Single Technology Appraisal

Dupilumab for treating prurigo nodularis [ID4054]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating prurigo nodularis [ID4054]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Sanofi**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. British Association of Dermatologists

3. **Comments on the Draft Guidance from experts:**
   a. Andrew Pink– Clinical Expert, nominated by Sanofi

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

National Institute for Health and Care Excellence,
2 Redman Place
London
E20 1JQ

14th September 2023

Re: Dupilumab for treating moderate to severe prurigo nodularis [ID4054]

Dear Professor Crawley,

Thank you for the opportunity to comment on the ACD for dupilumab in the prurigo nodularis (PN) indication.

The ACD highlighted that the committee has several concerns, and we would like to address these here. To do this, we focus on the following key themes in our response.

- Generalisability of the dupilumab PRIME clinical trials to the UK setting
- Maintenance of response for the BSC responder patients
- Calculation of the utility data and evolution over time.

We have carried out the following activities to respond to these points.

- Five individual interviews with UK practicing consultant dermatologists who have experience of using dupilumab in atopic dermatitis (AD) and in some cases PN.
- Further analysis of the PRIME clinical trial data
- Derivation of a 'UK-like' cohort from the PRIME clinical trial data
- Additional regression analysis to explore the impact of treatment and response covariates on the utility outcomes.
- Further economic modelling

These activities, in particular the expert clinical opinion we received, have emphasised some important points and so we have provided a new company base case to accommodate them, as well as addressing the concerns raised in the ACD. The new probabilistic base case ICER is £27,327 and the deterministic ICER is £27,510/QALY. We have also provided focused sensitivity analysis with estimates between £25k - £32k/QALY.

We hope that this additional analysis and expert opinion gives the committee confidence that the uncertainty related to the generalisability of the trials has been resolved and that when considered alongside the rarity of the condition and benefits that are unlikely to be well captured in the QALY, the committee will agree that dupilumab for the treatment of PN is a good use of NHS resources.

Our response is detailed and so we have provided an executive summary to orientate the reader to the main arguments presented.

We look forward to further discussion at the committee meeting on the 4th of October.

Best regards

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Executive summary

Generalisability of the dupilumab PRIME clinical trials to the UK setting

Best supportive care (BSC) in the PRIME trials

- The committee identified that BSC in the trials was not the same as in real world (RW) clinical practice and speculates that outcomes for these patients may have been underestimated.
- The clinicians we spoke to reassured us that although current clinical practice uses a basket of therapies, they are largely ineffective in the RW, and patients cycle through them, often discontinuing treatment and getting lost to the system as their outcomes are generally poor.
- The experts believe that regardless of the therapies used, outcomes would have been equivalent for the BSC patients and so the trials are fit for UK decision making purposes.
- The clinicians pointed out the cost of failure is high and so we have introduced additional disease management cost aligned to the RW therapies for non-responding patients.

Age and weight

- The experts told us that age and weight are not likely to be treatment effect size modifiers and that PN patients are typically not overweight (unlike psoriasis where this is an issue).
- They also told us that PN is closely related to AD where it has been established that outcomes are not affected by age or weight and that AD can be used as a proxy.
- We carried out further analysis of the PRIME data to explore the impact of age and weight and have developed a matched 'UK-like' patient cohort from them. This shows directionally better outcomes than the full study cohort.

Maintenance of response for the BSC responder patients

- The calculation for the current committee preferred ICER includes up to 4 years for loss of response (defined as WI-NRS 4+ and PN-S 1+) for all BSC responders.
- The clinicians we spoke to said that this is far too long and so we have implemented a new single parameter to correct this and allay concerns from the committee about the implementation of loss of response in the original model.

Calculation of the utility data and evolution over time.

- We show that the regression analysis to calculate utility from the original modelling does generate statistically significant differences for the BSC and dupilumab non-responders.
- Therefore, we argue that averaging utility for the BSC and dupilumab non-responders is not credible. The clinical experts we spoke to said that it is not plausible that BSC quality of life (QoL) would suddenly increase to the average directly after the observation period ends, and that dupilumab QoL would suddenly fall to the average value.
- We recognise that both BSC and dupilumab non-responder patients (who will be discontinued) will lose QoL on return to normal clinical practice and so have implemented the corrected EAG expression of our structured expert elicitation results to account for this.

Modelling

- The new base case aligns with the EAG preferred SEE implementation and includes updated costs for non-responders along with an amendment to loss of response; both taken from expert clinical opinion. The model retains the differential utilities for non-responders at week 24.
- The probabilistic base case ICER is £27,327/QALY. (Deterministic ICER = £27,510/QALY).
- This was tested in scenario analysis generating ICERs between £25k and £32k/QALY.

Conclusion

- PN is a rare multifactorial disease affecting all aspects of patients' lives and much of this impact is not well captured in the QALY. Dupilumab has the potential to address aspects of social functioning, stigma, system capacity and Type 2 comorbidity (AD, CRSwNP, EoE etc) cross-over benefits for which dupilumab has a licence and so is a good use of NHS resources.

1. Generalisability of the dupilumab PRIME clinical trials to the UK setting

Two potential areas of uncertainty in the clinical trial evidence base were identified by the committee. The committee is concerned that these may make the results uncertain and not generalisable to the NHS. The two areas of uncertainty are:

- BSC in the trials did not include many of the treatments that are usually used in the NHS.
- The age of patients in the clinical trial may be younger than those seen in clinical practice in England and consequently they may not weigh as much. NICE have identified weight as a potential treatment effect modifier.

1.1 Impact of trial based best support care on trial outcomes.

The PRIME clinical trials included emollients and mild to moderate potency topical corticosteroids (TCS) as BSC with escalation to high potency TCS if required. The committee identified antihistamines, oral steroids, phototherapy, immunosuppressive therapies and antidepressants as additional treatments that might be used in UK clinical practice. However, there is a lack of RCT evidence to support the efficacy of any of these agents. A recent pan-European physician consensus statement which included physicians from the UK, reported that immunosuppressants were effective in less than 27% of patients with PN. The panel also unanimously agreed that antihistamines are ineffective in the management of PN [Pereira, 2018]. BSC for PN is poorly defined in the UK and while these unlicenced medicines are often used as adjunct therapy to alleviate symptoms or for a patient in crisis, they are not effective long-term treatment solutions.

It is important to note that high and super-potent TCS were allowed in the PRIME studies as rescue treatment just as they would be in RW clinical practice. Although high potency or super potent TCS are only used for short bursts in PN (as they can't be used for long periods of time - clinical expert opinion) nearly a quarter of patients in the BSC arm received this form of rescue medication. (Table 1) [Note that in the modelling we follow the 'as observed approach' which means that responding patients were considered "responders" regardless of the rescue medications. This ensures all patients who are responders remain on treatment as they would in clinical practice. The 'primary' analysis method in the studies censors these patients].

Table 1. Concomitant rescue medications that potentially impacted efficacy during planned treatment period - Number of participants by category and standardized medication name – Pooled ITT population

Permitted rescue medication n (%)	Placebo (N=158)	Dupilumab 300 mg Q2W (N=153)
Any concomitant rescue medications impacting efficacy	36 (22.8)	11 (7.2)
High potency or super-potent TCS	34 (21.5)	11 (7.2)
TCI (Tacrolimus / Tacrolimus monohydrate)	3 (1.9)	0

n (%) = number and percentage of participants with at least one concomitant medication. TCS: Topical corticosteroid; TCI Topical calcineurin inhibitor.
Note: Concomitant medications are those the participant used at any time from first IMP intake up last IMP intake + 98 days

In our survey of five clinical experts, we asked if the fact that BSC in the studies didn't contain all the elements that might be variously found in real world (RW) clinical practice would mean that patients treated in the BSC study arm had worse outcomes than they would have done had all the therapies considered by the committee been available. The unanimous answer was that the outcomes for BSC would have been the same regardless of treatment used because currently available options are largely ineffective. The experts explained that unlicensed treatments have variable and unpredictable outcomes and are used because nothing else is available. The clinicians believed that the trial outcomes would be reflective of the relative effect size of dupilumab vs. BSC.

One clinician noted that for PN it is critical to consider the opinions of multiple experts practicing across the UK because otherwise a skewed view of current practice might be received, for example from the single tertiary centre consulted by the EAG. In the district general hospitals where most PN patients are treated few treatment options are offered and patients often refuse them because of poor prior experiences. The clinician noted that treatment is generally about 'tinkering' and often patients 'just give up'. For this reason, whilst the list of treatments discussed in the committee meeting can and is being used, this may not be the 'norm' for many patients who will either 'survive' on topical therapies or be lost to clinical practice as they have no expectation of good outcomes.

We heard from the clinicians that when many unlicensed options are available in a therapy area it is indicative that nothing really works. 'If there was an effective medicine, then that would be used'. PN patients often cycle through multiple treatments for which there is only anecdotal and level-C evidence, and they don't respond. One clinician stressed that time is an important factor here. People don't stay on treatment long and the drop off rate for methotrexate and cyclosporin is high due to intolerance adverse events or lack of efficacy. In the experience of clinicians dupilumab is used for many years without concerns and so comparison with short lived agents is not helpful.

There was agreement amongst the clinicians that currently available treatments such as gabapentinoids, antihistamines and immunosuppressants do not alter the underlying pathophysiology of PN and are used for symptom relief or in the case of antihistamines to help people sleep. These unlicenced agents are used since no alternatives exist, not because they are efficacious. All the experts we spoke to agreed that the mode of action of dupilumab is very important.

The majority of the experts said that immunosuppressants such as methotrexate are used, generally without an expectation of good long term response. Many patients don't tolerate them, and they are not used for long term treatment. One clinician characterised this as 'clutching at straws'. Another noted that the assumption made by the committee that BSC used in the RW is better than nothing and that it would 'narrow the gap' between outcomes seen for dupilumab versus BSC in the trials is not borne out by the evidence for BSC or from his long experience of using dupilumab for both AD and PN.

Another clinician pointed out that prior use of systemic treatments is likely to be a predictor of outcomes. He hypothesised that if outcomes were the same in the study with or without prior use then it would be unlikely that BSC trial outcomes would have been better if 'physicians' choice' had been used. A subgroup analysis of the pooled PRIME trial data for itch (WI-NRS), which is the main determinant of QoL, is presented below in Figure 1 and in Figure 2 for the other primary endpoint of IGA PN-S 0 or 1 score at Week 24. These data clearly indicate there is no influence on outcomes for this patient population regardless of prior treatment. This is also the pattern in the larger AD studies.

Figure 1 Proportion of participants with an improvement (reduction) in WI-NRS by >=4 points from baseline to Week 24 by subgroups - Pooled ITT population

[redacted]

Figure 2 Proportion of participants with IGA PN-S 0 or 1 score at Week 24 by subgroups - Pooled ITT population.

[redacted]

Although the frequency of previous methotrexate use itself is relatively low [redacted] in the PRIME trials, [redacted] (DUP: [redacted]) of patients in the PRIME trials had previous exposure to non-steroidal immunosuppressants (including methotrexate, ciclosporin and thalidomide). The clinical expert

consulted by the EAG estimated that ~50% of patients receive methotrexate and ~20% receive ciclosporin. This was presented in the committee meeting and whilst this is the opinion arising from a single major London tertiary centre there is no broad consensus in the UK on the primacy of methotrexate (unlike in other diseases). For example, this level of use does not appear to be consistent with the evidence from our review of patients in England, utilising CPRD data (N = 2,498) across the spectrum of treating centres and not just in the tertiary care setting. This RW evidence suggests that only [redacted] of PN patients receive immunosuppressants.

Indeed, it is important to consider that the choice to use systemic therapies is complicated due to the level of intolerance, comorbidities, and polypharmacy in PN patients. The clinicians we spoke to felt that older patients would not be treated with immunosuppressants such as methotrexate as readily as younger patients who, for example, may have AD. The lower use of these agents observed in the RW study than expressed at the committee meeting may be due to age, intolerance, comorbidities, and polypharmacy in the general PN population.

One clinician noted that the 'Cost of failure' is high for these patients. He suggested that the base case should include more costs for additional treatments for non-responders (but with equivalent outcomes to the PRIME studies for the reasons stated above). We have used the drug classes and proportions of patients taking them from the CPRD database study to estimate the additional costs and applied these to the non-responder patients (both BSC and dupilumab non-responders). The implementation is discussed in Appendix A and the results are provided in Section 4 below.

Overall, the clinicians we spoke to recognised that the trial BSC did not include all the possible PN treatments but felt that BSC outcomes from the trial and by extension the relative effect size of dupilumab could be relied upon for UK decision making. This is because the unlicensed treatments available to them have variable and unpredictable outcomes and are used, often in desperation with a low expectation of good efficacy, because nothing else is available. The outcomes from the PRIME trials are considered generalisable to the UK setting.

1.2 Impact of age and weight on trial outcomes.

The committee was concerned that the mean age of patients in the pooled analysis from the PRIME studies (49.5 years old) was lower than the mean age of patients included in the moderate to severe PN cohort identified in the company CPRD database study described in the company submission (61 years old). They also considered that the weight of study patients may be lower than RW patients because as people age, they have a tendency for weight gain. The committee speculated that age and weight might be treatment effect modifiers and so the PRIME clinical trial populations may not be generalisable to UK clinical practice.

1.2.1 impact of age on efficacy.

All of the clinical experts with experience of treating PN and managing patients with dupilumab that we consulted confirmed that age is not expected to be a treatment effect modifier.

This has been their experience in AD and is consistent for those who have used dupilumab to treat PN. The clinicians commented that the disease generally occurs in adults in their 40's, 50's and 60's but can be diagnosed at any age (although it is far less prevalent in younger people). They unanimously agreed that 61 years is too high an average age for diagnosis of PN today and that the trial average of 49.5 years was a more reasonable estimate for UK clinical practice.

