Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

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NICE National Institute for Health and Care Excellence

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

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Consultation on the draft guidance document – deadline for comments 5pm on 17 April 2025. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	This response is on behalf of Galderma, the submitting Company.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose.
Name of commentator person completing form:	Simon Keady

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	**Section 3.8 Discontinuation probability** **Summary** The Committee's preferred assumption to use a clinical trial-based discontinuation rate only for nemolizumab instead of the class-based discontinuation rate used for all other comparators

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	contradicts both current UK clinical expert opinion and the precedent set by NICE in TA986. The Committee's preferred discontinuation assumption cannot be considered a fair or reasonable interpretation of the evidence as there is a lack of consistency in the selection of the conditional discontinuation rate sources, which results in a lower conditional discontinuation rate assumed for the comparators versus both their clinical trial data and their real world evidence. In this response, we provided the additional information requested by the Committee in the draft guidance and have highlighted several areas of concern associated with both the Committee's preferred discontinuation probabilities and the use of trial-based discontinuation rates. The areas of concern include: 1. The consistency and clinical plausibility of Committee's preferred discontinuation assumption 2. NICE technology appraisal precedent and UK clinical expert opinion 3. Additonal discontinuation data from the ARCADIA clinical trials 4. Heterogeneity in trial designs 5. Variation in comparator discontinuation rates In addition, we have provided an appendix (Appendix A) with the complete discontinuation data in the ARCADIA 1, 2 and CYCLO clinical trials. The breakdown of discontinuation in the ARCADIA trials clearly indicates that nemolizumab treatment is not driving the higher discontinuation rate versus the value provided by clinical experts in TA986. Discontinuation of nemolizumab is significantly lower in the ARCADIA CYCLO trial, is either lower than or comparable to the placebo arms in all trials, and is primarily driven by participant's request, not lack of efficacy or adverse events. In the ACM, both patient and clinical experts highlighted that atopic dermatitis (AD) has a substantial impact on patient's sleep, quality of life, social lives and mental health, and they emphasised that there remains a significant unmet need for new and effective treatment options. Currently available Janus kinase (JAK) inhibitors are associated with safety concerns at the class level and currently available biologic treatments are associated with increased risk of ocular surface disease and conjunctivitis, which drives discontinuation in clinical practice. In the ARCADIA trials, nemolizumab demonstrated both efficacy and a favourable safety profile in patients with moderate-to-severe AD. Furthermore, in the Appraisal Committee Document (ACD) it states that nemolizumab is cost-effective versus the biologic comparators based on the Company, EAG and TA986 base-case discontinuation assumption. Therefore, we hope our response below addresses any remaining uncertainty and will result in the Committee aligning with the previously accepted class-based discontinuation rates in TA986 for all treatments and allowing patient's access to nemolizumab to address the unmet need for increased therapeutic diversity in moderate-to-severe AD. **1. The consistency and clinical plausibility of Committee's preferred discontinuation assumption** The Committee's preferred discontinuation assumption (based on the discontinuation probabilities from the EAG's scenario analysis 2) adopts an inconsistent approach to the selection of the conditional discontinuation rate sources for nemolizumab and the comparator products, which significantly biases the cost-effectiveness results against nemolizumab. The Committee's preferred approach assumes, based on the observed discontinuation rate from responders in the

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	ARCADIA 1 and 2 clinical trials, that nemolizumab has a conditional discontinuation rate at week 52 of [redacted]. In contrast to the approach used for nemolizumab, the Committee's preferred approach assumes that the comparators have a class-based discontinuation rate based on UK clinical expert opinion provided in TA986 and not based on their respective clinical trial data. Clinical experts consulted in TA986 stated that despite differences in discontinuation rates observed in the clinical trials, they would expect discontinuation for treatments within the same class to be similar. Therefore, the clinical experts recommended a discontinuation rate of 3.9% for biologics and 10% for JAK inhibitors, which the TA986 Committee considered suitable for decision making in May 2024.[1] In these circumstances, the use of a different and less favourable approach for nemolizumab despite conflicting expert opinion, is unfair and unreasonable. In the draft guidance, the Committee stated that in the absence of further information as to why discontinuation probabilities for nemolizumab in ARCADIA 1 and 2 were different to the consensus-based discontinuation rate assumed for other biological medicines, the Committee opted to use the value from the trials. However, Galderma want to clarify that, as indicated above, trial values have not been used for the biologic or JAK inhibitor comparators, which is driving the significant difference in discontinuation. The Committee have chosen to compare clinical trial data for nemolizumab versus clinical expert opinion for the comparators. Therefore, the Committee's preferred discontinuation probabilities cannot be considered a fair or reasonable interpretation of the evidence as there is a lack of consistency in the selection of the conditional discontinuation rate sources, with different criteria being applied for nemolizumab versus the comparators. Furthermore, the Committee has not clearly explained or justified why a different approach was chosen for nemolizumab versus the comparator products. Galderma would also like to clarify that the published clinical trial and real-world discontinuation rates for the biologic comparators are higher than the rate of 3.9% assumed by the Committee. In TA986, conditional discontinuation for lebrikizumab at week 52 was reported to be 6.9%; however, despite this higher trial-based discontinuation rate, both UK clinical experts consulted as part of TA986 and the TA986 Committee agreed that the assumption for a class-based biologic discontinuation rate of 3.9% was appropriate for decision making.[1] In addition to the higher discontinuation rate reported for lebrikizumab, higher discontinuation rates for the other biologics have also been reported and are presented in detail in a later section of this response. As the Committee's preferred discontinuation assumption uses a lower discontinuation rate for the biologic comparators compared to rates observed in both clinical trials and clinical practice, the use of clinical trial data to inform only the nemolizumab discontinuation rates biases the cost-effectiveness estimates against nemolizumab. Clinical data from the ARCADIA trials[2-4] and the long-term extension (LTE) study[5] have demonstrated that nemolizumab has durable efficacy and a favourable safety profile. In contrast to nemolizumab, JAK inhibitors are associated with increased risk of infections, venous thromboembolism, cardiovascular events and safety concerns at a class level, while other biologics are associated with increased risk of conjunctivitis and ocular surface disease complications. A patient expert in the ACM supported this, stating that current biologic treatments can have troubling side effects (such as eye problems) that could be avoided with nemolizumab. Therefore, it would not be clinically plausible that the discontinuation rate for nemolizumab is [redacted] as implied by the Committee's preferred discontinuation probabilities for nemolizumab. The clinical implausibility of the Committee's preferred discontinuation probabilities is supported by the views of UK clinical experts and statements by the NICE Committee as set out in section 3.8 of the draft guidance. When asked, one UK clinical expert at the ACM could not think of a reason why discontinuation for nemolizumab should be different to that of other biological medicines,

particularly because nemolizumab appeared to be better tolerated. This feedback is consistent with clinical experts consulted by both Galderma and the EAG during the submission. Similarly, the NICE Committee noted that given nemolizumab was generally better tolerated with lower rates of adverse events, it was unclear why discontinuation should be different for nemolizumab compared with other biological medicines.

2. NICE technology appraisal precedent and UK clinical expert opinion

As discussed in the ACM, the Company and EAG base-case assumption of class-based discontinuation rates is identical to the approach used in the recent NICE submission for lebrikizumab in moderate-to-severe AD, TA986. In TA986, the submitting Company stated that the use of treatment-specific discontinuation rates was unsuitable because of heterogeneity in the comparator trial populations and the use of different measurements of response that determined treatment discontinuation. As outlined above, in alignment with the submitting Company, clinical experts consulted in TA986 and the Committee concluded that class-based discontinuation rates of 3.9% for biologics and 10% for JAK inhibitors based on clinical expert opinion should be used in the base-case, rather than treatment-specific clinical trial data.[1]

The assumption of class-based discontinuation rates in both the Company and EAG base-case has been validated by multiple clinical experts consulted by different stakeholders. Clinical experts consulted by Galderma, the EAG and during both the TA986 and ID6221 ACMs all agreed that discontinuation for treatments within the same class would be comparable.

Therefore, the Committee's preferred assumption to apply trial-based conditional discontinuation rates to only nemolizumab or any additional scenario analysis without class-based treatment discontinuation for all treatments would contradict both UK clinical expert opinion and NICE Committee precedent set in TA986 and should not be considered a fair or reasonable interpretation of the evidence.

3. Additonal discontinuation data from the ARCADIA clinical trials

As requested by the Committee, in Appendix A we have presented the discontinuation data from the ARCADIA 1, 2 and CYCLO trials with the primary reason for discontinuation included. Galderma considers that this evidence has not been adequately taken into account by the Committee, and that, when considered in detail, it supports a conclusion that nemolizumab treatment is not driving the higher discontinuation rate seen in the ARCADIA trials versus the rate determined by clinical expert opinion in TA986.

At week 16 in the ARCADIA 1, 2 and CYCLO trials, discontinuation in the nemolizumab arms were comparable to the placebo arms. In the ARCADIA 1 and 2 trials, the proportion of participants who discontinued treatment at week 16 in the nemolizumab arms ([redacted]% and [redacted]%, respectively) were comparable to the placebo arms ([redacted]% and [redacted]%, respectively).[2,3] In the ARCADIA CYCLO trial, which included a second-line ciclosporin experienced population, the proportion of participants who discontinued nemolizumab treatment at week 16 was also comparable to the placebo arm ([redacted]% and [redacted]%, respectively) and significantly lower than the proportion who discontinued treatment at the same timepoint in the ARCADIA 1 and 2 trials.[4] The higher rate of discontinuation at week 16 in the ARCADIA 1 and 2 trials can be explained in part by the increased number of patients discontinuing due to participant's request. In the ARCADIA 1 and 2 trials, participant's request was the most common reason for discontinuation in the nemolizumab arms at week 16 ([redacted]% and [redacted]% of discontinuations, respectively) and not lack of efficacy or adverse events.[2,3] In

