59 (86.4%)	665/814 (81.7%)	20/20 (100%)	1088/1371 (79.4%)
Week 8	452/524 (86.3%)	306/347 (88.2%)	333/385 (86.5%)	52/56 (92.9%)	691/788 (87.7%)	6/6 (100%)	1149/1318 (87.2%)
Week 12	459/498 (92.2%)	296/328 (90.2%)	324/367 (88.3%)	51/56 (91.1%)	671/751 (89.3%)	5/5 (100%)	1135/1254 (90.5%)
Week 16	433/461 (93.9%)	289/313 (92.3%)	306/337 (90.8%)	50/55 (90.9%)	645/705 (91.5%)	0/0	1078/1166 (92.5%)
Week 20	337/357 (94.4%)	290/309 (93.9%)	220/238 (92.4%)	45/49 (91.8%)	555/596 (93.1%)	0/0	892/953 (93.6%)
Week 24	254/267 (95.1%)	285/298 (95.6%)	145/158 (91.8%)	31/35 (88.6%)	461/491 (93.9%)	0/0	715/758 (94.3%)
Week 28	216/224 (96.4%)	282/293 (96.2%)	116/120 (96.7%)	25/25 (100%)	423/438 (96.6%)	0/0	639/662 (96.5%)
Week 32	185/191 (96.9%)	279/291 (95.9%)	88/91 (96.7%)	21/21 (100%)	388/403 (96.3%)	0/0	573/594 (96.5%)
Week 36	158/164 (96.3%)	278/286 (97.2%)	70/72 (97.2%)	14/14 (100%)	362/372 (97.3%)	0/0	520/536 (97.0%)
Week 40	139/143 (97.2%)	269/281 (95.7%)	55/57 (96.5%)	12/12 (100%)	336/350 (96.0%)	0/0	475/493 (96.3%)
Week 44	122/126 (96.8%)	271/280 (96.8%)	49/52 (94.2%)	5/6 (83.3%)	325/338 (96.2%)	0/0	447/464 (96.3%)
Week 48	111/113 (98.2%)	270/277 (97.5%)	40/41 (97.6%)	5/5 (100%)	315/323 (97.5%)	0/0	426/436 (97.7%)
Week 52	93/97 (95.9%)	265/272 (97.4%)	28/30 (93.3%)	3/3 (100%)	296/305 (97.0%)	0/0	389/402 (96.8%)
Week 60	79/82 (96.3%)	246/253 (97.2%)	20/21 (95.2%)	1/1 (100%)	267/275 (97.1%)	0/0	346/357 (96.9%)
Week 68	73/75 (97.3%)	243/245 (99.2%)	16/17 (94.1%)	1/1 (100%)	260/263 (98.9%)	0/0	333/338 (98.5%)
Week 76	47/47 (100%)	202/206 (98.1%)	16/17 (94.1%)	1/1 (100%)	219/224 (97.8%)	0/0	266/271 (98.2%)
Week 84	40/40 (100%)	172/173 (99.4%)	15/16 (93.8%)	1/1 (100%)	188/190 (98.9%)	0/0	228/230 (99.1%)
Week 92	30/30 (100%)	103/104 (99.0%)	15/16 (93.8%)	1/1 (100%)	119/121 (98.3%)	0/0	149/151 (98.7%)
Week 100	14/14 (100%)	36/36 (100%)	9/9 (100%)	1/1 (100%)	46/46 (100%)	0/0	60/60 (100%)
Week 108	6/6 (100%)	7/7 (100%)	0/0	0/0	7/7 (100%)	0/0	13/13 (100%)
Week 116	2/2 (100%)	0/0	0/0	0/0	0/0	0/0	2/2 (100%)

Note: N1 stands for number of patients with non-missing EASI score at each week. Analysis groups were not randomized and not readily comparable.

At baseline of the parent study, the mean POEM score in all patients in the SAF was [redacted] (**Error! Reference source not found.**).

[redacted]

		Value at Visit								Percent Change from Baseline of Parent Study							
Treatment	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Total (N=1491)	Baseline of parent study	1374	21.2	5.62	1	18.0	22.0	26.0	28								
	Baseline of current study	1491	16.7	7.44	0	11.0	17.0	23.0	28	1374	-18.37	80.493	-100.0	-42.86	-18.75	0.00	2600.0
	Week 12	1276	8.1	6.24	0	3.0	7.0	12.0	28	1167	-59.14	48.404	-100.0	-85.00	-66.67	-41.67	1200.0
	Week 24	755	6.8	5.85	0	2.0	5.0	10.0	28	673	-64.11	80.512	-100.0	-88.89	-75.00	-50.00	1900.0
	Week 36	534	6.6	5.90	0	2.0	5.0	10.0	28	458	-68.04	27.993	-100.0	-89.29	-76.47	-50.00	57.1
	Week 48	435	6.0	5.41	0	2.0	4.0	9.0	27	363	-71.31	24.661	-100.0	-90.00	-78.26	-60.00	27.3
	Week 76	270	5.5	5.37	0	2.0	4.0	8.0	24	231	-73.06	25.176	-100.0	-92.31	-82.35	-57.14	21.4
	Week 100	60	5.3	5.28	0	2.0	3.5	6.5	22	45	-76.25	24.754	-100.0	-92.31	-84.62	-70.59	-13.3
	Week 124	1	9.0		9	9.0	9.0	9.0	9	0							
Dupilumab Naive (N=606)	Baseline of parent study	547	21.2	5.41	4	17.0	22.0	26.0	28								
	Baseline of current study	606	18.5	7.12	0	14.0	19.0	25.0	28	547	-10.61	39.431	-100.0	-32.00	-8.00	4.55	475.0
	Week 12	521	7.5	6.33	0	3.0	6.0	11.0	28	467	-63.14	31.240	-100.0	-87.50	-71.43	-45.45	87.5
	Week 24	267	6.7	5.87	0	2.0	5.0	10.0	28	237	-68.16	27.569	-100.0	-90.91	-76.47	-50.00	46.2
	Week 36	164	6.5	6.00	0	2.0	5.0	10.0	26	135	-68.12	28.893	-100.0	-91.30	-77.78	-47.62	6.3
	Week 48	113	6.3	5.46	0	2.0	4.0	10.0	24	85	-68.62	25.130	-100.0	-88.24	-75.00	-50.00	4.3
	Week 76	46	5.1	4.87	0	1.0	3.5	9.0	17	32	-72.48	26.468	-100.0	-92.30	-80.48	-57.69	21.4
	Week 100	14	4.1	4.19	0	2.0	2.5	5.0	14	7	-75.68	28.918	-100.0	-92.86	-84.00	-70.59	-14.3
	Week 124	1	9.0		9	9.0	9.0	9.0	9	0							
Total Previously Exposed with Dupilumab (N=850)	Baseline of parent study	792	21.3	5.79	1	18.0	22.0	26.0	28								
	Baseline of current study	850	15.6	7.36	0	10.0	16.0	21.0	28	792	-22.52	100.136	-100.0	-48.00	-26.32	-4.17	2600.0
	Week 12	750	8.5	6.16	0	4.0	7.0	12.0	28	695	-56.43	57.084	-100.0	-82.61	-64.00	-38.46	1200.0
	Week 24	488	7.0	5.84	0	3.0	6.0	10.0	28	436	-61.91	97.916	-100.0	-87.23	-73.80	-50.00	1900.0
	Week 36	370	6.6	5.87	0	2.0	5.0	10.0	28	323	-68.00	27.654	-100.0	-88.46	-76.47	-52.00	57.1
	Week 48	322	5.8	5.40	0	2.0	4.0	8.0	27	278	-72.14	24.502	-100.0	-90.00	-78.57	-60.00	27.3
	Week 76	224	5.6	5.48	0	2.0	4.0	8.0	24	199	-73.16	25.030	-100.0	-92.31	-82.61	-57.14	0.0
	Week 100	46	5.6	5.57	0	2.0	4.0	8.0	22	38	-76.36	24.352	-100.0	-92.31	-85.16	-70.00	-13.3
	Week 124	0								0							

From baseline of the parent study to baseline in the current study, the mean percent change in POEM score in all patients in the SAF was -[redacted] Additional reductions from baseline of the parent study in mean POEM scores, suggesting improvement in symptomatology with dupilumab

treatment, were observed beginning at week 12, and mean reductions in POEM score of [redacted] were maintained throughout the remainder of the relevant time points in the study.

Changes from baseline in peak pruritus

The percent change from baseline of the parent study in peak pruritus numeric rating scores at each week is shown in **Error! Reference source not found.** overleaf

From baseline of the parent study to baseline of the OLE, a mean reduction of [redacted] in peak Pruritus NRS was observed. Further reductions in peak Pruritus NRS relative to baseline of the parent study were observed during the current study through week 24 and reductions of [redacted] were maintained throughout the remainder of the relevant time points **Error! Reference source not found.**.

At baseline of the parent study, the mean peak Pruritus NRS was [redacted] in the dupilumab-naïve patient subset and [redacted] in the re-treatment patient subset. The mean percent change from baseline of the parent study to baseline of the current study in peak Pruritus NRS was [redacted] in the dupilumab-naïve subset and [redacted] in the re-treatment subset. Further reductions from baseline of the parent study were observed for peak Pruritus NRS in both subsets over the course of the current study, beginning as early as week 1. Reductions of approximately [redacted] were maintained during the remainder of the relevant time points in both patient subsets.

[redacted]

	Value at visit								Percentage change from baseline of parent study							
Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Baseline of parent study	[redacted]															
Baseline of current study	[redacted]															
Week 12	[redacted]															
week 24	[redacted]															
Week 36	[redacted]															
Week 48	[redacted]															
Week 60	[redacted]															
Week 76	[redacted]															
Week 100	[redacted]															
Week 124	[redacted]															

Changes from baseline in DLQI

At baseline of the parent study, the mean DLQI in all patients in the SAF was [redacted] A change in DLQI [redacted] was observed from baseline of the parent study to baseline of the current study in all patients. Additional reductions in DLQI from baseline of the parent study, suggesting increases in QoL, were observed and maintained throughout the remainder of the relevant time points.

The absolute change from baseline from the baseline of the parent study in the DLQI score is presented in **Error! Reference source not found.** below.

[redacted]

		Value at Visit								Change from Baseline of Parent Study							
Treatment	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Total (N=1491)	Baseline of parent study	1206	15.4	7.37	0	10.0	15.0	21.0	30								
	Baseline of current study	1491	10.1	7.39	0	4.0	9.0	14.0	30	1206	-5.6	6.90	-28	-10.0	-5.0	-1.0	17
	Week 12	1273	4.4	4.94	0	1.0	3.0	6.0	29	1001	-10.9	7.24	-29	-16.0	-10.0	-5.0	18
	Week 24	758	3.6	4.17	0	1.0	2.0	5.0	26	523	-11.3	7.06	-28	-16.0	-11.0	-6.0	12
	Week 36	534	3.4	4.13	0	1.0	2.0	5.0	25	348	-11.3	6.70	-29	-16.0	-11.0	-6.0	3
	Week 48	435	3.0	3.91	0	1.0	2.0	3.0	23	319	-11.3	6.74	-29	-16.0	-11.0	-6.0	3
	Week 76	264	2.8	3.77	0	0.0	1.0	4.0	21	225	-11.3	6.86	-28	-16.0	-10.0	-7.0	3
	Week 100	60	2.8	3.79	0	1.0	1.0	3.0	18	45	-13.3	7.80	-27	-19.0	-12.0	-8.0	1
	Week 124	1	1.0		1	1.0	1.0	1.0	1	0							
Dupilumab Naive (N=606)	Baseline of parent study	460	15.4	7.34	0	10.0	15.0	21.0	30								
	Baseline of current study	606	11.6	7.88	0	5.0	10.0	17.0	30	460	-4.1	6.89	-24	-8.0	-4.0	0.0	17
	Week 12	519	4.2	4.80	0	1.0	2.0	6.0	27	380	-11.0	7.29	-29	-17.0	-10.0	-5.0	9
	Week 24	268	3.2	3.83	0	1.0	2.0	4.0	21	161	-11.7	6.78	-28	-17.0	-11.0	-7.0	3
	Week 36	164	3.4	4.07	0	1.0	2.0	4.0	19	78	-10.6	6.49	-25	-16.0	-10.0	-6.0	2
	Week 48	113	3.0	3.64	0	1.0	2.0	3.0	17	64	-10.3	6.39	-26	-14.5	-10.0	-5.5	0
	Week 76	46	2.8	3.42	0	1.0	1.0	3.0	14	32	-11.2	6.54	-27	-16.0	-10.0	-7.0	-1
	Week 100	14	2.4	3.27	0	0.0	1.0	3.0	12	7	-11.3	8.06	-23	-19.0	-9.0	-5.0	-2
	Week 124	1	1.0		1	1.0	1.0	1.0	1	0							
Total Previously Exposed with Dupilumab (N=850)	Baseline of parent study	711	15.5	7.43	0	10.0	15.0	21.0	30								
	Baseline of current study	850	9.2	6.88	0	3.0	8.0	13.0	30	711	-6.4	6.73	-28	-10.0	-6.0	-2.0	13
	Week 12	749	4.6	5.00	0	1.0	3.0	6.0	29	616	-10.8	7.13	-28	-15.0	-10.0	-5.0	4
	Week 24	490	3.8	4.33	0	1.0	2.0	5.0	26	362	-11.1	7.18	-28	-16.0	-11.0	-6.0	12
	Week 36	370	3.4	4.17	0	1.0	2.0	5.0	25	270	-11.4	6.75	-29	-16.0	-11.0	-7.0	3
	Week 48	322	3.0	4.01	0	1.0	2.0	3.0	23	255	-11.5	6.81	-29	-16.0	-11.0	-7.0	3
	Week 76	218	2.8	3.85	0	0.0	1.0	4.0	21	193	-11.3	6.93	-28	-16.0	-11.0	-7.0	3
	Week 100	46	2.9	3.96	0	1.0	1.0	3.0	18	38	-13.7	7.81	-27	-20.0	-12.0	-10.0	1
	Week 124	0								0							

Changes from Baseline of Parent Study in EQ-5D and patient Global assessment

At baseline of the parent study, the mean EQ-5D utility score in all patients was [redacted] and the mean EQVAS score was [redacted]

. An increase in mean EQ-5D utility score of [redacted] from baseline of the parent study to baseline of the current study was observed in all patients. Further mean increases above in EQ-5D utility score were observed at week 12 and were maintained over the course of the OLE, suggesting improvements in QoL with dupilumab treatment which continues over time.

