NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Upadacitinib, abrocitinib and tralokinumab for dermatitis [ID3960]

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

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

2. **External Assessment Group/Assessment Group response to the ACD**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:

- Abbvie
- Leo Pharma
- Pfizer
- Eczema Outreach Support (EOS)
- British Association of Dermatologists

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

Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis [ID3960]

Multiple Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1.	Consultee	LEO Pharma	LEO Pharma would like to highlight the frustrations with the process that tralokinumab has been through over the last 12 months. The justification for using a hybrid Multiple Technology Appraisal (MTA) was to increase the speed of decision making and reduce the workload for NICE due to capacity reasons. Regrettably, this has not been the case and a standard Single Technology Appraisal (STA) would have been more timely and would also have given clarity and reduced the workload for all parties. LEO Pharma consider it imperative that further delays, which could adversely impact treatment access for patients with Atopic Dermatitis, are avoided.	Comments noted. NICE maintains that scheduling a single MTA has been quicker and more efficient than 3 separate STAs.
2.	Consultee	LEO Pharma	The hybrid MTA has been an 'off process' approach with no published documentation or project plan for companies to follow. All companies find themselves in the position of having to comment at the ACD stage on a model that has been deemed inappropriate for decision making by the NICE committee members. A crucial aspect seems to be the External Assessment Group (EAG) model's lack of consistency with the models used in the previous dupilumab appraisal (TA534); the unsuitability of the EAG model has limited LEO Pharma's ability to proactively input into this process.	Comments noted. This topic is an MTA not a hybrid MTA, this distinction was communicated to the companies. NICE believes that this topic has followed the MTA process. The committee considered the model structure to be fit for decision-making (section 3.17 of the FAD).
3.	Consultee	LEO Pharma	The economic model submitted as part of LEO Pharma's STA included assumptions that were more in line with previous STAs (TA534) and LEO Pharma believe that the revised EAG model should have greater consistency with the models used as the basis for decision making in these previous appraisals.	Comment noted. The committee considered EAG's models to be appropriate and were similar to models previously seen in atopic dermatitis appraisals. The committee discussed this issue in section 3.17.
4.	Consultee	LEO Pharma	LEO Pharma agree with the recommendation of the committee to explore a long-term utility waning effect in patients treated with BSC. This was an assumption in the tralokinumab STA model and also in previous appraisals such as TA534.	Comment noted. The relevant paragraph has been updated in the FAD. The committee discussed this issue in section 3.24.
5.	Consultee	LEO Pharma	Given the potential sources of heterogeneity across the evidence base, as discussed in LEO Pharma's STA submission, we consider the random effects approach to the NMA as more appropriate. Please see Section B.2.9.3 of LEO's STA	Comment noted. The EAG presented results using a fixed-effects model after consultation. The relevant paragraph has been updated in the FAD. The committee discussed this issue in section 3.15.
6.	Consultee	LEO Pharma	We note that LEO Pharma will not have sight of the updated EAG model in advance of the next committee meeting and so have no visibility on the final	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			assumptions that will be implemented following the feedback in the ACD.	
7.	Consultee	LEO Pharma	LEO Pharma would like to make the EAG and committee aware of the treatment option of Q4W dosing for tralokinumab. This will be an option in clinical practice based on feedback LEO Pharma has received from leading clinicians in the UK. In addition, Q4W dosing was one of the scenarios run by the EAG in the initial appraisal and we recommend this is revisited for the base case as this will become common practice.	Comment noted. The committee discussed the alternative dosing schedule in section 3.20 of the FAD.
8.	Consultee	Pfizer Ltd	Overarching statement Abrocitinib received its marketing authorisation (MA) in September 2021, the first MA worldwide. However, prior to the first committee meeting, we were already approximately 4–6 months delayed in terms of the appraisal process given that abrocitinib was re-routed from an STA to MTA process given capacity challenges at NICE. Patients now face a further 2-month delay based on a preliminary negative opinion which we strongly believe could have been avoided. We have been unable within the MTA process to impact the evidence seen by the committee in the meeting, given many of our comments in the EAG consultation period were not addressed, and evidence we submitted in our original STA was not provided for consideration with the first appraisal committee meeting. This is in the context of a successful baricitinib appraisal (TA681) in early 2021 in which the committee made a positive recommendation within one appraisal committee meeting. [redacted]. The adopted process for appraising abrocitinib is misaligned with NICE's ambition to provide "rapid, robust and responsive" technology evaluation and the recently published Life Sciences Vision for clinically and cost-effective innovations to be rapidly adopted.	Comments noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The lack of efficiency and pragmatism in the NICE process is illustrated by the contrasting approach of the SMC in relation to the appraisal of abrocitinib. [redacted]. Within the comments that follow (5-9) we have provided responses to the specific concerns of the committee identified within the appraisal consultation document (ACD) on page 22. We have highlighted both evidence from our initial STA submission which addresses these concerns and/or adaptations needed to the EAG NMA/model prior to the second appraisal committee meeting. Comments 10-13 relate to other sections of the ACD or the appraisal process thus far. We have sought a meeting with the NICE technical team/EAG on several occasions since the ACD was shared, in order to ensure we can contribute to the work required to ensure the appropriate evidence is provided to the committee during the second appraisal committee meeting. To date (28 April 2022) we have not received a response to this request. Finally, we want to emphasise that abrocitinib was granted a Promising Innovative Medicine (PIM) designation and a positive scientific opinion for Early Access to Medicine Scheme (EAMS) by the MHRA for the treatment of severe AD. This underlines the fact that severe AD is a seriously debilitating condition and that abrocitinib offers major advantages over existing systemic therapies. NICE have not met their commitment to prioritise PIM/EAMS treatments.	
9.	Consultee	Pfizer Ltd	[redacted]	Comments noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted] Clinical outcomes • In JADE COMPARE, EASI (±DLQI) response rates for abrocitinib 100mg and dupilumab are comparable. For several critical response measures (e.g., PP-NRS itch response at Week 2, [redacted] abrocitinib 200mg is statistically significantly better than dupilumab; otherwise no significant differences between these treatments were observed (Abrocitinib submission Document B, Section B.2.6.1 [page 68]). • [redacted] (Abrocitinib submission Document B, Section B.2.9.5 [page 113]). • Results from the NMA (Abrocitinib submission Document B, Section B.2.9.5 [page 113]) also suggests that [redacted] [redacted]	
10.	Consultee	Pfizer Ltd	**Inaccurate ACM summary** The ACD states on page 3 and 4: *"Standard treatment for moderate to severe atopic dermatitis (eczema) includes topical treatments such as emollients and corticosteroids. If these treatments are not effective, systemic immunosuppressants such as methotrexate and*	Comments noted. The recommendation section has been updated in the FAD. The committee discussed the key clinical evidence for abrocitinib in section 3.7.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			ciclosporin can be added. Dupilumab and baricitinib are used if these systemic treatments are not effective. *Clinical trial evidence shows that abrocitinib, tralokinumab and upadacitinib all reduce symptoms of atopic dermatitis compared with placebo. They have been indirectly compared with some standard treatments, but the results are highly uncertain.* *The limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a suitable cost- effectiveness estimate for abrocitinib, tralokinumab and upadacitinib. So, they cannot be recommended."* *****This statement is unacceptably misleading, vague and does not reflect the discussion at the first appraisal committee meeting. The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD was assessed in an extensive clinical trial programme, comprising four pivotal trials (COMPARE, TEEN, MONO-1, and MONO-2). All four trials were randomised, double-blind, and placebo controlled, representing the gold standard for evaluating treatment effectiveness.[1] Importantly, JADE COMPARE evaluated the efficacy and safety of abrocitinib (100 mg and 200 mg) and dupilumab in comparison with placebo. Moreover, JADE DARE was a head-to-head study comparing abrocitinib 200 mg and dupilumab, which is a key comparator relevant to this appraisal. Data are also available for a range of endpoints including those most relevant to decision-making (e.g., EASI-50 and DLQI ≥4) and those most relevant to patients (e.g., PP-NRS) We request that NICE reissue the ACD to clarify specifically the comment related to clinical evidence. It should be clear upfront in the ACD that as per our communication with NICE, the reason for the negative decision was that the committee did not see a model with its preferred assumptions. The paragraph in section 3.23 we believe more accurately reflects the reason for a negative ACM: **"***Because of the issues with the model inputs, the committee did not consider that it had seen analysis that represented its preferred assumptions, so it was unable to assess the cost-effectiveness of the treatments in the appraisal or recommend their use"*	
11.	Consultee	Pfizer Ltd	**Systemic naïve population** The recommendations from the committee related to the systemic naïve population are unclear. However, as per our request on 16 December 2021, prior to the first appraisal committee meeting, we request that abrocitinib be considered as a first-line systemic for adults and adolescents.	Comment noted. The committee discussed this issue in section 3.14 of the FAD.