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	contrast, in the ARCADIA CYCLO trial only one patient in the nemolizumab arm discontinued treatment at week 16 due to participant request.[4] In the maintenance period of the ARCADIA 1 and 2 trials, those who discontinued treatment by week 48 in the nemolizumab every 4 weeks (Q4W) to every 8 weeks (Q8W) arms ([redacted]% and [redacted]%, respectively) were lower than the nemolizumab Q4W to placebo arms ([redacted]% and [redacted]%, respectively) and lower or comparable to the placebo arms ([redacted]% and [redacted]%, respectively). In line with the week 16 data, in the nemolizumab Q4W to Q8W maintenance arms of the ARCADIA 1 and 2 trials, the most common reason for discontinuation was participant's request ([redacted]% and [redacted]% respectively) and not lack of efficacy or adverse events.[2,3] As discontinuation in the nemolizumab arms of the ARCADIA trials is consistently comparable to or lower than the placebo arms, this supports the conclusion that nemolizumab treatment specifically is not driving the discontinuation rates observed in the ARCADIA trials. Furthermore, discontinuation in the ARCADIA CYCLO trial, which includes a second-line ciclosporin experienced population aligned with the decision problem, is significantly lower than discontinuation in the mixed first- and second-line ARCADIA 1 and 2 trials. Due to the 16-week treatment period in ARCADIA CYCLO, the conditional discontinuation rate at week 52 of [redacted]% preferred by the Committee was based only on the ARCADIA 1 and 2 trials. Therefore, it can be considered that the Committee's conditional discontinuation rate selected for nemolizumab based on the ARCADIA 1 and 2 trials is a significantly high estimate versus anticipated clinical practice for nemolizumab. In clinical trials, Eczema Area and Severity Index (EASI)-75 and treatment-related adverse events are robust measures that can be compared between trials, as demonstrated by the comparable EASI-75 response at week 16 and safety profiles across the ARCADIA 1, 2 and CYCLO trials. However, the measurement of discontinuation in clinical trials can be influenced by multiple factors unrelated to the treatment, which results in a high level of uncertainty associated with direct comparison of trial-based discontinuation rates between treatments. The conclusion that nemolizumab treatment is not driving the higher discontinuation rate versus the value based on clinical expert opinion from TA986 is further supported by closer examination of the breakdown of reasons for patient discontinuation. The primary reason for discontinuation in the ARCADIA 1 and 2 clinical trials at both week 16 and during the maintenance period was participant's request and not lack of efficacy or adverse events. Documented reasons for participant's request included site's early closure, patients moving town due to the COVID-19 pandemic and patient's lack of time or transportation. Therefore, a major contributor to overall nemolizumab discontinuation rate is due ultimately to factors unrelated to nemolizumab treatment. This is further supported by the EASI score at the point of discontinuation in patients who discontinued due to participant's request. Figure 1 shows that in the ARCADIA 1 and 2 maintenance periods, with one exception, all patients in the nemolizumab Q4W to Q8W arms who discontinued due to participant's request had no worsening of EASI score prior to discontinuation. The one exception presented in Figure 1 reported no adverse events and discontinued due to 'subject's schedule'. Overall, this evidence supports that the nemolizumab discontinuation rate of [redacted]% assumed by the Committee is driven by patients discontinuing due to participant's request, which is related to trial protocol and healthcare setting rather than issues with nemolizumab treatment itself. **[redacted]Figure 1. EASI score in patients who discontinued from the nemolizumab Q4W to Q8W arms due to participants request during the maintenance period of the ARCADIA 1 and 2 trials** Abbreviations: BL, baseline; EASI, Eczema Area and Severity Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

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	The higher rates of discontinuation in the ARCADIA 1 and 2 trials may also be partly explained by the COVID-19 pandemic. The ARCADIA 1 and 2 trials commenced in June 2019 and finished in August and September 2022. In contrast, the ARCADIA CYCLO trial commenced in November 2021 and finished in April 2023. The significantly lower rate of discontinuation (especially as a result of participants request) in the ARCADIA CYCLO trial, which was not conducted during the peak of the COVID-19 pandemic, supports that the COVID-19 pandemic may have impacted the higher rate of discontinuation in the ARCADIA 1 and 2 trials. The impact of the COVID-19 pandemic on the ARCADIA 1 and 2 trials is corroborated by the increased rate of COVID-19 vaccination and infection between the initial treatment period and maintenance phase. In the ARCADIA 1 and 2 trials, in the nemolizumab Q4W to Q8W arms, the rate of COVID-19 vaccination in the maintenance period ([redacted]% and [redacted]%, respectively) increased significantly from the initial treatment period ([redacted]% and [redacted]%, respectively). Similarly, in the nemolizumab Q4W to Q8W arms of the ARCADIA 1 and 2 trials, the rate of COVID-19 infections in the maintenance period ([redacted]% and [redacted]%, respectively) also increased from the initial treatment period ([redacted]% and [redacted]%, respectively).[2,3] The COVID-19 pandemic has been demonstrated to have a significant impact on both patient recruitment into clinical trials and patients' willingness to come to their trial site.[6] A cross-sectional study on the conduct of oncology trials reported that 54.8% of respondents reported an observed decrease in patient's willingness to come to their site.[6] **4. Heterogeneity in trial designs** In line with the submitting Company rationale in TA986, Galderma does not consider it appropriate to use treatment-specific discontinuation rates. There is significant heterogeneity in the trial designs and in the exact measures of conditional discontinuation used in the previous NICE AD technology appraisals that make direct comparison of the discontinuation rates inappropriate. The source of heterogeneity in trial designs includes the trial population, patient randomisation and use of concomitant therapy: • Firstly, there are a number of differences in the populations included in the different clinical trials. In TA814 and TA986, the conditional discontinuation rate for dupilumab and lebrikizumab were based on a mixed first- and second-line population in CHRONOS and ADhere, respectively, whereas the conditional discontinuation rate for upadacitinib was based on the second-line only subgroup of the AD UP study. Furthermore, CHRONOS included an adult only population, whereas AD UP and ADhere included a mixed adult and adolescent population.[1,7,8] • Secondly, there are differences in trial design and how patients are randomised to treatment. In the ECZTRA 1 and 2 and ARCADIA 1 and 2 trials, patients who were randomised to treatment in the initial treatment period and achieved clinical response at week 16 were re-randomised, whereas in the CHRONOS trial all subjects continue treatment to week 52 as assigned at baseline, regardless of response status at week 16.[2,3,7,8] In addition, unlike the majority of conditional discontinuation rates, which are based on a single clinical trial, the conditional discontinuation rate for lebrikizumab presented in TA986 is based on patients that transition from the 16-week ADhere trial to the LTE study, ADjoin.[1] • Finally, in TA814, the conditional discontinuation rate for tralokinumab was based on the ECZTRA 2 monotherapy trial, whereas the conditional discontinuation rates for comparators were based on combination therapy trials.[7] Furthermore, between

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combination trials, there are observed differences in both the potency and frequency of topical corticosteroid and topical calcineurin inhibitor treatment.

These points outline just a few examples of the heterogeneity in trial design between the comparators and serve to demonstrate why direct comparison of clinical trial values would be associated with significant uncertainty and the requirement of multiple assumptions. The impact that heterogeneity in trial design has on discontinuation rates is highly uncertain, hence why UK clinical experts and the TA986 Committee considered class-based discontinuation rates for all treatments appropriate for decision making. In addition to heterogeneity in trial design, conditional discontinuation rates in the previous NICE AD technology appraisals are not available for all comparators. In TA814, conditional discontinuation rates for abrocitinib and baricitinib were not available and were assumed to be equal to upadacitinib. Furthermore, conditional discontinuation rates for a number of comparators are redacted and are not publicly available. Overall, this results in an additional level of uncertainty and lack of transparency with the use of treatment-specific discontinuation rates.[7]

The measure of response used to calculate conditional discontinuation also impacts the discontinuation rate. Conditional discontinuation for nemolizumab in the Q4W to Q8W arm of the ARCADIA 1 and 2 trials was [redacted] based on EASI-75 and [redacted] based on the composite endpoint EASI-50 + Dermatology Life Quality Index (DLQI) > 4. Based on the lack of consistency and/or lack of transparency in relation to the measure of response used to calculate comparator conditional discontinuation rates, any direct comparison of trial-based discontinuation rates would be associated with significant uncertainty and would not be appropriate. Furthermore, the impact of measure of response on the conditional discontinuation rate adds additional uncertainty to the Committee's preferred discontinuation probabilities, as it is unclear what measure of response the UK clinical expert opinion assumption of 3.9% for biologics is based on.

In the ACD, the Committee noted that the different mechanism of action of nemolizumab versus the other biologics could result in the difference in discontinuation. However, a UK clinical expert consulted by Galderma following the ACM confirmed that in clinical practice discontinuation is driven by lack of efficacy or adverse events, and not by mechanism of action. In the ARCADIA 1 and 2 maintenance periods, nemolizumab has demonstrated a favourable safety profile and maintained EASI-75 response up to week 48. In the pooled ARCADIA 1 and 2 maintenance periods, [redacted]% of patients in the nemolizumab Q4W to Q8W arms maintained EASI-75 at week 48 (Figure 2).[9] Similarly, maintenance of EASI-75 for tralokinumab every 2 weeks (Q2W) at week 52 was reported to be 60% and 56% in ECZTRA 1 and ECZTRA 2 respectively,[10] and maintenance of EASI-75 for lebrikizumab Q4W at week 52 was reported to be 81.7% in the pooled ADvocate 1 and ADvocate 2 trials.[11] As previously discussed, EASI-75 and treatment-related adverse events are robust measures; however, the measurement of discontinuation in clinical trials can be influenced by multiple non-treatment related factors. Therefore, given nemolizumab has demonstrated maintained efficacy and a favourable safety profile, the most clinically plausible justification for any significant difference in discontinuation between the biologics is non-treatment related factors and heterogeneity in trial design, rather than differences in mechanism of action as suggested by the Committee.

[redacted]Figure 2. Proportion of patients with EASI-75 during pooled ARCADIA 1 and 2 maintenance periods

Abbreviations: EASI, Eczema Area and Severity Index; Q4W, every four weeks, Q8W, every 8 weeks, TCI, topical calcineurin inhibitors; TCS, topical corticosteroid.
Source: Galderma data on file ARCADIA 1 and 2 pooled analysis[9]

Galderma would also like to clarify that the comparator biologics do not have identical mechanisms of action, and despite observed differences in efficacy the Committee have still considered it appropriate to apply a class-based discontinuation rate of 3.9% for these treatments.