In the words of one dermatologist PN is 'grossly under reported'. In the CPRD-HES study the enrolment period started in 2007 and finished in 2019. Over this time the prevalence and incidence

of the disease appears to have risen by between three and four times respectively. It is improbable that this is entirely due to an underlying increase in PN and is likely due to better diagnosis and recording in recent years. We heard from the clinician and from the patient group at the committee meeting, that people can spend a long time before receiving a diagnosis of PN. Therefore, it may be the case that the CPRD data is skewed to an older average age of 61 years because patients from the earlier part of the CPRD data collection period were diagnosed at an older age than patients are diagnosed (and recorded) today.

We have carried out post-hoc analysis on the pooled PRIME dataset to examine the impact of age on outcomes. The proportion of patients with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at week 24 by age subgroup is plotted in Figure 3 overleaf.

In the patient age group below 30 years the relative proportion of patients achieving the efficacy response criterion for dupilumab versus BSC is lower than in patients above 30 years old. However, the trials were not powered to identify differences in efficacy based on age or weight and the sample size is small in this age group, so it is difficult to fully interpret this finding. Clinicians told us that this is not generally an age group in which PN is prevalent. For the age groups above 30 years old the proportion of responders and non-responders is similar.

Figure 3. Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24 by age subgroup

The committee was concerned about the average age in the CPRD-HES study, so we have carried out an analysis to examine outcomes for patients above and below 60 years old to capture the relative proportions responding and not responding in these age groups. This is tabulated below (Table 2). The proportion of responders in dupilumab treated patients aged above 60 is numerically similar than those below 60 years old [redacted] but the sample size is low.

Table 2. Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24 for patients under and over 60 years.

	BSC (N=158) n (%)	Dupilumab (N=153) n (%)
Patients under 60 years (n)	121	109
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
OR, 95% CI vs. placebo	[redacted]	
P-value vs. placebo	<.0001	
Patients over 60 years (n)	37	44
Responder	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]
OR, 95% CI vs. placebo	[redacted]	
P-value vs. placebo	0.0008	

Real world data on the off-label use of dupilumab in PN does not suggest that age (or weight) is a treatment modifier. A published investigator-initiated retrospective study of dupilumab data prior to licensure in PN did not identify age as a potential response predictor, defined as a reduction in the NRS score by >4. [Gael, 2022] There are several case reports in the literature which provide further

evidence of efficacy in older patients and the results show efficacy in PN comparable to AD. We have summarised these cases in elderly patients ≥65 years and older successfully treated with dupilumab in Appendix B.

The clinicians we spoke to agreed that the AD studies could be used as a proxy to examine the effect of age as AD is closely related to PN. Analogous results to those shown above for the populations above and below 60 years old are presented in Table 3 for the recently published pooled analysis from the AD study programme for the key primary endpoints of IGA and EASI-75. [Silverberg, 2023]

Table 3. Efficacy outcomes from the pooled phase III studies in AD

AD pooled Ph3 study outcomes	Efficacy <60ys (BSC vs. Dup Q2W) (n=616 vs. n=827)	Efficacy≥60ys (BSC vs. Dup Q2W) (n=54 vs. n=56)
IGA	12.1% vs. 37.8%	7.1% vs. 44.4%
EASI-75	22.1% vs. 55.2%	14.3% vs. 63%

These data are in a much larger cohort than the PN results from the PRIME studies and show a numerical bias in favour of the older age group.

Finally, it is important to note that the SmPC states that:

'The pharmacokinetics (PK) of dupilumab is similar in patients with atopic dermatitis, asthma, CRSwNP, PN and EoE' and *'Age was not found to be associated with any clinically meaningful impact on the systemic exposure of dupilumab determined by population PK analysis.'* [Dupixent SmPC, 2023]

1.2.2 Impact of weight on efficacy.

Pharmacokinetic modelling

Consistent with the known effect of body weight as a covariate influencing the exposure of monoclonal antibodies in general, the pharmacokinetic (PK) data from the dupilumab phase I and II studies did suggest a diminished exposure with increasing body weight on pharmacokinetics. However, PK by age group was similar indicating there is no correlation of age and body weight.

The effect of body weight on exposure was modest within the range of adult body weights in the phase I and II studies. As dupilumab has a wide therapeutic index and weight accounts for a small portion of variance, it has been concluded that no dose adjustment for weight is warranted based on the phase I and II studies. [Kovalenko, 2016] This is reflected in licence wording (See above and at the end of this section).

Post-hoc analysis of the pooled PRIME studies

We have carried out further analysis on the pooled PRIME data to examine differences between weight subgroups. Figure 4 shows a breakdown of the weight profile for the pooled ITT population. Only around 15% of patients weighed more than 90 kg in the studies.

Figure 4. Description of weight (kg) at baseline - Pooled ITT population

The proportion of patients meeting the efficacy response criteria agreed by the committee (WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at week 24) above and below the weight thresholds of 60, 70, 80 and 90 kg is presented in Table 4 below.

Table 4 Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24 by weight. Pooled ITT population.

Weight cut off	Response status	BSC (N = 158)		Dupilumab (N = 153)	
		Weight < cut off	Weight >= cut off	Weight < cut off	Weight >= cut off
60kg	Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
70kg	Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
80kg	Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
90kg	Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]

The dupilumab responders are balanced in the groups above and below 70kg and 80kg at ~55%. However, the study is not powered to deliver on an efficacy by weight analysis and for the lighter patients below 60kg and the heavier patients above 90kg there are less than 30 patients in each subgroups and so it is difficult to interpret these data.

The clinicians we spoke to all stated that they have not seen an efficacy response relationship with weight in either AD or PN. This contrasts with psoriasis in which there is a demonstrated influence of weight on dosing requirement for biologic treatment. The experts unanimously agreed that PN is not related to psoriasis which often has accompanying metabolic syndrome and significant obesity associations. One clinician commented that when he thinks about a waiting room full of PN patients he does not see an overweight group however, this would be the case with psoriasis patients. Another clinician said that his database of PN patients does not support a weight effect and it is not borne out by the evidence or his extensive experience. The clinicians recognised that the PRIME studies might show a directional treatment effect for very heavy patients but that basing a reimbursement decision on the outcomes from the 'very few heavier' patients in the PRIME studies which are not powered to deliver on that outcome in that patient group, is not robust. One of the clinicians noted that even if there is a treatment effect it would be at the very margin in PN patients with a very high BMI patients, and this is '*not something to worry about*'.

We discussed at the committee meeting how the AD data suggests no concerns about the impact of body weight or BMI on efficacy and this has been demonstrated across all the different dupilumab indications However in the ACD the committee did not agree that AD could be transposed to PN. In contrast, the experts we consulted all agreed that the outcomes from the AD studies (and their RW clinical experience treating AD) could be used as a proxy for PN. For example a Forest plot for the percentage of patients by weight and BMI achieving the two primary endpoints of EASI-75 and IGA 0-1 from the AD study CHRONOS (which included concomitant use of TCS and rescue treatment when required) is presented in Figure 5 below. This indicates no important age or weight influence on outcomes. Similar profiles are observed in the asthma and chronic rhinosinusitis with nasal polyps indications. [Bachert, 2020; Bourdin 2022].

Figure 5. Forest plot for the percentage of patients by weight and BMI subgroup achieving the two primary endpoints of EASI-75 and IGA 0-1 from CHRONOS (FAS)

[redacted]

Finally, it is worth noting that Sections 5.2 and 4.2 respectively of the SmPC state that:

- *Dupilumab trough concentrations were lower in subjects with higher body weight with no meaningful impact on efficacy.*
- *No dose adjustment for body weight is recommended for patients with asthma and EoE 12 years of age* and older or in adults with atopic dermatitis or CRSwNP, or PN

1.3. Matching analysis

We have shown above that the clinical data from the PRIME studies does not support a clinically important age or weight-based treatment effect size modifier and that the clinicians we spoke to agreed. Nonetheless we recognise that the committee had concerns over the generalisability of the data to the UK population based on age and weight. To provide further assurance that the PRIME trial data are suitable for decision making we carried out a sensitivity analysis, matching on age and BMI observed in the CPRD RW study to generate a 'UK-like' patient population. We noted in Section 1.2.1 above that the CPRD data may be skewed towards older patients due to the historic nature of the data potentially confounded by poor diagnosis and recording practices but have used the baseline age and weight patient characteristics from the CPRD-HES database study for the moderate to severe PN population without adjustment. These are presented below in Table 5.

Table 5. Baseline characteristics, Moderate to severe PN population taken from the company CPRD-HES database study.

		Pooled ITT analysis from PRIME	
	CPRD study	**BSC**	**Dupilumab**
Characteristic	**N = 2,498**	**158**	**153**
Female n, (%)	1,582 (63)	99 (62.7)	104 (68.0)
Male n, (%)	916 (37)	59 (37.3)	49 (32.0)
Mean age (SD)	61 (15)	48.8 (15.6)	50.1 (16.6)
Mean BMI (SD)	31 (7)	26.71 (5.83)	27.47 (6.07)

A simple matching exercise inspired by the Matching Adjusted Indirect Comparisons (MAICs) methodology was carried out on these parameters with no preselection of patients. To ensure comparability of the population at baseline, age and BMI were weighted in the PRIME pooled population to match to the baseline characteristics of the CPRD-HES study population (Table 5). Before matching the sample size was 311 and after matching the effective sample size (ESS) was 143.

A comparison of the age and weight baseline characteristics before and after matching is tabulated below in Table 6. As can be seen the populations before and after matching are broadly similar for these parameters. There are slightly fewer males after matching and the mean weight of patients is higher (+9 kg) as expected. The full demographics and baseline characteristics are provided in Appendix D.

Table 6. Comparison of age and weight baseline characteristics before and after matching. Pooled ITT population.

Characteristic	**Before matching (N = 311)**			**After matching (ESS = 143)**		
	BSC	**Dupilumab**	**All**	**BSC**	**Dupilumab**	**All**
Mean Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Male (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A descriptive analysis of responder status at week 24 was carried out to compare the matched populations with the ITT pooled population.

The DLQI score at baseline was lower in the matched versus ITT population, but the WI-NRS scores were comparable. The change from baseline (CFB) between the ITT and matched populations for both DLQI and WI-NRS were similar [redacted] (See appendix D for detailed breakdown including the 'Primary analysis').

More importantly the responder analysis is presented in Table 7 below. There is a numerically higher proportion of dupilumab responders in the matched group than in the ITT population and a lower proportion of BSC responders. Formal statistical testing has not been carried out, but this analysis suggests that dupilumab is at least as effective in achieving response status relative to BSC in the 'UK-like' population as in the ITT pooled trial population.

Table 7. Responder status at week 24 according to WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline. Matching on age (mean=61 years old) and BMI (mean=31 kg/m^2). (As observed analysis)

	Before matching (ITT, N= 311)		**After matching (ESS = 143)**	
	BSC	**Dupilumab**	**BSC**	**Dupilumab**
Scenario 2: Matching on age (mean=61 years old) and BMI (mean=31 kg/m^2). ESS=143				
Responder (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder (%)	[redacted]	[redacted]	[redacted]	[redacted]

The data from the clinical studies (both the ITT population analysis and the descriptive matched 'UK-like' population analysis) along with licence wording and clinical opinion from the experts we consulted, supports the generalisability of the PRIME clinical trials to UK populations. We hope that this additional analysis and expert opinion gives the committee confidence that the uncertainty related to the generalisability of the trials previous identified has been resolved.

2. Maintenance of response

An important part of the economic modelling is the handling of loss of response for patients who have achieved the efficacy response criteria of WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline by week 24. In our original modelling we had included two parameters to describe this. It is critical to note that this does not address return to baseline levels for QoL (that process is examined in Section 3 below). Instead, this parameter describes how quickly patients move between the binary responder and non-responder states. At this point (week 24 in the model) they will still have some residual response.

For dupilumab we included the observed rate of discontinuation from the PRIME data which was [redacted] due to AE's and patient/clinician preference ('all cause discontinuation') and a probability of loss of response intended to capture further attrition over time. This is the way in which overall loss of response was handled in each of the AD HTA appraisals and agreed by the committees at the

time. In the absence of further data for PN to support the probability of dupilumab loss of response we used the rates from the dupilumab AD appraisal TA534.

In the original submission, while there is no observed rate of discontinuation of BSC because patients do not switch treatments after loss of response, to be consistent with the calculations used for dupilumab we applied an 'all-cause' discontinuation rate (calculated to be [redacted] annualised from the proportion of BSC responders at 24 weeks who lost response by 36 weeks) and a probability of loss of response, again taken from the AD appraisal.

We understand the concerns of the committee that the rationale for the inclusion of two parameters for BSC was unclear in the original submission. However, we are pleased to see the committee does maintain a preference to include a loss of response parameter. This is because when patients treated with BSC return to RW clinical practice, the improvement in outcomes driven by the trial protocol will diminish over time and BSC responders will all eventually lose response (defined in the model as WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 at week 24 from baseline). This rate of loss of response was agreed by the committee as a linear loss of 25% of patients per year, resulting in complete loss of response by the end of the 5th year after trial start.

The committee thought that this resulted in a 'fairly rapid loss of response' in the BSC arm, so we felt it was worthwhile to test this assumption further because it was slower than our effective original level and we asked the five clinicians we spoke to if this rate of response loss was reasonable. All the experts were very firm in their belief that it was far too slow and indeed by the end of [redacted] (or even earlier) all BSC patients would have dropped below the efficacy response criterion cut-off. One expert explained that this is because the trial has very intensive management for BSC including monitoring of adherence. After patients leave the trial setting, they will 'ease off' their treatment quickly and return to old habits.