[1] Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005;90(8):840-4.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			We request that the EAG incorporate the data provided previously within the NMA and model prior to the second appraisal committee meeting	
12.	Consultee	Pfizer Ltd	**Data from the adult population to generalise to the adolescent population (section 3.12)** It is appropriate to reflect on the analysis that have been conducted within the adolescent population although we recognise that it is only feasible to conduct a 'monotherapy comparison' versus dupilumab based on EASI75, given the limitations in the evidence available in adolescents available for dupilumab. Therefore, we agree with the approach proposed by the committee to assume that the results from the 'combination therapy' analysis for adults who were previously exposed to a systemic immunotherapy (and based on EASI 50 + DLQI≥4) would be generalisable to the adolescent population. Only the comparison with dupilumab would be relevant given that baricitinib is licensed for adults only.	Comment noted.
13.	Consultee	Pfizer Ltd	**A fixed effect model for the network meta-analysis (section 3.15 in ACD)** The committee highlighted that they would want to see a fixed effects NMA, given that random effect models with uninformed priors may not be appropriate because of the small number of trials for each treatment arm. We presented fixed effects NMA analyses in our base case within our initial submission and agree with the committee's assessment of the limitations associated with random-effects analysis. However, as also critically highlighted in our original submission, the overall conclusions are largely comparable regardless of approach (fixed or random effects) It is important to ensure that both fixed effects and random effects-are explored in the EAG NMA. Both should be presented to the committee in the next appraisal committee meeting, to ensure that the full complement of evidence is available to ensure rapid decision making and avoid any further delays.	Comment noted. The EAG presented results using a fixed-effects model after consultation. The relevant paragraph has been updated in the FAD. The committee discussed this issue in section 3.15.
14.	Consultee	Pfizer Ltd	A pooled cost-effectiveness estimate for each of the treatment options that have high and low doses (section 3.18 in ACD) In our initial submission (Document B, Section B.3.8.3 [Table 104]) we explored a scenario with a pooled cost-effectiveness estimate for abrocitinib 200 mg and 100 mg doses. An assumption was made that [redacted] of patients would receive abrocitinib 200mg and [redacted] would receive abrocitinib 100mg. [redacted]	Comments noted. The EAG presented scenarios which pooled the cost-effectiveness results of the high and low doses. The committee discussed this issue in section 3.19 of the FAD.