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Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor IL-4Rα/IL-13Rα.[12] In contrast, tralokinumab only binds IL-13 and inhibits its interaction with the IL-4Rα/IL-13Rα1 complex and does not block IL-4 signalling.[13] Finally, lebrikizumab binds to IL-13 with high affinity and a slow off-rate, selectively inhibiting IL-13 signalling through the IL-4Rα/IL-13Rα1 heterodimer complex.[14]

5. Variation in comparator discontinuation rates

Based on the significant heterogeneity in comparator trial design, precedent set in TA986 and UK clinical expert opinion, Galderma does not consider it appropriate to conduct an NMA for discontinuation at week 16. However, we have sourced the discontinuation at week 16 for the comparator biologics, which are all between the discontinuation at week 16 for nemolizumab in the ARCADIA CYCLO trial ([redacted]%)[4] and the ARCADIA 1 and 2 trials ([redacted]% and [redacted]%, respectively):[2,3]

- Discontinuation for dupilumab Q2W at week 16 in the CHRONOS trial was reported to be 6.6%.[15]
- Discontinuation for lebrikizumab Q2W at week 16 was reported to be 7.1%, 7.8% and 7.6% in the ADvocate 1, ADvocate 2 and ADhere trials, respectively.[16,17]
- Discontinuation for tralokinumab Q2W at week 16 in the ECZTRA 1, ECZTRA 2 and ECZTRA 3 trials was reported to be 8.5%, 5.6% and 6.7%, respectively.[10,18]

This data supports that discontinuation at week 16 for nemolizumab is, overall, comparable to the biologic comparators. Therefore, it would not be clinically plausible that conditional discontinuation for nemolizumab at week 52 is [redacted] higher than the biologic comparators, as implied by the Committee's preferred discontinuation probabilities.

In addition to the week 16 discontinuation rates, we have provided a number of additional published discontinuation rates for the biologic comparators. The impact of trial design on treatment discontinuation is clearly supported by the published biologic discontinuation rates, which demonstrate significant variation both versus the Committee's preferred assumption of 3.9% and versus individual publications for the same biologic treatments.

A significant number of discontinuation rates for dupilumab have been published which range from 5.1% to 23.8%. In the CHRONOS trial, the number of non-completers in the 52-week treatment period among EASI-75 responders at week 16 was reported to be 5.1%.[7] However, higher rates for those who discontinued by week 52 among those who completed treatment at week 16 have been reported in CHRONOS (13.13%)[15] and SOLO CONTINUE (8.28%).[19] In addition, retrospective studies of dupilumab in AD reported the discontinuation in clinical practice to be 15.5% at a median of 20 weeks[20] and 19.6% at a mean of 29.9 weeks.[21] Furthermore, a long-term cohort study demonstrated that 23.8% of patients discontinued dupilumab after a median 54 weeks, mainly due to adverse events and/or ineffectiveness.[22]

There is also significant variation in the discontinuation rates for lebrikizumab and tralokinumab. The discontinuation rate for lebrikizumab Q4W between week 16 and week 52 in ADhere going to ADjoin conditional on achieving EASI 75 at week 16 was reported to be 6.9%.[1] In addition, in the maintenance period of ADvocate 1 and ADvocate 2, discontinuation of lebrikizumab Q4W by week 52 among those who responded at week 16 was reported to be 7.9% and 5.5%, respectively.[11] For tralokinumab, in the pooled analysis of the ECZTRA 1 and ECZTRA 2 trials, discontinuation of tralokinumab Q2W by week 52 was reported to be 7.55% based on those who completed week 16.[10] In the ECZTRA 7 trial, discontinuation of tralokinumab by week 26 was reported to be 9.4%.[23] In line with dupilumab, cohort studies for tralokinumab in AD have demonstrated increased

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	discontinuation rates in clinical practice versus the clinical trials with discontinuation being reported to be 27.4% due to adverse events and/or ineffectiveness after 28 weeks[24] and even 41% after an average treatment duration of 14 weeks.[25] In addition to the lack of consistency in trial design for biologic treatments, the variation in published discontinuation rates can be explained in part by the increasing number of alternate treatments for patients with moderate-to-severe AD that have become available over time. For example, the dupilumab CHRONOS study enrolled patients between October 2014 and July 2015.[15] Therefore, patients taking part in this trial would not have access to the diverse range of treatments currently available for patients with moderate-to-severe AD, which may have resulted in a lower discontinuation rate versus current clinical practice. This possible interpretation was supported by a UK clinical expert in the ACM who stated that the different probability may be explained by the increased number of alternative treatment options currently available for this condition compared with when biological medicines were first recommended. Therefore, given the significant change in AD treatment landscape over time, direct comparison of discontinuation rates from trials conducted several years apart would be associated with significant uncertainty and may underestimate discontinuation for treatments that were earlier to market. The published discontinuation data clearly support the uncertainty in direct comparison of clinical trial discontinuation rates between biologics and highlight that rather than being strictly corelated to specific treatment received, multiple non-treatment related factors can significantly impact upon treatment discontinuation. This further emphasises how the Committee's preferred assumption to apply a conservative conditional discontinuation of 3.9% to the biologic comparators but not nemolizumab is not a fair or reasonable interpretation of the evidence and significantly biases the cost-effectiveness estimates against nemolizumab. Therefore, based on the significant variation in trial designs and published discontinuation rates for the biologic treatments, and in light of the additional evidence provided, the company would like to request that the Committee reconsider the use of class-based discontinuation rates for all treatments as the most appropriate approach for decision-making. **Conclusion** In conclusion, the Committee's decision to apply a lower conditional discontinuation rate for the comparators versus their respective clinical trial data and real-world evidence but not to adopt a consistent approach for nemolizumab biases the cost-effectiveness estimates against nemolizumab and does not constitute a fair or reasonable interpretation of the available evidence. Discontinuation in clinical trials is impacted by multiple factors unrelated to treatment such as trial design, the COVID-19 pandemic, current AD treatment landscape, trial protocol and healthcare setting. This is demonstrated by the lower discontinuation rate for nemolizumab in the ARCADIA CYCLO trial and the significant impact of participants' requests to discontinue treatment on the ARCADIA 1 and 2 trials. Therefore, any direct comparison of clinical trial-based discontinuation rates would be associated with significant uncertainty and would require multiple assumptions. As nemolizumab has demonstrated both durable efficacy and a favourable safety profile, which are key factors impacting discontinuation or continuation of therapy in clinical practice, Galderma hope that the additional evidence provided has addressed any remaining uncertainty and will result in the Committee aligning with UK clinical expert opinion and the previously accepted class-based discontinuation rates in TA986 for all treatments.
2	**Section 3.9 Utility values**

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	The health state utility values in the Company and EAG base-case economic model are based on clinical trial data for nemolizumab in moderate-to-severe AD from the ARCADIA 1, 2 and CYCLO trials and LTE study and have been further validated by a UK clinical expert as generalisable to UK clinical practice.[26] The approach to cap the utility for responders at general population levels results in the utility values in the economic model no longer reflecting the difference in utility between responders and non-responders observed in the clinical trial data. Furthermore, the approach to cap the utility values for responders at the general population level results in the removal of the increase in utility for responders over time in the economic model. UK clinical experts validated the assumption that the utility for responders would increase over time, as although itch relief is observed shortly after treatment initiation, it can take more time (approximately one year) for skin lesions to fully heal.[26] Therefore, the application of the utility cap would contradict both UK clinical expert opinion and clinical trial data. Galderma consider that the utility cap for responders should be removed, to ensure the difference in the health state utility values reflect the clinical trial data and UK clinical expert opinion. If a utility cap is applied, then an equal utility decrement should be applied to all health states to ensure that the utility difference between responders and non-responders is accurately captured and the utility for responders increases over time.
3	**Economic model shared by the EAG** Galderma would like to clarify that the economic model shared by the EAG prior to the ACM has hard coded odd ratios for all comparators in the Parameter Sampling sheet. Consequences of hard coding the odds ratios for the comparators include that the odds ratios are not included in the probability sensitivity analysis, do not change when the population is updated (e.g., from adults to adolescents) and do not change when the measure of response is amended. Therefore, if the Committee request any additional analysis from the EAG following the second ACM, this incorrect implementation in the model must be amended.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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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.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 17 April 2025. Please submit via NICE Docs.

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

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

References:

1. National Institute of Health and Care Excellence. Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [TA986]. 2024. Available at: https://www.nice.org.uk/guidance/ta986 [Accessed 15/08/2024].
2. Galderma Data on File. ARCADIA 1 Clinical Study Report. 2023.
3. Galderma Data on File. ARCADIA 2 Clinical Study Report. 2023.
4. Galderma Data on File. ARCADIA-CYCLO Clinical Study Report. 2023.
5. Galderma Data on File. ARCADIA LTE Interim Study Report (Week 56). Data on file. 2024.
6. Sathian B, Asim M, Banerjee I, et al. Impact of COVID-19 on clinical trials and clinical research: A systematic review. Nepal J Epidemiol. 2020;10(3):878-87.
7. National Institute of Health and Care Excellence. Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis [TA814]. 2022. Available at: https://www.nice.org.uk/guidance/ta814 [Accessed 20/02/2023].
8. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis. Technology appraisal guidance [TA534]. 2018. Available at: [Accessed 12/12/23].
9. Galderma Data on File. ARCADIA 1 and 2 Pooled Maintenance Analysis. 2023.
10. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2021;184(3):437-49.
11. Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. British Journal of Dermatology. 2023;188(6):740-8.
12. Electronic Medicines Compendium. Dupilumab - Summary of product characteristics. 2025. Available at: https://www.medicines.org.uk/emc/product/8553/smpc/print [Accessed 15/04/2025].
13. Electronic Medicines Compendium. Tralokinumab - Summary of product characteristics. 2025. Available at: https://www.medicines.org.uk/emc/product/12725/smpc/print [Accessed 15/04/25].
14. Electronic Medicines Compendium. Lebrikizumab - Summary of product characteristics. 2025. Available at: https://www.medicines.org.uk/emc/product/15367/smpc/print [Accessed 15/04/25].
15. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD

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

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CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-303.
16. Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. New England Journal of Medicine. 2023;388(12):1080-91.
17. Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA Dermatology. 2023;159(2):182-91.
18. Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021;184(3):450-63.
19. Worm M, Simpson EL, Thaçi D, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(2):131-43.
20. Marniquet ME, Seneschal J, Darrigade AS, et al. Reasons for discontinuation of dupilumab in adult atopic dermatitis in clinical practice. British Journal of Dermatology. 2022;186(4):733-5.
21. Kang D-H, Kwon S-H, Lew B-L. 52501 4-year long-term drug survival of dupilumab analyzed by treatment period and predictive factors of discontinuation in moderate to severe atopic dermatitis patients: A real-world retrospective study. Journal of the American Academy of Dermatology. 2024;91(3):AB100.
22. Boesjes CM, Kamphuis E, de Graaf M, et al. Long-Term Effectiveness and Reasons for Discontinuation of Dupilumab in Patients With Atopic Dermatitis. JAMA Dermatol. 2024;160(10):1044-55.
23. Gutermuth J, Pink AE, Worm M, et al. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7)*. British Journal of Dermatology. 2022;186(3):440-52.
24. Dekkers C, Zuithoff N, Bakker D, et al. Tralokinumab Treatment in Adult Atopic Dermatitis Patients: 28-Week Evaluation of Clinical Effectiveness, Safety, Serum Proteins and Total IgE Levels. Allergy. 2024.
25. Schlösser AR, Shareef M, Olydam J, et al. Tralokinumab treatment for patients with moderate-to-severe atopic dermatitis in daily practice. Clin Exp Dermatol. 2023;48(5):510-7.
26. Galderma Data on File. UK clinical expert interview report. 2024.