The mean EQ-5D utility score at baseline of the parent study was [redacted] in the subset of patients with previous exposure to dupilumab. Increases in EQ-5D utility score from baseline of the parent study to baseline of the current study were observed [redacted]). Additional mean increases in EQ-5D utility score were observed at week 12 and were maintained over the course of the study in both patient subsets.

A similar pattern was observed in dupilumab naïve patients.

[redacted]

		Value at Visit								Change from Baseline of Parent Study							
Treatment	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Total (N=1491)	Baseline of parent study	1206	0.5923	0.33645	-0.594	0.2640	0.7250	0.7960	1.000								
	Baseline of current study	1491	0.7544	0.25809	-0.484	0.6890	0.7960	1.0000	1.000	1206	0.1645	0.31718	-0.841	0.0000	0.0710	0.2750	1.484
	Week 12	1275	0.8763	0.18368	-0.239	0.7960	1.0000	1.0000	1.000	1004	0.2900	0.33029	-0.672	0.0010	0.2040	0.4215	1.484
	Week 24	758	0.9052	0.13751	0.028	0.7960	1.0000	1.0000	1.000	523	0.3125	0.31657	-0.275	0.0710	0.2040	0.4840	1.319
	Week 36	536	0.9050	0.16320	-0.239	0.7960	1.0000	1.0000	1.000	349	0.3082	0.31438	-0.708	0.1070	0.2280	0.3800	1.239
	Week 48	435	0.9185	0.14988	0.028	0.8480	1.0000	1.0000	1.000	319	0.3069	0.30309	-0.661	0.1230	0.2040	0.3800	1.239
	Week 76	270	0.9210	0.16961	-0.077	0.8480	1.0000	1.0000	1.000	231	0.2981	0.30646	-0.532	0.1170	0.2400	0.3440	1.239
	Week 100	60	0.9249	0.11270	0.656	0.8315	1.0000	1.0000	1.000	45	0.4098	0.37109	0.000	0.1230	0.2750	0.8070	1.239
	Week 124	1	1.0000		1.000	1.0000	1.0000	1.0000	1.000	0							

		Value at Visit								Change from Baseline of Parent Study							
Treatment	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Total Previously Exposed with Dupilumab (N=850)	Baseline of parent study	711	0.5885	0.33968	-0.594	0.2640	0.7250	0.7960	1.000								
	Baseline of current study	850	0.7783	0.23933	-0.484	0.7250	0.7960	1.0000	1.000	711	0.1906	0.31868	-0.807	0.0000	0.1050	0.3110	1.484
	Week 12	751	0.8735	0.18505	-0.239	0.7960	1.0000	1.0000	1.000	618	0.2926	0.32851	-0.568	0.0360	0.2040	0.3800	1.484
	Week 24	490	0.9023	0.14084	0.028	0.7960	1.0000	1.0000	1.000	362	0.3131	0.32042	-0.273	0.0710	0.2040	0.4150	1.319
	Week 36	372	0.9015	0.17319	-0.239	0.7960	1.0000	1.0000	1.000	271	0.3115	0.31622	-0.708	0.1070	0.2040	0.4150	1.239
	Week 48	322	0.9185	0.14822	0.028	0.8480	1.0000	1.0000	1.000	255	0.3134	0.30443	-0.661	0.1170	0.2400	0.4150	1.239
	Week 76	223	0.9124	0.18168	-0.077	0.8480	1.0000	1.0000	1.000	198	0.2964	0.30773	-0.532	0.1070	0.2400	0.3440	1.239
	Week 100	46	0.9138	0.11991	0.656	0.7960	1.0000	1.0000	1.000	38	0.4177	0.37147	0.000	0.1170	0.2575	0.8070	1.239
	Week 124	0								0							

		Value at Visit								Change from Baseline of Parent Study							
Treatment	Visit	n	Mean	SD	Min	Q1	Median	Q3	Max	n	Mean	SD	Min	Q1	Median	Q3	Max
Dupilumab Naive (N=606)	Baseline of parent study	460	0.5950	0.33209	-0.484	0.2910	0.7250	0.7960	1.000								
	Baseline of current study	606	0.7138	0.28197	-0.248	0.6890	0.7960	0.8480	1.000	460	0.1184	0.31213	-0.841	0.0000	0.0360	0.2075	1.000
	Week 12	519	0.8815	0.18090	-0.016	0.7960	1.0000	1.0000	1.000	381	0.2882	0.33387	-0.672	0.0000	0.2040	0.4990	1.170
	Week 24	268	0.9104	0.13130	0.193	0.7960	1.0000	1.0000	1.000	161	0.3113	0.30873	-0.275	0.0710	0.2400	0.5320	1.077
	Week 36	164	0.9132	0.13801	0.291	0.8300	1.0000	1.0000	1.000	78	0.2968	0.30964	-0.152	0.0520	0.2400	0.3110	1.008
	Week 48	113	0.9182	0.15516	0.088	0.8480	1.0000	1.0000	1.000	64	0.2812	0.29868	-0.152	0.1230	0.2040	0.3100	1.051
	Week 76	47	0.9619	0.08277	0.689	1.0000	1.0000	1.0000	1.000	33	0.3082	0.30325	-0.071	0.1520	0.2040	0.3110	1.029
	Week 100	14	0.9614	0.07748	0.796	1.0000	1.0000	1.0000	1.000	7	0.3669	0.39544	0.055	0.1760	0.2750	0.3440	1.239
	Week 124	1	1.0000		1.000	1.0000	1.0000	1.0000	1.000	0							

The proportion of patients who rated the way that their eczema responded to treatment with dupilumab during the OLE as 'very good' or 'excellent' increased in all patients from baseline of the OLE to week 12, and the majority of patients [redacted] rated treatment as 'very good' or 'excellent' throughout the study (**Error! Reference source not found.**). In addition, the proportion of patients who rated the way their eczema responded to treatment as 'poor' or 'fair' remained low (<10% of all patients) during the study.

[redacted]

Question	Baseline	Week 12	Week 24	Week 36
How Well You Are Doing				
Poor (Scale = 1)	[redacted]	[redacted]	[redacted]	[redacted]
Fair (Scale = 2)	[redacted]	[redacted]	[redacted]	[redacted]
Good (Scale = 3)	[redacted]	[redacted]	[redacted]	[redacted]
Very good (Scale = 4)	[redacted]	[redacted]	[redacted]	[redacted]
Excellent (Scale = 5)	[redacted]	[redacted]	[redacted]	[redacted]
Rate Way Eczema Responded to study medication to study medication				
Poor (Scale = 1)	[redacted]	[redacted]	[redacted]	[redacted]
Fair (Scale = 2)	[redacted]	[redacted]	[redacted]	[redacted]
Good (Scale = 3)	[redacted]	[redacted]	[redacted]	[redacted]
Very good (Scale = 4)	[redacted]	[redacted]	[redacted]	[redacted]
Excellent (Scale = 5)	[redacted]	[redacted]	[redacted]	[redacted]

Table 10 continues at week 48…

	Week 48	Week 76	Week 100	Week 108	Week 124
How Well You Are Doing					
Poor (Scale = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fair (Scale = 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good (Scale = 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very good (Scale = 4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excellent (Scale = 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate Way Eczema Responded to study medication to study medication					
Poor (Scale = 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fair (Scale = 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good (Scale = 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very good (Scale = 4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excellent (Scale = 5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix B. Evidence from EAMS

Description of the study

PLACEBO RESPONSES

We are aware that the dupilumab trial data is the first AD trial that has been assessed by the committee. Placebo rates in the trials were noted to be high. The same has been demonstrated to be true across a number of investigational products currently in trials in AD. Given this finding, it is an area that the International Eczema council (IEC) are in the process of writing a position paper on placebo responses in AD trials (http://www.eczemacouncil.org/news/whats-next-iec/).

There are several other trials that corroborate this finding in AD trials (Table 3). In Table 3 all patients were using protocol mandated concomitant topical corticosteroids.

Table 3. Placebo response in AD trials

Product	Phase	Placebo response (EASI 50 unless otherwise stated)	Best response (EASI 50 unless otherwise stated)
Dupilumab (CAFÉ and CCL)	3	27.8 (EASI 50 and DLQI 4)	73.1 (EASI 50 and DLQI 4)
Dupilumab (CAFÉ and CCL)	3	37.9	83.1
Tralokiumab	2	51.7	73.1
Lebrikizumab	2	62.3	82.4
Nemolizumab	2	39.7	53.7
Baricitinib	2	37	61

The company has discussed with a number of UK and international experts, and there is general consensus that the contributory factors to this response include the increased contact with health care professionals (up to weekly) in the trial setting which, in turn, leads to high (protocol mandated) compliance with topical medications. In addition, it provides regular psychological support to patients.

Low discontinuation rate also supported by Anti-drug antibody (ADA) data

One potential reason for discontinuation might be the formation of anti-drug antibodies (ADAs). In CHRONOS and the OLE study the formation of ADAs was low, and didn't appear to affect efficacy (note, the numbers were small and underpowered to make this comparison).

In CHRONOS (52 week data), in the dupilumab treatment arms (Q2W) treatment-emergent ADAs were [redacted] in the placebo arm. At week 52, [redacted] of the dupilumab arm and [redacted] of placebo arm met the primary end point (EASI-75), comparable to the total trial population. There was only 1 patient with positive neutralising status, and they met the primary end point.

In the OLE study, the relationship between ADA and clinical response relative to baseline of the parent study) was investigated in the small number of patients who were positive in the ADA assay. There was no evidence of loss of efficacy among these patients.

Overall, [redacted] had treatment-emergent ADAs in the OLE, of whom [redacted] in the re-treatment subgroup and [redacted] in the dupilumab-naive subgroup reported treatment-emergent ADAs; [redacted] had ADA responses lasting >12 weeks. Low-titer ADAs did not have an impact on functional dupilumab concentrations, which were similar in treatment emergent ADA-positive and ADA-negative patients. There was no meaningful difference in efficacy between ADA-positive and ADA-negative patients, and no AEs associated with ADAs. Table x shows the efficacy (EASI-75) by neutralising status

Table 4. Efficacy by neutralising status.

Time (weeks) in OLE	Patients achieving EASI 75 n/N (%)	Patients achieving EASI 75 n/N (%)
	Neutralising status: positive	Neutralising status: negative
24	[redacted]	[redacted]
52	[redacted]	[redacted]
84	[redacted]	[redacted]
92	[redacted]	[redacted]

In summary, there was a very low rate of ADA detected in patients, and no trend for reduced efficacy on these patients.

Real World Efficacy Demonstrated in EAMS

The company were able to collect follow up data on a cohort from EAMS.

35 patients had baseline and follow up data, at a mean follow up 86 days (12.3 weeks).

There was a significant improvement in EASI score. Median scores at baseline were 24.9 (range 4.3 to 72.0) vs 7.5 (range 0.0 to 35.0) at 12 weeks (Wilcoxon p<0.001).

Dupilumab efficacy (as demonstrated by EASI-50), from EAMS, appears to be comparable with clinical trial data from CHRONOS / CAFÉ (Table 5). 52% of patients in EAMS were on an immunosuppressant at the point of severity scoring, making the EASI-50 score more difficult to achieve than in the clinical trials.

Table 5. Patients meeting EASI-50 response criteria in RCTS compared to real-world EAMS study

Clinical setting	Q2W dosing (n)	EASI 50 at 12 weeks
CHRONOS trial	106	79.2
CAFÉ trial	107	87.9
EAMS	35	72.7

The composite end point, EASI-50 & DLQI 4 was met by 65.6% of patients, which is comparable to the same population from CAFÉ and CCL used in the economic modelling (68.5% for the primary analysis). Note that the EAMS end point data are from 12 weeks whereas the modelling uses 16 week data. Based on the trajectory of response seen in the clinical trials it is likely that the response in EAMS will continue to improve.

Physicians were also asked to rate patient response to treatment (Much worse; worse; about the same; somewhat better; much better)

At mean follow up of 24 days, 92% of patients were deemed to be somewhat better or much better.

At mean follow up of 63 days, 89% of patients were deemed to be somewhat better or much better.

Appendix C. Calculation of updated resource use estimates

Costings are taken from the Unit Costs of Health and Social Care 2016 and the National Schedule of Reference Costs - NHS trust and NHS foundation trusts. Both of these sources are now available with 2016-17 costs and these have been updated in the model. This update causes minimal changes to the ICERs.

We have re-examined the estimates for resource use counts used in the base case and implemented updates in the following way.

1.1. Data for 'non-responders'

Data from a review of secondary care case notes for patients not controlled with systemic therapy forms the basis for resource use estimates in the economic model. At the time of submission only the results from an interim analysis of 30 records were available. However the study is now complete and data is available on 60 patients.

The study was designed to capture the 3 years of data from the patient records by counting backwards from the data collection date. However not all patients enrolled in the study had 3 years'

worth of data in the secondary care record. For this reason we submitted only the most recent years' data in the company submission but provided the entire data set within the appendices for full disclosure. The ERG preferred method to utilise all the data was to count events by patient years. However this did not take into account the fact that only partial years were available for some patients. In order to follow the ERG preferred method of counting by per patient year we have updated the estimates for resource use based on the following count of full patient years (Table 6) utilising only the data from patients with full year data in years 2 and 3 (only one patient had a full year of data in the first year and this was not included in the analysis for expediency).