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			[redacted]. The wording in the SmPC related to dosing is as follows: Abrocitinib is to be taken orally with or without food. It is recommended at 200 mg or 100 mg once daily. For most patients, particularly those with severe disease, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions. The maximum daily dose is 200 mg. During treatment, the dose may be decreased or increased based on tolerability and efficacy. Dose reduction can be considered after disease control is achieved in patients receiving 200 mg. Some patients may experience a disease flare after dose reduction. A higher risk of disease flare after dose reduction is associated with history of receiving systemic treatments for atopic dermatitis and extensive disease involving >50% of body surface area (BSA). [redacted] Nonetheless we would ask that the committee have access to Table 104 in our initial submission where this is explored. Further, we would request that the EAG build this scenario into their model to share with the committee ahead of the second appraisal meeting so that all information required for the committee to make a decision in that meeting is available.	
15.	Consultee	Pfizer Ltd	**Additional utility values scenarios based on degree of change observed in the trials, health-state specific values rather than treatment-specific utility values and utility values used in TA534 (section 3.20 in the ACD)** We agree with the committee's concerns around the utility data incorporated within the EAG model and the clinical plausibility of the inputs. The two key issues are as follows: • **Utility data at baseline:** we agree with the committee that there is no clinical rationale for the EAG's use of different baseline utility values across therapies. Although improvement in utility may differ, a common baseline should be applied in the EAG model. • **Assumptions around utility for responders**: o We agree with the suggestion from the EAG that the utility associated with being a responder may differ by treatment which was also recognised by the NICE committee in the ACD *"it plausible that there may be some differences in utility values based on responses to treatment" (page 19)*	Comments noted. The committee discussed this issue in sections 3.21 and 3.22 of the FAD.

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			o It is logical to expect that responders (defined as EASI 50 + DLQI ≥4) on a treatment providing higher thresholds of response (e.g., EASI90) would have a higher utility score. o We strongly disagreed with the EAGs assumption that the utility associated with being a responder on baricitinib 4mg would be comparable to the higher doses of abrocitinib (200mg) and upadacitinib (30mg), although under the proposals from the NICE committee this assumption would no longer apply which is appropriate given the lack of clinical plausibility. The baricitinib 4mg dose, whilst being the 'higher-dose,' in the arbitrary sense of being the highest marketed dose, has substantially lower efficacy compared with both doses of abrocitinib and upadacitinib (see Pfizer submission Document B, Section B.2.9.6 [Table 47]). The committee's conclusion in the ACD is two-fold: 1. *"To explore treatment-specific response utilities"* by using *"a single baseline value and apply changes in utility based on the degree of change observed in the trials. Ideally, this would include a single synthesis of the utility evidence linked via the common comparator of placebo, similar to the network meta-analysis approach used for the effectiveness data"* 2. "*See analysis that used health-state utility values, in order to more clearly see the effect of using treatment-specific utility values.* The first proposal needs careful consideration & evaluation given the potential heterogeneities between the trials as recognised by the NICE committee (ACD, page 19). An alternative and more appropriate approach would be to apply a common baseline utility and utility value associated with being a EASI 50 + DLQI ≥4 responder to all treatments, with additional utility benefits applied based on the proportion of patients achieving EASI75 and EASI90 within the trials. The additional utility benefit associated with being a EASI75 or EASI90 responder could be deduced from regression analysis. In our original submission (Abrocitinib submission Document B, Section B.3.4.5 [Table 71]), we presented this analysis, including for DLQI ≥4 response and for different levels of EASI response. The relevant table is copied below. EASI response categories have been defined in a mutually exclusive way, with categories for patients with an EASI-50 response, but not and EASI-75 response, patients with an EASI-75 response but not an EASI-90 response and patients with an EASI-90 response. This analysis demonstrated that higher levels of EASI response are associated with greater improvements in utility. Treatment covariates were also included but were not significant, suggesting that differences in EASI response sufficiently explained variations in utility between treatments.	

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<tr><td></td><td></td><td></td><td>
COMPARE EQ-5D analysis including EASI-75 and EASI-90 response
<table>
<tr><th></th><th>Coefficient</th><th>Standard error</th><th>LCI</th><th>UCI</th></tr>
<tr><td>Age</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Baseline EQ-5D</td><td></td><td></td><td></td><td></td></tr>
<tr><td>DLQI ≥4</td><td></td><td></td><td></td><td></td></tr>
<tr><td>EASI-50 to -74</td><td></td><td></td><td></td><td></td></tr>
<tr><td>EASI-75 to -89</td><td></td><td></td><td></td><td></td></tr>
<tr><td>EASI-90</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Abrocitinib 100 mg</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Abrocitinib 200 mg</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Dupilumab</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Constant</td><td></td><td></td><td></td><td></td></tr>
</table>
Abbreviations: DLQI, disease quality of life index; EASI0, Eczema Area and Severity Index; LCI, lower confidence; UCI, upper confidence interval.

<u>Critical request:</u>
Explore within the model a baseline utility and utility value associated with being a EASI 50 + DLQI ≥4 responder to all treatments, with an uplift based on the proportion of patients achieving EASI75 and EASI90 within the trials.
</td><td></td></tr>
<tr><td>16.</td><td>Consultee</td><td>Pfizer Ltd</td><td>
Analysis that represents best supportive care treatment waning over time and sensitivity around the modelled time horizon (section 3.21)

While BSC is not a comparator in the EAG model, the utility values for patients ending up on BSC remains an important factor. The EAG model assumed that there is a waning in the utility benefit associated with active treatment and that the response rates seen in clinical trials will not hold in the long-term. However, the model does not include any waning of BSC utility and instead models the BSC as a weighted average of responders and non-responders to BSC, with efficacy taken from the placebo arms of AD UP or MEASURE UP 1 and 2. This is in line with the ERG's preferred approach in TA681, however is at odds with clinical opinion, the approach taken in the company submissions and the committee's preferred assumptions in the baricitinib appraisal (TA681).