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Single Technology Appraisal

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

Draft guidance consultation form Appendix A: Discontinuation in ARCADIA trials

April 2025

File name	Version	Contains confidential information	Date
[ID6221] Appendix A 2024.04.17 [REDACTED]	1	Yes	17th April 2025

Discontinuation at week 16 in ARCADIA 1, ARCADIA 2 and ARCADIA CYCLO

Discontinuation during the initial treatment period (up to week 16) in the ARCADIA 1, 2 and CYCLO clinical trials are presented in Table 1, including the primary reason for discontinuation to treatment.

Table 1. Treatment discontinuation at week 16 in ARCADIA 1, ARCADIA 2 and ARCADIA CYCLO

	ARCADIA 1		ARCADIA 2		ARCADIA CYCLO	
	Initial treatment period (to Week 16)		Initial treatment period (to Week 16)		Treatment period (to Week 16)	
	ITT population		ITT population		ITT population	
	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W	Nemolizumab 30 mg Q4W	Placebo Q4W
Total, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomised, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]‡	[redacted]‡
Discontinued treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]§	[redacted]§
Primary reason for discontinuation of treatment, n (%)						
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician/principle investigator decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Participants in ARCADIA 1 and 2 placebo group are not part of ITT population. Placebo group in maintenance period is for all placebo-treated participants who were randomised.
‡Percentages were based on the number of participants screened.
§Percentages were based on the number of randomised participants

Abbreviations: AE, adverse event; ITT, intention to treat; LTE, long term extension; n, number; NA, not applicable, Q4W, every 4 weeks; Q8W, every 8 weeks
Source: Galderma data on file ARCADIA 1, 2 and CYCLO CSR[1-3]

Discontinuation during the maintenance period in ARCADIA 1 and ARCADIA 2

Discontinuation during the maintenance period (week 16 to week 48) in the ARCADIA 1 and 2 are presented in Table 2, including the primary reason for discontinuation to treatment.

Table 2. Treatment discontinuation during maintenance period in ARCADIA 1 and ARCADIA 2

	ARCADIA 1					ARCADIA 2				
	ITT population				Re-assigned to Placebo**	ITT population				Re-assigned to Placebo**
	Nemo 30 mg Q4W to Q4W	Nemo 30 mg Q4W to Q8W	Nemo 30 mg Q4W to Placebo	Total*		Nemo 30 mg Q4W to Q4W	Nemo 30 mg Q4W to Q8W	Nemo 30 mg Q4W to Placebo	Total*	
	N=90	N=91	N=91	N=272	N'=100	N=79	N=78	N=78	N=235	N'=85
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Re-randomised/re-assigned	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Re-randomised/re-assigned but not treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed treatment maintenance period treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued treatment maintenance period treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Primary reason for discontinuation of treatment										
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject's request	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					
Physician/principal investigator decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed/exited the study after maintenance period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from the study during maintenance period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note. Percentages were based on the number of subjects in each treatment group.

* Total is for all subjects who were re-randomised to the Maintenance Period from Nemolizumab 30mg group in the Initial Period.

** Subjects in Placebo group are not part of ITT population. Placebo group in Maintenance Period is for all placebo-treated subjects who were randomised and responded to Placebo during Initial Period and continued to receive Placebo during Maintenance Period.

Abbreviations: ITT, intent-to-treat; N, number of subjects in the treatment group; N', number of subjects who responded to placebo and continued to receive placebo in Maintenance Period; n, number of subjects with available data; Nemo, nemolizumab; Q4W, every 4 weeks; Q8W, every 8 weeks
Source: Galderma data on file ARCADIA 1, 2 CSR[1,2]

References:

1. Galderma Data on File. ARCADIA 1 Clinical Study Report. 2023.
2. Galderma Data on File. ARCADIA 2 Clinical Study Report. 2023.
3. Galderma Data on File. ARCADIA-CYCLO Clinical Study Report. 2023.

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 17 April 2025. Please submit via NICE Docs.

	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):	Eczema Outreach Support

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Eczema Outreach Support has received no funds form Galderma in the last 12 months. We were granted £3,254 from Pfizer in November 2024 towards our resource packs for families with eczema. It was a one-off grant. There was no relevance to any products. For full transparency, on 31/04/25 we applied for a one-off grant from AbbVie to support our support services for families. We have now received communication that we will be awarded this grant.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation may increase health inequalities experienced by patients who are neurodiverse and are unable to utilise other treatments that have a higher dosing frequency and/or require more frequent medical appointments. Young people with autism and their

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	carers share with Eczema Outreach Support how travel to appointments via public transport, busy waiting rooms and long waits to see clinicians can all negatively impact the wellbeing of the young person and their ability to engage with treatment and care. Frequent injections or other treatment applications can also be very challenging for many of these young people. Nemolizumab offers an option with reduced injection frequency and therefore reduced hospital visits, which would make it more accessible to many patients with autism or those with other sensory challenges.
2	We are concerned that young people may be negatively impacted by the recommendation due to the higher treatment/administrative burden of other existing treatment options. Young people with eczema share their struggles to comply with treatment regimes due to the range of priorities, concerns and challenges they face in their wider lives. The current recommendation prevents the availability of a treatment option that would offer a reduced administrative burden, which subsequently could increase the treatment's accessibility to young people compared to other options.
3	We are concerned that the recommendation may have negative impact on the already compromised mental wellbeing of patients and their carers. New treatment options for patients are essential in bringing hope for a better future to families. This hope can particularly enhance the wellbeing of a parent/carer and help them to continue to be the vital support and champion that their child needs. "Please do not underestimate the need for hope when dealing with eczema. Hope for better treatments brings hope for a better life for my child." (Eczema Outreach Support Member Carer, online discussion).
4	We are concerned that the recommendation may cause more young people with eczema to further disengage from mainstream, evidence-based treatments due to their concerns about the side effects of current treatment options. Many young people are turning to "natural" products advertised on social media that claim to cure their eczema quickly or completely avoid side effects. Nemolizumab has so far offered a reduced cancer risk and a reduced risk of ocular issues which may lower the risk of young people turning to unsafe sources for treatment options.
5	
6	

Insert extra rows as needed

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

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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:	[redacted], [redacted], [redacted] and [redacted], on behalf of the British Association of Dermatologists' Therapy & Guidelines Sub-committee

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	Thank you for the opportunity to comment on the current stage of this consultation. We are concerned that not recommending nemolizumab for treating moderate-to-severe atopic dermatitis (AD) would limit the treatment options available to some patients with severe AD. AD is a heterogenous disease and patient response to other biologics and JAK inhibitors is variable, so they might need other treatment options if they fail to respond adequately or are unable to tolerate existing treatments. Nemolizumab can be valuable in people with AD who experience severe itch

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	due to its anti-IL-31 effect, improving the symptoms and quality of life for these patients. About 30% of clinical trial participants do not achieve the primary endpoint of EASI75 or IGA 0/1. Nemolizumab is an IL-31 blocker and evidence was presented which indicates that it is that which enables this medication to be effective in treating the itch related to AD. None of the other medications currently available have this mode of action, and some patients have either primary or secondary failure to currently available agents. It is the itch of AD which is so catastrophically associated with anxiety and/or depression, and evidence has shown that recalcitrant itch is most associated with suicidal ideation in patients with AD. Pruritus may be extremely distressing in people with AD, with the major contributor being due to cytokines, particularly IL-31, which is the reason for antihistamines not being effective in relieving itch in AD – nemolizumab would be particularly effective here. Additionally, there is a strong association with psychological comorbidities (depression and anxiety) plus impact on work/productivity/schooling/families as a whole.
2	**Has all of the relevant evidence been taken into account?** We have been made aware of an *upcoming*, 'living' network meta-analysis publication comparing different agents for AD with dupilumab in terms of EASI responses from baseline to 12-16 weeks which, unfortunately, are not yet able to share, even marked as confidential in this response.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The EAG and committee did not agree with the company's assumption of clinical equivalence, i.e. there was no significant difference between nemolizumab and its comparators in the network meta-analysis (NMA), and that there is uncertainty surrounding relative benefits of treatments included within the NMA; however, might there still be a case for recommending it in people with AD who have not responded adequately to other biologics or JAK inhibitors, or in those with a greater burden of itch, especially when it had been noted that it has a lower rate of adverse events?
4	**Are the recommendations sound and a suitable basis for guidance to the NHS?**
5	**Are there any aspects of the recommendations that need particular consideration to ensure there is no 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?** None that we are aware of.

Insert extra rows as needed

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 17 April 2025. Please submit via NICE Docs.

separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- 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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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Neonatal and Paediatric Pharmacy Group (NPPG)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] (as [redacted] NPPG)

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	This is a fair assessment as there is no data to support superiority in effect or better safety compared with current biologics or JAK inhibitors used in this condition.
2	

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3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	Andrew Collinson

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	I am concerned that there are a percentage of patients who are profoundly suffering, who have come to the end of the available medication options and are being denied a new and novel treatment.

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2	I am concerned that the life changing results due to recent medication developments brought to market by huge investment from Pharmaceutical companies will be disincentivised to continue if they are not reliably approved.
3	I am concerned that the profound suffering of those living with chronic Atopic Dermatitis is not being truly recognised.
4	I am concerned that those who are unable to tolerate the other approved medications available due to far worse safety profiles are still yet to have any viable option for relief.
5	I am concerned that people with neurodivergence will be denied access to a biologic which has a far more agreeable injection interval.
6	I am concerned at the mention of cost effectiveness when it seems, when injection interval is taken into account, there is very little difference with the biologics currently available.
7	I am concerned that those of us who are making it through each day on the hope that one day a medication will become available which can give some relief will lose hope and then be at a greater risk of suicide.
8	I am concerned that a medication which targets one of the most fundamentally all-encompassing and torturous part of Atopic Dermatitis; the itch, is being denied to patients. I would ask you to imagine going about your day when covered head to toe in itching powder and the effects this would have on every area of life.