Table 6. Number of patients in the final analysis and number with full year data

Year	Total number of patients included	Total number of patients with full within year data
1	48	1
2	59	48
3 (index data of data collection)	60	59

A summary of the updated estimates for the resources used in the modelling are provided in Table 7 below.

Table 7. Estimates for the key resources used in the modelling counted per patient year using only data from patients with full within year data recorded in the secondary care record.

Encounter	Visits	Patient Year	Mean	SD	LCI	UCI	Median	Range
OP visits to dermatologist (total pt visits/yr)	652	107	6.093	5.057	5.124	7.063	4	0 - 27
A&E attendance (total visits/ year)	10	107	0.093	0.323	N/A	N/A	0	0 - 2
Hospital admissions (total admissions/year)	13	107	0.100	0.700	N/A	N/A	0	0-7
OP visits to dermatology nurse (total visits/yr)	59	107	0.551	1.057	0.349	0.754	0	0
Day case	23	107	0.200	1.000	N/A	N/A	0	0 - 8

1.2. Data for 'responders'

In the absence of data to describe the likely resource use by a patient responding to dupilumab we used the consensus of clinical opinion obtained from an advisory board of experts with experience of treating patients with dupilumab in the EAMS program for the number of dermatologist and primary care visits. For all other estimates multipliers were used from the market research. The ERG adjusted figures used multipliers for all the categories of resource use.

In this instance we believe that it is more appropriate to use the opinion of experts with experience of treating patients in busy clinics, often at capacity and who have direct knowledge of how patients respond to dupilumab to provide the estimates for dermatology visits. These clinicians told us that a patient who responds to dupilumab would be seen every 3 months in the first year and then 2 clinic visits per year would be sufficient thereafter. We validated this with 3 more clinicians with experience of treating patients in EAMS scheme for the purposes of this ACD response and received the same answer. This estimate is also applied in the BSC arm although this is likely to be conservative. The clinicians stated that they would not expect any day cases for dupilumab responders. Similarly they would not expect that there would be more than 2 GP visits over and above the usual number of visits observed in the general population. (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(10). We have assumed

that this is the case in both arms of the model and only considered additional visits directly related to AD in the analysis). Again this is applied in the BSC arm and is likely to be conservative.

Therefore we have not used multipliers taken from the market research to estimate GP or dermatologist visits as was the case in the ERG adjusted model. This takes account of the feedback obtained from clinicians who felt that it was not credible that responding patients would be seen more than 4 times a year by a consultant in perpetuity. It is also worth noting that in the recent apremilast guidance (TA419) the committee concluded that 4 visits per year including visits to GPs was appropriate. This is in line with our estimate of 2 GP visits and 2 dermatologist visits.

Table 8. Updated resource use estimates.

Encounter	Non-responder	Multiplier	Responder Year 1	Responder Yr 2+
Visits to the GP (total pt visits/year)	12.8	N/A	2.00	2.00
OP visits to dermatologist (total pt visits/yr)	6.09	N/A	4.00	2.00
A&E attendance (total pt visits/ year)	0.09	0.25	0.02	0.02
Hospital admissions (total pt admissions/year)	0.12	0.13	0.02	0.02
OP visits to dermatology nurse (total pt visits/yr)	0.55	0.77	0.42	0.42
day case	0.21	N/A	0.00	0.00

Additional elements included in the updated resource use estimates

Average resource use is discussed in Section 3.23, 3.4 and 3.6 in the ACD. The committee agreed that the base case '*definition of best supportive care is* appropriate' but stated that it '*does not include all the elements likely to be offered in clinical practice'* in particular, phototherapy, education, psychological support, bandages and hospitalisation. (Section 3.4 of the ACD). We address each of these points below.

1.1. Phototherapy

The IEC recommend phototherapy as a second-line or adjuvant therapy, especially in adults or older children with moderate-to-severe AD but place it ahead of the use of immunosuppressants.(5) The ERG and committee noted that it is not a comparator in this assessment but it may be used as a constituent of BSC. Both the case notes review and baseline data from the EAMS patients recorded data on the use of phototherapy. In the case notes review 15 out of the 60 (25%) patients had received UV over the 3 year observation period. This corresponds to 0.06 (SD:0.3) course per person per year. At baseline in EAMS it was around 31% in total. (Table 9).

Table 9. Distribution of UV therapy at baseline in EAMS

Therapy	Young Adults (*n*=72)	Middle-Aged Adults (*n*=68)	Older Adults (*n*=25)	Total (*n*=165)
Narrowband UVB	20 (27.8%)	19 (27.9%)	4 (16.0%)	43 (26.1%)
PUVA	3 (4.2%)	6 (8.8%)	2 (8.0%)	11 (6.7%)
One or more specified [a]	**23 (31.9%)**	**23 (33.8%)**	**6 (24.0%)**	**52 (31.4%)**
UVB unspecified	10 (13.9%)	2 (2.9%)	1 (4.0%)	13 (7.9%)
Phototherapy unspecified	6 (8.3%)	13 (19.1%)	2 (8.0%)	21 (12.7%)

The value recorded in at baseline in EAMS was not the number of events per year, rather it was the proportion of patients who had received phototherapy in the recent past. We interpret these values to provide a range for BSC but use the number of events per patient per year from the case notes review (6%) in the base case. Clinical experts at the advisory board told us that a patient responding to dupilumab would not require phototherapy.

The outpatient procedure tariff for the reference cost JC47A (Phototherapy or Photochemotherapy, 13 years and over), is £86.85 (2016/17 National Prices and National Tariff Workbook). Literature values suggest that typically phototherapy is administered 3 to 5 times a week for up to 12 weeks.(6, 7) The British Association of Dermatologists state that the treatment schedule varies from two to five times a week and an average course lasts between 15 and 30 treatments.(8) On the basis of these data we include 22 treatments (mean umber) at £86.85 each in the modelling to give a cost for a typical course at £1,910.70 and vary this in sensitivity analysis. A course of phototherapy is recognised in the literature as burdensome but we do not include out of pocket expenses for patients or a decrement in QoL.

1.2. Psychological support and education

Very few visits to a psychologist were recorded in the case notes review. A summary of the observed resource use is provided below.

Table 10. Clinical psychology*

Visits	Patient Year	Mean	SD	LCI	UCI	Median	Range
7	107	0.065421	0.24843	0.017805	0.113036	0	0-1

* See Point 7 below for a description of the calculation

This is likely to be an underestimate for the use of psychology in patients with significant disease burden.

The service code for Clinical psychology is WF01A - 656 and the unit cost is £189.28 (National Schedule of Reference Costs - Year 2016-7 - NHS trust and NHS foundation trusts).

1.3. Bandages

Bandaging was recorded as a component of day case visits in the case notes review and so we have assumed that this is already captured in the overall estimates for day case. However this may also represent an underestimate of this resource. (Table 11).

Table 11. Reasons for day case admissions (overall per patient year)*

	Visits	Patient years	Mean	SD	Median	Range
All	23	107	0.2	1.0	0	0-8
Flare	2	107	0.0	0.2	0	0-2
Treat admin	16	107	0.2	0.9	0	0-8
Bandage	2	107	0.0	0.1	0	0-1
Other	1	107	0.0	0.1	0	0-1
Not known	0	107	0.0	0.0	0	0-0

* See Point 7 below for a description of the calculation

1.4. Hospitalisation

Hospitalisations were recorded at a very low rate in the case notes review (Table 8), however the committee heard that 'hospitalisations for 1 week to 2 weeks to intensify treatment and provide respite for people having to apply topical medications' may be employed. In order to examine the effect of this on the ICER we have included 2 hospital visits per year for non-responders according to the clinical opinion expressed during the committee meeting.

Appendix D: A&E tariff.

Table 12. A&E tariff from the 2016/17 National Prices and National Tariff Workbook

		Tariff (£)	
HRG code	**HRG name**	**Type 1 and 2 Departments**	**Type 3 Departments**
VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	246	57
VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	232	57
VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	197	57
VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	174	57
VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	150	57
VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	105	57
VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	132	57
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	119	57
VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	83	57
VB10Z	Emergency Medicine, Dental Care	58	57
VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	57	57

Appendix E. Comparison of aggregate and split utilities in the BSC arm of the model

Table 13. Comparison of total discounted utility values for the BSC arm by aggregate and split health states.

	Together	Split by response	Increment
Decision Tree	0.7759	0.7685	0.0074
Markov	13.3888	13.3621	0.0267
Total QALYs	14.1647	14.1306	0.0342

Appendix F: Calculations for the maintenance of treatment effect using a factor derived from the use of TCS

The rates for concomitant use of TCS corresponding to BSC and dupilumab from CAFE are shown in Table 14. The factor corresponding to this pairing is tabulated.

Table 14. Rates for proportional reduction with derived factor.

Source	Dupilumab treated patients	BSC treated patients (CHRONOS)	Factor
Proportional reduction in TCS in CAFE	19.30%	50.30%	38.40%

According to the suggested methodology this factor are applied to the proportion of patients where by '*if at year 1, the quality of life improvement in the model for the placebo arm is discounted by 66%, then a 22% discount should be applied to the dupilumab arm, and 100% in the placebo arm would be 33.3% in the dupilumab arm'*

Two key waning estimators for BSC are used in the modelling.

1. Weibull estimate providing the most credible fit to the Kaplan Meier data for time to first rescue treatment or withdrawal from study for BSC patients in CHRONOS. (Figure 1)
2. Conservative linear fit declining as 75%, 50%, 25% and 0% maintenance of treatment effect over four years post trial.

The factors are applied to the discounted annual amount in each of the key assumptions:

Table 15. Calculations for the year on year waning estimators for BSC and dupilumab

Year	BSC QoL maintained	Discount for QoL BSC	QoL maintained in dupilumab arm (1-discounted BSC QoL * factor)
			Factor
			38%
	Weibull estimator for BSC waning		
2	18.2%	81.8%	68.6%
3	10.3%	89.7%	65.6%
4	6.2%	93.8%	64.0%
5	3.9%	96.1%	63.1%
	Linear estimator for BSC waning		
2	75%	25%	90%
3	50%	50%	81%
4	25%	75%	71%
5	0%	100%	62%

Appendix G: Model fits with time to first rescue treatment or withdrawal from CHRONOS for BSC treated patients.

We have discussed the credibility of lengthy times to rescue for this patient cohort above and believe that 5 years is a very conservative estimate before receiving rescue treatment and by analogy for return to baseline quality of life. This was supported by the clinicians at the committee meeting and also in discussion with dermatologists during the preparation of the dossier and for this response. There are minimal differences between the AIC, AICC, BIC and Loglikelihood criteria for these estimators (Table 16) so with these considerations in mind the Weibull estimate provides the most credible fit to the Kaplan Meier data. (Figure 1).

Figure 1. Time to first rescue treatment or withdrawal from study with Weibull fit (years) (BSC patients; full analysis set)

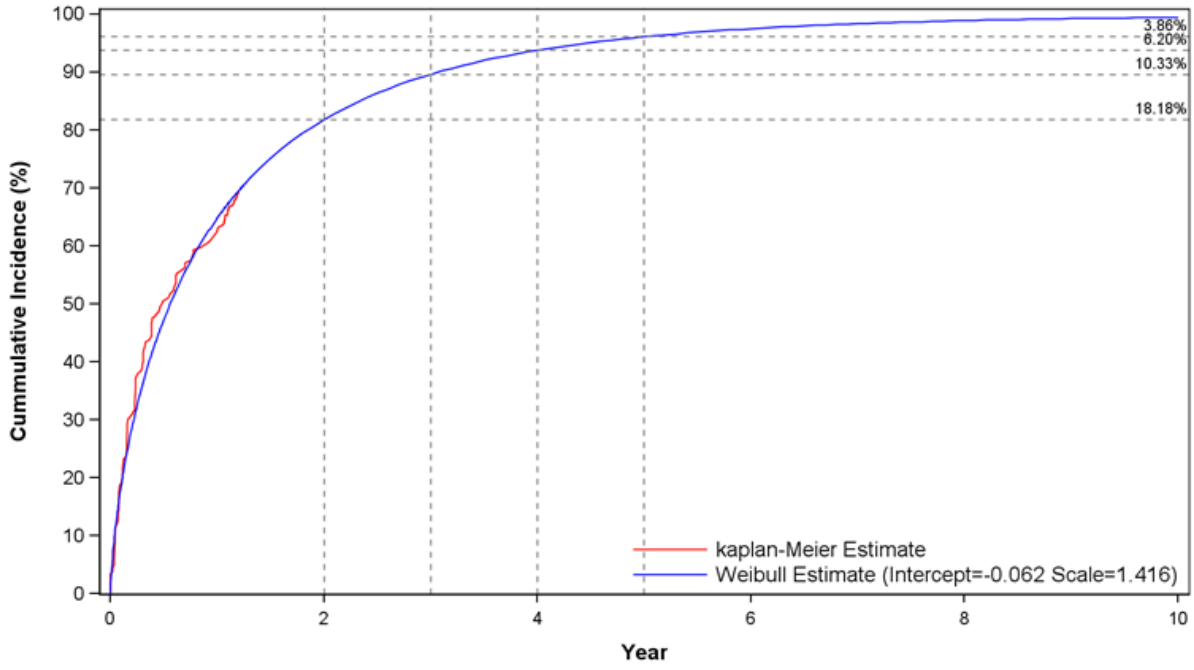

Figure 2. Time to first rescue treatment or withdrawal from study with Gamma fit (years) (BSC patients; full analysis set)