The approach from the EAG produces counterintuitive results as in overestimating the utility values for patients receiving BSC in the long-term, the model overstates the QALY gains for treatments with lower response rates and higher rates of discontinuation.
</td><td>Comments noted. The EAG presented a scenario which included best supportive care waning after consultation. The committee discussed this issue in sections 3.23 and 3.24 of the FAD.</td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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We were reassured to see that the committee are requesting additional scenarios related to the waning of BSC within the model and we would propose scenario 2 in the below table in the base case, which aligns with the base case in our initial submission.

Clinical opinion provided to the company indicated that the response to BSC seen in clinical trials would be expected to drop off quickly, with one clinician stating that utility for BSC would be more comparable to that of non-responders. Scenario 2 also represents one of the preferred scenarios from the dupilumab appraisal (TA534) based on long-term CHRONOS data.

Waning of utility benefit for BSC in the model, scenarios for consideration
<table>
<tr><th>Year</th><th>Abrocitinib, dupilumab and baricitinib</th><th>BSC – scenario 1</th><th>BSC – scenario 2</th><th>BSC – scenario 3</th></tr>
<tr><td>2</td><td>98%</td><td>43%</td><td>18%</td><td>18%</td></tr>
<tr><td>3</td><td>95%</td><td>18%</td><td>10%</td><td>10%</td></tr>
<tr><td>4</td><td>93%</td><td>8%</td><td>6%</td><td>10%</td></tr>
<tr><td>5</td><td>92%</td><td>3%</td><td>4%</td><td>10%</td></tr>
</table>
We also explored additional scenarios for BSC waning in our initial submission.
Scenario 1 is additional scenario from the dupilumab appraisal based on CHRONOS that was preferred by the committee

Scenario 3 reflects assumptions that are between the company and ERG base cases in the baricitinib appraisal. In this appraisal in the revised base case the company applied waning assumptions from CHRONOS as per the dupilumab appraisal whereas the ERG preferred no application of treatment waning. The committee commented that the true value was likely somewhere between the company and ERG assumptions. Scenario 3 matches the base case (scenario 2), however there is assumed to be no further waning beyond year 3.

<u>Critical request:</u>
• For the EAG to explore scenarios related to BSC waning including the three scenarios presented in the above table which represent the two preferred scenarios (1 & 2) from
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>the dupilumab appraisal (TA534).

[redacted]</td><td></td></tr>
<tr><td>17.</td><td>Consultee</td><td>Pfizer Ltd</td><td>Limitations related to the comparison with baricitinib
A broader consideration related to the utility data applied within the EAG model is the absence of reliable baricitinib data, given there was no utility gain associated with being in a maintenance health state (i.e., a responder) based on trial data, as discussed in the final guidance from TA681 (page 17).

Further, baricitinib discontinuation data (as per the below table) were provided to Pfizer, with permission from Eli Lilly, for inclusion within our initial STA submission for abrocitinib. This data is highly relevant given that discontinuation is a significant driver of the ICER; however, permission has not been given for this data to be used within the ongoing MTA.

Summary of baricitinib discontinuation rates, annual discontinuation week 52 +
<table><tr><th colspan="2">NICE baricitinib appraisal TA681[a]</th><th colspan="2">EAG model</th></tr><tr><th>EASI 75</th><th>EASI 50 + DLQI≥50</th><th></th><th>EASI 50 + DLQI≥50</th></tr><tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>-</td></tr></table>[a]Slide 47 appraisal committee slides; company and ERG alignment

We strongly disagreed with the EAGs initial assumption that the discontinuation associated with baricitinib 4mg would be comparable to the higher doses of abrocitinib (200mg) and upadacitinib (30mg). The baricitinib 4mg dose, whilst being the ‘higher-dose,’ in the arbitrary sense of being the highest marketed dose, has substantially lower efficacy compared with both doses of abrocitinib and upadacitinib (see Pfizer submission Document B, Section B.2.9.6 [Table 47]).

We appreciate from reading the ACD (section 3.19, page 19) that the EAG also presented to the committee a scenario where baricitinib 4mg was instead assumed to be comparable to the lower doses of abrocitinib (100mg) and upadacitinib (15mg) although the committee’s comments on this are unclear.

We request that the scenario whereby baricitinib is assumed to be equivalent to the high dose JAKs is not presented to the committee as it is not a plausible scenario. As per the recently published NICE manual:</td><td>Comments noted. The committee considered uncertainty surrounding discontinuation rates and the comparison with baricitinib as part of the discussion of best supportive care waning in sections 3.23 and 3.24 of the FAD.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			"*all model parameter values used in base-case, sensitivity, scenario and subgroup analyses should be both clinically plausible and should use methods that are consistent with the data. Results from analyses that do not meet these criteria will not usually be suitable for decision making*[2]*"* More generally, given the challenges related to utility and discontinuation data for baricitinib we question the reliability of comparisons with baricitinib based on a cost-effectiveness analysis. We would defer the NICE committee to our cost-minimisation analysis in relation to the comparison of abrocitinib versus baricitinib as the economic case is more clearly illustrated. **Critical requests:** • Remove the scenario where baricitinib discontinuation is assumed to be equivalent to the high doses of abrocitinib (200mg) and upadacitinib (30mg) as this is not clinically plausible and therefore not appropriate for consideration. [redacted]	
18.	Consultee	Pfizer Ltd	Data from JADE DARE Data from a Phase 3 active-controlled study to assess efficacy of abrocitinib 200mg versus dupilumab 300mg, was requested during the committee meeting. This was shared by us on 17 September 2021 as soon as it was available internally, however it was not incorporated within the NMA/model developed by the EAG even after the consultation period. Given the comments from the committee in the first appraisal meeting we would ask the EAG to incorporate these data within the NMA and modelling. The data from JADE DARE comparing abrocitinib and baricitinib aligns broadly with the narrative from JADE COMPARE as per our initial submission. It is unlikely to change markedly the overall conclusions but add additional weighting to these. **Critical request:** For the EAG to add JADE DARE into the network for indirect comparisons with baricitinib and dupilumab to ensure that this data is captured prior to the second appraisal committee meeting.	Comment noted. The recommendation section has been updated in the FAD. The committee discussed the key clinical evidence for abrocitinib including JADE DARE in section 3.7.
19.	Consultee	Pfizer Ltd	**Modelling treatment sequencing (section 3.6)** In our initial submission we presented exploratory analysis looking at treatment	Comment noted.