Insert extra rows as needed

Checklist for submitting comments

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

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	healthcare professional
Organisation	n/a
Location	London

Comments on the DG:

I am a healthcare professional specialised in dermatological conditions working in London. There is a significant need for a new treatment option for atopic dermatitis that specifically focuses on itch. All other advanced therapies are not effective in addressing this key symptom. Therefore I am disappointed to see NICE rejecting this treatment option for patients based on such minor issues and would kindly ask you to reconsider this position

Has all of the relevant evidence been taken into account?

No. the discontinuation of all biologics in atopic dermatitis is similar and therefore I am disappointed to see NICE rejecting this treatment without any valid clinical evidence

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The discontinuation of biologics is similar across the board and thereore its disappointing to see NICE treating this innovation in a different way

Are the recommendations sound and a suitable basis for guidance to the NHS?

We would like to have in our clinic access to a new treatment and therefore would kindly ask NICE to reconsider its position

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?

None

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

EAG critique of the company's response to the draft guidance

Produced by	School of Health and Related Research (SCHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK Mon Mon Yee, Research Associate, SCHARR, University of Sheffield, Sheffield, UK George Daly, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
Date completed	1st May 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR169836.

1. Introduction

In March 2025, the National Institute for Health and Care Excellence (NICE) published a Draft Guidance (DG[1]) which gave a negative recommendation for nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over with a body weight of 30kg or more. The DG highlights uncertainty around (i) the company's assumption of clinical equivalence between nemolizumab and the comparators based on the credible intervals within the indirect comparison crossing unity (Section 3.6) and (ii) the potential that nemolizumab had a greater probability of discontinuation compared with other biologics (Section 3.8). The Appraisal Committee "*concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained), for both adults and young people*" and that that "*the cost-effectiveness estimates for nemolizumab are above the range that NICE normally considers an acceptable use of NHS resources.*" This document should be read alongside the initial External Assessment Group (EAG) report.[2]

The EAG extracted what it believes are the Appraisal Committee's preferred model assumptions from the DG, which were as follows:

- Using the estimates of efficacy from the EAG's network meta-analysis (NMA)
- Using the discontinuation probability of nemolizumab observed in the ARCADIA 1 and ARCADIA 2 studies, in the absence of further information explaining the discrepancy between trial-based values and the Committee's previously preferred assumptions in TA986.
- Capping utility values when they are higher than the general population level

The DG stated that more information from the company related to discontinuation would be helpful, and listed the following areas, noting that these were not exhaustive.

- Discontinuation probabilities for the ARCADIA 1, ARCADIA 2 and ARCADIA-CYCLO trials separately with any differences explained • corresponding discontinuation probabilities for the placebo arm
- The reasons for discontinuation of treatment in all trials across both treatment arms
- Examples of other trials or treatments that have shown a trend for increased discontinuation because of the COVID-19 pandemic, for example, trials for nemolizumab in other indications
- If feasible, discontinuation rates from trials of other biological medicines
- If feasible, an NMA for discontinuation of nemolizumab compared with other biological medicines for the initial 16-week treatment period.

In April 2025, the company submitted a response to the DG which included two Word documents[3, 4], which provided further details regarding the discontinuation probabilities of nemolizumab and placebo

groups observed in the ARCADIA 1 , ARCADIA 2, ARCADIA-CYCLO and LTE studies. No indirect treatment comparison (ITC) for discontinuation probability of nemolizumab relative to other biologics was conducted by the company. As neither additional analyses nor a mathematical model were provided by the company, it is assumed that the company's base case remains unchanged, as is the Patient Access Scheme (PAS) discount for nemolizumab, which is [redacted].

The structure of this document is as follows: Section 1 provides an introduction, Section 2 provides a summary of the results of the Appraisal Committee's preferred analysis, together with the company's base case and the previous EAG base case, assuming the PAS for nemolizumab only. Section 3 provides a brief summary of the company's response to DG and the EAG critique of this. Section 4 provides the details of additional analyses undertaken by the EAG related to an ITC of the discontinuation rates within the first 16 weeks for nemolizumab and comparators, and in changing the measure of response. Section 5 provides the results generated by the analyses described in Section 4.

Results incorporating the PASs for comparators are provided to the Appraisal Committee in a confidential appendix.

2. Summary of the results from the company's base case, the previous EAG base case 2 and the Appraisal Committee's preferred assumptions

The results presented start with the company's base case. The notable change to form the EAG base case 2 was the rejection of the assumption of clinical equivalence when the credible intervals from the EAG's NMA cross unity, with the Convergence Diagnostic and Output Analysis from the NMA used instead. The Appraisal Committee's believed preferred assumptions change EAG base case 2 to assume a discontinuation rate for nemolizumab ([redacted]) based on trial data, that is considerably higher than that for other biologic drugs (3.90%) and to cap the utility at a value of 0.90 such that the population did not have a higher utility than an age- and sex-matched population.

Table 1 and Table 2 summarise the results of the Appraisal Committee's preferred analysis for adults and adolescents, respectively. Only deterministic results are presented as the probabilistic values were similar to the deterministic. All results included the PAS for nemolizumab, but not those for comparators.

Table 1: Deterministic results: adults

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs †	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£673,855	[redacted]	£673,855
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EAG's base case 2							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,203,560
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£553,553	[redacted]	£553,553
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,189,283
Appraisal Committee's preferred base case[§]							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,531	[redacted]	£3,531
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£51,138
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	£220,643
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£238,741
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£166,086
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£609,671	[redacted]	£157,446
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£194,469

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

[§] *The utility was capped at the general population level only for responders.*

Table 2: Deterministic results: adolescents

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs †	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Company's base case, using 1L adolescent data							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
EAG's base case 2, using 1 L adolescent data							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,832,902
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£416,634
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£119,625	[redacted]	£119,625
Appraisal Committee's preferred base case, using 1 L adolescent data[§]							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£32,601
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£45,827
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£223,610
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£140,578
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£125,162	[redacted]	£76,085
EAG's base case 2, using 2 L adult data (SA3)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£551,422
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£416,303	[redacted]	£416,303
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£908,679
Appraisal Committee's preferred base case, using 2 L adult data[§]							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£33,205
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£45,794
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£223,440
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£673,958	[redacted]	£140,473
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£180,113

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line, SA: scenario analysis

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

[§] *The utility was capped at the general population level only for responders.*

3. Summary and critique of the company's DG response

The company's response to the DG discusses three key issues: (1) uncertainty around the discontinuation probability of nemolizumab, (2) capping of utility values for responders, and (3) the economic model shared by the EAG. These key points are summarised by the EAG and critiqued in individual sections.

3.1. Uncertainty around discontinuation probability of nemolizumab (Company's DG response, Issue 1)

In response to the Committee's request in the DG, the company provided the following:

a) observed discontinuation probabilities for the nemolizumab and placebo arms in the ARCADIA 1, ARCADIA 2 and ARCADIA-CYCLO studies during the induction period (from week 0 to week 16)

b) observed discontinuation probabilities (conditional on response) for the nemolizumab and placebo arms in the ARCADIA 1 and ARCADIA 2 during the treatment maintenance period (from week 16 to week 48)

c) a detailed breakdown of reasons for discontinuation in specific arms

d) discussion of the discontinuation probabilities of biologic comparators

e) potential reasons to explain different discontinuation probabilities in the nemolizumab studies

The company highlighted five areas of concerns "*associated with both the Committee's preferred discontinuation probabilities and the use of trial-based discontinuation rates*". These are discussed individually with the exception of the first two areas raised by the company which have been combined into one point. Where company responses could fit into more than one point the EAG has selected the one that it feels is most appropriate.

3.1.1. The consistency and clinical plausibility of Committee's preferred discontinuation assumption and NICE technology appraisal precedent and UK clinical expert opinion

The company stated that in TA986 "*the Committee's preferred approach assumes that the comparators have a class-based discontinuation rate based on UK clinical expert opinion … and not based on their respective clinical trial*" and that "*the use of a different and less favourable approach for nemolizumab despite conflicting expert opinion, is unfair and unreasonable*". The company highlights that "*trial values have not been used for the biologic or JAK inhibitor comparators, which is driving the significant difference in discontinuation. The Committee have chosen to compare clinical trial data for nemolizumab versus clinical expert opinion for the comparators*" and states that "*TA986, conditional discontinuation for lebrikizumab at week 52 was reported to be 6.9%*".

The company further states that "*it would not be clinically plausible that the discontinuation rate for nemolizumab is* [redacted] *as implied by the Committee's preferred discontinuation probabilities for nemolizumab.*"

The company also states that "*The assumption of class-based discontinuation rates in both the Company and EAG base-case has been validated by multiple clinical experts consulted by different stakeholders. Clinical experts consulted by Galderma, the EAG and during both the TA986 and ID6221 ACMs all agreed that discontinuation for treatments within the same class would be comparable. Therefore, the Committee's preferred assumption to apply trial-based conditional discontinuation rates to only nemolizumab or any additional scenario analysis without class-based treatment discontinuation for all treatments would contradict both UK clinical expert opinion and NICE Committee precedent set in TA986 and should not be considered a fair or reasonable interpretation of the evidence*."

3.1.2. Additional discontinuation data from the ARCADIA clinical trials

The company provided discontinuation data from the ARCADIA 1,2, and CYCLO trials stating that "*when considered in detail, it supports a conclusion that nemolizumab treatment is not driving the higher discontinuation rate seen in the ARCADIA trials versus the rate determined by clinical expert opinion in TA986.*" At 16 weeks, discontinuation was [redacted]% in the nemolizumab arm and [redacted]% in the placebo arm (ARCADIA 1), was [redacted]% in the nemolizumab arm and [redacted]% in the placebo arm (ARCADIA 2) and was [redacted]% in the nemolizumab arm and [redacted]% in the placebo arm (ARCADIA CYCLO). The company states that at week 16, participants request was the most common reason for discontinuation, not lack of efficacy or adverse events, being [redacted]% in ARCADIA 1 and [redacted]% in ARCADIA 2.