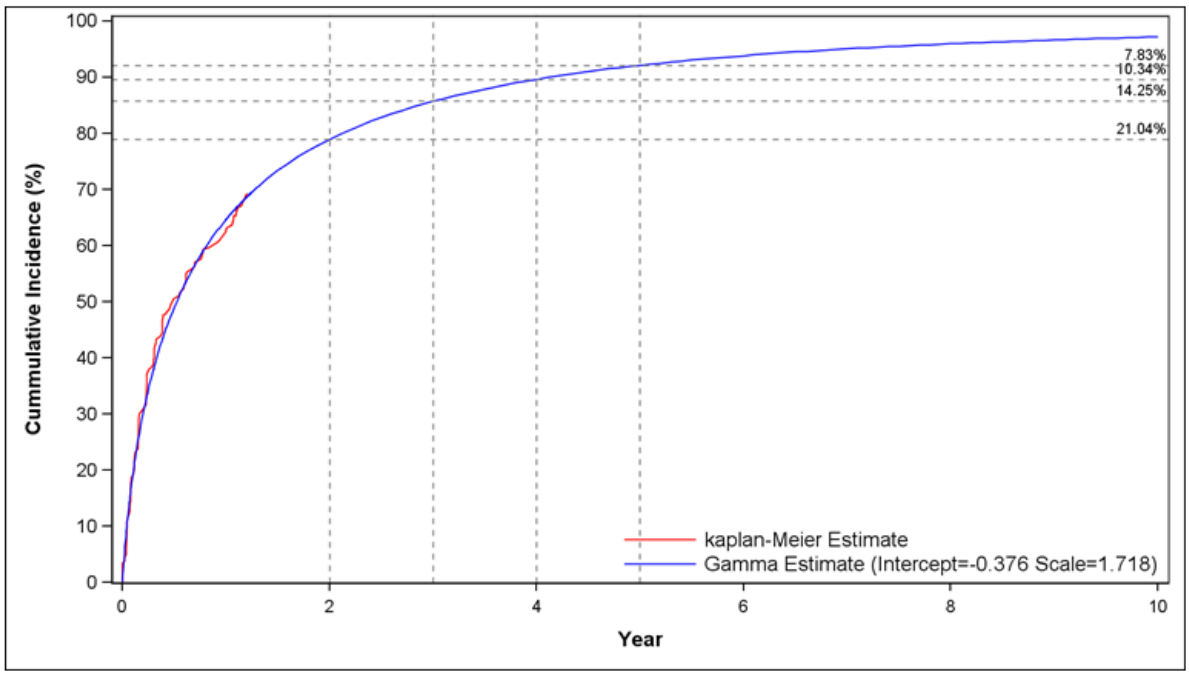

Figure 3. Time to first rescue treatment or withdrawal from study with LogLogistic fit (years) (BSC patients; full analysis set)

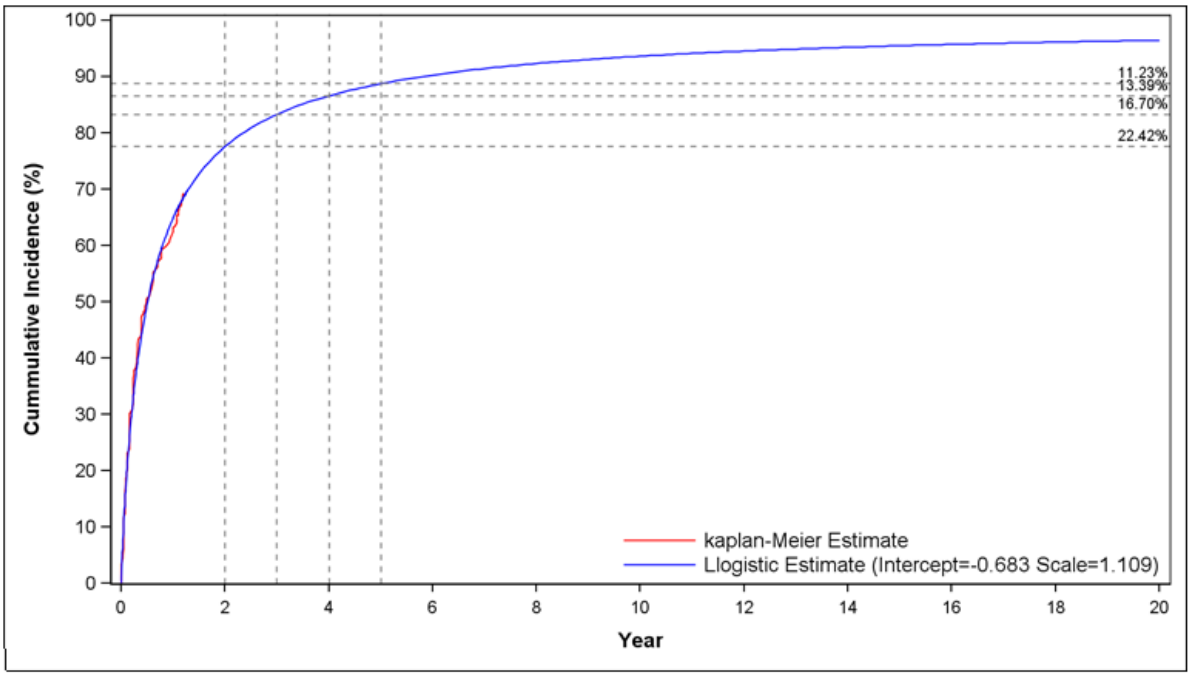

Figure 4. Time to first rescue treatment or withdrawal from study with LogNormal fit (years) (BSC patients; full analysis set)

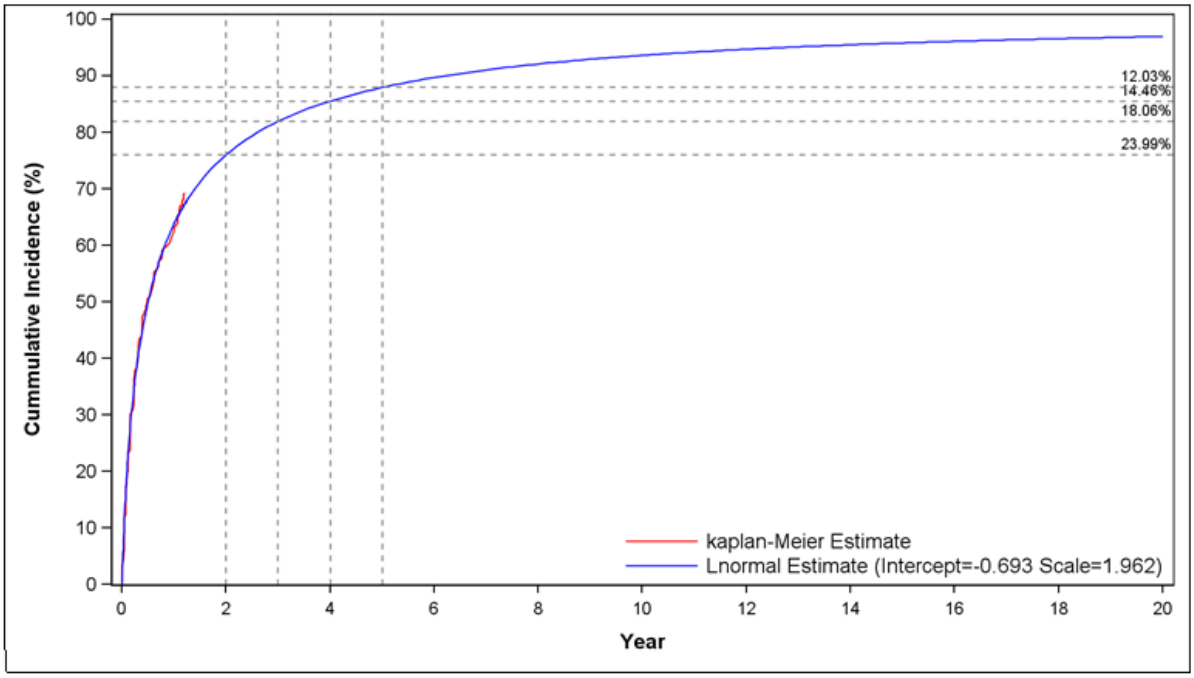

Table 16. Criterion results for model fits with Time to First Rescue Treatment or Withdrawal from Study.

-2 Log Likelihood	1076.223	LNORMAL
AIC (smaller is better)	1080.223	LNORMAL
AICC (smaller is better)	1080.261	LNORMAL
BIC (smaller is better)	1087.728	LNORMAL
-2 Log Likelihood	1076.814	WEIBULL

AIC (smaller is better)	1080.814	WEIBULL
AICC (smaller is better)	1080.853	WEIBULL
BIC (smaller is better)	1088.319	WEIBULL
-2 Log Likelihood	1071.207	LLOGISTIC
AIC (smaller is better)	1075.207	LLOGISTIC
AICC (smaller is better)	1075.246	LLOGISTIC
BIC (smaller is better)	1082.713	LLOGISTIC
-2 Log Likelihood	1071.958	GAMMA
AIC (smaller is better)	1077.958	GAMMA
AICC (smaller is better)	1078.035	GAMMA
BIC (smaller is better)	1089.216	GAMMA

Appendix H. Settings for simplistic testing of extreme resource use

For this scenario the following settings are varied:

Table 17. Settings to test the hospitalisation assumption.

Variable	Setting	Change on spreadsheet
Waning estimator	No waning applied	Use waning assumptions set to NO on Clinical sheet
BSC non-responder utility	Set to responder utility	G49, E59 and AD68 on the BSC Calcs Sheet
Dupilumab non-responder utility	Set to Dupilumab responder utility	G49 and E59 in the DUP Q2W Calcs Sheet
Resource use BSC	*In the first year:* • All patients receive the Number of hospitalisations used in the base case *At the end of the study period Years 2+:* • 2 hospitalisations per year to maintain effect for all patients (trial effect is assumed gone for BSC 'responders')	On Resource use sheet Q38:39 unchanged W38:39 set to 2
Resource use dupilumab	*In the first year:* • All patients receive the number of hospitalisations used in the base case *At the end of the study period Years*	On Resource use sheet E38:39 unchanged K39 set to 2

	2+: • 2 hospitalisations per year to maintain effect for non-responders • Base case number of hospitalisations for responders	

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Patient organisation submission

Dupilimab for severe atopic dermatitis

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Allergy UK
3. Job title or position	Head of Clinical services
4a. Brief description of the organisation (including who funds it). How many members does it have?	**About Allergy UK** We are the leading national patient charity for people living with all types of allergy. We work with government, professional bodies, Healthcare Professionals and corporates towards our vision and to help improve the lives of the millions of people with allergic disease. It is estimated that 21 million people in the UK live with allergic disease. But there remains a gap in healthcare services for those affected by this disease of the immune system. Our mission is to raise the profile of allergy at all levels, with a vision for everyone affected by allergy to receive the best possible care and support. Our dedicated free Helpline is there for people who need our help and support. Our free Factsheets provide information to explain the symptoms and triggers that people with allergy are dealing with. We are not a member organisation. We have corporate sponsorship for activities to deliver our objectives as well as a business arm of the charity which comes under the British Allergy foundation.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	**Via a patient experience survey of living with atopic dermatitis**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	305 people were surveyed. 58% said it impacts on their personal relationships. 10% spent over 30 days a year managing their eczema eg by applying creams. With 86% said that the management of the condition impacts their day to day activities. 7 in 10 said their sleep was affected. 1 in 10 consume more alcohol when their eczema is at it's worst. Over 70% reported feeling depressed. Nearly ¼ missed more than 6 days of work per year due to their condition, whilst approx. 15% missed 16 or more days
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Applying emollients very time consuming. In words of one patient 'I'm constantly physically and mentally exhausted. I have blood and skin in my bed every morning, skin coming off in my clothing, and have to cover myself in emoliients etc. My children do not want me to be near them when I'm sticky'.
8. Is there an unmet need for patients with this condition?	Yes, education of patients in their disease area. Lack of knowledge at primary care level in adequate management of eczema. Toxic and unacceptable side effects of long term use of immunosuppressants and steroid treatment. Need to more targeted therapy with minimal side effects for severe disease and better long term management.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Less side effects
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Long term effects unknown
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People with severe eczema, who have historically failed previous treatments. People whose quality of life has been seriously impacted from their severe eczema People who have unacceptable side effects from previous treatments

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Would this be accessible to all people who fit an agreed criteria for treatment or would some CCG's provide and some not**
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- A targeted therapy focuses on the immunological correction of a malfunctioning pathway. It has less side effects, so potentially less problematic for the patient. Current immunosuppressive treatments can have horrendous toxic side effects and have to be monitored very closely, so alternative treatments with less side effects are welcomed
- There should be a consensus on best scoring system to use
- NICE should also consider creating guidelines to treat eczema, with referral pathways

- prompt referrals from primary care for moderate/severe eczema and treatment failures are the people most likely to benefit from this drug, from evidence provided.
- Impact on quality of life (lack of sleep, employment productiveness, personal/social aspects) are all subjective and often difficult to quantify by a measurement tool, but these are key issues that need to be considered in severe eczema, as the psychological and impact on relationships was a key reoccurring theme of respondents to our eczema survey and how their self-esteem had been seriously eroded by the long term chronic effect of severe eczema

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National Eczema Society We are a charity registered in England and Wales and also in Scotland. Our role is to support people living with eczema and those who care for them in order to improve their quality of life. We support millions of people with information and advice about eczema and its management and treatment, which we deliver through our website, social media, publications and nurse-supported helpline.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this