Our original calculations are tabulated below to show the overall effect of the combination of both parameters for BSC loss of response.

Table 8. Maintenance of response for BSC responder patients

End of year…	'Discontinuation rate'	Maintenance of response (current committee preferred rates)	Effective level of maintained response	New base case for maintained response
2*	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]

*This modelling applies to the Markov portion of the economic modelling which is the extrapolation of the data over time. Therefore the 2nd year after the start of treatment applies.

Given the very clear direction from the experts, we believe that whilst the handling of the calculations was unclear in the original submission, the effective level of maintained response shown in Table 8 is more clinically plausible than the much slower loss imposed by a linear [redacted] decline over 4 years. However, taking into account the opinion of the experts even this rate might to be too slow and so we have adjusted this in the base case to approximate our original assumption in the first year [redacted] and in the subsequent years to reflect half of the EAG preferred maintenance proportion for years 3 and 4. The experts we spoke to felt that all response would be lost after [redacted] for BSC responders so we have tested this scenario along with the current committee

preferred rates and the original company effective rates in sensitivity analysis. See section 4.3 below.

3. Calculation of the utility data and evolution over time.

Two key areas related to utility data were debated at the committee meeting.

- The regression equations used for the calculation of the utility values.
- The extrapolation of utility data over time after the end of the observation period in the studies.

3.1 Exploration of the regression parameters for the calculation of utility

The committee was concerned that because the economic model includes a difference in utility between the BSC and dupilumab non-responders they would expect to see treatment and response status as significant covariates in the regressions used to calculate utility. It requested analyses from the company including treatment arm and response status in the regression modelling to examine the difference in utilities at week 24. Therefore, we developed two alternative regression models which included these variables. The original model and the two scenarios explored are shown below in Table 9. The models and residuals are provided in Appendix E.

Table 9. Exploration of regression models to calculate utility.

Variable	Unit	Original model		Scenario model 1		Scenario model 2	
		Coef.	p-value	Coef.	p-value	Coef.	p-value
Intercept		[redacted]	<.0001	[redacted]	<.0001	[redacted]	<.0001
Treatment	Dupilumab (ref: Placebo)	[redacted]	-	[redacted]	0.3175	[redacted]	0.0571
Age	1 year	[redacted]	0.0955	[redacted]	-	[redacted]	0.4655
Gender	Male (ref: Female)	[redacted]	0.0526	[redacted]	-	[redacted]	0.0351
Baseline EQ-5D-5L	1 point	[redacted]	<.0001	[redacted]	-	[redacted]	<.0001
Baseline DLQI total score	1 point	[redacted]	0.0002	[redacted]	-	[redacted]	-
DLQI Total Score at visits	1 point	[redacted]	<.0001	[redacted]	-	[redacted]	-
WI-NRS Score at visits	1 point	[redacted]	0.0723	[redacted]	-	[redacted]	-
Response status (WI-NRS improvement >=4 and IGA PN-S improvement >=1)	(Responder (ref: Non-responder)	[redacted]	-	[redacted]	0.0018	[redacted]	0.0013
Treatment * Response status	Dupilumab *Responder	[redacted]	-	[redacted]	0.4600	[redacted]	0.4186

The most appropriate model to use for the estimation of utility is the one included in the original company submission.

The variables included in this model were identified though discussion with clinicians which generated 10 variables to test, and a stepwise approach (forward selection) was used to determine which ones to keep. The three criteria below for determining the “best fit” model were applied. This follows the generally accepted approach to adjust for covariates and was tested and agreed at an ad board.

- Are the covariates included significant?
- Does the regression prediction approximate the observed baseline utility weight?
- Does the regression prediction approximate the observed 24-week values for each treatment (Dupilumab Q2W, and placebo) for each analysis method?

We observed that most of the treatment effect was captured by the post-baseline DLQI total score and WI-NRS covariates. The final model did not include the treatment covariate as it was non-significant. (With treatment included as a co-variate in the model the p-value for treatment was 0.4774). It did reach significance when DLQI and NRS-WI were removed (see discussion about model scenario 2 below) but we kept DLQI and NRS-WI in the model as these measures provide a broader estimate of QoL and are drivers of the regression. Importantly the magnitude of the CFB for BSC is significantly less than for dupilumab in both quantities. Table 10 indicates that the difference in CFB for WI-NRS and DLQI is statistically significant.

Table 10 Change from baseline for WI-NRS and DLQI to 24 weeks for dupilumab and BSC patients judged to be non-responders according to WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at week 24.

	WI-NRS	DLQI
Baseline (pooled)	[redacted]	[redacted]
Dupilumab (LS mean CFB)	[redacted]	[redacted]
Dupilumab (LS mean CFB)	[redacted]	[redacted]
p-value Dupilumab vs BSC	0.0013	<0.0001

For WI-NRS, studies have shown that the clinically important change score depends on the baseline. For a severe baseline score of between of 7 to 9 (note the trial baseline was [redacted]) a reduction of -3.65 is considered clinically significant. [Riepe, 2019] (The MCID does appear to reduce as severity reduces. For example, for a baseline score of 3 to <7, a 1.34 point decrease is sufficient). The difference observed in the PRIME studies for dupilumab non-responders according to the efficacy response criteria agreed by the committee was greater than this within group threshold at [redacted] whereas BSC fell below at [redacted]. This indicates that for itch, dupilumab non-responders had a clinically important difference but BSC non-responders did not. It is therefore critical to maintain this parameter in the regression modelling.

The utility values predicted for dupilumab and BSC non-responders using this original model were [redacted] and [redacted] respectively. The difference in the utility value is [redacted]. This is statistically significant with a p-value of <0.0001 (Table 11).

Table 11. Statistical testing for the difference between the non-responder (WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24) utility values.

Dupilumab non-responder	BSC Non-responder	Estimate of the difference	95% CI	Standard Error	P Value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<.0001

We tested the committee suggestion of modelling only the treatment and response covariates. This is scenario model 1 in Table 9 above. In this case the p-value for the treatment covariate is 0.3175 and so it is not statistically significant. When the model is used to estimate utilities for non-responders the 'response status' and 'response status * treatment' interaction terms both disappear

(because the reference is non-responder). Therefore, for non-responder utilities the model is driven solely by the intercept and treatment covariate. We believe this very simple model is not an appropriate estimator of utility because it does not consider patient characteristics at baseline (age, gender, and baseline EQ-5D-5L) or clinical responses for the key determinant of QoL (WI) and a measure of QoL impact (DLQI) for which the differences between BSC and dupilumab responses are statistically significant. (Table 10).

To test the impact of the baseline patient characteristics of age, gender, and baseline EQ-5D-5L on the regression we included them in a second model. (See scenario model 2 in Table 9). In this case the p-value for the treatment covariate is 0.0571 which marginally mises conventional levels of significance. However, it is important to note: 1) data collection efforts were not powered for this endpoint; 2) scenario model 2 still lacks the statistically significant DLQI and NRS-WI treatment covariates which we believe are important to fully describe QoL impact; 3) the findings cohere with the results of the model in indicating dupilumab has a significant benefit on improving patients' position on the continuum of disease such that 'non responding' dupilumab patients have a better HRQL than 'non responding' BSC patients.

We then calculated p-values for the difference between the non-responder utilities for BSC and dupilumab. These are tabulated overleaf in Table 12 along with the original model for reference.

Table 12 Difference in utility values for the dupilumab and BSC non-responders.

	Original model		Scenario model 1		Scenario model 2	
	Responder	**Non-responder**	**Responder**	**Non-responder**	**Responder**	**Non-responder**
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE (non-responder difference)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%CI (non-responder difference)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value (non-responder difference)		<.0001	-	0.318	-	0.057

The original model remains our preferred option for calculating utilities for the reasons described above but we have implemented the utilities from the two additional scenarios into the economic model to test the impact on the cost effectiveness estimate. This is provided in Section 4.3 below.

3.2 Non-responder utility at 24 weeks and waning of quality of life over time

The committee was concerned that different utility values were applied for dupilumab and BSC at 24 weeks from which to begin the long-term extrapolation in the Markov portion of the model for non-responders. The committee agreed with the EAG that a pooled utility value should be used. We disagree with this assumption for several reasons.

1. We have examined the results from three regression models above and shown that the most suitable model at 24 weeks predicts a statistically significant difference in utility for BSC and dupilumab non-responders ($p < 0.0001$). (Table 11). We have also shown that it is important to include patient characteristics at baseline and key clinical responses in the regression analysis.

2. Pooling the utility between the non-responders results in an immediate increase in utility value for BSC patients from [redacted] to [redacted] which is the pooled average, as they leave the clinical trial environment. This is an implausible assumption because it represents an improvement in QoL for BSC patients when they re-enter RW clinical practice. The experts we have consulted strongly expect QoL to dimmish quickly for these patients, not go up.
3. Similarly, it is not reasonable to expect an immediate drop in HRQoL for dupilumab patients from [redacted] to [redacted] the day after discontinuation.
4. The findings from the structured expert elicitation (SEE) indicate that both the BSC and dupilumab non-responders will lose any trial benefit gained relatively rapidly and return to baseline levels but this will not be on immediate withdrawal from the study. (See section 3.2 below).
5. The clinical experts we consulted agreed that there would be a difference in outcomes for non-responder versus responder patients and that benefit beyond the study for dupilumab patients which would persist versus BSC for a period of time. They agreed that the EAG suggested pooling of utility directly after week 24 in the model was not clinically plausible for the following reasons:
    a. Response in the model is judged on a binary endpoint, but the disease is a continuum.
    b. The efficacy response criterion is a high bar and patients not reaching this bar have a spread of outcomes from no response all the way up to nearly responder. (No to Partial-responder).
    c. Dupilumab is an active compound which works on the underlying pathophysiology whereas BSC is largely just transitory symptom control.
    d. The evidence shows that dupilumab provides better outcomes than BSC even for non-responders (see Table 10 above).

It is critically important to recognise that there is a clinical and QoL difference in outcomes between BSC and dupilumab non-responders at week 24 in the PRIME trials and to follow the advice of clinicians on how this might diminish, not immediately, but over time (SEE methodology) rather than applying an oversimplifying assumption. (See Section 3.2 below)

3.3 Waning of utility over time.

After patients leave the protocol driven setting of the clinical trial and return to real world clinical practice assumptions must be made about how utility might evolve over time.

From experience of AD we have good reason to believe that dupilumab treated patients who remain controlled will not lose QoL over time:

- The open label extension (OLE) data from the AD studies shows continued improvement in QoL to 4 years
    - Self-reported compliance was 98.1%, and most (98.9%) patients reported ≥80% injection compliance.
    - At week 204, 71% of patients had achieved >=4 point change in weekly average pruritus NRS

    - For EQ-5D more than 90% of patients reported No impact for mobility, Self care and Usual activities and 70-80% reported No impact for Pain/discomfort and Anxiety/depression
- The 'Satisfaction with dupilumab in clinical practice over 36 months in Real world' study shows high levels treatment satisfaction and good outcomes
    - Overall satisfaction (extremely, very, or somewhat satisfied) 87% at months 30–36. (75.5% extremely or very satisfied)
    - 84.9% of patients experienced the more than the minimally clinically important difference in DLQI scores (≥4-point change from baseline) at months 30–36.
    - More than half of patients reported DLQI of 0/1 by months 30–36

It is less clear how QoL for patients (dupilumab or BSC) who are judged to be non-responders at week 24 will evolve in the long term.

The committee has agreed with the EAG that after 6 months the average utility (see Section 3.2 above) they applied to both BSC and dupilumab non-responders should fall abruptly to baseline. We believe this simplifying assumption does not fully account for what might be expected to occur in RW clinical practice for non-responders following a period of treatment with either dupilumab or BSC in the trial setting. The clinicians we spoke to for the purposes of this ACD response agreed that it is entirely reasonable for there to be a difference in QoL for BSC and dupilumab non-responders and that this differential could persist for a while.

Unfortunately, this decline in utility is not an observable quantity as it takes place outside the confines of the trial. Therefore, for our original submission we sought the advice of clinical experts using structured expert elicitation (SEE) to populate this part of the model. The methodology and results were described in the original company submission.

In the original company submission, our implementation of the structured expert elicitation resulted in a residual utility difference between dupilumab and BSC responders (~0.01) who became non responders and were both treated with BSC for the remainder of their time in the model. As part of their assessment the EAG suggested an alternative implementation of the SEE which removed this difference and they provided the utility values shown in Table 13 below. This was scenario 11 in the EAG report and is reproduced from page 96, Table 28 in the EAG report. We agree that this is a more appropriate use of the SEE data, than originally implemented by the company because it does not introduce a long-term quality of life benefit for a discontinuing patient who had been treated with dupilumab rather than BSC.

Table 13. Utility values used in EAG scenario 11 for non-responders to treatment over time according to time since becoming a non-responder and according to previous response status. Response criterion of WI-NRS improvement ≥4 AND IGA-PN-S reduction ≥ 1 at week 24 from baseline. (Reproduced from page 96, Table 28 in the EAG report).

Time in model	Dupilumab non-responder having previously responded at week 24		Dupilumab plus BSC non-responder at week 24		BSC non-responder having previously responded at week 24		BSC non-responders at week 24	
	SEE % of gained QoL remaining	Utility	SEE % of gained QoL remaining	Utility	SEE % of gained QoL remaining	Utility	SEE % of gained QoL remaining	Utility
0 - 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 - 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+ years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For their Scenario 11, the EAG helpfully provided outcomes from their updated model. Using the original company submission model (which estimated an ICER of £27,100/QALY) we implemented the utility values used in scenario 11 (Table 13 above) and checked the updated model outcomes against the EAG results to ensure that we had implemented the utilities correctly. We are grateful to the EAG for providing this alternative implementation and have used this to update our model base case which is described in Section 4 below along with scenario and sensitivity analysis. One of which removes the final [redacted] benefit for non-responders who have previously responded, shown in Table 13 and sets all the non-responder patients to baseline at 2+years (Scenario 8, 12 and 13). In these cases the ICER remains below £30,000/QALY.