In the maintenance period the discontinuation rates were noted to be [redacted]% (ARCADIA 1) and [redacted]% (ARCADIA 2) for patients moving from nemolizumab Q4W to Q8W, which were lower than, or comparable to, values for patients moving from nemolizumab to placebo or remaining on placebo ([redacted]% and [redacted]% respectively in ARCARDIA 1, and [redacted]% and [redacted]% respectively in ARCARDIA 2). As in the induction phase, the most common reason for discontinuation from nemolizumab treatment was participant request ([redacted]% in ARCADIA 1 and [redacted]% in ARCADIA 2). Figure 1 in the company's response "*shows that in the ARCADIA 1 and 2 maintenance periods, with one exception, all patients in the nemolizumab Q4W to Q8W arms who discontinued due to participant's request had no worsening of EASI score prior to discontinuation. The one exception … reported no adverse events and discontinued due to 'subject's schedule'*".

The company highlights that the studies were undertaken during the COVID-19 pandemic and noted the number of COVID-19 infections in the maintenance period ([redacted]% (ARCADIA 1) and [redacted]% (ARCADIA 2)) and provided a reference (Sathian *et al*.[5]) reporting an observed decrease in the willingness of patients to visit sites in 55% of respondents from clinical trial sites.

3.1.3. Heterogeneity in trial designs

The company stated that it is not appropriate to have a direct comparison of discontinuation from clinical trials due to the heterogeneity of trial design. Heterogeneity could exist in: the trial population in terms of the number of treatment lines and age of patients; differences in patient randomisation and duration of treatment; the efficacy of concomitant therapy; and the measure of treatment response in deciding treatment duration (whether EASI-75 (a [redacted]% discontinuation rate in ARCADIA 1 and 2) or EASI-50+ DLQI >4 (a [redacted]% discontinuation rate in ARCADIA 1 and 2)). The company also highlights that the maintenance of an EASI-75 response up to week 48 for nemolizumab ([redacted]%) is similar to that of tralokinumab every 2 weeks (Q2W) at week 52 of 60% in ECZTRA 1 and 56% in EZCTRA 2, and to the 81.7% value for lebrikizumab when pooling Advocate 1 and Advocate 2 studies, although this comparison represents a naïve indirect comparison.

The company stated that the variation in published discontinuation rates may also be explained by the increasing number of available treatments for atopic dermatitis over time which could results in earlier trials conducted at an earlier point having lower discontinuation rates compared to more recent studies.

3.1.4. Variation in comparator discontinuation rates

The company stated that "*Based on the significant heterogeneity in comparator trial design, precedent set in TA986 and UK clinical expert opinion, Galderma does not consider it appropriate to conduct an NMA for discontinuation at week 16*" but instead reported the trial-based discontinuation probabilities of biologic comparators at week 16, ranging from 5.6% to 8.5%, which was stated to "*supports that discontinuation at week 16 for nemolizumab is, overall, comparable to the biologic comparators*". The company additionally provide reported discontinuation probabilities (at different time points) for biologic comparators, ranging from 5.5% to 41%, based on clinical trials and cohort studies, however these are all naïve indirect treatment analyses.

EAG critique of the company's response

The EAG notes that the company is factually correct when stating that the Appraisal Committee has used a class effect for other biologic treatments (dupilumab, lebrikizumab and tralokinumab) but not for nemolizumab, however this is a decision for the Appraisal Committee. The EAG will instead comment on the data presented by the company.

The EAG has calculated odds ratios (ORs) and confidence intervals associated with the key nemolizumab studies. Table 3 presents data on discontinuation during the initial treatment period (up to week 16) whilst Table 4 presents discontinuation during the maintenance period (week 16 to week 48).

Table 3: Treatment discontinuation and odds ratios at week 16 in ARCADIA 1, ARCADIA 2 and ARCADIA-CYCLO

Study	Nemolizumab 30mg Q4W		Placebo		Odds Ratio (95% CI)
	d_i	c_i	d_c	c_c	
ARCADIA 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCADIA 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCADIA-CYCLO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: d, number of discontinuations; c, number who completed treatment; CI, confidence interval; Q4W, every 4 weeks

[redacted]

Table 4: Treatment discontinuation and odds ratios during maintenance period in ARCADIA 1 and ARCADIA 2 (adapted from Appendix A, Table 2)

Trial	Intervention	Comparator	Intervention		Comparator		Odds Ratio (95% CI)
			d_i	c_i	d_c	c_c	
ARCADIA 1	Nemolizumab 30mg Q4W to Q8W	Nemolizumab 30mg Q4W to placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCADIA 2			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCADIA 1	Nemolizumab 30mg Q4W to Q8W	Remaining on placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ARCADIA 2			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: d, number of discontinuations; c, number who completed treatment; CI, confidence interval; Q8W, every 8 weeks

[redacted]

The EAG believes that the naïve indirect comparisons presented by the company are not useful, particularly when there is significant heterogeneity between studies and thus does not place much weight on the company's reported values. A more appropriate way to compare relative discontinuation is through an ITC, which considers discontinuation from both the intervention and control from the individual studies. To provide the Appraisal Committee with additional information, the EAG conducted an NMA for discontinuation probabilities of nemolizumab compared with comparators (biologics and JAKI) at week 16. Details of this analysis is provided in Section 4.

3.2. Capping of utility values for responders (Company's DG response, Issue 2)

The company's response highlights that the health state utility values in the company's and the EAG's base case model were based on the data from the ARCADIA 1, ARCADIA 2, ARCADIA CYCLO, and long-term extension studies which have been further validated by a UK clinical expert as being generalisable to UK clinical practice. The company also stated that the observed utility differences between responders and non-responders were no longer reflected in the economic model when a cap was applied to the utility values for responders at the general population level (as the cap was only applied to responders and thus reducing the difference in utility between responders and non-responders).

In addition, the company highlights that the cap removes the pattern of increasing utility value for responders over time which is likely as "*although itch relief is observed shortly after treatment initiation, it can take more time (approximately one year) for skin lesions to fully heal*". The company suggested two alternative approaches: (i) removing the utility cap so that the observed utility differences between responders and non-responders are adequately reflected in the model, and (ii) if a cap is applied, ensuring that an equal utility decrement is applied to both responders and non-responders to maintain the observed difference from the studies, whilst also allowing the utility for responders to increase over time.

EAG critique

The EAG notes that the cap was contained within the Appraisal Committee's preferred assumptions (See Section 3.9 of the DG) and therefore did not remove the cap. However, the EAG has conducted additional scenario analyses applying an equal utility decrement to both responders and non-responders: the utility was capped at 0.90 for responders at all timepoints, with the utility for adult non-responders becoming [redacted] ([redacted] minus a decrement of [redacted]) and the utility for adolescent non-responders becoming [redacted] ([redacted] minus a decrement of [redacted]). The decrement for non-responders ([redacted]) was based on the difference between the year 3+ utility value of [redacted] (week 104 data of LTE study) and the general

population utility value of 0.90. The results are summarised in Table 5 for adults and Table 6 for adolescents. Whilst the EAG notes the company's comments relating to the increase in utility for responders over time, this has not been incorporated in the model due to time constraints although the EAG believes that this is likely to have only a small impact on the ICER. The EAG highlights that the reduction of the utility for non-responders to maintain the difference observed in the studies between responders and non-responders has resulted in nemolizumab becoming less cost-effective compared with the comparators when using the Appraisal Committee's preferred assumptions although the efficiency frontier remains unchanged.

Table 5: EAG's deterministic analysis capping utility for responders but maintaining the difference in utility between responders and non-responders: adults

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Appraisal Committee's preferred base case[§]							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£3,531	[redacted]	£3,531
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£51,138
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	£220,643
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£238,741
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£166,086
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£609,671	[redacted]	£157,446
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£194,469
Appraisal Committee's preferred base case, with equal utility decrement for both responders and non-responders							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£2,365	[redacted]	£2,365
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£34,214
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	£147,229
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£160,921
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£111,040
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£417,065	[redacted]	£106,027
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£131,261

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

[§] *The utility was capped at the general population level only for responders.*

Table 6: EAG's deterministic analysis capping utility for responders but maintaining the difference in utility between responders and non-responders: adolescents

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
Appraisal Committee's preferred base case, using 1 L adolescent data§							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£32,601
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£45,827
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£223,610
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£140,578
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£125,162	[redacted]	£76,085
Appraisal Committee's preferred base case, using 1 L adolescent data , with equal utility decrement for both responders and non-responders							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£20,021
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£28,136
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£138,073
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£86,443
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£78,091	[redacted]	£47,079
Appraisal Committee's preferred base case, using 2 L adult data§							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£33,205
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£45,794
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£223,440
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£673,958	[redacted]	£140,473
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£180,113
Appraisal Committee's preferred base case, using 2 L adult data , with equal utility decrement for both responders and non-responders							
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	-	[redacted]	Dominates
Nemolizumab	[redacted]	[redacted]	-	-	Dominated	-	-
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£20,391
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£28,115
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£137,968
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£424,382	[redacted]	£86,379
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£111,373

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

§ *The utility was capped at the general population level only for responders.*

3.3. Economic model shared by the EAG (Company's DG response, Issue 3)

The company response stated that, in the economic model shared by the EAG prior to the 1st ACM, the ORs for comparators in the parameter sampling sheet were hard-coded with the implications that "*that the odds ratios are not included in the probability sensitivity analysis, do not change when the population is updated (e.g., from adults to adolescents) and do not change when the measure of response is amended*."

EAG critique

The EAG does not agree with the company's statement. The ORs values are not hard-coded but are introduced via a macro called "EA2". The macro brings in the values from column D25:D33 to column J25:J33 in the parameter sampling sheet. As stated in Appendix 1 of the EAG report (post-FACT check version), the macro called "EA2" should be run when the user changes assumptions relating to the ORs, such as when the population is changed.

Regarding measure of responses, the EAG explored the impact of using EASI-50 and DLQI ≥ 4 by assuming that ORs of comparators are generalisable from the EASI-75 analysis, see SA1 (page 91 of the EAG report, post-FACT Check version, Section 4.6.2) which as detailed above are implemented correctly. No other measures of response were evaluated.

4. Description of additional analyses undertaken by the EAG

The EAG conducted its own NMA in a Bayesian framework using binomial likelihood with a logit link function for binary endpoints, performed for discontinuation at week 16 in mixed cyclosporine-naïve/experienced (first and second line) adolescent and adult population. Due to time constraints, only the studies used in the NMA for efficacy (see Table 16 of the main EAG report) were used in this NMA. The data used in the NMA is presented in Table 7. Data for time periods beyond 16 weeks were largely redacted and were not available to the EAG so no analysis was performed in the maintenance period.