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	table.
1	We are concerned that NICE has not considered fully the physical health, psychological and social impacts on quality of life of people with moderate to severe atopic dermatitis (referred to henceforth as simply 'severe eczema' for brevity). The most harrowing calls to the National Eczema Society Helpline service are from adults with severe eczema who tell us their life is a torment, that there is no let-up in their symptoms and no hope despite trying current treatments. We talk to people with severe eczema who wish for the courage to end their own life and sometimes they are parents of young children who haven't left the house for several weeks. Many other long-term health conditions come with periods of remission and symptom respite through effective drug treatment. One of the hardest things for others to grasp about severe eczema is there is no end to the daily suffering, people can see no future for themselves and are held prisoner by their condition. National Eczema Society fundamentally opposes the decision to reject funding for this effective new treatment in the NHS.
2	We are concerned that NICE has not considered fully the side effects of current systemic treatment options for severe eczema, which is not responsive to topical management. People are currently faced with the choice of managing the best they can with topical treatments, in great pain and discomfort, and/or starting systemic treatments of uncertain efficacy with the potential for significant long-term harm through severe adverse side effects. Only one systemic treatment, ciclosporin, is licenced and with a usual maximum duration of 8 weeks. Dupilumab offers the potential of safer therapy and the opportunity for significantly reduced topical steroid treatment, which people with severe eczema so desperately want and deserve.
3	We are concerned that NICE has not considered fully the overall impact of severe eczema, and is not demonstrating parity with other severe chronic conditions like psoriasis, urticaria, asthma and arthritis, all of which have had life-changing biologic treatments approved by NICE that have been life-transforming for patients. It seems especially harsh to withhold funding from the first game-changing new drug treatment for severe eczema in many years. The trial data results are impressive, both for symptom improvement and reduction in topical steroid use, which for the first time in decades gives people with severe eczema the prospect of an effective treatment.
4	We are concerned that NICE has not considered fully the opportunities for greater treatment accessibility provided by dupilumab. It can be incredibly difficult and painful for people with severe eczema to travel to medical appointments in specialist dermatology centres. Dupilumab offers the potential for people to self-administer their treatment injections at home under supervision, and for the treatment to be supervised through all hospitals and not just specialist centres.
5	We are concerned that NICE has not considered fully the variable availability of systemic treatments and local clinical preferences in prescribing. There is no NICE quality standard or clinical guideline for the treatment of atopic eczema in adults, and people with eczema tell us about the varying ways they are treated. Phototherapy, for example, is not universally available and patients often find it extremely difficult to travel for frequent therapy sessions. Hence National Eczema Society believes it is only fair that the eligibility for dupilumab must be that patients have tried and failed on one systemic treatment only.
6	We are concerned that NICE has not considered fully the impact on people's ability to study

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	in further and higher education, as well as people's inability to maintain paid employment, because of the pain, constant discomfort and disrupted sleep caused by severe eczema. It is cruel that people's life chances are so negatively affected by this condition as a result of the limitations of current systemic treatments that offer only temporary respite from symptoms and topical treatments that for people with severe eczema are ineffective.
7	We are concerned that NICE has not considered fully the negative impact of severe eczema on relationships and family life. Severe eczema ruins relationships and often prevents individuals from entering into relationships. Those in a relationship tell us they can't bear their partner to see their body or touch their rough, scaly inflamed skin. Teenagers fear never getting married or never having the chance to experience sex.
8	We are concerned that NICE has not considered the social impact of living with severe eczema. People with severe eczema usually cannot hide their disease - facial and hand eczema in particular are on show to the public. People tell us they are often very self-conscious about their skin, and sadly eczema is still often perceived as infectious and a result of poor personal hygiene. Many people with severe eczema are subject to cruel comments about their skin condition and will isolate themselves socially for fear of rejection.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and

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transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**British Association of Dermatologists (the BAD)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[redacted] **on behalf of the Therapy & Guidelines and A*STAR sub-committees of the British Association of Dermatologists**

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	From a clinical perspective, following experience of limited use in trials and during the EAMS phase, the BAD would like to highlight the life-transforming nature of dupilumab treatment in many patients. People with severe atopic eczema are a high-need population who have few treatment options (most of which are unlicensed and have very little or no evidence base) [Roekevisch, J Allergy Clin Immunol 2014,133: 429-38]. As dermatologists, we are exposed to NICE-approved, high-cost drugs for dermatological disease and have gained experience of the appropriate ratio for cost effectiveness in clinical practice. We strongly believe that the benefit accrued by dupilumab to patients with (severe) atopic dermatitis should be supported by the NHS and disagree with the decision to reject funding for this treatment.
2	Based on expert opinion, the BAD considers that best supportive care is not well represented by the placebo arm of these trials. The reduction of topical corticosteroids usage amongst those on the dupilumab arm (despite failure to achieve 100% clearance) as shown in the CAFÉ trial, but continued use in the placebo arm, suggests that the observed positive effects of dupilumab vs. placebo would have been greater if topical corticosteroids usage had been continued. We predict that the placebo response would regress towards baseline if followed for a longer time period as patients gradually give up on the intensive topical therapy required to maintain the placebo response. This is supported by the NICE analysis which shows that *with* best supportive care, EASI50 & DLQI $\geq$ 4 responders drop off much more significantly in the placebo/best supportive care groups (25% loss) than in the dupilumab groups (4-5% loss) between 16 and 52 weeks across all studies. Loss of placebo effect should be incorporated into the model.
3	The health economic model needs to reflect the fact that patients with severe disease are likely to benefit more in terms of QALY change than those with moderate disease. Bearing in mind that disease severity data was captured for all patients, it would be relatively straightforward for Sanofi to provide a subgroup health economic analysis for the cohort of patients with severe disease.
4	Patients with severe disease are highly unlikely to remain on best supportive care as this is not tolerable for them (as described in the trial) as they require systemic therapy. Therefore, this group will generate increased costs from other areas not currently included in the model. These may include the cost of increased visits to GPs and dermatologists, admissions, complications from inappropriate use of prednisolone and toxicities from high dose systemic immunosuppression (for example nephrotoxicity with ciclosporin, skin cancer with azathioprine)
5	We suggest that 'severe' disease (as opposed to moderate) should be defined clinically by atopic dermatitis requiring systemic therapy because of its profound impact on patients' quality of life [Simpson, J Am Acad Dermatol 2017, 77: 623-33] For the purposes of the health economic evaluation, 'severe' atopic dermatitis corresponds to an EASI score of $\geq$ 21.1 [Leshem, Br J Dermatol 2015,172: 1353-7],

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	mirroring the severity inclusion criterion for the CAFÉ trial (EASI score ≥ 20 at screening and baseline).
5	
6	
7	
8	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Centre of Evidence-Based Dermatology at the University of Nottingham
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this

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	table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Dupilumab is a real innovation** in a field that has been devoid of much progress for 30 years. I welcome such efforts very much. The studies have also been well reported. Dupilumab may be life transforming for those with severe disease, but I can see no data on just severe disease.
2	I strongly disagree with the idea of applying for a marketing authority for moderate atopic eczema. Some moderate cases are challenging, but the real problem in atopic dermatitis is severe disease. **We do not have a problem in treating moderate disease** with good education and adequate and safe use of topical corticosteroids including proactive (weekend therapy) control. We do not often need to resort to systemics or UV light for such moderate cases. **The problem is the very small proportion with severe disease.** These are the poor folk who we try with UVB and systemics, with mixed success. The company probably realise that the population in need (ie those with severe disease) are too small to offer adequate financial returns for their investment, and therefore are understandably targeting and including the much larger moderate severity atopic eczema population where it is questionable if new drugs are needed. I have yet to see the vital data that shows evidence of effectiveness in just the severe atopic eczema population. Please see: Thomson J, Wernham AGH, Williams HC. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. Br J Dermatol. 2018 Jan 6. doi: 10.1111/bjd.16317. [Epub ahead of print] PubMed PMID: 29315479
3	There is, as is so often the case, a **complete absence of active comparator trials** eg against standard systemic treatments such as ciclosporin or methotrexate or azathioprine, nor can I see any evidence of any plans to conduct further randomised trials against active comparators ie the most relevant comparison group in order to best understand the role of dupilumab in the treatment pathway. Very few doctors use placebos these days. I would have thought that NICE would at least have done a simple network meta-analysis using available data from existing RCTs on existing comparator systemics in your STA background document – this was a bit casual since the data is there. Thankfully, Cochrane Skin are doing one this year, so that should help you.
4	The concept of randomising people with atopic eczema who according to the Lancet abstract had ‘an inadequate response to topical corticosteroids’ to be randomized to a control group of yet more topical corticosteroid plus placebo for a whole year seems rather **unethical**.
5	Dupilumab used **every 2 weeks is probably just as good as weekly** in terms of trade-off between effectiveness and adverse events in the Liberty and CHRONOS trials, but the study report was strangely silent on making any recommendations on this issue
6	**The concept of treatment failure in existing studies and the post-hoc subgroup analysis is unconvincing**. I appreciate they only refer to ciclosporin (which is the only other licensed systemic), but in reality, it can only be used for around 4 months due to potential kidney damage. We use methotrexate for severe cases with good results and it can be used for years not “short periods” as implied on page 7 of the appraisal. The company should be encouraged to now evaluate dupilumab in those severe cases that have failed on ciclo, methotrexate, azathioprine or MMF as they encourage key dermatologists around the world to try out dupilumab for free.
7	It is completely **unclear from the evidence presented how long dupilumab should be** continued – for 6 months to induce remission in order to return to topical therapy for the rest of a person’s life?
8	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.

Please return to: **TACommB@nice.org.uk**

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 24th April **email:** TACommB@nice.org.uk

- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD Received from the Public through the NICE Website

Role	Patient
Other role	Professor
Organisation	West Virginia University
Location	United States
Conflict	No
Notes	

Comments on the ACD:

I am an American who lived in Europe for nine years, up until 2017. I suffered from increasingly severe eczema beginning in 2010, and by the time I returned to the US, I was in such bad condition that I often couldn't sleep and I had to cancel my teaching at times after a bad flare up. During the years from 2012-2017, I spent a lot of time at the dermatologist, who monitored my condition, prescribed increasingly powerful steroid creams and pills, and provided UV treatments three times a week. I can't even guess how much I cost the Austrian national health service from what must have been over a hundred office visits.

I started with a new dermatologist upon arriving in the US who saw my condition, listened to my history, and immediately suggested Dupixent. I got insurance approval and I've been on it for the past six months. It has reduced my symptoms by about 80%, and returned me to what I could finally describe as a normal life. Severe eczema means living your life in extreme discomfort, with little chance for relief. This includes at night when you try to sleep, at work, taking a shower - it affects everything in your life, and for many people it never goes away on its own.

Eczema is a condition that is not yet well-understood, and dermatologists have been limited in the tools they have to treat it. Steroids are generally very effective at tamping down flare-ups temporarily, but they are clearly not a long-term solution. Other forms of treatment are much less effective at addressing symptoms, and also don't address the underlying cause of the condition. Dupixent is the first sign that this condition might be controllable in a sustainable way, allowing people like me to return to normal, productive lives. It has brought about a complete turning point in my life, to give a single data point.

I understand that your recommendation to reject Dupixent isn't based on its efficacy, but rather its cost to benefit ratio. I completely agree that the $37k sticker price is ridiculous, and I'm sure that whatever price the UHS is negotiating with Sanofi is just as unreasonable. I just hope that this initial recommendation to reject the drug is a negotiating tactic, and that the message is well-understood, that this medicine is about as valuable to sufferers of severe eczema as a drug could be. For someone who can't even sleep through the night without waking up constantly to intensely itchy skin, Dupixent is a life-changer, and I think you should weigh the "value" side of the equation very highly.

Role	Patient

Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

My name is [redacted] and I've suffered from eczema for almost my entire life.

The past thirty years have been spent using steroid creams that has left my already damaged skin thin and fragile, taking oral steroids that only ever bring temporary relief, and taking immunosuppressants that leave me open to infections and possibly even cancer further down the line. And not one of these treatments has ever worked to the extent where I can live a normal life, with the exception of Cyclosporin, which unfortunately I couldn't continue to take due to the fact it rose my blood pressure to extremely dangerous levels.

My eczema is very severe. Covering over 80% of my body severe. I'm in constant pain from my sore and open skin, and I feel extremely self conscious going out in public; I'm a young woman who should be making the most of her youth, and instead I'm hiding my skin and staying out of social situations because I feel like a monster. I had to miss my best friend's wedding because I was in the middle of an incredibly debilitating flare, not only could I not travel, I didn't want to ruin her wedding with my disgusting appearance. Holidays have been ruined because my skin was so bad, while my friends were having fun, I had to keep out of the sun and douse myself in moisturiser and take pain killers just to cope.

I have to take painkillers every day to cope with the pain, and even then that doesn't always help.

I have no job prospects outside of my low-level retail job because of my skin, I have no chance of meeting anyone when I look so hideous, and I have no future while my skin is so bad. I'm overweight because eating is the one thing I can do when I'm stuck inside alone because my skin is so bad. I'm lonely, I'm depressed, and sometimes I hate myself so much because of my awful skin.

I won't lie, I've entertained suicide. The only things keeping me here are my family and my dog. Without them, I dread to think of where I would be. All because of the pain, emotional and physical, that I'm in almost every single day.

I started Dupilumab/Dupixent just two days ago. And I've already seen an improvement in my skin. I couldn't believe it, I thought it was to good to be true, but there's already signs of improvement when it was so painfully bad before. The redness is receding, I can see patches of my unblemished skin appear. My eczema has become dry and peeling, but the painful sores are gone already. I think this is the first day in a very long time where I could move my arms without pain, I've not even taken any painkillers.

It's early days, but Dupilumab has already given me so much hope for the future. I can finally see a future, one where I can function like anyone else. I don't have any grand dreams, but I would love to find a job that isn't restricted by my skin, I'd love to meet someone, I'd love to be able to travel and not have to spend my days frozen up because of how much pain I'm in. I'm looking forward to when I can just jump in the shower and not have to worry about the pain that comes with it.

Please consider making Dupilumab available on the NHS. It's the biggest breakthrough in eczema treatment for a long time, and there are countless success stories out there where people like me are finally able to do things that normal people take for granted. I've been in such a dark place for such a long time, and now I can finally see light at the end of the tunnel. I know there are others out there who are still suffering, and they should get the chance to live a normal life.

Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	

Comments on the ACD:

I am a university student in Scotland, and would like to input my experience with atopic dermatitis and why I am very saddened at the potential of this ground breaking drug not being approved by the NHS.

I have suffered with atopic dermatitis (AD) all my life, and it was in my early teens when it got completely out of control. From that point on my entire youth had a damper put on it and affected me both physically and mentally. At certain points it was too painful to wake up in the morning, and my high school attendance suffered as a result. Furthermore, my friend circle had shrunk due to my lack of being able to feel confident enough to engage with people outside school due to being in pain, or feeling unconfident about how I looked. AD has been the toughest hurdle in my life and I feel like I am far from over coming it.

When I heard of news that Dupilumab would potentially be available to AD sufferers in the UK I finally felt that I may see a day where I wont have to plan my entire schedule and life around the condition of my skin at that time...

I sincerely hope that this decision is considered thoroughly, through the input of other sufferers and those that have experienced this life destroying condition.

Role	Patient
Other role	Software Developer
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

I have severe atopic eczema. It's a painful and debilitating condition that means I'm not able to concentrate on work and spend a lot of my life in pain or with severe irritation. My condition also leads to a weak immune system which means that I am usually in a state of permanent illness. These factors also have a big impact on my mental health, further inhibiting the activities I can take part in and the work I can do. Being in my final year of university, my condition has had a big impact on my grades and has lead to me submitting work late and under extenuating circumstances. A treatment such as Dupilumab would go a long way to helping me regain control of my life and realise my full potential as a software engineer.

Role	Patient

Other role	IT MANAGER
Organisation	
Location	Other
Conflict	No
Notes	

Comments on the ACD:

As a sufferer of Severe Atopic Dermatitis I believe you should reconsider this drug. At the moment the treatments available as immunosuppressant or the other don't work and the quality of life of people like me is so poor that you can not even imagine. If there is another option available it should be approved for the severe cases. Thank you for your understanding. Kind Regards

Role	Patient
Other role	Student (Bachelor's degree)
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

Pre-face: I am an adult with severe eczema currently prescribed 4th line systemic treatments (methotrexate) which has been met with a positive response, and blood tests have revealed that I have adequate tolerance to the drug to use as a long-term treatment. I now endure more manageable eczema ranging from mild to moderate for most of my days, but further treatment methods including regular application of moisturising ointments and occasional corticosteroid ointments. Despite the effort and risk of my treatments, I still live a life plagued by past mental damage and poor skin generally.

The document, which I have read in its entirety, is a breath of fresh air regarding the appreciation of atopic eczema symptoms, physical and mental, in adults, where we are otherwise ignored or misunderstood. It has taken 21 years of NHS care with countless physicians and treatments tested to finally have my condition taken seriously. This is not an attack on the NHS as an institution, but rather of the perceptions of atopic eczema until recently being fundamentally flawed. Immune system treatment is pivotal to many patients who feel they have tried everything to no avail, and if it wasn't for extensive research, I wouldn't even know of their availability, much less has it been even mentioned by GPs.

If not for dermatologists at the Leicester Royal Infirmary treating me for my 4th bout of infected eczema last summer, I would have certainly killed myself should the 5th have shown itself. Systemic treatment is a necessity for me to have skin in a condition where infections are not nearly as high a concern, i.e. less areas of damaged skin, but despite this I now forever live in fear of infections happening again. If 4th line treatments were not effective for me, then I would have no other options, and suicide would be entirely a plausible release from the suffering this condition has caused to my life.

I hope that whether Dupilumab is accepted or not in its current state, it will lead to a shift in awareness for the underlying causes of the debilitating, life consuming illness. As a 5th line treatment the idea of cost effectiveness should be more critically evaluated as a last resort for people with no other options than to suffer tremendously or brave the side effects of systemic treatments. Would it be fair in this case to consider that cost effectiveness for eczema treatment is based on generations of poor perceptions and factually flawed opinion? I believe that at least having it available as a last resort to a very select group of people

should be a necessity in a 5th line context, considering NICE has already identified so many reasons why adults with severe atopic eczema need treatments.

Role	NHS Professional
Other role	Consultant Dermatologist
Organisation	Poole Hospital NHS Foundation Trust
Location	England
Conflict	No
Notes	

Comments on the ACD:

As a skin specialist caring for patients with severe eczema, I was very disappointed to hear that NICE approval for dupilimumab has not been granted. There is a pressing need to find more effective systemic therapies for our patients and this drug has shown to be effective both in clinical trials and the early access scheme. This drug should be made available to patients who have failed to respond to conventional treatments and it is concerning that NICE has not granted patients access to it. I hope the decision will be reconsidered.

Role	Patient
Other role	Student
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

Having this disease is extremely debilitating physically and psychologically. So much so that I have considered suicide. Existing treatments don't work properly and if there is a glimmer of a chance that Dupixent will help patients it should be given without hesitation.

Role	mother of chronic AD sufferer
Other role	in this context: mother
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

For the attention of the National Institute for Health and Care Excellence (NICE):
I am writing with reference to the recent recommendation not to back use of Dupixent as treatment for severe atopic dermatitis (AD).
My son has suffered from this disease since his birth in 1978. Its effect is often underestimated, since it is seen as â€œonlyâ€ a skin problem. However, I can testify that it is excruciatingly painful and profoundly debilitating, leading to acute infections, sleep deprivation, inability to concentrate, impaired capacity for social interaction and chronic depression which, coupled with the perpetual agony, can turn suicidal.

With discipline and strength of character, my son managed to complete his degree in Physics at the University of Edinburgh and get a PhD from Imperial College London. He is neither a complainer nor a quitter, but it was clear that his life and opportunities were critically diminished. Awake all night, in a daze all day, he would spend hours applying creams merely to keep the worst at bay. He visited countless specialists and tried every treatment on offer - each new option raising hopes only to be dashed, and all at great expense to the NHS, ultimately to no effect.

The advent of Dupixent has completely changed, one might even say: saved his life. In his late thirties, he is finally able to get a healthy nightâ€™s sleep, concentrate with success on a demanding job, pursue sports and generally enjoy being alive. He shares this transformative experience with many other former sufferers.

Dupixent is an expensive drug, but from what I hear, it was also very expensive to develop, so Sanofi is not being greedy. And the financial cost is offset by the fact that people like my son can now work full-time, pay taxes and contribute to society, rather than suffer chronic pain and frustration that leave them a burden to society, their families and most tragically: themselves.

Given the price tag, nobody expects the NHS to resort to Dupixent as the first port of call when treating AD. It is perfectly legitimate to try other treatments and medications first. But in cases like my sonâ€™s, where nothing else has worked, Dupixent should please be available as a last resort.

Please reconsider this decision!

With thanks for your attention and best regards,

[redacted]

Role	Patient
Other role	Public Sector Account Manager of NHS accounts
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

As someone who has tried all available therapies for atopic dermatitis and found no relief, it is deeply disappointing and shocking to find the initial NICE guidance is to reject Dupilumab as a treatment for eczema.

For many eczema sufferers the current therapies (which are cost effective) are sufficient, but in my personal case my life has been torn apart by eczema for over 20 years with no light at the end of the tunnel. This treatment must be made available for severe eczema sufferers who have no other sustainable alternatives. Dupilumab for the first time in a long time has provided hope for those without sufficient treatment.

Whilst i understand the cost is high for Dupilumab, it would not be needed for every single eczema patient in the UK, and i implore the committee to understand that life sufferers of eczema are individuals that are regularly suffering from mental illness. This includes depression, severe sleep loss, anxiety, self loathing and suicide to name a few. These can be alleviated to an extent with the control of an individuals eczema. Surely these mental illnesses also provide a cost to the NHS? Certainly in terms of hours of treatment/ counselling and medication. The use of Dupilumab could help severe sufferers like myself come out of the darkness and control mental illnesses with the improvement of ones eczema. This opportunity cost must be considered

The real life of eczema is hard to understand for a non sufferer, it is a highly visible and painful underserving condition which can debilitate a person physically and mentally. Personally speaking and from what i can gauge from fellow sufferers is that once the eczema is sub dued individuals can start to rebuild their life and feel a sense of normality and crucially build momentum towards life goals. However with eczema flares which in severe sufferers are prolonged and regular, this halts any progress you have made in your personal and professional life, inhibiting any success you had been working towards. It is this constant 'one step forward, two steps back' approach which can drive a eczema sufferer towards severe mental illness, something i can speak for personally.

The current eczema treatments are unsustainable which really provides no hope for ones life. Personally i have reacted badly to topical steroids with peri-oral and orbital dermatitis and been recommended by a NHS dermatologist to cease use. Immunosuppressants such as ciclosporin and methotrexate have cause strong painful side effects and do not present a long term solution for myself without incurring other painful side effects a 'catch 22 situtation'. UVB treatment has provided n relief and after 2 separate periods of maximum treatment with UVB (in 2008 and 2017). I have also tried Elidel and protopic multiple times to no avail with a painful burning sensation side effect. So my question is for someone in my position...What do i do? What NHS resources are dedicated to helping me? What does the NHS recommend i do? Before Dupilumab,

I had NHS dermatologists simply say their was nothing more they could offer me and they 'wish and hope for a turn in my fortunes in the furture'. This is completely unacceptable, especially when there is a treatment option available in existence.

UKâ€™s Medicines and Healthcare Products Regulatory Agency (MHRA) granted dupilumab, an investigational treatment for atopic dermatitis (AD), a positive scientific opinion through the Early Access to Medicines Scheme (EAMS).

The aim of EAMS is to provide early availability of innovative new unlicensed medicines to UK patients that have a high degree of unmet clinical need.

Crucially from my understanding Dupilumab was added to EAMS to help patients with a high degree of unmet clinical need. Hypothetically speaking if Dupilumab is rejected as a treatment for atopic dermatitis by the NHS, how would this unmet clinical need have been met?

I find it difficult to understand how a medicine which was added to EAMS because of an 'unmet clinical need' is now being rejected. Essentially demonstrating the NHS/NICE is neglecting severe eczema sufferers with no options moving forward into the future.

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

Dear Amanda Adler, dear members of the Appraisal Committee,

Thank you for giving me this opportunity to comment on NICEâ€™s draft guidance on dupilumab, published in March 2018. Please allow me to convey some of my personal

experience with Atopic Dermatitis (AD) and dupilumab from the perspective of a patient. I am 39 years old and have been affected by severe AD for most of my life. As you know, AD covers a broad spectrum and can manifest itself in a wide range of clinical presentations, with the vast majority of patients affected by a mild form of the disease which is more easily managed. As a result, the rarer, severe form of AD is often misunderstood or underappreciated. Your draft guidance repeats a common misconception about severe AD, by implicitly tying the burden experienced by the patient to the â€œstigmaâ€ associated with the disease. My quality of life was severely impacted, not because of embarrassment about my physical appearance, but because of the incessant and intolerable physical discomfort. It is difficult to describe the intense itch which I would experience and the persistent chronic pain from my oozing, cracked and bleeding skin, which was often infected. The itch and pain caused chronic sleep deprivation, which condemned me to live a zombie-like existence during my formative years and beyond, contributing to deep depression, despair and a profound sense of helplessness. Effective relief from the itch was only temporarily available through short-term courses of systemic cortisone and immunosuppressants (ciclosporin and off-label mycophenolate mofetil), but always in the uncomfortable knowledge that these therapies posed a serious risk of severe adverse effects in the long term and that their discontinuation would immediately trigger a violent relapse.

Having long since exhausted the arsenal of therapies available to me through current â€œBest Supportive Careâ€ , I was excited to learn that dupilumab was being tested as the first new AD drug to directly target the inflammatory pathway, rather than merely suppress the immune system indiscriminately. The AD patient community had been hoping for this development for some time, given that similar biologics had already proven to be extremely effective in the treatment of psoriasis for many years. Although fully aware of the potential risks inherent in using an experimental drug, I decided to enrol in a Phase 2 study for dupilumab, and eventually a Phase 3 open-label extension study at Guyâ€™s Hospital in London (principal investigator: Prof. Catherine Smith). The experience was transformational, causing my quality of life to improve radically and sustainably. Rapid onset of action occurred within the first two weeks of therapy, the itch abated substantially and my skin soon cleared completely. Furthermore, I have been able to maintain this radical improvement through monotherapy, alone, without the need to resort to topical corticosteroids. It is no exaggeration to credit dupilumab with giving me a new lease on life.

I was therefore shocked and surprised when I learned that NICEâ€™s draft guidance recommended against providing access to dupilumab through the NHS on the grounds of cost effectiveness. Clearly, dupilumab is not appropriate as first-line therapy, and every attempt should be made to control the disease through traditional therapies first. But to force patients with severe AD to continue to rely on ciclosporin for episodic management of symptoms, when dupilumab has been shown to be a far safer, more effective and better tolerated long-term treatment option for this chronic relapsing condition, is surely unconscionable. It seems to me that thereâ€™s a significant risk of underestimating both, dupilumabâ€™s radical improvement to patientsâ€™ quality of life, and the substantial costs associated with current Best Supportive Care, which, in my personal experience, includes frequent visits to the GP and dermatologist, the use of topical and systemic corticosteroids, topical and systemic immunosuppressives, phototherapy sessions, regular treatment of infections (antibiotics, antivirals, antifungals, antiseptics), as well as the use of sleeping pills; all of these costs have fallen away, now that Iâ€™m being treated with dupilumab as monotherapy. And thatâ€™s before taking into account the increase in productivity from this patient population (I was unemployed, and frankly unemployable, for 3 years prior to my treatment with dupilumab) and the benefit that accrues to society in general as a result

of this whole population no longer being marginalized.