4. Cost effectiveness analysis

4.1 Updated base case summary

We have updated our base case to reflect the issues raised in the ACD and discussed in Sections 1-3 above. Table 14 below provides an overview of the key differences between the current committee preferred analysis and our updated base case with rationale.

Table 14. Comparison of the current committee preferred assumptions and the new company base case.

	Committee preferred assumptions	Updated company base-case	Rationale
Response waning	• All-cause discontinuation rate for BSC set to 0%. • Maintenance of response at [redacted]	• All-cause discontinuation rate for BSC set to 0%. • Maintenance of response set at [redacted]	• We agree that the rationale for the use of two parameters may be unclear. • Only the maintenance of response parameter is used. • Clinical opinion supports a faster loss of response than the committee preferred assumptions.
Utility values for non-responders at week 24	Same utility value by treatment arm for non-responders based on week 24 pooled value for non-responders.	We have maintained the different utilities values for responder and non-responder based on the original regression equation.	• Supported by trial data • Pooling the utility is not consistent with the observed evidence. • The difference in the non-responder utilities estimated using the original regression analysis does reach statistical significance (p<0.000.1)
Utility waning	Utility values for non-responders are assumed to hold constant only for the first six months after treatment discontinuation and then rebound to baseline utility.	We have retained the expert opinion gathered using the SEE approach to inform utility waning. The implementation has been updated to reflect Scenario 11 suggested by the EAG.	The EAG corrected SEE implementation is the best available evidence.
Updated cost for BSC	None	Additional drug costs are included for non-responders	According to clinical opinion the cost of drugs for non-responder BSC (which included dupilumab patients who do not respond) is likely to be higher than originally modelled.
Probabilistic ICER	**£35,700**	**£27,327**	

4.2. Updated base case results.

The estimated ICER using the updated company base case is presented in Table 15 below and the disaggregated cost and QALYS are provided in Appendix F.

Table 15. Updated base case results.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Probabilistic (base case)							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,327
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]				
Deterministic							
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,510
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]				

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

The probabilistic results are presented in Figure 6 and Figure 7 below. Results show that at a willingness-to-pay (WTP) of £30,000, the probability of being cost-effective is 82.9%; at £20,000 it is 0.0%.

Figure 6. Cost effectiveness acceptability curve (10,000 iterations)

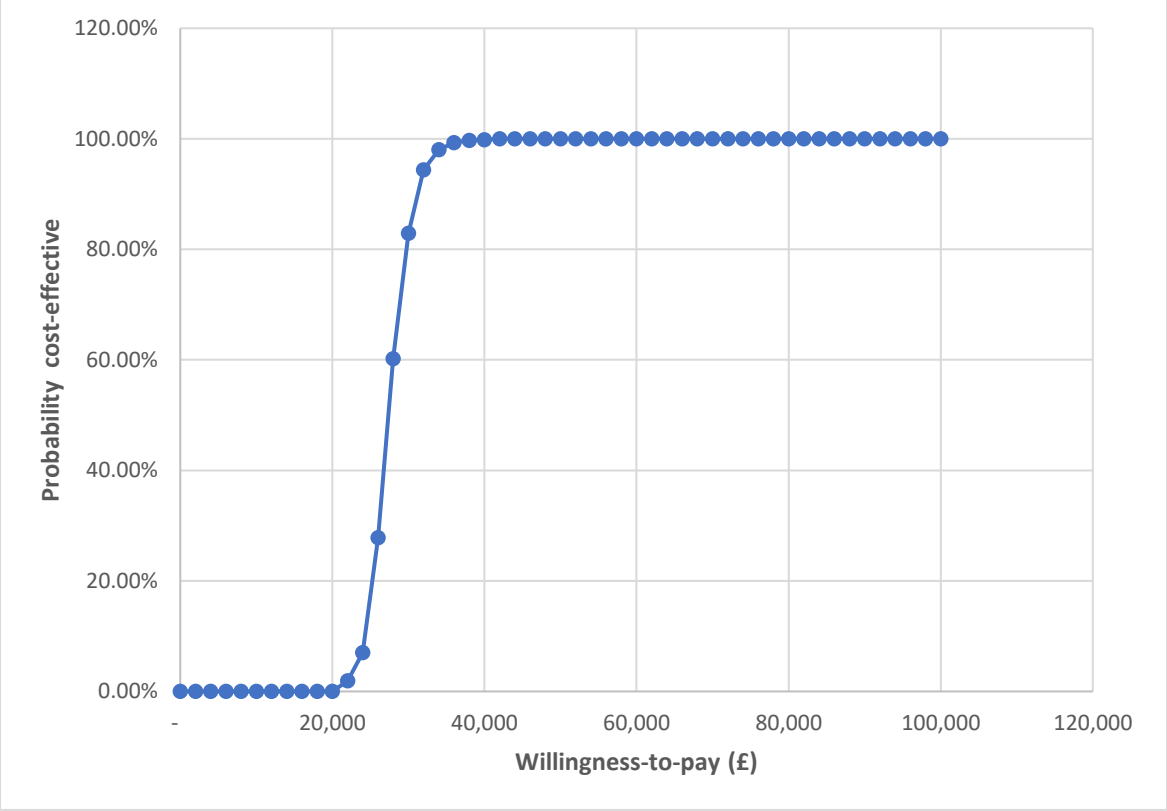
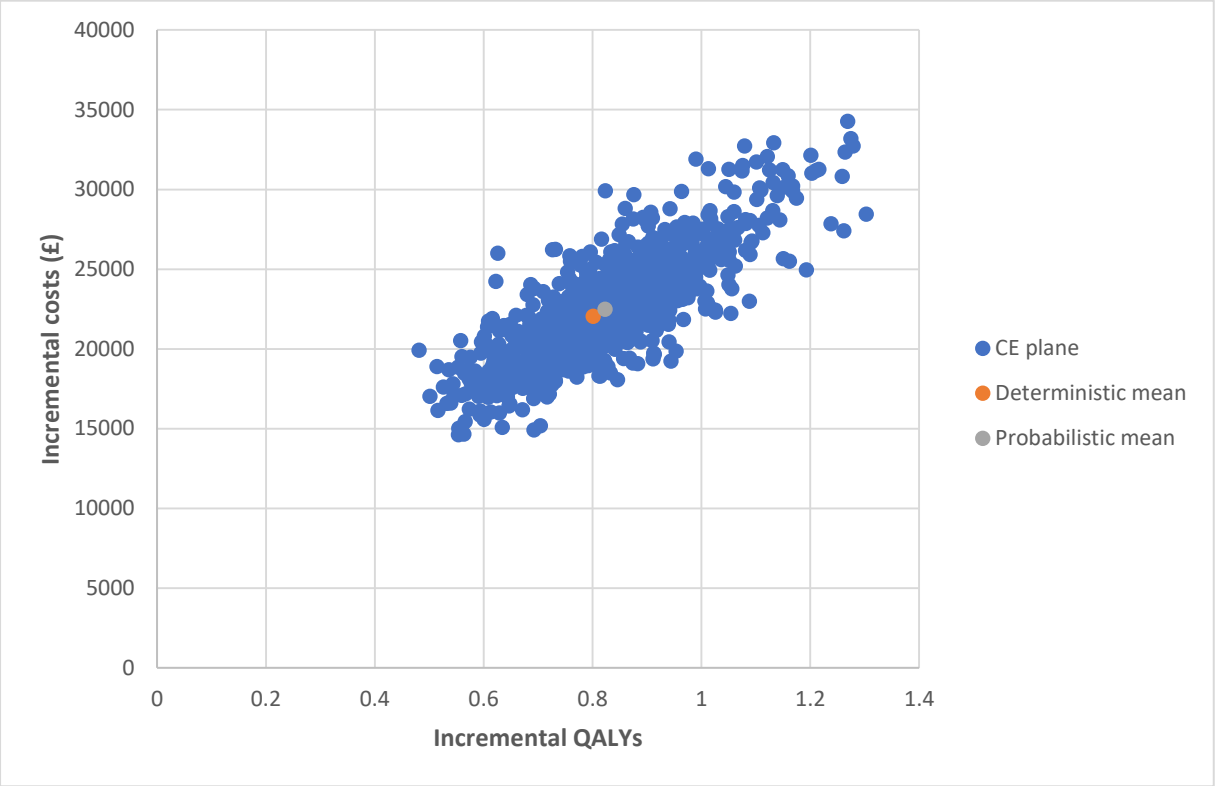


Figure 7. Scatter plot for incremental cost effectiveness results (10,000 iterations)



CE = cost-effectiveness; QALYs = quality-adjusted life years

4.3. Sensitivity analyses

Several scenario analyses were explored in which model assumptions or parameters were altered in line with requests from the committee. The rationale and results of the scenario analyses carried out are presented in Table 16 below.

Table 16. Scenario analyses (deterministic results)

No.	Scenario	Rationale	Incremental costs	Incremental QALYs	ICER (£/QALY)	Difference
	Company Base case	**See above**	[redacted]	[redacted]	**27,510**	-
1	Utility regression scenario model 1	The committee requested further analysis using treatment and response as covariates in the utility regression model (See Section 3.1). *Modelling note: See Cell F19 on the [Utilities] sheet to select the regression*	[redacted]	[redacted]	32,242	+4,732
2	Utility regression scenario model 2		[redacted]	[redacted]	31,107	+3,597
3	Inclusion of the 'UK-like' population, matching on age AND BMI	The committee requested modelling to include an average age of the population at 61 to reflect a more 'UK-like' population as observed in the CPRD-HES database study.	[redacted]	[redacted]	26,687	-823

No.	Scenario	Rationale	Incremental costs	Incremental QALYs	ICER (£/QALY)	Difference
		It is not appropriate to simply change the age in the base case model as this will not properly reflect the expected outcomes in the population of interest. We have modelled the outcomes (including utilities derived from the matched cohort) associated with the matched populations described in Section 1.3. *Modelling note: See Cell F13 on the [Settings] sheet to select the regression*				
4	More rapid loss of response for BSC Non-responders. All patients have lost response within 1 year	According to clinical opinion BSC responders would be likely to lose response within 1 year judged against the efficacy response criteria of WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 at week 24 from baseline	[redacted]	[redacted]	26,241	-1,269
5	Current committee assumptions. 75%, 50%, 25% and 0% maintenance of response in following years	To test the impact of the current committee assumptions on the new base case	[redacted]	[redacted]	28,297	+787
6	Original company assumptions (See Table 8)	To test the impact of the original company estimates on the new base case	[redacted]	[redacted]	27,525	+15
7	Exclusion of the additional non-responder drug costs	To align with the originally submitted base case the additional disease management costs are removed. According to clinical opinion disease management drug costs for non-responders were likely underestimated in the original model so the originally submitted ICER may represent an overestimate.	[redacted]	[redacted]	29,359	+1,849
8	Removal of difference in QoL for non-responders at 2+years	The clinical experts consulted in the SEE said that a residual QoL benefit would be retained in perpetuity for non-responders who had previously responded. The EAG was concerned about this point and so we have tested a return to baseline for all non-responders at 2+years (Cells CD11 and CE11 set to baseline utility on the engine sheets).	[redacted]	[redacted]	29,851	+2,341
9	3+4	Including the 'UK-like population matching on age AND BMI and	[redacted]	[redacted]	25,659	-1,851

No.	Scenario	Rationale	Incremental costs	Incremental QALYs	ICER (£/QALY)	Difference
		inclusion of the expert view of loss of response				
10	3+7	Including the 'UK-like population matching on age AND BMI but without the additional non-responder drug costs	[redacted]	[redacted]	28,494	+984
11	3+4+7	Including the 'UK-like population matching on age AND BMI and the expert view of loss of response but without the additional non-responder drug costs	[redacted]	[redacted]	27,495	-15
12	3+8	Removal of difference in QoL for non-responders at 2+years and the 'UK-like population matching on age AND BMI	[redacted]	[redacted]	28,472	+962
13	3+4+8	Including the 'UK-like population matching on age AND BMI and the expert view of loss of response but with removal of difference in QoL for non-responders at 2+years	[redacted]	[redacted]	27,260	-250

4.4 Discussion of the cost-effectiveness results

The updated company base case includes adjustments to align with the EAG implementation of the SEE, updated costs for non-responders to align with clinical expert opinion and an amendment to the loss of response parameter for BSC responders for clarity and to take clinical opinion into account. The model retains the differential utilities for non-responders at week 24. This is supported by significance testing and further exploration of the regression equations used to calculate utility.

The updated probabilistic base case ICER is £27,327/QALY and the deterministic ICER is £27,510/QALY. This was tested in scenario and sensitivity analysis discussed below.

Using two new regression equations for utility calculation suggested by the committee which included the treatment and response covariates with or without baseline characteristics, increased the deterministic ICER to just above £30,000/QALY. (Scenario analyses 1 and 2). However, we argue that the key drivers of QoL (which are statistically significant in their own right) are not captured in these analyses and the treatment covariate alone is insufficient. We have retained the original regression developed using a forward selection methodology according to guidelines for utility analysis.

To allay the concerns of the committee we have provided evidence that age and weight should not be a concern. For the modelling we have not simply changed the age in the model to 61 years as requested because this would use data from the trials based on a younger cohort with no further adjustment to outcomes. Rather we have derived a 'UK-like' cohort matching the RW evidence we obtained from the CPRD on age and BMI. Implementation of these cohorts in the model reduces the ICER by £823 to £26,687/QALY (scenario 3).