[2] Developing NICE guidelines: the manual paragraph 4.6.27

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			sequencing although we highlight several of the limitations associated with the analysis (see Pfizer submission Document B, Section B.3.10). Efficacy data for patients who received their second systemic therapy was assumed as equal to the base-case model data with no adjustment made given that there is no data on sequential effectiveness. We agree with the committee that for that reason cost-effectiveness analysis based on treatment sequencing would be associated with significant uncertainty that is unresolvable.	
20.	Consultee	Pfizer Ltd	**Minor wording change** • Paragraph 3.4. 'used in inflammatory disorders' is repeated in this paragraph	Comment noted. This has been amended.
21.	Consultee	Abbvie ltd	This document outlines AbbVie's perspective on the ACD. AbbVie welcome the Committee's conclusions which were broadly positive for upadacitinib. However, AbbVie were disappointed to learn that the Committee issued an appraisal consultation, bearing in mind the recent positive Scottish Medicines Consortium (SMC) decision for upadacitinib for people over 12 years with moderate to severe atopic dermatitis. Unfortunately, AbbVie did not receive the updated External Assessment Group (EAG) model by 4th May 2022. Therefore, AbbVie adapted the original EAG model to address issues in the ACD, using the second-line, combination treatment effectiveness inputs for both adults and adolescents. While the ACD focussed on specific modelling assumptions, it is important to highlight to the Committee that upadacitinib has been studied in a head-to-head study against dupilumab. The effectiveness of upadacitinib 30 mg monotherapy compared to dupilumab monotherapy was established in the Heads UP trial. At 16 weeks, patients aged over 18 years with moderate to severe atopic dermatitis achieved an EASI 75 improvement of 71% (247/348) in the upadacitinib arm and 61.1% (210/344) in the dupilumab arm (mean adjusted difference: 10 %, 95% confidence interval (CI) for difference 2.9 to 17.0, p=0.006), which supports the conclusions of the fixed effects and random effects network meta-analysis that upadacitinib 30 mg is more effective than dupilumab 300 mg. To address the Committee's key concern regarding counter-intuitive results (issue 4 and 5), AbbVie thoroughly queried interactions between clinical and cost-effectiveness, the inputs for conditional discontinuation, best supportive care (BSC) and health state utility values (HSUV). The combination of data inputs applied in the initial EAG model including baseline HSUV utilities, responder HSUV and conditional discontinuation produces a scenario where interactions between the inputs lead to counter-intuitive results. Once the model is updated with common baseline utilities and responder utilities rather than treatment arm-specific utilities, the direction of the cost-effectiveness results follows the clinical effectiveness. While applying responder utilities improves the intuitiveness of the model outputs, it does have its own limitations. Given that conditional discontinuation is	Comments noted. The committee discussed this issue in sections 3.21 and 3.22 of the FAD.