I am reassured by the committeeâ€™s acknowledgement that dupilumab â€œis innovative and a step change in managing atopic dermatitisâ€ , and I remain optimistic that a way will be found to secure access through the NHS to this revolutionary treatment that is so vital to improving the quality of life of patients with severe AD. As a participant in the clinical trial, I have been assured that I would be guaranteed access to dupilumab for at least the next 12 months, but Iâ€™d like to advocate on behalf of the many other AD patients who are not so fortunate and risk being denied access to dupilumab and, by extension, the entire new class of biologics currently being developed.

Thank you for your consideration. I remain at your disposal for any further information.

Sincerely yours,

[redacted]

PS: I would ask that you please keep my full name confidential and out of the public domain

Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

My name is Annie and I've suffered from eczema for almost my entire life. I have posted my comment here before after being on Dupilumab for just two days, but I feel that I must update my situation now that I've been on it for over two weeks.

My skin is around 70% healed. My hands and wrists are still very sore, but they were very bad before I started Dupilumab, but they're starting to finally heal. What sore skin I have left is peeling and growing soft and healthy. I have absolutely no pain at all now, asides from the odd twinge from a sore on my shin. I can actually see my skin again, my actual skin, and not layers of rashes and sores. I've also learnt that my fingers and wrists were actually swollen from the severity of my eczema now that they've gone down to a normal size.

Dupilumab has changed my life. I can do so much more than I used to be able to. I can jump in the shower without having to worry about pain or an extensive moisturising routine afterwards. I can do housework without having to take painkillers just to cope with moving around the house. I can sleep peacefully at night, and when I wake up it's not in pain, it's in amazement that my skin is only getting better and better with each passing day.

I feel like a new person. People have commented, not just on my skin, but on how positive I am lately. My nephew expressed amazement that I wasn't 'in a bad mood' like usual, and my customers have told me that I'm happier. I feel happier. I feel so happy right now, because I'm pain free. My skin not only looks good, it feels good, and I feel good because of that. I just can't get over not being in any pain, after I've been in so much pain for so long.

I can't recommend Dupilumab enough. It truly is a life changer.

Role	Patient
Other role	
Organisation	
Location	England
Conflict	I am currently employed by Tudor Reilly Health, a company that provides clinical trial recruitment and retention services to pharmaceutical companies. We do not provide services in the areas of pricing & reimbursement or market access. We have never been engaged to support the clinical development of dupilumab. My knowledge of dupilumab is and has always been limited to information available in the public domain.
Notes	

Comments on the ACD:

As a 40-year-old atopic dermatitis (AD) patient, I have lived with my condition for around 30 years. In recent years, my condition has become increasingly difficult to manage: I am now on fourth-line treatment, having rapidly progressed through topical corticosteroids, a topical calcineurin inhibitor, and phototherapy, to no avail. Having kept a close eye on research into dupilumab throughout its clinical development (see disclosure comment), I had high hopes it would one day be a drug I could access through the NHS.

Having read the project documents, I believe the impact on the individual AD patient has been described well, and I can identify with all of the experiences documented within them. But in my view, a fundamental missing piece in the analysis is alluded to in slide 39 of the public committee slides, titled â€˜Innovationâ€™, namely the statement: â€œBenefit to society, carers and family not included in quality-adjusted life yearâ€ . Why is this the case?

When I was a child and teenager with AD, it could have been argued that the impact of my AD did not extend far beyond myself. However, as an adult with AD, the situation is markedly different. There are many times when I simply cannot interact with family members in a normal way. In addition, at work, I am increasingly challenged in meeting the expectations of those to whom I have professional responsibilities, including: the people I manage; my companyâ€™s management team, of which I am a member; and the clients our business serves.

I propose that a broader review be conducted, taking into account the impacts of AD not only on patients but also on these numerous other parties. It might lead to a more favourable conclusion about the cost-effectiveness of dupilumab.

Dupilumab for treating adults with moderate to severe atopic dermatitis

ERG critique of the new economic evidence submitted by the company in response to the ACD

Produced by: Aberdeen HTA Group

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Date completed: 3rd May, 2018

Contains AiC

This report provides the ERG's brief commentary and critique of revised economic evidence submitted by the company (Sanofi Genzyme) on 24/04/2018 in response to the ACD and in advance of the second AC meeting for this appraisal. The commentary/critique provided below is structured into two sections:

- Section A: Comments on supporting data from the Open Label Extension (OLE) study
- Section B: ERG critique of the company's revisions to the economic model

This ERG commentary/critique should be read in conjunction with the company's submitted document: ID1048_Dupilumab_24-04-2018_company ACD response - JP 240418 [ACIC]

Section A: Comments on supporting data from the Open Label Extension (OLE) study

The company submitted evidence from the Open Label Extension study (OLE). The primary purpose of the study was to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD.

The study population consisted of patients who had previously participated in phase I, II and III controlled clinical trials of dupilumab for AD or had been screened for a phase III study but could not be randomised because of randomisation closure.

The OLE study consists of a treatment period [redacted], during which patients received weekly (QW) doses of 300 mg subcutaneous dupilumab, and [redacted].

A total of [redacted] patients were enrolled in the OLE; [redacted] were included in the safety analysis set.

Additional information about the OLE study was derived from the clinical study report (CSR) that the company made available. [redacted]

Patients could receive rescue treatments [redacted] at the discretion of the investigator. Rescue treatments included systemic corticosteroids, nonsteroidal immunosuppressants and phototherapy.

[redacted]

[redacted]

The company clarifies that *"four patient subsets were identified in the OLE study based on patients' prior experience with dupilumab in the parent studies. These subsets included dupilumab-naïve patients (patients who did not receive any dupilumab doses in the parent study), re-treated patients (patients who came from the dupilumab arm of parent studies and had a gap of >13 weeks between the last injection in the parent study and the first injection in the current study), interrupted-treatment patients (patients who came from the dupilumab arm of parent studies and had a gap of ≥6 weeks but ≤13 weeks between the last injection in the parent study and the first injection in the current study), and continuously-treated patients (patients who came from the dupilumab arm of parent studies and had a gap of <6 weeks between the last injection in the parent study and the first injection in the current study)".*

Table 1 shows the baseline characteristics of patients enrolled in OLE and those enrolled in previous relevant dupilumab trials.

Table 1 Baseline characteristics of patients in OLE and previous relevant trials

	CAFÉ + CHRONOS-CAFÉ-like			SOLO-CAFÉ like subgroup			OLE
	Placebo QW + TCS	Dupilumab Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo QW + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Dupilumab Total
	N=169	N=130	N=163	N=88	N=104	N=96	[redacted]
EASI (0-72, 20=severe), mean (SD)	34.8 (12.0)	33.6 (10.5)	34.2 (11.7)	35.6 (14.3)	36.9 (14.6)	35.7 (14.7)	
Weekly average of peak daily pruritus NRS (0-10, >6=severe), mean (SD)	6.9 (2.1)	6.9 (2.1)	6.6 (2.0)	7.8 (1.5)	7.6 (1.6)	7.4 (1.8)	[redacted]
DLQI score (0-30, >10=very large effect), mean (SD)	14.8 (7.7)	14.6 (7.5)	15.0 (8.0)	16.6 (7.9)	15.7 (6.8)	16.8 (7.8)	[redacted]
EQ-5D utility, mean (SD)	0.632 (0.324)	0.719 (0.249)	0.646 (0.282)	0.520 (0.377)	0.575 (0.315)	0.540 (0.382)	[redacted]

The table of baseline data suggests that while the patients in OLE would be classed as [redacted], the severity of the disease is [redacted] than in either the CAFÉ + CHRONOS-CAFÉ like subgroup or SOLO-CAFÉ like subgroup. This is also suggested by the peak daily pruritus NRS and DLQI score. The EQ-5D score at baseline is also [redacted] in the OLE study than it was in the data provided in the original company submission indicating [redacted] quality of life.

Table 2 Patients efficacy response in OLE and previous relevant trials

	CAFÉ + CHRONOS-CAFÉ-like			SOLO-CAFÉ like subgroup			OLE
	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	Dupilumab Total
	N=169	N=130	N=163	N=88	N=104	N=96	[redacted]
Proportion of patients who achieved EASI-50 and DLQI>4 at week 16	47/169 (27.8%)	92/130 (73.1%)	117/163 (71.8%)	21/88 (23.9%)	61/104 (58.7%)	58/95 (61.1%)	
Proportion of patients who achieved EASI-50 and DLQI>4 at week 48							[redacted]
Proportion of patients who achieved EASI-50 and DLQI>4 at week 100							[redacted]
Proportion of patients who achieved EASI-75 at week 16	51/169 (30.2%)	87/130 (66.9%)	103/163 (63.2%)	15/88 (17.0%)	47/104 (45.2%)	49/95 (51.6%)	[redacted]
Proportion of patients who achieved EASI-75 at week 48							[redacted]
Proportion of patients who achieved EASI-75 at week 100							[redacted]
EQ-5D utility change from baseline to week 16	0.256 (0.0259)	0.257 (0.0209)	0.246 (0.0180)	0.291 (0.0422)	0.313 (0.0281)	0.353 (0.0271)	
EQ-5D utility change from baseline to week 24							[redacted]
EQ-5D utility change from baseline to week 100							[redacted]

The composite EASI-50 and DLQI is not presented at 16 weeks in order to make a direct comparison with the CAFÉ + CHRONOS-CAFÉ like subgroup or SOLO-CAFÉ like subgroup. The outcome is, however, available at 48 weeks and 100 weeks and shows over [redacted] of participants in OLE achieve this outcome. It is possible to make a direct comparison with EASI-75 at week 16 and this shows [redacted] of participants attaining this response at 16 weeks which is [redacted] than both the placebo arms and the intervention arms of the trial

subgroups. The proportion attaining the EASI-75 also [redacted] at the subsequent time points. Again it is not possible to compare the EQ-5D utility change in OLE with the CAFÉ + CHRONOS-CAFÉ or SOLO-CAFÉ like subgroups due to timing of response though the change at week 24 in OLE is [redacted] with the change at week 16 in the two subgroups and subsequent time points show that this change [redacted] (see Table 2 above).

Information on safety events has been obtained from the CSR. In the trials reported in the original company submission exacerbation of AD and infections and infestations were the most frequent adverse events while in OLE the most common events are [redacted] (see Table 3 below). As was the case with the different trials included in the original company submission there are varied frequencies of these events.

The CSR indicates that during the OLE study, a total of [redacted] patients had at least 1 TEAE, including [redacted] patients who had at least 1 SAE and [redacted] who had a TEAE resulting in permanent treatment discontinuation.

A total of [redacted] patients reported the use of a rescue medication. According to the CSR, rescue medications included [redacted]

At the time of the first interim analysis, [redacted] patients were ongoing in the OLE study and [redacted] were withdrawn from the study. The most frequently cited reasons (Table 8 of the CSR) for patients withdrawal from the study were [redacted].

In general, the results of the OLE study indicate that dupilumab 300 mg QW - a higher dose than that of the licence indication – [redacted] in previous dupilumab controlled clinical trials.

Table 3 Safety events

	CHRONOS (16 weeks) (n=740)			CAFÉ (n=325)			SOLO 1 (n=669)			SOLO 2 (n=707)			OLE
	Placebo + TCS (n=315)	Dupilumab Q2W + TCS (n= 110)	Dupilumab QW + TCS (n= 315)	Placebo + TCS (n=108)	Dupilumab Total	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)	Dupilumab Total
Nasopharyngitis	10.5%	13.6%	11.7%	16.7%	20.6%	15.5%	7.7%	9.6%	11.5%	9.4%	8.5%	8.4%	[redacted]
Headache	4.8%	3.6%	6.3%	8.3%	9.3%	9.1%	5.9%	9.2%	5.0%	4.7%	8.1%	9.3%	[redacted]
Upper respiratory tract infection	6.3%	6.4%	6.7%	0.9%	0.9%	2.7%	2.3%	2.6%	5.0%	2.1%	3.0%	3.8%	[redacted]
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%	[redacted]
Exacerbation of atopic dermatitis	27.3%	10.9%	7.9%	14.8%[a]	7.5%[a]	8.2%[a]	30.2%	13.1%	9.6%	34.6%	13.6%	16.0%	[redacted]
Infections and infestations	35.2%	35.5%	34.6%	40.7%	45.8%	42.7%	28.4%	34.9%	33.9%	32.5%	27.5%	28.7%	[redacted]
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%	[redacted]
Conjunctivitis	0.6%	0	1.40%	2.8%	11.2%	7.3%	0.9%	4.8%	3.2%	0.4%	3.8%	3.8%	[redacted]

It is worth noting that the OLE study was not a controlled, randomised study. According to the information provided by the company and presented in the CSR, patients were enrolled from several parent studies [redacted] as well as different intervals between the last treatment in the parent study and the first treatment in the OLE. [redacted] Patients were allowed concomitant use of topical corticosteroids, topical calcineurin inhibitor [redacted] Additionally, patients could receive rescue treatments [redacted] Rescue treatments included systemic corticosteroids, nonsteroidal systemic immunosuppressive medications, [redacted]

Due to these factors the results of the OLE study should be interpreted with caution.

Section B: ERG critique of the company's revisions to the economic model

The company provided a document detailing a revised economic analysis incorporating a number of changes from their previous base case. The company's response is structured around the eight bullet points that summarise the Committee preferred assumptions as documented in section 3.25 of the Appraisal Consultation Document (ACD). The concerns of the committee were that the company's base case:

1. "*included only part of the best supportive care likely to be offered in NHS practice*
2. *used data that included patients who had rescue therapy ('all observed' analyses)*
3. *pooled 'responders' and 'non-responders' in best supportive care*
4. *applied a constant annual stopping rate of 3.7%, which appeared low*
5. *generalised the utility value for 'responders' and 'non-responders' in the best supportive care arm to dupilumab 'non-responders'*
6. *applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms*
7. *overestimated the long-term costs of best supportive care*
8. *underestimated the cost of injection site reactions, and accident and emergency visits*"

Summary

In the ERG's opinion, the company have provided an updated economic base case incorporating changes that address points 1 to 3, and 7 and 8. In relation to point 5, the company have justifiably applied an approach that transitions dupilumab non-responders at week 16 to the utility value of non-responders in the BSC arm by week 52, rather than applying the utility value "*specific to people whose condition had not responded to dupilumab plus topical corticosteroids at 16 weeks*" as the ACD suggested. In relation to points 4 and 6, the company have provided further justification for retaining the original assumption of a constant annual stopping rate (3.7%), and have partially modified the waning assumptions for clinical and utility benefits in the BSC arm of the model.