The experts we consulted said that BSC responders would lose response quickly when they returned to the RW and so we have tested a scenario (scenario 4) in which this loss occurs by the end of the first year post trial exit. The deterministic ICER decreases by £1,269. When this was tested in the 'UK-like' population the ICER fell by £1,851 to £25,695/QALY which is the lowest ICER of the scenario analyses. (Scenario 8). The current committee preferred assumptions for response loss and the original company submitted 'effective rates' are examined in scenarios 5 and 6 resulting in marginal impact on the ICER.

We have introduced new costs into the base case to account for the clinical opinion that we received suggesting cost of treatment failure in patients is much higher than we originally modelled. To test the impact of including this extra cost on the ICER we removed it and the ICER rises to £29,359/QALY. (Scenario 7). However, when the extra cost is removed but the scenario is combined with the UK-like population and the expert view of rapid loss of response for BSC responders the ICER is equivalent to the base case at £27,495/QALY (-£15) (Scenario 11).

The clinical experts consulted in the SEE said that a residual QoL benefit ([redacted] % of the benefit gained) would be retained in perpetuity for non-responders who had previously responded. This was based on the observation that some people who are predisposed to good habits might be able to retain some of the adherence and other behaviours that contributed to their response status in the studies. However, the EAG was concerned about the retention of any QoL benefit for any patient in the long run and so we have tested a return to baseline for all non-responders at 2+years (the end of the period informed by the SEE). In this case the ICER increases by £2,341 to £29,851/QALY. (Scenario 8). When tested in the UK-like population this ICER falls to £28,472 (+£962 from base case). (Scenario 12). If the expert view of rapid loss of response is included the ICER falls still further to £27,262 which is a decrease of £250 from base case (scenario 13).

5 Conclusion

PN is a multifactorial disease affecting all aspects of patients' lives and much of this impact is not well captured in the QALY. We heard the patients at the committee meeting eloquently describe the profound effect on social functioning which leads many to become reclusive, shunning social interaction. The stigma associated with physical appearance can be debilitating and the literature describes a significant proportion of PN patients reporting past or present suicide ideation.

In addition to the bearing of PN on patients there is the healthcare system capacity impact of multiple touch points in dermatology and primary care. For example, our CPRD study found more than 20 touch points in primary care alone and the testing and monitoring of patients treated with immunosuppressants is significant in secondary care.

Dupilumab has been shown to impact itch and the signs and symptoms of PN and so is well placed to address many of these wider points which are not necessarily represented in the QALY.

Furthermore, dupilumab is indicated in several other 'Type 2' inflammatory conditions such as AD, asthma and chronic rhinosinusitis with nasal polyps and other related indications may follow. 'Type 2' patients are often comorbid with several of these conditions and so the cross-over benefits not captured in this appraisal could be profound in some cases.

We have provided evidence and clinical expert opinion to allay the concerns of the committee over the generalisability of the clinical trial evidence to the UK population and discussed how there is likely to be significant benefit not captured in the QALY. The ICERs we have estimated are all below £30,000/QALY apart from when the alternative regression equations for the calculation of utility are implemented. However, we believe these do not capture the key determinants of quality of life and that the original regression equation should be used.

The new probabilistic base case is £27,327/QALY (deterministic = £27,510/QALY) and so we hope that the committee is reassured that dupilumab is a good use of NHS resources.

One of the clinicians we spoke to told us that he considers '*Dupilumab to be a game changing drug in dermatology*' and he often tells his patients that after many years without effective treatments '*we can now change your life'*.

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Appendix A. Calculation of the additional BSC drug costs for non-responder patients.

We heard during the clinician interviews we carried out for the purposes of this ACD response that the cost of failure is high for moderate to severe PN patients because they cycle through multiple medications. To reflect this important aspect of RW treatment outside the confines of the trial setting that was missed in the original modelling, we have included an additional cost associated with non-response post 24 weeks for BSC non-responders or dupilumab patients who move to BSC. To calculate this, we used the proportions of patients receiving the range of medicines observed in our CPRD study multiplied by the average cost of representative examples of each class. Clinical expert opinion suggested that the majority of immunosuppressant use would be with methotrexate and so we have included only the methotrexate cost for this class. (Note that we have shown the alternatives in Table 17 below). The expert pointed out that methotrexate use requires considerable resource use for monitoring and testing but this has not been included as healthcare resource use (HCRU) from the CPRD study has already been included in the model.

The full list of drug classes for the moderate to severe cohort from the study along with proportions receiving the medicine at any time observed in the study is shown in Table 17 below. Some of these medicines are already reflected in the economic model so to avoid double counting a subset was chosen for inclusion in the additional cost analysis.

Table 17 Treatments observed in the real-world Sanofi observational study. Moderate to severe PN cohort.

Treatments	**N = 2,498**	**Included (Y/N)**
Topical Calcineurin inhibitors (TCI)	187 (7.5%)	N
Tricyclic antidepressants	532 (21%)	Y
First generation H1 antihistamine	1,607 (64%)	Y
Second generation H1 antihistamine	1,811 (72%)	Y
Gabapentinoids	832 (33%)	Y
Topical corticosteroids (TCS) - Mild potency	2,108 (84%)	N
Topical corticosteroids (TCS) - Moderate/potent/Very Potent	2,136 (86%)	N
Systemic Corticosteroids (oral only)	1,367 (55%)	N
Systemic Corticosteroids (injectable route only)	344 (14%)	Y
Immunosuppressant	367 (15%)	Y

Representative drugs for these classes, doses and costs taken from the BNF are presented overleaf in Table 18. The average model cycle cost is also shown.

Table 18. List of drugs included in BSC for non-responders, dose, cost, and average model cycle cost.

Drug and class		Pack size	Pack size unit	Strength numerator (mg)	Acq. cost per pack (£)	Cost per dose unit (£)	Prescribed dose (mg)	No. doses	Time interval (days)	Total dose (mg) received per model cycle	Cost per model cycle - individual drugs	Average model cycle per drug class
1st gen. antiH1	promethazine	56	tablets	10	31.22	0.05575	10	3	1	2520	140.49	140.49
2nd gen. antiH1	Ketotifen	60	tablets	1	14.56	0.242667	1	1	1	84	20.384	9.525333
	fexofenadine (in combination)	30	tablets	120	1.49	0.000414	120	1	1	10080	4.172	
	montelukast (in combination)	28	tablets	10	1.34	0.004786	10	1	1	840	4.02	
Gabapentinoids	gabapentin	100	capsules	300	3.19	0.000106	300	3	1	75600	8.0388	7.4694
	pregabalin	56	capsules	150	2.3	0.000274	150	2	1	25200	6.9	
Antidepressants	paroxetine	30	capsules	20	1.71	0.00285	20	1	1	1680	4.788	4.54896
	mirtazapine	28	tablets	15	1.04	0.002476	15	1	1	1260	3.12	
	amitriptyline	28	tablets	10	0.75	0.002679	10	1	1	840	2.25	
	nortriptyline	100	tablets	10	2.02	0.00202	10	1	1	840	1.6968	
	duloxetine	28	capsules	60	3.63	0.002161	60	1	1	5040	10.89	
Immunosuppressants	cyclosporin	30	capsules	100	68.28	0.02276	100	1	1	8400	191.184	4.1904*
	methotrexate	100	tablets	2.5	5.82	0.02328	15	1	7	180	4.1904	
	thalidomide	28	capsules	50	298.48	0.2132	50	1	1	4200	895.44	
	azathioprine	56	tablets	50	1.85	0.000661	50	1	1	4200	2.775	
Parent. corticoids	triamcinolone acetonide	5	vial	40	7.45	0.03725	40	1	1	3360	125.16	125.16

*Methotrexate is the assumed immunosuppressant of choice.

The cost per cycle and cost per year was calculated according to the proportion of patients receiving the medicines taken from Table 17 above. This is shown in Table 19 below.

Table 19 Cost per cycle and cost per year for the basket of therapies included in BSC for non-responders, dose, cost, and average model cycle cost.

	Cost per model cycle (£)	Cost weight	Adjusted cost (£)
First generation H1 antihistamine	140.49	0.64	89.91
Second generation H1 antihistamine	9.525333	0.72	6.86
Gabapentinoids	7.4694	0.33	2.46
Antidepressants	4.54896	0.21	0.96
Immunosuppressant	4.1904	0.15	0.63
Systemic Corticosteroids (injectable route only)	125.16	0.14	17.52
Total non-resp. BSC cost per cycle			118.34
Total non-resp. BSC cost per year			514.59

Modelling note 1: These calculations are found on the [Model_mechanics] sheet.

Modelling note 2: To toggle this cost on and off use cells G35 and H35 on the [Other_costs] sheet.

Appendix B. Exploration of age and weight by subgroup.

Table 20. Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24 by age subgroup

	Age									
Baseline age group 1 (years)	**<30 years**		**≥30-45**		**≥45-<55**		**≥55-<65**		**≥65**	
Weekly average WI-NRS improvement ≥ 4 points from baseline and IGA PN-S ≥ 1 point reduction from baseline at Week 24	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**
Number of patients (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed non-responder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value vs. placebo[b]		0.2354		0.0002		<.0001		0.0002		0.0164

Pool of EFC16459 and EFC16460 studies
CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval.
a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator.
b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no) and study indicator (EFC16459 or EFC16460).
c Logistic regression model was used for the interaction test including intervention group, adjusted documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no), study indicator (EFC16459 or EFC16460), plus the subgroup variable and the subgroup-by-intervention in the model.
Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and missing data at Week 24 were considered as non-responders.

RW evidence data on off-label use of dupilumab in PN does not suggest that age or weight are treatment modifiers. A retrospective study of the published literature did not identify age as a potential response predictor, defined as a reduction in the NRS score by >4. [Gael, 2022] Table 21 and Table 22 below summarise case studies in elderly patients ≥65 years and older successfully treated with dupilumab.

Table 21. Case studies in elderly patients ≥65 years and older successfully treated with dupilumab.

Reference	Age	History of atopy	Treatment Failures Before Dupilumab Therapy	Effected Evaluation of Dupilumab Therapy	Adverse events
Beck KM et al. Dupilumab Treatment for Generalized Prurigo Nodularis. JAMA Dermatol. 2019;155(1):118-120.	70s	NA	Corticosteroids, hydroxyzine hydrochloride, doxepin, dronabinol, gabapentin, phototherapy, cryotherapy	Pruritus and skin lesions improved within 8 weeks	No
Giura MT et al. Efficacy of dupilumab in prurigo nodularis in elderly patient. Dermatologic Therapy. 2020; 33:e13201.	85	NA	Topical and systemic corticosteroids	Itch reduced by about 3 points in 1 week and completely disappeared after 6 months, skin improved	No
Kovács B et al Dupilumab for treatment-refractory prurigo nodularis. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2020;18: 618-624.	80	AD	Topical corticosteroids, topical calcineurin inhibitors, antihistamines, antidepressants, gabapentin, cyclosporine, methotrexate, naloxone, UVB irradiation	Pruritus improved within 10 weeks	NA
Liu T et al. Effectiveness of Dupilumab for an Elderly Patient with Prurigo Nodularis Who Was Refractory and Contradicted to Traditional Therapy. J Asthma Allergy. 2021;14:175-178.	85	No	gabapentin, thalidomide, ketotifen, NB-UVB, TCS Note: Mtx/CsA not recommended due to age-related comorbidities	Improvements in itch, prurigo activity score and DLQI within 12 weeks	No

Criado PR et al. Dupilumab as a useful treatment option for prurigo nodularis in an elderly patient with atopic diathesis. Int J Dermatol. 2020; 59: e358-e361.	87	AD, rhinitis	Topical, intralesional, and systemic corticosteroids, mirtazapine, pregabalin, hydroxyzine, methotrexate, cyclosporine	Pruritus improved within 4 weeks. Pruritus and skin lesions disappeared within 16 weeks	No
Wieser JK et al. Resolution of Treatment-Refractory Prurigo Nodularis With Dupilumab: A Case Series. Cureus. 2020;12(6):e8737	66	No	Topical corticosteroids, antihistamines, prednisone, methotrexate	Pruritus improved within 20 weeks, skin lesions improved within 16 weeks	No
Wieser JK et al. Resolution of Treatment-Refractory Prurigo Nodularis With Dupilumab: A Case Series. Cureus. 2020;12(6):e8737	65	No	Thalidomide, intralesional triamcinolone, gabapentin, phototherapy	Pruritus and skin lesions improved with in 4 weeks	No
Wieser JK et al. Resolution of Treatment-Refractory Prurigo Nodularis With Dupilumab: A Case Series. Cureus. 2020;12(6):e8737	65	No	Topical corticosteroids, tacrolimus 0.1% ointment, antihistamines, gabapentin, hydroxyzine	Pruritus and skin lesions improved within 28 weeks	No

Table 22. Summary of case series of ≥10 patients and median age of the included cohort

Reference	**Number of patients**	**Age**	**Previous treatments**
Chiricozzi A et al. Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. J Am Acad Dermatol. 2020;83(1):39-45	27	Mean 52 (23-83)	Systemic corticosteroids, phototherapy, MTX, CSA, azathioprine
Calugareanu A et al. Effectiveness and safety of dupilumab for the treatment of	16	Median 56	TCS, TCI, phototherapy, MTX, CSA, azathioprine, cryotherapy, topical capsaicin, antihistamines, dapsone, systemic retinoids, mycophenolate mofetil, thalidomide,

prurigo nodularis in a French multicenter adult cohort of 16 patients. J Eur Acad Dermatol Venereol. 2020; 34: e74-e76.			anti-IL-17, anti-TNF alfa, nemolizumab or placebo as part of a clinical trial, Ig IV
Ferrucci S et al. Dupilumab and prurigo nodularis-like phenotype in atopic dermatitis: our experience of efficacy. J Dermatolog Treat. 2021;32(4):453-454.	11	19-88	TCS, TCI, corticosteroids, MTX, CSA, antihistamines
Tilotta G et al. Our experience with prurigo nodularis treated with dupilumab. J Eur Acad Dermatol Venereol. 2021; 35: e285-e287.	11	Median 67 (62-78)	Emollients, TCS, antihistamines, CSA, systemic corticosteroids
Wieser JK et al. Resolution of Treatment-Refractory Prurigo Nodularis With Dupilumab: A Case Series. Cureus. 2020;12(6):e8737	19	Median 56 (44-67)	Phototherapy, MTX, triamcinolone acetonide, prednisone, CSA, azathioprine, mycophenolate mofetil

Appendix C. Exploration of weight by subgroup.