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			currently derived as naïve rates from each trial without adjustment for potential differences, expanding the assumption of responder-derived values to also cover conditional discontinuation represents a consistent approach and removes a source of bias where the evidence-base for treatment differences remains unclear. Therefore, AbbVie carried out a scenario whereby discontinuation rates were based on TA534 (3.7%) or AD UP ([redacted]) across all agents. The inputs for BSC HSUV (high or low), baseline HSUV and conditional discontinuation (AD UP or TA534) influence the ICERs and are interactive between each other. If it is assumed that conditional discontinuation is treatment-specific rather than responder-specific, this further complicates the issue as different treatments benefit from BSC at different time-points depending on which effectiveness and conditional discontinuation rates are applied in the cost-effectiveness model (CEM). However, the direction of results is consistent with expected clinical effectiveness results if disease specific responder values are applied rather than treatment-specific values. AbbVie agrees with the Committee's preference for a common HSUV baseline value (Section 3.20), where it is assumed that randomisation to placebo or active treatment do not impact on baseline HSUV. AbbVie believe that applying the upadacitinib clinical trial data from AD UP and dupilumab clinical trial data from TA534 for HSUV are reasonable options, since this reflects the available evidence for responders. However, due consideration for the results of Heads UP is appropriate as additional benefit is likely to be conferred on patients with response per EASI 90 or EASI 100 criteria. The Committee recognised the burden of disease of atopic dermatitis and the need for alternative treatments. Combining these scenarios yields cost-effectiveness results for upadacitinib that represent good use of NHS resource and will enable people with atopic dermatitis who have failed least one conventional systemic immunosuppressant, such as ciclosporin, to benefit from a clinically effective agent.	
22.	Consultee	Abbvie ltd	Response to Appraisal Consultation Document Although the Committee were unable to come to a decision after the first Committee meeting, the discussion at the Committee meeting was broadly positive: • Recognition of the burden of disease of atopic dermatitis (Section 3.1) and the need for alternative treatments (Section 3.1, 3.3). • Adult evidence is generalisable for adolescents (Section 3.12). In the meeting, one of the clinical advisors pointed out that equal access for adolescents and adults is important. • Abrocitinib, tralokinumab and upadacitinib are clinically effective vs placebo (Section 3.10). The network meta-analysis with dupilumab or baricitinib is appropriate for decision-making (Section 3.13) and the fixed effects results (AbbVie original choice) may be more appropriate than the random effects (EAG choice) (Section 3.15). • The structure of the economic model is appropriate for decision-making	Comments noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			(Section 3.17). • Combination therapy as base case (Section 3.5), with AD UP providing evidence for upadacitinib (Section 3.8). • EASI 50 + Dermatology Life Quality Index (DLQI) 4 is the most relevant endpoint for decision-making (Section 3.11). Scenario analyses to existing model Unfortunately, AbbVie did not receive the updated EAG model by 4th May 2022 and had to adapt the existing EAG model to address issues in the ACD, using the second-line, combination treatment effectiveness inputs for both adults and adolescents. AbbVie further requests that cost-effectiveness results presented by the EAG include the PAS prices that [redacted] The issues are addressed as per the bullet points for additional analysis requested by the Committee on page 22 of the ACD.	
23.	Consultee	Abbvie ltd	Issues 4 and 5: Counter-intuitive results in the model vs clinical response Discontinuation as a model driver As discussed in the summary, the model ceases to produce counter-intuitive results (i.e., decreasing effectiveness improves cost-effectiveness) when data inputs for HSUV and conditional discontinuation are assumed to be for responders rather than being treatment-specific. The Committee has requested analyses which assess disease health state utilities, it is important to note the limitations with this approach (see Alternative active treatment utility values). To avoid biasing the results without robust evidence, the Committee should also consider disease-specific conditional discontinuation rates, as was the case in TA681 (baricitinib appraisal in moderate-severe AD). Responder conditional discontinuation rates In the previous EAG base case, the conditional discontinuation rates were [redacted] for upadacitinib 15 mg, [redacted] for upadacitinib 30 mg (both from AD UP) and 3.7% for dupilumab from TA534 (dupilumab appraisal in moderate to severe AD). As conditional discontinuation is currently derived from each trial without adjustment for differences, expanding the assumption of responder-derived values to also cover conditional discontinuation is consistent and removes a potential bias where the evidence-base for differences remains unclear. Therefore, AbbVie carried out a scenario whereby discontinuation rates were based on TA534 (3.7% across all agents), together with a scenario using AD UP-derived value of [redacted] across all agents. More recent clinical trials, such as AD UP, were conducted at a time when treatment choice in clinical practice and the clinical trial setting had drastically improved. Clinical expert opinion suggests that availability of alternative treatments is likely to influence patient discontinuation. Therefore, extending the	Comments noted. The committee discussed utility values used in the economic model in section 3.21 and 3.22 of the FAD. It also discussed best supportive care assumptions in sections 3.23 and 3.24 of the FAD.

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			assumption of responder values for HSUV to also cover conditional discontinuation from AD UP is a reasonable assumption when considering disease specific utilities. Patients with a response to treatment were assumed to have similar risk of discontinuing treatment, and the AD UP conditional discontinuation rates were pooled ([redacted] and this rate applied across all treatments. In summary, both doses of upadacitinib remained cost-effective compared to dupilumab, when a consistent discontinuation rate was used across all treatments. Utility values for BSC The ACD stated that utility values for the BSC health state are highly uncertain and have a large impact on the cost-effectiveness results (Section 3.21). Utility values for the BSC health state were derived using a weighted average of the utility values for responders and non-responders at week 16. The current base case BSC utility for the second-line adult combination population is [redacted], based on the average of responders and non-responders to placebo in the AD UP trial (see Table 45 of the MTA report). AbbVie has explored the issue by varying the BSC HSUV higher and lower than [redacted] as follows: • TA534 generalised BSC non-responders (0.7732): week 16 non-responder utility for BSC from TA534 (Higher BSC HSUV). • TA534 baseline combination (0.663): baseline utility from TA534 for combination treatment to model complete treatment effect waning for BSC (Lower BSC HSUV). For upadacitinib 15 mg, ICERs are in the SW quadrant, while cost-effective, ICER decrease with a lower BSC HSUV due to higher proportion of patients in BSC. For upadacitinib 30 mg, ICERs remain in the NE quadrant. A low BSC HSUV results in marginally improved ICERs (lower NE quadrant ICERs) as more patients are on modelled on BSC for dupilumab. Alternative active treatment utility values The Committee suggested that treatment-specific utility values are uncertain and alternative utility value scenarios should be explored (Section 3.20). The Committee suggested that alternative utility values could be based on degree of change observed in the trials, HSUV rather than treatment-specific utility values, and utility values used in TA534. AbbVie has carried out scenarios based on the following: • Common baseline and responder utilities based on TA534 (baseline utility = 0.663; responder utility = 0.8979). • Common baseline utility based on AD UP ([redacted] made up of an average of current high and low dose JAK inhibitor utilities for second-line combination population ([redacted]) and responder utilities for active treatment based on combined AD UP results for both doses from upadacitinib	