In addition to addressing these points, the company have proposed an updated patient access scheme (PAS); See Table 1 of the company's response to the Appraisal Committee Document (ACD).

In brief, most of the proposed changes have a modest impact to the incremental cost-effectiveness ratio (ICER), some reducing it and others increasing it. The assumptions that have a relatively higher impact on the ICER correspond to points 1 (the costs components of best supportive care), 4 (the annual discontinuation rate for dupilumab responders after year one) and point 6 (the waning assumptions applied for both dupilumab responders and best supported care). Please see the company's response to the ACD for details of the company's justification for the changes proposed. Each of these are commented on below by the ERG.

The ERG believe that issues 4 and 6 are the main issues the committee need to consider further.

1. **(The company) included only part of the best supportive care likely to be offered in NHS practice (ACD sections 3.4 and 3.6)**

The Committee noted that while BSC in the model reflected many of the elements used in clinical practice, it excluded education, psychological support, bandages and hospitalisations for "*1 week to 2 weeks to intensify treatment and provide respite for people having to apply topical medications*".

The company incorporated the cost of phototherapy (6% rate per year) and psychological support (i.e. psychologist visits at a rate of 7% per year) using data from their updated case note review study (based on 107 patient years of data). One uncertainty here relates to whether inclusion of these cost components is in keeping with the model of BSC in the relevant LIBERTY trials, from which BSC effects were derived. Bandages were included in the original costing as part of the day cases. The company was unable to find a suitable cost for an educational programme and this was not included.

Hospitalisation cost were originally included in the model and the company's revised base case also includes an update of all non-responder resource use data based on the updated case note review (see point 7 below). With the above combined changes, the annual costs for BSC non-responders and responders decrease slightly compared with the previous model.

To accommodate the ACD view that hospitalisations for 1 week or 2 weeks may be employed to provide respite for people having to apply topical medication, the company conducted scenario analyses assuming one or two hospital admissions per year for non-responders (Company's response to ACD, Table 22). It is worth noting that this is well above the rate of hospitalisations observed in the company's own case note review study (i.e. 0.12 per patient year).

The ERG have checked and understand that the company's revisions for resource use, and consider that they have addressed the committees concerns.

2. (The company) used data that included patients who had rescue therapy ('all observed' analyses; ACD section 3.11)

The originally submitted model provided a switch to run the analysis according to 'all observed' or 'primary analysis' groups, with the primary analysis method treating dupilumab patients who required rescue therapy as non-responders. The company have re-run all their analyses using 'primary analysis' method, and as such the ERG consider that committees preference has been met. With this change the dupilumab and BSC responder proportions are reduced at 16 and 52 weeks, resulting in a minor impact on the ICER in the company's revised model ('Primary analysis': ICER = £28,495 ; 'All observed' analysis: ICER = £28,432).

3. (The company) pooled 'responders' and 'non-responders' in best supportive care

In the originally submitted model, the company had applied the aggregate utility value for responders and non-responders for the BSC arm. The company's revised model provides separate utility weights for BSC responders and non-responders responders, addressing the committee's request. This model structural change on its own has very limited impact on the ICER (e.g. reduced the ICER by £653 from the revised base case), because it only has an impact on BSC utility in the short-term due of the waning assumptions applied to BSC.

4. (The company) applied a constant annual stopping rate of 3.7%, which appeared low (ACD section 3.17)

As stated in the company's response to ACD, patients were assessed for response at 16-weeks and 52-weeks in the model leading to cumulative discontinuation rates of 31.5% and

36.9% by these time points respectively; based on the 'primary analysis' method of CAFÉ+CCL for the 16 week response and 'primary analysis' method of CHRONOS for maintained response at 52 weeks. Note, the corresponding discontinuation proportions were 26.9% and 31.4% in the original base under the "all observed" analysis method. Thereafter, the discontinuation rate of 3.7% has been retained based on data from the CHRONOS study, and only applies to the responders remaining on treatment at 52 weeks.

The company reports further discontinuation data from the Open Label Extension (OLE) study for the composite endpoint (EASI50 and DLQI ≥4) according to patient status at entry to the OLE (dupilumab naïve, with previous exposure to dupilumab, treatment blinded in the parent study). All the discontinuation rates are [redacted] than the assumed 3.7% (see Company response to ACD, Table 7). The company use this as justification for maintaining the original 3.7% annual discontinuation rate from year 1 onwards and tested alternative rates in scenario analysis.

It should also be noted, that in addition to the ongoing annual 3.7% discontinuation rate, the company base case waning assumptions for dupilumab response result in a further 2% discontinuing for loss of response in years 2 and 4, 3% discontinuing in year 3, and 1% per year from year 5 onwards. Table 1 is provided below to clarify the proportion of survivors that remain on dupilumab treatment at selected time points in the model, according to the companies revised base case assumptions and the other scenarios provided.

Table 1: Proportion of the surviving cohort remaining on dupilumab treatment - Revised base case assumptions and scnarios assessed (model starting age 38.1 years)

	Annual probability of discontinuation (primary analysis method)					Company's original base case
Time point	[redacted]	[redacted]	**3.7%***	[redacted]	[redacted]	**3.7%**
zero	100%	100%	100%	100%	100%	100%
16-weeks	68.5%	68.5%	68.5%	68.5%	68.5%	73.1%
1 year	63.1%	63.1%	63.1%	63.1%	63.1%	68.6%
5 years	53.3%	52.3%	49.9%	47.1%	44.6%	54.3%
10 years	45.5%	43.4%	39.2%	34.3%	30.3%	42.6%
20 years	33.0%	29.9%	24.1%	18.3%	14.1%	26.2%
30 years	24.0%	20.6%	14.9%	9.7%	6.5%	16.1%

*Company revised base case

The ERG are of the opinion that the applied longer term discontinuation rates appear reasonable and consistent with available data.

5. (The company) generalised the utility value for 'responders' and 'non-responders' in the best supportive care arm to dupilumab 'non-responders' (ACD section 3.18)

The utility weight used for those individuals that discontinue dupilumab in the original model was set to the pooled BSC utility weight. After discussion the Committee concluded that "it was more appropriate to use the utility value specific to people whose condition had not responded to dupilumab plus topical corticosteroids at 16-weeks". The company argue in their response to the ACD that fully implementing this suggestion (i.e. assuming the dupilumab non-responder utility weight at 16-weeks, when patients were still on treatment) would not acknowledge that utility is likely to reduce once dupilumab treatment is discontinued. The company revised base case analysis therefore assumes:

- The average of the 16 week utility weights for dupilumab and BSC non-responders for the first year
- The BSC non-responder utility weight from 52-weeks and thereafter

The ERG are satisfied with the company's approach, and the proposed changes have a minor impact on the ICER. This is because they only affect the utility of those who discontinue dupilumab in the short term given the company's BSC waning assumptions. Furthermore, any changes that increase the utility weights of dupilumab non-respondents, such as assuming the dupilumab non-respondent utility weight beyond 52-weeks, would reduce the ICER.

6. (The company) applied different assumptions for the decline in the clinical and utility benefits of best supportive care in the dupilumab and best supportive care arms

In relation to this point the Committee stated three observations in their ACD:

- Using data rather than opinion is preferable for estimating the decline in quality of life for patients after dupilumab or best supportive care
- The quality of life waning assumptions for best supportive care are a source of uncertainty
- Quality of life waning assumptions for dupilumab should be based on all available data and consider the relative use of topical corticosteroids in trials

The ERG agree with the company that data from the OLE can inform the possible waning effect or loss of efficacy for the dupilumab arm of the model and that there are no equally meaningful data to inform the waning effect for BSC. The company proposed to treat these issues separately for dupilumab and BSC, respectively.

Dupilumab maintenance of treatment effect and utility benefits over time.
The committee suggested that data on the reduction of use of TCS from the CAFÉ study (i.e. 51% for dupilumab and 17% for BSC) could be used to weight the waning effect in the dupilumab and BSC arms of the model. The Committee "considered this to be a good proxy for the relative effect of best supportive care on health-related quality of life in each arm. The same assumption about the waning effect of best supportive care could then be applied to different proportions of people in each arm, based on the relative use of topical corticosteroids in that arm in CAFÉ" study.

The company presents data from the OLE study to argue against this suggestion and to support their base case assumptions for treatment effect maintenance on dupilumab. Available data on [redacted] patients observed to [redacted], show that [redacted] of individuals met the response status of EASI50 and DLQI reduction ≥ 4 points at this time point (see Table 10 of company response to ACD). The company use these data together with the observed reduction in the use of topical medications of over [redacted] in the OLE, to dispute the idea that the "reduction of use of TCS" can be used to represent the relative effect of best supportive care on health-related quality of life in the dupilumab arm. They further argue that it is not possible to disentangle the isolated effect of BCS in the dupilumab arm of the trials on page 19 of their response to the ACD. The ERG would tend to agree that the committee's suggestion requires a number of strong assumptions which are difficult to justify based on the observed data.

Therefore, the company have retained their original waning assumptions for dupilumab maintenance treatment in their revised base case analysis. The ERG are not certain about what the committee's preferred analysis would be with respect to the waning assumptions in the dupilumab arm, but note that the company have tried to implement a scenario analysis based on the proportional use of TCS in each arm of the CAFÉ trial (Company response to ACD, Table 19).

Best supported care maintenance of treatment effect and utility benefits over time.
The company note that there are no data from the available studies to inform this crucial variable in the model. Therefore, the company have used one of the scenarios from their original submission to model waning of clinical and utility benefit on BSC. This assumes that 75%, 50%, 25% and 0% of responders retain the observed 52 week clinical and utility benefits by 2, 3, 4, and 5 years, respectively. This is less pessimistic compared to the company's original base case analysis where 37%, 9% and 0% of BSC patients were assumed to retain the clinical and utility benefits by years 2, 3 and 4. However, the new waning assumptions still assume that all BSC patients return to and remain at baseline utility for the majority of the model time horizon. In addition, this assumptions means that 100% of BSC patients accrue non-responder costs from year five onwards.

The company also provided an alternative approach to model decline in BSC response, based on survival analysis for the time to rescue treatment or withdrawal from the BSC arm in the CHRONOS study. For this analysis, Weibull, lognormal, log-logistic and gamma models were considered. The company present the results using the Weibull function in Table 19 of their response to ACD. This results in an initially more rapid decline in response, but does predict a small proportion retaining clinical and quality of life benefit beyond year five.

It is unclear to the ERG that only data on those individuals that were respondents (e.g. at 16-weeks) were used in this analysis, since the assumption is used to wane the trial observed utility gain for all BSC patients. Moreover, the ERG do not believe the use of rescue therapy to be a good proxy for permanent loss of clinical and utility benefits of BSC, as rescue therapy is essentially part of BSC and can presumably improve patients quality of life and in some case restore responder status for a time. The ERG still have some reservations about the plausibility of the assumption to return all BSC patients to baseline utility and non-responder status for the long-term duration beyond year 5. This assumption remains an important driver of the model results. For example, assuming that 25% of BSC patients retain the trial observed utility benefit and the 52 week responder status, this increases the ICER from the base case of £28,495 to £31,792.

The company have supplied two scenario analyses where no waning is assumed for BSC, but in conjunction with one or two hospital admissions per year for all non-responders in both arms. The additional costs are assumed to maintain all patients in both arms under the appropriate (BSC or dupilumab) responder utility (Company response to ACD, Table 22).

7. (The company) overestimated the long-term costs of best supportive care

The Committee was concerned that the implication of the waning assumption for BSC implied that all individuals in the BSC arm would accrue the cost of non-respondents in the long-term. The committee suggested using the average resource use from all patients "rather than assuming everyone is a 'non-responder'". In addition, the committee preferred the resource use data to be gathered from the now available 60 patient case notes review study than the original data based on 30 participants.

The company have revised and updated the resource use data for non-responders based on more complete case not review data; 48 patients in year 2 and 59 patients in year 3 (107 patients years). See the company's response to ACD (Appendix C) for details.

The company did not incorporate the committee suggestion of using average resource use data for responders and non-responders. The company justified their decision on the grounds that the case note data have been collected for non-responders only and that the amended model allows for utility and resource use to be treated by responder/non-responder status. The ERG accept that the model allows resource use to be treated by responder/non-responder status, but notes that the base case waning assumptions will still result in all BSC patients accruing these estimated non-responder costs in long-term (beyond year 5). Assuming a proportion of patients under BSC retain their responder status would partially address the committee concerns.

There were further concerns by the committee on the number of dermatologist visits assumed in the model for patients on systemic therapy or new drugs (i.e. "generally seen 3 to 4 times per year by dermatologists and probably more often by GPs). The company have retained the original number of visits for dupilumab: 4 dermatology visits for the first year and 2 visits thereafter; 2 primary care visits per year.

8. (The company) underestimated the cost of injection site reactions, and accident and emergency visits

The company original model assumed injection site reactions for dupilumab as a one off event happening at start of treatment. This assumption has been amended and now injection site reactions are considered on a yearly basis.

The company has also revised the cost of A&E attendance using the average of NHS National Prices and National Tariffs for Emergency Medicine (excluding attendances related to dental care or with no investigations and no significant treatment).

The ERG is satisfied with these changes and agree that these changes have minor impact on the ICER.

The company have provided all their additional analysis results in their response to the ACD, with further modelling details in the appendix.