Table 23 Proportion of participants with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at Week 24 by weight

	Weight cut off = 60kg		Weight cut off = 70kg		Weight cut off = 80kg		Weight cut off = 90kg	
	BSC	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**	**BSC**	**Dupilumab**
Weight < cut off (kg)								
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value vs. placebo[b]		0.0079		<.0001		<.0001		<.0001
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]		[redacted]
Weight >= cut off								
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Imputed non-responder n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OR, 95% CI vs. placebo[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P-value vs. placebo[b]		<.0001		<.0001		<.0001		0.027
RRD (%), 95% CI vs. placebo[a]		[redacted]		[redacted]		[redacted]		[redacted]
Overall p-value for interaction[c]		0.8913		0.7671		0.8098		0.4428

CMH: Cochran-Mantel Haenszel; WI-NRS: worst-itch numeric rating scale; CI: confidence interval.

a OR: odds ratio; RRD: response rate difference; derived from the Mantel-Haenszel estimator. b CMH test was performed on the association between the responder status and intervention group, adjusted by documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no) and study indicator (EFC16459 or EFC16460). c Logistic regression model was used for the interaction test including intervention group, adjusted documented history of atopy (atopic or non-atopic), stable use of TCS/TCI (yes or no), region, baseline anti-depressant use (yes or no), study indicator (EFC16459 or EFC16460), plus the subgroup variable and the subgroup-by-intervention in the model.

Note: Participants who received the prohibited medications/procedures and/or rescue medications that impacted efficacy before Week 24 were considered as non-responders, and missing data at Week 24 were considered as non-responders

Appendix D. Matching analysis.

Table 24. Demographics and baseline characteristics before and after matching on age (mean=61 years old) and BMI (mean=31 kg/m^2).

	Before matching (ITT, N= 311)			After matching on age and BMI (ESS=143)		
	BSC	**Dupilumab**	**All**	**BSC**	**Dupilumab**	**All**
Age (years)						
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight group (kg) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60 to <90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI group (kg/m^2) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25-<30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PN (year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stable use of TCS/TCI (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline WI-NRS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA PN-S score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline IGA PN-S categorical score(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0 (clear)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Before matching (ITT, N= 311)			After matching on age and BMI (ESS=143)		
	BSC	Dupilumab	All	BSC	Dupilumab	All
1 (almost clear)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 (mild)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 (moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 (severe)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT=Intent-to-treat; ESS=Effective Sample Size

Table 25. Change from baseline in DLQI and WI-NRS at Week 24 before and after matching on age (mean=61 years old) and BMI (mean=31 kg/m^2). (Primary method)

	Before matching (ITT, N= 311)			After matching (ESS = 143)		
	BSC	Dupilumab	All	BSC	Dupilumab	All
Change from baseline in DLQI score at Week 24						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in WI-NRS at Week 24						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26. Change from baseline in DLQI and WI-NRS at Week 24 before and after matching on age (mean=61 years old) and BMI (mean=31 kg/m^2). (As observed method)

	Before matching (ITT, N= 311)			After matching (ESS = 143)		
	BSC	Dupilumab	All	BSC	Dupilumab	All
Change from baseline in DLQI score at Week 24						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in WI-NRS at Week 24						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 27. Responder status at week 24 according to WI-NRS improvement ≥4 and IGA-PN-S reduction ≥ 1 from baseline before and after matching on age (mean=61 years old) and BMI (mean=31 kg/m2). (Primary analysis)

	Before matching (ITT, N= 311)		After matching (ESS = 143)	
	BSC	Dupilumab	BSC	Dupilumab
Responder (%)	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder (%)	[redacted]	[redacted]	[redacted]	[redacted]

Appendix E. Linear regression models

Table 28. Scenario model 1: Linear regression of EQ-5D-5L Single Index Score (UK Crosswalk tariffs, Hernandez 2020) all observed data - Pooled ITT population

Parameter	Class or Unit	Estimate [95% CI]	p-value
Intercept		[redacted]	<.0001
Treatment	Dupi. 300mg qw (ref: Placebo)	[redacted]	0.3175
Response status (WI-NRS improvement >=4 and IGA PN-S improvement >=1)	Responder (ref: Non-responder)	[redacted]	0.0018
Treatment*Response status (WI-NRS improvement >=4 and IGA PN-S improvement >=1)	Dupi. 300mg qw*Responder	[redacted]	0.46

Figure 8 Scenario model 1: Linear regression of EQ-5D-5L Single Index Score (UK Crosswalk tariffs, Hernandez 2020), all observed data, Conditional Residuals - Pooled ITT population

Table 29 Scenario model 2: Linear regression of EQ-5D-5L Single Index Score (UK Crosswalk tariffs, Hernandez 2020), all observed data - Pooled ITT population

Parameter	Class or Unit	Estimate [95% CI]	p-value
Intercept		[redacted]	<.0001
Treatment	Dupi. 300mg qw (ref: Placebo)	[redacted]	0.0571
Age	1 year	[redacted]	0.4655
Gender	Male (ref: Female)	[redacted]	0.0351
EQ-5D-5L single index score (UK Crosswalk tariffs, Hernandez 2020) at baseline	1 point	[redacted]	<.0001
Response status (WI-NRS improvement >=4 and IGA PN-S improvement >=1)	Responder (ref: Non-responder)	[redacted]	0.0013
Treatment*Response status (WI-NRS improvement >=4 and IGA PN-S improvement >=1)	Dupi. 300mg qw*Responder	[redacted]	0.4186

Figure 9 Scenario model 2: Linear regression of EQ-5D-5L Single Index Score (UK Crosswalk tariffs, Hernandez 2020), all observed data - Conditional Residuals - Pooled ITT population

[redacted]

Appendix F. Disaggregated costs and QALYs

Table 30. Probabilistic costs and QALYs

	Dupilumab	Comparator	Incremental
Costs (£) - discounted			
DECISION TREE			
Dupilumab acq.	[redacted]	[redacted]	[redacted]
BSC acq.	[redacted]	[redacted]	[redacted]
Rescue medication acq.	[redacted]	[redacted]	[redacted]
Drug adm.	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Drug acquisition cost			
Responder - dupilumab	[redacted]	[redacted]	[redacted]
Responder - BSC	[redacted]	[redacted]	[redacted]
Responder - rescue medication	[redacted]	[redacted]	[redacted]

Non-responder - BSC	[redacted]	[redacted]	[redacted]
Non-responder - rescue medication	[redacted]	[redacted]	[redacted]
Total Markov drug acq. cost	[redacted]	[redacted]	[redacted]
Drug administration cost			
Drug adm.	[redacted]	[redacted]	[redacted]
Disease management cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov dis. management cost	[redacted]	[redacted]	[redacted]
AE cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov AE cost	[redacted]	[redacted]	[redacted]
Indirect cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov indirect cost	[redacted]	[redacted]	[redacted]
QALYs - discounted.			
DECISION TREE			
QALYs in decision tree	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Responder QALYs	[redacted]	[redacted]	[redacted]
Non-responder QALYs	[redacted]	[redacted]	[redacted]
Total Markov QALYs	[redacted]	[redacted]	[redacted]
Life years - discounted			
DECISION TREE			
Life years in decision tree	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov life years	[redacted]	[redacted]	[redacted]

Table 31. Deterministic costs and QALYs

	Dupilumab	Comparator	Incremental
Costs (£) - discounted			
DECISION TREE			
Dupilumab acq.	[redacted]	[redacted]	[redacted]
BSC acq.	[redacted]	[redacted]	[redacted]
Rescue medication acq.	[redacted]	[redacted]	[redacted]
Drug adm.	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]
Indirect costs	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Drug acquisition cost			

Responder - dupilumab	[redacted]	[redacted]	[redacted]
Responder - BSC	[redacted]	[redacted]	[redacted]
Responder - rescue medication	[redacted]	[redacted]	[redacted]
Non-responder - BSC	[redacted]	[redacted]	[redacted]
Non-responder - rescue medication	[redacted]	[redacted]	[redacted]
Total Markov drug acq. cost	[redacted]	[redacted]	[redacted]
Drug administration cost			
Drug adm.	[redacted]	[redacted]	[redacted]
Disease management cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov dis. management cost	[redacted]	[redacted]	[redacted]
AE cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov AE cost	[redacted]	[redacted]	[redacted]
Indirect cost			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov indirect cost	[redacted]	[redacted]	[redacted]
QALYs - discounted.			
DECISION TREE			
QALYs in decision tree	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Responder QALYs	[redacted]	[redacted]	[redacted]
Non-responder QALYs	[redacted]	[redacted]	[redacted]
Total Markov QALYs	[redacted]	[redacted]	[redacted]
Life years - discounted			
DECISION TREE			
Life years in decision tree	[redacted]	[redacted]	[redacted]
MARKOV MODEL			
Responder	[redacted]	[redacted]	[redacted]
Non-responder	[redacted]	[redacted]	[redacted]
Total Markov life years	[redacted]	[redacted]	[redacted]

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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):	British Association of Dermatologists (the BAD)

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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:	Dr Ser-Ling Chua on behalf of the BAD's Therapy & Guidelines sub-committee, Prof Anthony Bewley, on behalf of the BAD's guideline development group for prurigo nodularis (currently in development)

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	**Has all of the relevant evidence been taken into account?** We acknowledge the original scope of the appraisal had intended to include both topical treatments as well as systemic immunosuppressive treatment, antidepressants, gabapentinoids, etc. Due to the limited evidence available to support systemic treatments for prurigo nodularis (PN), best supportive care (BSC) was defined as a combination of

	emollients, topical corticosteroids and topical calcineurin inhibitors. Evidence for the efficacy of BSC in the management of PN is limited. The comparisons made in the draft guidance were between dupilumab (+ topical therapy) and topical therapy alone for those with prurigo nodularis (PN), however, the clinical trial evidence compared dupilumab plus BSC (with topical corticosteroids and emollients) with placebo plus BSC. There is a significant difference between BSC defined for the purpose of this appraisal and standard of care (SOC) in the NHS. Typically, SOC by NHS dermatologists includes topical treatments in combination with systemic therapy which may be a combination of immunosuppressants, anti-depressants, thalidomide, etc. Despite the fact that there is little to no high quality-evidence on the efficacy of conventional systemic therapy for managing PN, there is considerable real-world, and other evidence into the management of people with PN. However, NHS dermatologists still have to cycle through various treatments due to loss of efficacy, adverse effects and/or the need to find a combination of treatments that will help control PN sufficiently for patients. We are concerned that there is a considerable underestimation of the actual health utilisation cost (or clinical cost) and psychosocial cost associated with the current BSC/SOC management of patients living with PN, especially those with moderate-to-severe disease, in primary, secondary and tertiary care. They include: a. Monitoring required for their systemic therapy, which includes systemic anti-inflammatories (e.g. methotrexate and ciclosporin), systemic steroids, phototherapy, antidepressants, and a range of off-licence treatments such as thalidomide. The efficacy of these medications is variable, but some patients do respond to them. However, they might require more frequent blood tests and other clinical monitoring than patients receiving treatment with dupilumab. b. As their responses to treatment are variable, and it may take a long time to cycle through multiple treatments (that are licensed for other conditions, e.g. atopic dermatitis) in order to come to a treatment regimen that might help control their PN, they have frequent visits to primary, secondary and/or tertiary care until amelioration or (somewhat rarely) remission of their disease is achieved. It is common for people with PN to have disease flares and to request extra appointments. c. Their significant psychological co-morbidities including anxiety, depression and suicidal ideation (Brenaut *et al.* 2019 JEADV) add to their health care costs. Treating these patients in multidisciplinary clinics that include dermatologists, psychiatrists and psychologists are ideal, but are not readily available throughout the UK. d. There is also data from the US that suggests that they have a higher burden of other health issues including cardiovascular, pulmonary and other systemic disease, resulting in high cost of utilisation of healthcare resources (Wongvibulsin *et al.* 2021). e. Their healthcare utilisation costs is greater compared to age- and sex-matched controls with atopic dermatitis and psoriasis (Huang *et al*. 2020). Please see algorithm of management for the treatment of PN in *Psychodermatology in Clinical Practice* (Springer, 2021, eds Bewley et al., pages 185-90). Also, please see Diagnostic and treatment algorithm for chronic **nodular prurigo**. Ständer HF, Elmariah S, Zeidler C, Spellman M, Ständer S. J Am Acad Dermatol. 2020 Feb;82(2):460-468.