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			applied to all responders on upadacitinib or dupilumab. Notably, this should be considered a conservative analysis for upadacitinib 30 mg vs dupilumab due to the positive results for upadacitinib vs dupilumab in the Heads UP trial. While using upadacitinib clinical trial data from AD UP is an appropriate approach given that it is a recent high quality clinical trial and considered representative of clinical practice, using disease-specific responder utilities has the limitation of not considering the impact of clinical effectiveness improvements on quality of life. Applying disease-specific responder conditional discontinuation rates as an appropriate extension to this scenario further establishes that upadacitinib 15 mg and upadacitinib 30 mg represent a cost-effective use of NHS resources. Shorter time horizon for consideration Applying a time horizon of 5 or 10 years has significant limitations. Atopic dermatitis is a chronic condition, and as suggested by NICE methods and previous precedent, a life-time horizon is most appropriate, therefore the base case considered a life-time time horizon (100 years). AbbVie modelled a 5-year and 10-year time horizon as scenarios to reflect [redacted]. These shorter time horizons reflect that patients may switch to another active agent, rather than remain on BSC. Reducing the time horizon in this way results in upadacitinib remaining cost-effective vs dupilumab.	
24.	Consultee	Abbvie ltd	Issue 1: Adult results generalisable to adolescent population Section 3.12 concluded that the results of the 'combination therapy' analysis for adults who had tried systemic immunotherapy would likely be generalisable to the adolescent population. A scenario analysis was carried out running the adolescent baseline characteristics in the adult model (second-line combination data). Results from the original adolescent model showed that upadacitinib 15 mg was dominant vs dupilumab. The scenario showed that upadacitinib 15 mg remained cost-effective with ICERs in the SW quadrant. Due to the preference of adolescents, the results based on adolescent clinical trial participants should not be ignored for decision making.	Comment noted. The committee discussed this issue in section 3.12 of the FAD.
25.	Consultee	Abbvie ltd	Issue 2 – Fixed effect network meta-analysis Section 3.15 states that random effect models with uninformed priors may not be appropriate because of the small number of trials for each treatment arm. The Committee concluded it would like to consider the results of the fixed effects analysis, which may reduce the width of the credibility intervals and also may plausibly affect the point estimates of the results used in the deterministic base case analysis. This is shown in Table 2 below, which is taken from the Appendices submitted by AbbVie in our initial Single Technology Appraisal submission (Table 49). We acknowledge that the use of a random effects model is often preferred in a	Comment noted. The EAG presented results using a fixed-effects model after consultation. The relevant paragraph has been updated in the FAD. The committee discussed this issue in section 3.15.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Bayesian indirect comparison, as it allows for between-studies heterogeneity in the estimates of treatment effect. However, where there is a single data source for the treatment, as is the case for many treatments in this analysis, this benefit is negated. Furthermore, in the situation where single studies feed into the analysis, a random effects model will yield zero-estimates for type I error, probably reflecting unchanged non-informative priors2,3. This effect results in the lack of face validity seen in the random effects model, which yielded an estimate of 95% CI that substantially exceeded the 95% CI seen in the source study. Results from the random and fixed effects models are similar, in particular the point estimates. The credible intervals are wider for the random effects model. However, this is a function of small numbers of studies feeding into the analyses causing the posterior of between trial standard deviation to be sensitive to the prior4. The vague prior therefore results in posteriors which allow for unrealistically high levels of heterogeneity. Consequently, in this situation the fixed effects model is the appropriate network meta-analysis model for base case analysis due to the low number of trials used to estimate between study variability.	
26.	Consultee	British Association of Dermatologists	We agree with the committee that all the available evidence was not included in the original document but needs to be considered. This includes data from studies that were not available in the original analysis, e.g. JADE-DARE, AD-UP, RISING-UP	Comments noted.
27.	Consultee	British Association of Dermatologists	The committee may wish to consider the results of the TREAT trial (ciclosporin vs. methotrexate in adolescents), although we realise these treatments are not currently licensed in adolescents with eczema. The investigators would be happy to share the results confidentially with NICE in a few months' time when they have been accepted for publication. There is also additional published evidence regarding methotrexate in adults which would ideally be considered because methotrexate is the most commonly used first-line treatment for eczema and is much cheaper than ciclosporin or the new drugs	Comments noted. The committee discussed this issue in section 3.14 of the FAD.
28.	Consultee	British Association of Dermatologists	Evidence from trial situations is limited because trial data necessarily exclude some patients, e.g. significant mental health difficulties, patients who have not responded to other treatments, patients with very severe disease who it would be unethical to randomise to placebo or who would drop out of the standard run-in period due to disease flares when their current systemic therapy needs to be stopped. Hence, real-world effectiveness data, such as that from the A-STAR registry, are likely to be more representative of the patient populations treated within NHS clinics than cohorts enrolled in trials	Comments noted. The committee discussed this issue in section 3.26 of the FAD.

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29.	Consultee	British Association of Dermatologists	There are many patients who have been treated with abrocitinib under the Early Access to Medicines Scheme (EAMS) and with tralokinumab and upadacitinib via free-of-charge (FOC) or nearly FOC schemes from their respective manufacturers. Such patients would have not only failed treatment with at least one conventional systemic but also a novel agent (most likely dupilumab). This shows the need for additional systemic therapies and the companies may have data from enrolment into these schemes that could be additionally used for the NICE technology assessment	Comments noted. The committee discussed this issue in section 3.26 of the FAD.
30.	Consultee	British Association of Dermatologists	It is essential that patients commencing new treatments for eczema are entered into an independent research data platform, such as A-STAR, to allow evidence of comparative effectiveness, safety and treatment effect waning to be taken into account for future appraisals. A-STAR also collects health resource use data that could be used for the health economic evaluation that forms part of the NICE technology assessments	Comments noted. The committee discussed this issue in section 3.26 of the FAD.
31.	Consultee	British Association of Dermatologists	The summary statement that the drugs in question 'have been indirectly compared with some standard treatments, but the results are highly uncertain' seems disingenuous in the light of overwhelming data showing clinical benefit, including the living NMA (Drucker et al.) just published in JAMA Dermatology. This NMA has conducted indirect comparisons between the novel systemics using much of the same data as NICE, and demonstrated evidence of efficacy against conventional and other novel drugs, in particular dupilumab., Drucker states, ''This systematic review with meta-analysis found that compared with dupilumab, abrocitinib, 200 mg daily, and upadacitinib, 30 mg daily, were associated with reductions in EASI scores; upadacitinib, 15 mg daily, was associated with similar reductions, and tralokinumab, 300 mg every other week, and baricitinib, 2 and 4 mg daily, were associated with fewer reductions''. The uncertainty identified by NICE principally surrounds the meta-analysis approach taken, which essentially favours head-to-head clinical trial data with IMP vs. best supportive care. Unfortunately, such data largely does not exist, and therefore, it seems unreasonable to derive a model that favours it. However, the efficacy of the medications under review against placebo was undoubted and agreed in the report. Indeed, it was a drug vs. placebo technology appraisal model that has been applied for novel AD therapies until now. The uncertainty of effect size due to a circuitous indirect comparison with ciclosporin, risks loss of sensitivity. This results in a negative appraisal which would exclude highly effective treatments from clinical use for our patients. In the single area where head-to-head data is available (albeit not as primary endpoint) abrocitinib vs. dupilumab data, the clinical efficacy of abrocitinib is demonstrated, supporting	Comments noted. The committee discussed the indirect comparison of interventions with ciclosporin in section 3.14 of the FAD.