The EAG also carried out a separate NMA analysing discontinuation at week 16 of nemolizumab against classes of treatments (biologics, and JAKIs) according to whether treatments belonged to the same intervention class. The exception was for nemolizumab which was regarded as its own class as this had been questioned by the Appraisal Committee.

Table 7: Input data for discontinuation at 16 weeks in adolescent and adult 1L + 2L population

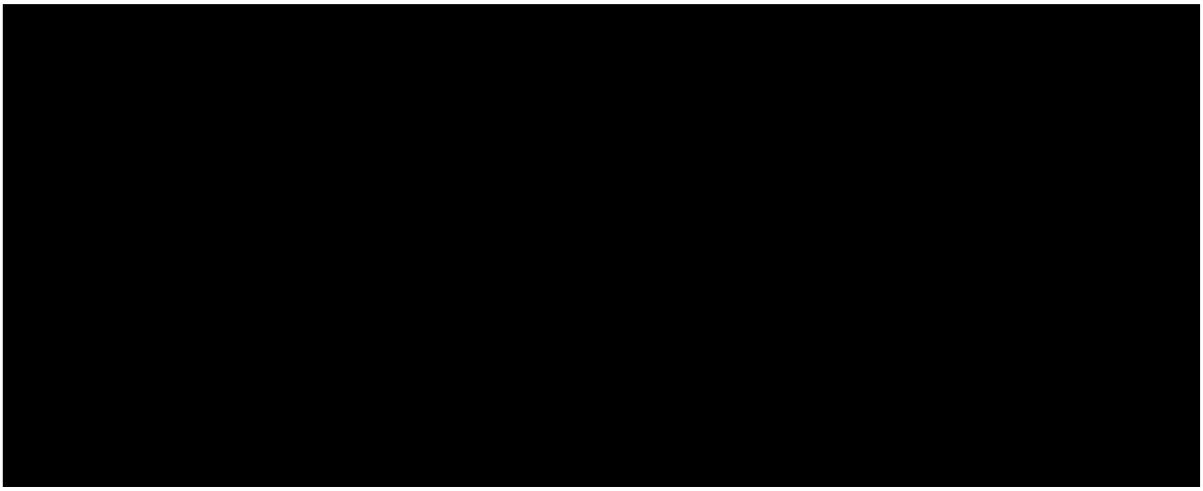
Trial	Population	Treatment	Number of Discontinuations, d	Number of patients, n
ARCADIA 1[6]	Adolescent and adult 1L + 2L	Nemolizumab 30mg	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]
ARCADIA 2[7]	Adolescent and adult 1L + 2L	Nemolizumab 30mg	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]
ARCADIA-CYCLO[8]	Adult 2L	Nemolizumab 30mg	[redacted]	[redacted]
		Placebo	[redacted]	[redacted]
AD UP[9]	Adolescent and adult 1L + 2L	Upadacitinib 15mg QD	10	300
		Upadacitinib 30mg QD	8	297
		Placebo	21	304
Adhere[10]	Adolescent and adult 1L + 2L	Lebrikizumab 250mg Q2W	11	145
		Placebo	8	66
ADhere-J[11]	Adult 1L	Lebrikizumab 250mg Q4W	1	81
		Lebrikizumab 250mg Q2W	3	123
		Placebo	0	82
Advantage[12]	Adult 2L	Lebrikizumab 250mg Q2W	8	220
		Placebo	11	111
BREEZE AD-4[13]	Adult 2L	Baricitinib 2mg QD	11	185
		Baricitinib 4mg QD	7	92
		Placebo	21	93
BREEZE AD-7[14]	Adult 2L	Baricitinib 2mg QD	9	109
		Baricitinib 4mg QD	4	111
		Placebo	7	109
ECZTRA 7[15]	Adult 2L	Tralokinumab 300mg Q2W	15	140

		Placebo	17	137
ECZTRA 8[16]	Adult 1L	Tralokinumab 300mg Q2W	0	53
		Placebo	1	53
JADE COMPARE[17]	Adult 1L	Abrocitinib 100mg QD	21	238
		Abrocitinib 200mg QD	18	226
		Dupilumab 300mg Q2W	19	242
		Placebo	14	131
JADE DARE[18]	Adult 2L	Abrocitinib 200mg QD	35	362
		Dupilumab 300mg Q2W	31	365
JADE TEEN[19]	Adolescent 1L	Abrocitinib 100mg QD	3	95
		Abrocitinib 200mg QD	3	94
		Placebo	6	96
LIBERTY AD CAFÉ[20]	Adult 2L	Dupilumab 300mg Q2W	1	107
		Dupilumab 300mg QW	1	110
		Placebo	1	108
RISING UP[21]	Adolescent and adult 1L	Upadacitinib 15mg QD	2	91
		Upadacitinib 30mg QD	3	91
		Placebo	3	90

The EAG used a random effects (RE) model and vague prior distributions to allow the data to dominate. Where there were a small number of trials included in the network, an informative prior (Turner et al.[22] for pharmacological vs placebo/control comparison for subjective outcome type) was used for the heterogeneity parameter in the RE model to help estimate the between-study standard deviation. All NMAs were conducted in WinBUGs. For all outcomes, a burn-in of 20,000 iterations of the Markov chain was used with a further 30,000 iterations retained to estimate parameters.

Relative discontinuation rates are presented as ORs (median) for binary endpoints with an OR more than one in favour of nemolizumab (as this indicates there is a higher chance to discontinue in the comparator arm). The results of the NMA for all the relevant comparators and for nemolizumab versus biologics, JAK inhibitors and placebo are presented in Figure 1 and Figure 2, respectively.

Figure 1: Forest plot of relative discontinuation rates versus nemolizumab for discontinuation at week 16 in first- and second-line adolescent and adult population



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

The odds ratios for relative discontinuation rate versus nemolizumab at week 16, show

Figure 2: Forest plot of class-based relative discontinuation rates versus nemolizumab for discontinuation at week 16 in first- and second-line adolescent and adult population

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

The EAG notes that the data used in the NMAs are only for the initial treatment period. Any extrapolation of these ORs to the maintenance period and to the conditional discontinuation based on response at week 16 would rely on assumptions that discontinuation rates are generalisable across treatment periods and between populations (responders only versus the full population. Comparison of

the odds ratios calculated in Table 3 and Table 4 suggests that discontinuation rates compared with placebo may not be generalisable across treatment periods. Additionally, the relatively low discontinuation rate associated with JAKIs in our NMA, is in conflict with expert opinion used in TA986, where the discontinuation rate associated with JAKIs was assumed to be considerably higher than for biologics. For these reasons, the EAG suggests caution should be used when interpreting the results of the EAG's NMA.

Compared with biologic comparators, the EAG's NMA [redacted] for the discontinuation probability at the week 16. However, the point estimate for the OR was [redacted].

Due to the lack of conditional discontinuation probability data at week 52 for placebo arms in most clinical studies included in the NMA, the ORs for the induction period were assumed generalisable to the maintenance period, which is a strong assumption, which has been discussed as a potentially important limitation.

The EAG present two new base cases, denoted EAG's base case 3 and EAG's base case 4 to avoid confusion with earlier base cases. Base case 3 differs from Base Case 2 by applying a utility cap at 0.90 for responders; Base case 4 differs from Base Case 2, by applying the cap of 0.90 for responders, but maintaining the absolute difference in utility between responders and non-responders by decreasing the utility associated with non-responders as detailed in Section 3.2.

Both Base case 3 and 4 assume that the conditional discontinuation probability at week 52 is the same as other biologics (at 3.90%) due to clinical advice received by the EAG, the company and in the Appraisal Committee, [redacted]. The EAG has run a scenario analysis assuming a higher conditional discontinuation probability for nemolizumab at week 52, being [redacted]%. The value of [redacted]% was calculated by applying an OR of [redacted] to the 3.90% conditional discontinuation probability assumed for biologics as a class. The EAG notes that conditional discontinuation probability relates to the period from week 16 to week 52, thereafter, annual discontinuation probabilities were applied for all analyses. As an example, the annual discontinuation probability was 5.58% for the biologic class (when assumed to be 3.90%); and [redacted]% for nemolizumab when the conditional discontinuation probability was assumed to be [redacted]%.

Following discussions with NICE it was believed that the 3.90% conditional discontinuation probability for the biologics class (and the 10% value for JAKIs) were not supported by published evidence. Therefore, the EAG undertook an NMA of the placebo discontinuation probability in the first 16 weeks, using the studies in Table 7 and using ORs generated from an NMA. These results are shown in Table

8. Our NMA estimated a probability of discontinuation for placebo of 6.88%, with other values marked as confidential.

Table 8: Probability of discontinuation at 16 weeks

Intervention	Referent	Odds Ratio (95% CI)	Discontinuation probability- placebo	Discontinuation probability
Biologics (including nemolizumab)	Placebo	[redacted]	6.88%	[redacted]
Biologics (excluding nemolizumab)		[redacted]		[redacted]
Nemolizumab 30mg		[redacted]		[redacted]
JAK inhibitors		[redacted]		[redacted]

Scenarios were run using the values in Table 8, assuming that nemolizumab had the same discontinuation probability as other biologics ([redacted]) and assuming that it had a higher discontinuation probability ([redacted]) with that for other biologics at [redacted]%. For all analyses, the conditional discontinuation probability for JAKi were maintained at 10% - whilst this is not a consistent approach, clinical advice is that there would be fewer discontinuations of biologics than of JAKi. This highlights limitations in the NMA in that we have had to assume that the ORs for discontinuation in the induction period were assumed generalisable to the maintenance period, which is a strong assumption.

Deterministic results are presented as probabilistic results were similar to deterministic ones.

Based on the additional request by the NICE technical team, a scenario exploring the use of EASI 50 and DQLI ≥ 4 as the response criteria in the Appraisal Committee's preferred analysis, rather than EASI has also been presented. This scenario is only applicable to adult population and has a minor impact on the results.

5. Results generated from the additional analyses undertaken by the EAG

Results for the EAG base cases and scenario analyses are shown in Table 8 for adults, Table 9 for adolescents, using first-line adolescent data only and in Table 10 for adolescents using efficacy data from adults in second-line treatment.

For adults, in all scenarios, the cost per QALY gained for all comparators compared with nemolizumab was in excess of £60,000 (Table 8). For adolescents using first-line adolescent data, this value dropped to £48,000 (Table 9) and fell to £38,000 when second-line adult data were used (Table 10). These results, however, could be misleading due to the omission of comparator PASs, which would decrease the cost-effective of nemolizumab. These results are provided to the NICE Appraisal Committee in a confidential appendix.