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	Finally, the BAD is in the process of publishing national evidence-based guidelines for the management of people with PN. The guideline development group have met and assessed the evidence *prior* to the publication of the RCTs cited in the NICE draft guidance but have indicated that the management of PN is likely to change rapidly and considerably with the licensing of biologics for managing people with PN.
2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We are concerned that the appraisal committee has not weighted sufficiently the clinical and psychosocial costs of managing people with PN in primary, secondary and tertiary care with BSC/SOC (please see section '1' above). Although the committee recognised that BSC in isolation is not likely to be the only treatment available for patients with PN and that SOC is commonly applied, we believe that the trials of dupilumab vs BSC are generalisable in the NHS as a background of basic care for patients with PN. The systemic medicines used as part of NHS SOC are unlicensed, and hence, they would not usually be included in clinical trials. The true cost of current NHS SOC for PN which includes systemic therapy, phototherapy and topical therapy, is far greater than that for BSC (topical therapy only). In addition, we have the below concerns: 1. The assumption in the EAG report around the age and weight of patients in the cited RCTs of dupilumab in people with PN may not be accurate, and that age and weight being treatment effect modifiers is speculative in this scenario. 2. From Section 3.9 *"It considered only using the probability of sustained response and thought that this resulted in a fairly rapid loss of response in the best supportive care arm"*. The EAG may have underestimated the attrition rate of loss of responsiveness for patients treated with BSC. In our experience the loss of responsiveness is rapid and likely to be 100% by the end of 12 months. 3. From Section 3.10 "*In the company's base case, dupilumab non-responders had a higher initial utility value when starting the Markov model than best supportive care non-responders"* and "*The committee agreed with the EAG, that in the absence of statistically significant and clinically meaningful differences in utility values between treatment arms in the trials, a pooled utility value for non-responders should be used in the model"*. The EAG has graded the QoL assessments as being different between non-responders to dupilumab and patients who were treated with BSC. The committee assumed that the non-responders to dupilumab have a significantly greater benefit in QoL compared with the BSC-treated patients. This does not correspond to clinical experience. 4. Both the company and the EAG have omitted the use of phototherapy in its modelling of the management of patients with PN. This is a SOC management tool for many patients with PN. As the committee will recognise from previous appraisals, it is HCP-intensive.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?**

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	It was mentioned in the committee papers that in Morgan *et al.* 2022 study, "PN has a prevalence of 3.27 per 10,000 in England and is considered a rare disease; 26.8% of the patients with PN have moderate-to-severe inadequately controlled disease", its debilitating effect on patients lead to "decreased productivity and substantial healthcare resource use" (*Nodular Prurigo* in *Psychodermatology in Clinical Practice* (Springer, 2021, eds Bewley *et al.*, pages 185-90) and that current topical *plus* systemic therapy do not sufficiently help a substantial group of these patients, there is an important unmet need in a significant proportion of the PN population that can be addressed by treatment with dupilumab. Currently, there is no effective (or in fact, licensed) treatment for PN. Patients affected by PN are at higher risk of developing anxiety, depression and suicidal ideation. We are concerned that the appraisal committee has not weighted sufficiently the clinical and psychosocial costs of managing people with PN in primary, secondary and tertiary care with BSC/SOC agents identified in the above algorithms. We are also concerned that the current treatment of people with PN is currently variably effective, and that newer treatments which have been reported as significantly superior to BSC are made available to people with moderate-to-severe PN.
4	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?** Research and expert consensus indicate that there is a higher prevalence of PN amongst those of African-American (in the US) and that there is a possibility that different ethnic groups may have a different propensity to develop PN, with erythema being more challenging to identify in people with different skin tones, leading to difficulty in diagnosis, evaluation of disease severity and treatment outcomes, etc. We are concerned that the recommendations as they stand may not fully appreciate the burden of PN disease (and the difficulties in assessing and managing the erythema and hyperpigmentation) in patients with darker skin tones. Non-Atopic Chronic Nodular Prurigo (Prurigo Nodularis): A Systematic Review of Best-Evidenced Treatment Options. Frølunde AS, Wiis MAK, Ben Abdallah H, Elsgaard S, Danielsen AK, Deleuran M, Vestergaard C. Dermatology. 2022;238(5):950-960.

Insert extra rows as needed

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- 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 draft guidance document, please submit these separately.

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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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Andrew Pink

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.
Example 1	We are concerned that this recommendation may imply that ……..
1	Relating to BSC and generalisability: a. Whilst used, anti-histamines are rarely of benefit in nodular prurigo (not a histamine driven itch) and anti-depressants are of limited value, with no robust evidence.

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	b. Whilst treatments such as phototherapy, prednisolone and ciclosporin are used they are time-limited (eg. ciclosporin 6-12 months, phototherapy 4-6 months, prednisolone 1-2 months) due to toxicity, practicality, durability etc. I fully agree MTX can be a durable treatment in those that respond and tolerate it.
2	Relating to response criteria: A composite response of clear/ almost clear (IGA 0/1) with a reduction in pruritis score of >4 is a very high bar in this disease at 24 weeks. I (and likely patients) would regard an IGA of 2 (mild disease) and an itch response of >4 to also represent a very meaningful improvement, ie "response". Indeed, a meaningful improvement in itch and only a 1 point change in IGA would be deemed a "response" by many given that itch is the key factor highlighted by NP patients as the most burdensome in multiple international studies.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
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External Assessment Group (EAG) Critique of the Company's Response to the Appraisal Consultation Document (ACD)

Dupilumab for treating moderate to severe prurigo nodularis [ID4054]

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Date completed 22/09/2023

Note on the text

All commercial-in-confidence (CIC) data have been [redacted].

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1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE ACD

The EAG provides a summary of the key themes covered in the company's response to the Appraisal Consultation Document (ACD). The following key themes are covered:

- Generalisability of the dupilumab PRIME clinical trials to the UK setting;
- Maintenance of response for best supportive care (BSC) responders;
- Calculation of the utility data and evolution over time;
- Updated costs for BSC in the model.

Under these key themes the company have provided a response to the following points:

Point 1: Generalisability of BSC in the PRIME trials to NHS clinical practice;

Point 2: Impact of age and weight on trial outcomes and efficacy;

Point 3: Maintenance of response for best supportive care (BSC) responders;

Point 4: Exploration of regression parameters for the calculation of utility values;

Point 5: Non-responder utility at 24 weeks and waning of quality of life over time; and

Point 6: Additional drug costs for non-responders in the model.

The company have updated their base case assumptions and provided the corresponding cost-effectiveness results, with additional scenario analyses.

Within the short timelines available to the EAG (a few working days), the EAG provides a critical evaluation of the company's key response points to the ACD and the company's new base case and scenario analyses following ACD. The EAG critique should be read in conjunction with the company's ACD response document and the EAG report.

2 CRITIQUE OF THE COMPANY'S POINTS IN RESPONSE TO THE ACD

2.1 Point 1: Generalisability of BSC in the PRIME trials to NHS clinical practice

The company surveyed five clinical experts about the issue of the absence of several best supportive care (BSC) therapies in the PRIME trials. The company stated that the unanimous answer was that the outcomes for BSC would have been the same regardless of treatment used because currently available options are largely ineffective. The clinicians also thought that variation in the use of BSC therapies across the NHS was likely, especially with regard to immunosuppressants. The clinicians nevertheless recognised that the trial BSC did not include all the possible treatments.

The company did not provide methods or full results for its clinician survey, so the EAG could not appraise the validity of this exercise. Although the EAG acknowledges that there is likely to be variation across the NHS in the type and uptake of BSC therapies used, this does not allay the serious concerns about the impact (on trial effect estimates) of prohibiting and restricting the use of numerous treatments which are available in the NHS. The EAG also makes the following observations on the statement that "currently available BSC options are largely ineffective": Why was it deemed necessary to prohibit and restrict the use of so many BSC treatments (in the PRIME trials) if they are largely ineffective? Why are BSC treatments used in the NHS if they are largely ineffective?

2.2 Point 2: Impact of age and weight on trial outcomes and efficacy

The company carried out post-hoc analyses on the pooled PRIME dataset to examine the impact of age on the proportion of patients with WI-NRS improvement (reduction) ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at week 24. This analysis differed from the original subgroup analysis in terms of outcome (originally WI-NRS improvement ≥ 4 points) and age cut-offs (originally <65, ≥65 to <75, ≥75). The company noted that the proportion of responders in dupilumab treated patients aged above 60 was numerically similar to those below 60 years old.

The company stated that although in the ACD the committee did not agree that results for dupilumab in atopic dermatitis (AD) could be transposed to prurigo nodularis (PN), in contrast, the company's experts all agreed that the outcomes from the AD studies (and their RW clinical experience treating AD) could be used as a proxy for PN.

The company also carried out a further analysis of the PRIME trial data - a "*sensitivity analysis, matching on age and BMI observed in the CPRD RW study to generate a 'UK-like' patient population*". A descriptive analysis of responder status at week 24 was reported to compare the matched population with the ITT pooled population. The company concluded that this analysis suggests that dupilumab was at least as effective in achieving response status relative to BSC in the 'UK-like' population as in the ITT pooled trial population.

The EAG had concerns that [redacted] This was important because [redacted] of patients in the PRIME trials weighed ≥90kg and the proportion of NHS patients weighing ≥90kg was thought likely to be higher than [redacted]. Age was of interest only with respect to its relationship to weight, given that the mean age in the PRIME trials was thought to be about [redacted] than would be expected in the current NHS population.

The company's new analyses do not reduce the EAG's concerns. The company has attempted to address the issue of a significant subgroup effect by re-categorising and re-analysing the same dataset. These new post-hoc analyses have less validity than the original, pre-specified analysis. Both the new age subgroup analysis and the matched, weighted analysis were performed using a post-hoc outcome: WI-NRS improvement ≥ 4 points and IGA PN-S ≥ 1 point reduction from baseline at week 24. Presentation of results for either the primary outcome (WI-NRS improvement ≥ 4 points) or the pre-specified composite outcome (WI-NRS improvement ≥ 4 points and an IGA PN-S 0 or 1 score at week 24) would have been a more valid approach. Even if such analyses had been done, it is unlikely that they would allay concerns about weight being an effect modifier, as they are more indirect in their focus.

2.3 Point 3: Maintenance of response for best supportive care (BSC) responders

The company's original model included both an all-cause annual discontinuation rate ([redacted]) and a probability of loss of sustained response for BSC responders. This resulted in the number of BSC responders rapidly falling to zero (incurring lower utility and higher resource use and costs associated with non-response to treatment). The committee concluded that the EAG's preference for only including loss of sustained response was preferable, i.e., the all-cause annual discontinuation rate for BSC is set to 0%. The company's new base case analysis accepts the committee's preferred assumption to include only one parameter for loss of response for BSC responders.

The rate of loss of response for BSC was agreed by the committee as a linear loss of 25% of patients per year, resulting in complete loss of response by the end of year 5, i.e., 25% of the benefit would be lost by the end of year 2, 50% by end of year 3, 75% by end of year 4, and 100% by the end of year 5. This was based on the assumptions used in the company's original model, which were based on the same assumptions used in TA534 for AD.

Following the ACD, the company asked five clinicians if this rate of response loss was reasonable. The company states that all the experts were very firm in their belief that it was too slow and by the end of [redacted] (or even earlier) all BSC patients would have dropped below the efficacy response criterion cut-off. The company states that one expert explained that "this is because the trial has very intensive management for BSC including monitoring of adherence. After patients leave the trial setting, they will 'ease off' their treatment quickly and return to old habits." As a consequence, the company have revised their original assumptions such that their new base case now includes a loss of [redacted] of patients responding by the end of year 2 (approximating the company's original assumption with both an all-cause annual discontinuation rate of [redacted] and a maintenance loss of 25% of patients by the end of year 2) and a loss of [redacted] of the benefit by the end of year 3, [redacted] by the end of year 4, and [redacted] by the end of year 5.

The EAG would like to highlight the following key points in relation to the company's revised assumptions for maintenance of response on BSC:

- If the main purpose of the response waning is to account for the high response rates seen in the placebo arm of the PRIME trials (due to improved adherence to BSC treatment that is unlikely to be sustainable for a prolonged period of time outside a clinical trial setting), then any benefit from improved adherence would be expected to be applied equally to both arms of the clinical trials (dupilumab plus BSC and BSC alone) which should not affect how the treatments perform relative to one another. Note that the company have also adjusted down the utility values for patients who become non-responders (having previously responded to treatment at week 24) at three time points (6 months, 1 year and ≥2 years based on the results of the structured expert elicitation exercise) to reflect the exit from the protocol-driven environment of the PRIME2 and PRIME trials and the return to real-world clinical practice. This means that both a response waning effect (affecting the movement of patients from the 'Response' to 'No response' states in the model) and a waning of health-related quality of life for non-responders to treatment is included in the model to account for lower adherence to BSC in clinical practice.
- The committee's preference for a linear loss of 25% of patients per year, resulting in complete loss of response by the end of year 5 came from the company's original model (not the EAG) based on the assumptions used in TA534 for AD. The EAG notes that in TA534 the estimates of 25% (year 2), 50% (year 3), 75% (year 4) and 100% (year 5) were used to adjust down the utility value applied over time such that by the end of year 5, everyone in the BSC arm returned to the baseline utility for the remainder of their time in the model. In contrast, in the company's model for PN, it is the proportion of responders that is adjusted downwards over time, incurring lower utility values (based on time since discontinuation due to loss of response and higher resource use and costs associated with non-response). The appraisal committee for TA534 concluded that there was uncertainty surrounding the assumptions on loss of utility benefit for BSC in AD.