Analyses related to the use of EASI50 and DQLI≥ 4 as the measure of response for adults are contained in Appendix1, as these do not change the efficiency frontier or change the signs of any incremental net monetary benefit for comparators compared with nemolizumab.

Table 9: Deterministic results for the EAG's additional base cases plus scenario analyses using a higher discontinuation probability: adults

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 3 (EAG's base case 2 + utility capping at 0.90 for responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,107,578
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£946,952
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£726,987	[redacted]	£726,987
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,559,561
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£125,426	[redacted]	£125,426
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£279,344
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£5,359,217
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£356,591
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£609,671	[redacted]	£318,368
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£445,617
EAG's base case 3 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-		
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£226,770	[redacted]	£226,770
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£541,362
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£725,302
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£873,606	[redacted]	£476,089
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,600,001
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£93,119	[redacted]	£93,119
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£211,341
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£3,232,573
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£311,959
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£797,062	[redacted]	£307,167
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£429,382
EAG's base case 4 (EAG's base case 2 + applying equal utility decrement for both responders and non-responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£685,317
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£614,042
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£485,247	[redacted]	£485,247
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,043,147

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£83,257	[redacted]	£83,257
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£184,308
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£3,442,620
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£236,611
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£417,065	[redacted]	£213,858
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£300,276
EAG's base case 4 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-		
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£149,405	[redacted]	£149,405
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£351,601
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£484,133
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	£579,171	[redacted]	£314,421
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,070,214
EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£61,961	[redacted]	£61,961
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£140,018
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£2,117,748
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£207,362
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£547,670	[redacted]	£206,370
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£289,373

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 10: Deterministic results for the EAG's additional base cases plus scenario analyses using a higher discontinuation probability: adolescents, using first-line adolescent data

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 3 (EAG's base case 2 + utility capping at 0.90 for responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,227,791
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£3,546,903
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£644,123
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£181,616	[redacted]	£181,616
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£111,434	[redacted]	£111,434
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£199,814
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£314,109
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£7,760,587
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£285,522
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£125,162	[redacted]	£121,914
EAG's base case 3 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-		
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£210,784
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£357,660
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£726,317
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£644,847
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£187,553	[redacted]	£187,553
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£80,393	[redacted]	£80,393
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£153,295
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£226,997
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£3,875,933
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£275,849
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£136,106	[redacted]	£120,548
EAG's base case 4 (EAG's base case 2 + applying equal utility decrement for both responders and non-responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£649,292
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,806,742
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£390,221
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£112,280	[redacted]	£112,280

EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£67,058	[redacted]	£67,058
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£121,521
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£190,006
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£4,431,663
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£174,815
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£78,091	[redacted]	£75,408
EAG's base case 4 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£125,304
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£215,546
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£429,638
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£390,655
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£115,950	[redacted]	£115,950
EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£48,565	[redacted]	£48,565
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£93,481
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£137,972
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£2,302,440
Dupilumab	[redacted]	[redacted]	-	-	ED	[redacted]	£168,941
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	£84,975	[redacted]	£74,564

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Table 11: Deterministic results for the EAG's additional base cases plus scenario analyses using a higher discontinuation probability: adolescents, using second-line adult data

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 3 (EAG's base case 2 + utility capping at 0.90 for responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£591,153	[redacted]	£591,153
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£4,424,536
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£673,958	[redacted]	£643,634
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,390,817
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£86,977	[redacted]	£86,977
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£203,936
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£313,883
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£7,750,554
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£673,958	[redacted]	£285,307
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£410,968
EAG's base case 3 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-		
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£158,530	[redacted]	£158,530
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£367,991
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£725,809
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£644,360
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,435,480
EAG's base case 3 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£62,775	[redacted]	£62,775
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£156,125
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£226,833
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£3,871,958
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£934,411	[redacted]	£275,642
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£397,044
EAG's base case 4 (EAG's base case 2 + applying equal utility decrement for both responders and non-responders)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£336,097	[redacted]	£336,097
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£2,161,435
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£424,382	[redacted]	£389,931
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£852,115
EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% (other biologics = 3.90%)							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£52,512	[redacted]	£52,512
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£123,997
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£189,873
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£4,426,371

Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£424,382	[redacted]	£174,685
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£253,674
EAG's base case 4 + conditional discontinuation probabilities at week 52: all biologics at [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£94,878	[redacted]	£94,878
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£221,637
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£429,351
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Dupilumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£390,366
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£879,474
EAG's base case 4 + conditional discontinuation probabilities at week 52: nemolizumab = [redacted]% and other biologics = [redacted]%							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£38,014	[redacted]	£38,014
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£95,191
Abrocitinib 100 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£137,874
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£2,300,171
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£593,184	[redacted]	£168,816
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£245,112

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

Appendix: Additional exploratory analyses using EASI 50 and DQLI ≥ 4 response measure

Table 12: Additional exploratory analyses using EASI 50 and DQLI ≥ 4 response measure, adults, deterministic

Option	Total costs	Total QALYs	Inc Costs†	Inc QALYs†	ICER†	iNMB vs nemolizumab*	ICER vs nemolizumab
EAG's base case 3, using EASI 50 and DQLI ≥ 4							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£3,863,265
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£1,428,469
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£824,673	[redacted]	£824,673
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,736,213
EAG's base case 4, using EASI 50 and DQLI ≥ 4							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£2,008,982
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	Dominated
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£909,230
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£549,636	[redacted]	£549,636
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£1,159,899
Appraisal Committee's preferred base case, using EASI 50 and DQLI ≥ 4[§]							
Nemolizumab	[redacted]	[redacted]	-	-	-	-	-
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	£9,912	[redacted]	£9,912
Baricitinib	[redacted]	[redacted]	-	-	Dominated	[redacted]	£242,738
Abrocitinib 200 mg	[redacted]	[redacted]	-	-	Dominated	[redacted]	£62,250
Tralokinumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£244,572
Upadacitinib 30 mg	[redacted]	[redacted]	-	-	ED	[redacted]	£189,111
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£558,834	[redacted]	£169,454
Lebrikizumab	[redacted]	[redacted]	-	-	Dominated	[redacted]	£203,335

ED: extendedly dominated; ICER: incremental cost-effectiveness ratio; iNMB: incremental net monetary benefit; Inc: incremental; LYs: life years; QALYs: quality-adjusted life years, 1 L: first-line; 2 L: second-line

**at £25,000 per QALY gained threshold*

† incremental costs and QALYs vs next least costly non-dominated or extendedly dominated option

[§] *The utility was capped at the general population level only for responders.*

REFERENCES

1. National Institute for Health and Care Excellence. Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over. Draft Guidance Consultation. 2025.
2. Stevenson M, Ren S, Pandor A, Mon-Yee M, Daly G, Clowes M*, et al.* Nemolizumab for treating moderate to severe atopic dermatitis in people 12 years and over. A Single Technology Appraisal. . 2024.
3. Galderma. Nemolizumab for treating moderate to severe atopic dermatitis in people 12 and over. Draft Guidance Comments. 2025.
4. Galderma. Nemolizumab for treating moderate to severe atopic dermatitis in people 12 and over [ID6221]. Draft Guidance Consultation form Appendix A: Discontinuation in ARCADIA Trials. 2025.
5. Sathian B, Asim M, Banerjee I, al. e. Impact of COVID-19 on clinical trials and clinical research: A systematic review. *Nepal J Epidemiol* 2020;10:878-87.
6. ARCADIA 1 CSR version 2.0. In.
7. ARCADIA 2 CSR. In.
8. Galderma Data on File. ARCADIA-CYCLO Clinical Study Report. 2023.
9. Silverberg JI, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Costanzo A*, et al.* Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. *Journal of Allergy and Clinical Immunology* 2022;149:977-87 e14.
10. Simpson E HHEKTJSMAAEHAHCSZJ. Lebrikizumab treatment improves four EASI clinical signs over 16 weeks in moderate-tosevere atopic dermatitis. *Journal of Clinical and Aesthetic Dermatology* 2023;16:S13.
11. ClinicalTrials.gov. A Study of Lebrikizumab (LY3650150) in Combination With Topical Corticosteroids in Japanese Participants With Moderate-to-Severe Atopic Dermatitis (ADhere-J). 2023. https://clinicaltrials.gov/study/NCT04760314 (Accessed March 2024).
12. Warren RB, de Bruin-Weller M, Tsianakas A, Khemis A, Szepietowski JC, Chih-Ho Hong H*, et al.* 619 - Lebrikizumab improves signs and symptoms of moderate-to-severe atopic dermatitis in patients not adequately controlled or non-eligible for cyclosporine: a placebo-controlled, randomized phase 3 clinical study (ADvantage). *British Journal of Dermatology* 2024;191:ljae266.005.
13. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP*, et al.* Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4). *British Journal of Dermatology* 2022;187:338-52.
14. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T*, et al.* Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. *JAMA Dermatology* 2020;156:1333-43.
15. Gutermuth J, Pink AE, Worm M, Soldbro L, Bjerregard Oland C, Weidinger S. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). *British Journal of Dermatology* 2022;186:440-52.
16. ClinicalTrials.gov. Tralokinumab in Combination With Topical Corticosteroids in Japanese Subjects With Moderate-to-severe Atopic Dermatitis (ECZTRA 8). 2022. https://clinicaltrials.gov/study/NCT04587453 (Accessed March 2024).
17. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE*, et al.* Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. *New England Journal of Medicine* 2021;384:1101-12.
18. Reich K, Thyssen JP, Blauvelt A, Eyerich K, Soong W, Rice ZP*, et al.* Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. *Lancet* 2022;400:273-82.

19. Eichenfield L, Flohr C, Sidbury R, Szalai Z, Galus R, Yao Z*, et al.* Efficacy and safety of abrocitinib in adolescent patients with moderate-to-severe atopic dermatitis (AD): results From the Phase 3 JADE TEEN study. *Journal of Allergy and Clinical Immunology* 2021;147:AB146.
20. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A*, et al.* Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *British Journal of Dermatology* 2018;178:1083-101.
21. Katoh N, Ikeda M, Ohya Y, Murota H, Hu X, Liu J*, et al.* Safety and Efficacy of Upadacitinib for Atopic Dermatitis in Japan: Analysis of the 3-Year Phase 3 Rising Up Study. *Dermatology And Therapy* 2024;14:213-32.
22. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol* 2012;41:818-27.