2.4 Point 4: Exploration of regression parameters for the calculation of utility values

The company's original model used regression analysis with EQ-5D-5L responses (mapped to EQ-5D-3L) as the dependent variable with several covariates, including baseline age, gender, baseline EQ-5D-5L, baseline DLQI total score, DLQI total score at visits (12- and 24-week timepoints), WI-NRS score at visits, treatment arm, response status (WI-NRS improvement ≥4 AND IGA-PN-S reduction ≥ 1 at week 24) and an interaction term for treatment and response status. A stepwise approach (using forward selection) was used to determine the final model based on examining the statistical significance of the covariates and how well the regression predictions approximated the

baseline and observed 24-week values for each treatment arm. The final model showed that the difference in EQ-5D utility score by treatment arm was captured by the DLQI and WI-NRS follow-up scores (see Table 9 of company response to the ACD), while the treatment and response status covariates were not statistically significant and excluded from the final model. The EAG considers the general regression-based approach and methods used by the company to be reasonable, in light of the correlation between clinical measures of disease burden and health-related quality of life outcomes in PN.

The company demonstrates that the difference in the resulting utility values from the regression model for dupilumab plus BSC non-responders ([redacted]) and BSC non-responders ([redacted]) at week 24 is statistically significant (see Table 11 of company response to ACD). However, the EAG notes that the company have not demonstrated that the difference in the resulting utility values predicted for dupilumab plus BSC responders ([redacted]) and BSC responders ([redacted]) at week 24 is statistically significant. In particular, the EAG notes that only a small difference in utility between treatment arms is predicted in responders to treatment ([redacted]), while a much larger difference between treatment arms is predicted in those who do not respond to either treatment by week 24 ([redacted]).

The company tested the committee suggestion of modelling only the treatment and response covariates in the regression analysis (see Scenario model 1 and Scenario model 2 in Table 9 of company response to ACD). In these regression models, the treatment covariate is not statistically significant. The difference in the resulting utility values from these models for dupilumab plus BSC non-responders and BSC non-responders is not statistically significant (see Table 12 of company response to ACD). For Scenario model 1, the resulting utility value for BSC responders is higher than dupilumab plus BSC responders. The EAG believes that this model is less suitable for decision making than the company's original regression model.

2.5 Point 5: Non-responder utility at 24 weeks and waning of quality of life over time

Non-responder utility at week 24

The company maintains the position that the different utility values for dupilumab non-responders ([redacted]) and BSC non-responders ([redacted]) at week 24 based on the original regression equation should be used in the model. The committee agreed with the EAG, that in the absence of statistically significant and clinically meaningful differences in utility values between treatment arms in the trials, a pooled utility value for non-responders should be used in the model. The company disagrees with this assumption for several reasons, outlined on page 17 of company response to the ACD. One of the reasons is that the pooled estimate for non-responders at week 24 ([redacted]) would represent an improvement in quality of life for BSC patients on return to real-world clinical practice after exiting the trial setting, where experts strongly advocate a reduction outside the protocol-driven environment

of the trials. EAG Scenario 8 in the EAG report addresses this concern by presenting the cost-effectiveness results using the week 24 utility value for BSC non-responders ([redacted]) for all non-responders in the model, which is still higher than the baseline utility value of [redacted]. The company states that the clinical experts who they consulted agreed that there would be a difference in outcomes for non-responder versus responder patients and that benefit beyond the study for dupilumab patients would persist versus BSC for a period of time. The EAG notes that the disagreement is not about the difference in utility between non-responder versus responder patients, but rather the differential utility between treatment arms for non-responders, all of whom do not reach the efficacy response criterion at week 24 (WI-NRS improvement ≥4 AND IGA-PN-S reduction ≥ 1) and receive BSC treatment only. The company makes the argument that the response criterion in the model is binary, whereas in reality response to the disease is a continuum and therefore treatment with dupilumab could result in partial response to the disease. Again, the EAG does not disagree that there could be partial response with dupilumab, but the way the model is structured by the company does not permit consideration of partial response to treatment. The model is structured such that once patients become non-responders to dupilumab plus BSC they receive treatment with BSC only. Therefore, it would seem implausible to apply two separate utility values for non-responders by treatment arm when all non-responders receive BSC only in the model [redacted]. One potential way around the model structure to account for partial response is to assume that a higher utility value for dupilumab plus BSC non-responders persists for a short period (through utility waning assumptions for dupilumab plus BSC non-responders); however, estimating what proportion of dupilumab plus BSC non-responders are actually partial responders, and for how long, creates additional uncertainty for model outcomes. Importantly, the EAG does not consider it appropriate to apply a higher utility value for dupilumab plus BSC non-responders versus BSC non-responders for the duration of the modelled time horizon as done in the company's original model. The company's revised base case in response to the ACD maintains the different utility values for non-responders by treatment arm but the duration of the difference is changed to reflect alternative assumptions for the waning of quality of life over time (see below).

Waning of quality of life over time

The company conducted a structured expert elicitation (SEE) to elicit how health-related quality of life might evolve in the short and longer term after patients leave the protocol-driven environment of the PRIME trials and return to real-world clinical practice (see details in the company submission and EAG report). The EAG noted a number of concerns with the SEE and the implementation of the data in the model (see Section 4.2.8.4 of the EAG report). The EAG suggested an alternative implementation that removed the inconsistencies in the way that the results of the SEE were

implemented in the company's original model (EAG Scenario 11 in the EAG report). In response to the ACD, the company agrees that the implementation in EAG Scenario 11 is a more appropriate use of the SEE data than that implemented in the company's original base case. Consequently, the company have revised their base case following the ACD to include the utility values used in EAG Scenario 11 for non-responders to treatment over time, according to time since becoming a non-responder and according to previous response status (i.e., whether a non-responder having previously responded at week 24, or non-responder at week 24). The resulting utility values for non-responders used in the company's revised base case following ACD are presented in Table 13 of company response to ACD (note that the utility values for responders are not reported in this table because these are held constant over time until treatment discontinuation).

The company believes that in patients who achieved the high level of response required by the efficacy response criterion (WI-NRS improvement ≥4 AND IGA-PN-S reduction ≥ 1 at week 24) there would likely be a residual long-term benefit derived from learned behaviours during the trial after they withdraw from treatment. This is quantified in the SEE (and shown in Table 13 of company response to ACD) at a final [redacted] of quality of life gained, and applied over the remainder of the patient's life. This means that a [redacted] gain in utility is applied, even after 5+ years loss of treatment response. The EAG notes that in NHS clinical practice, a prerequisite for treatment with dupilumab would not be a requirement for patients to be enrolled in a clinical trial in order to develop the learned behaviours during the trial (protocol driven clinical trial setting) and apply those after treatment withdrawal.

[redacted]

The company have presented alternative scenarios where this [redacted] gain in utility is removed and all non-responders return to baseline utility at 2+ years. The EAG believes that these scenarios are more appropriate than the company's revised base case following ACD. The committee strongly agreed that for people who initially had a response and later became non-responders, final utility should be the same in each arm and noted that the small difference in utilities that still remained should be removed.

2.6 Point 6: Additional drug costs for non-responders in the model

The company have revised their original model following the ACD to include additional drug costs for non-responders on BSC. In the company's original model, drug acquisition costs for BSC were the same for all patients (including those on dupilumab plus BSC arm), irrespective of response status.

Only disease management costs and costs of rescue therapies were different depending on response status, such that non-responders incurred higher disease management and rescue therapy costs than responders. The company have revised their model following the ACD to include additional drug costs for non-responders on the basis that clinical opinion carried out for the purpose of the ACD response indicated that the cost of failure is high in moderate to severe PN because non-responders cycle through multiple medications. The details of the additional costs are presented in Appendix A of the company response to ACD. The additional cost amounts to £439 per year for non-responders.

The EAG is unable to validate all the additional costs within the short timelines for this response and because the resource use data are provided by Sanofi's medical department. The EAG believes that limited justification has been provided for including these additional costs, which include first and second generation H1 antihistamines, gabapentinoids, immunosuppressants (including cyclosporin and methotrexate) and systemic corticosteroids by injectable route. The EAG is concerned that on one hand the company is very confident in making its case that the PRIME trials are generalisable to the NHS in terms of the medications used for BSC and resulting outcomes, while on the other hand the drug costs for BSC and the concomitant rescue therapies from the trials are underestimated in the model. Importantly, the addition of drug costs for BSC based on response status (responders versus non-responders) means that the response rates used in the model for BSC (see point 3 above) becomes an even more important parameter for driving the results of the cost-effectiveness analysis.

3 CRITIQUE OF THE COMPANY'S NEW BASE-CASE AND SCENARIO ANALYSES FOLLOWING ACD

The company presents new base-case results and scenario analyses following the ACD. The company's revised base case assumptions differ from the committee's preferred assumptions in the following ways (see Table 14 of company response to ACD):

1. Response waning - Maintenance of response for BSC responders is set to [redacted] in year 2, [redacted] in year 3, [redacted] in year 4, and [redacted] by the end of year 5 (see point 3 above). In contrast, the committee preferred assumption was 75% in year 2, 50% in year 3, 25% in year 4, and 0% by the end of year 5.
2. Utility values for non-responders at week 24 – The company maintains different utility values for dupilumab plus BSC non-responders ([redacted]) and BSC non-responders ([redacted]) at week 24 (see point 4 above). In contrast, the committee preferred assumption was week 24 pooled utility value ([redacted]) for non-responders.

3. Utility waning – The company uses SEE data to match EAG Scenario 11 in the EAG report (see point 4 above). In contrast, the committee preferred assumption was to hold the utility value of responders constant for the first six months after treatment discontinuation and then rebound to baseline utility (EAG base case).
4. Additional cost for non-responders on BSC – The company includes additional drug costs for non-responders (see point 5 above). These were not included in the company's original model or discussed at the first appraisal committee meeting.

The company have presented cost-effectiveness results for their new base-case in Table 15 of the company response to ACD, while additional scenario analyses are presented in Table 16.

3.1 Critique of the company's base case results

The EAG validated the company's revised base case results and model implementation. The EAG identified an error in the implementation of the utility waning assumptions based on the SEE data: In the model workbook, the utility value for BSC non-responders at week 24 was reduced by 20% from [redacted] to [redacted] (cell CB8 in worksheet BSC Calcs). With this error corrected, the company's deterministic base case ICER increases from £27,510 to £28,179.

Table 1 summarises the results of the company's revised base case following ACD with the EAG correction.

Table 1 Results of EAG-corrected company revised base case following ACD (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,179
BSC	[redacted]	[redacted]			

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

In order to understand the key drivers of the difference in the cost-effectiveness results between the committee's preferred assumptions (resulting deterministic ICER = £35,381) and the company's revised base case (deterministic ICER = £28,179), the EAG has examined the individual effect and cumulative effect of the alternative assumptions for (1) response waning; (2) utility values for non-responders at week 24; (3) utility waning; and (4) additional cost for non-responders on BSC.

The individual effect of each of the company's alternative assumptions on the committee preferred base case is shown in Table 2, while the cumulative effect is shown in Table 3. The alternative assumptions for utility waning have the largest impact on the ICER (reducing it by approximately £4,000). This is due to the [redacted] of quality of life gained for dupilumab plus BSC non-responders that is

applied over the remainder of the patient's life, even after 5+ years loss of treatment response, whereas the committee preferred assumption is based on the EAG base case with the utility value held constant for the first six months after treatment discontinuation and then non-responders rebound to baseline utility. The company have explored alternative assumptions for the duration of quality of life gain after treatment discontinuation in their scenario analyses.

Table 2: Individual effect of the company's revised changes to the committee's preferred assumptions

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Committee preferred assumptions	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£35,381
		BSC	[redacted]	[redacted]			
1	Response waning	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£34,276
		BSC	[redacted]	[redacted]			
2	Utility values for non-responders at week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£34,814
		BSC	[redacted]	[redacted]			
3	Utility waning	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£31,417
		BSC	[redacted]	[redacted]			
4	Additional cost for non-responders on BSC	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£33,227
		BSC	[redacted]	[redacted]			

Table 3: Cumulative effect of the company's revised changes to the committee's preferred assumptions

Scenario #	Name	Option	Costs	QALYs	Inc. Costs	Inc. QALYs	ICER, /QALY
	Committee preferred assumptions	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£35,381
		BSC	[redacted]	[redacted]			
1	Response waning	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£34,276
		BSC	[redacted]	[redacted]			
1+2	Utility values for non-responders at week 24	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£33,741
		BSC	[redacted]	[redacted]			
1+2+3	Utility waning	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£30,074
		BSC	[redacted]	[redacted]			
1+2+3+4 (company revised base case)	Additional cost for non-responders on BSC	Dupi	[redacted]	[redacted]	[redacted]	[redacted]	£28,179
		BSC	[redacted]	[redacted]			

3.2 Critique of the company's scenario analyses

Table 16 of the company's response to the ACD presents the results of the company's scenario analyses. Of the scenarios presented, the EAG believes that scenario 8 may be most relevant to committee discussions. In this scenario, the company removes the [redacted] of quality of life gained for dupilumab plus BSC non-responders that is applied over the remainder of the patient's life after treatment discontinuation and explores a return to baseline for all non-responders after two years (i.e., after treatment discontinuation, the utility benefit from treatment is maintained for a period of two years whilst receiving BSC only and, after two years, patients return to baseline utility). However, as noted above, the EAG identified an error in the model, which also affects the results of this scenario.

Table 4 presents the results of the company's scenario 8 with the EAG correction.

Table 4 Results of EAG-corrected scenario 8 in company response to ACD (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	£30,641
BSC	[redacted]	[redacted]			

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

Table 5 presents the results of the committee's preferred assumptions with the utility waning for non-responders changed to that of scenario 8 (i.e., the utility benefit from treatment is maintained for a period of two years after treatment discontinuation rather than six months in the committee's preferred assumptions).

Table 5 Results of committee preferred assumptions with utility benefit from treatment maintained for a period of two years after treatment discontinuation rather than six months

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Dupilumab plus BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,348
BSC	[redacted]	[redacted]			

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.