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			the argument that the indirect comparison model used in the NMA by Drucker et al. is robust. Another possible reason for difference in analysis results between NICE and Drucker include the categorical/dichotomous outcomes used in the NICE analysis vs. continuous outcomes in Drucker.	
32.	Consultee	British Association of Dermatologists	The cost economic modelling is problematic for several reasons highlighted by the committee in the consultation document. The committee have suggested a number of areas where changes are needed, which we broadly agree with.	Comments noted.
33.	Consultee	British Association of Dermatologists	We are very concerned that different methodology used in the appraisals for novel eczema treatments to date (dupilumab, baricitinib and this one) has led to different conclusions regarding cost effectiveness. For example, the utility value of best supportive care in this model was associated with higher quality of life and lower costs compared with the dupilumab appraisal. The consequence of this is that dupilumab, which was previously recommended, now appears less cost effective. We feel strongly that this needs to be addressed because of the implications for future NICE appraisals of new eczema treatments.	Comments noted.
34.	Consultee	British Association of Dermatologists	It was stated in the ACD document that "The limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a suitable cost-effectiveness estimate for abrocitinib, tralokinumab and upadacitinib. So, they cannot be recommended." However, when dupilumab and baricitinib were being appraised by NICE, the evidence available was more limited.	Comments noted. The recommendation section has been updated in the FAD.
35.	Consultee	British Association of Dermatologists	'Best supportive care' (BSC) is defined in this model as a single health care state. Costs of BSC are calculated by the weighted average of responders and non-responders at 16 weeks (as guided by the NMA of clinical effectiveness). This is likely to be an underestimate of true costs of BSC (see below). We do not feel it is appropriate to have a single BSC state or that this state should be assumed to be stable for the duration of modelling (5 years). In the current modelling, BSC is associated with high quality of life and low costs. This is incorrect and leads to favouring of ineffective treatments.	Comments noted. The relevant paragraphs have been updated in the FAD. The committee discussed this issue in sections 3.23 and 3.24.
36.	Consultee	British Association of Dermatologists	Patients in BSC are likely to require high-cost, ongoing care, including: i. Ongoing hospital outpatient attendances and investigations. ii. Alternative systemic drugs requiring hospital follow-ups, blood tests, other monitoring and management of drug side effects and toxicity. iii. GP support. iv. Hospital admission for severe uncontrolled disease. v. Mental health input due to impact of severe disease. vi. High social costs due to inability to work, costs of carers and impact on	Comment noted.

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			family.	
37.	Consultee	British Association of Dermatologists	Costs of being on different classes of drugs is not considered in the model (apart from the actual drug costs). Conventional systemic drugs and JAK inhibitors require frequent blood tests. Biologics including dupilumab and tralokinumab require minimal blood tests, and less frequent hospital attendances once stable.	Comment noted.
38.	Consultee	British Association of Dermatologists	The BAD does not consider these recommendations, as they stand, to be sound or a suitable basis for guidance to the NHS, for reasons outlined above and below.	Comment noted. The recommendation section has been updated in the FAD.
39.	Consultee	British Association of Dermatologists	The most important group of patients who need these drugs are those who have tried all existing treatments for eczema, and none have worked. These patients are desperately in need of new treatments to allow them to return to productive living, as evidenced by the uptake of JAK inhibitors on the EAMS and FOC schemes, where these drugs have proved life-changing for some.	Comment noted.
40.	Consultee	British Association of Dermatologists	There is a need for drugs of different classes to be available because eczema is a long-term disease affecting patients of all ages and with differing co-morbidities and preferences. Clinical judgement will influence treatment choice for individual patients, based on efficacy, adverse effects profile, pre-existing co-morbidities and cost. For this reason, it is not appropriate to dictate a rigid sequence of treatments.	Comment noted.
41.	Consultee	British Association of Dermatologists	Currently, the free of charge schemes run until October 2022, after which patients may not be able to access drugs which are currently working for them	Comment noted.
42.	Consultee	British Association of Dermatologists	We agree with the committee decision to recommend that adolescents are treated the same as adults to avoid age discrimination.	Comment noted.
43.	Consultee	British Association of Dermatologists	We note that the Scottish Medicines Consortium has approved tralokinumab (https://www.scottishmedicines.org.uk/medicines-advice/tralokinumab-adtralza-full-smc2403/) and upadacitinib (https://www.scottishmedicines.org.uk/medicines-advice/upadacitinib-rinvoq-full-smc2417/), and our understanding is that abrocitinib may be approved shortly. The current recommendation would therefore create a situation where patients in Scotland have access to the medications under assessment, while patients in England might not.	Comment noted. The recommendation section has been updated in the FAD.
44.	Consultee	Eczema Outreach Support (EOS)	EOS are concerned that the recommendation that abrocitinib and upadacitinib are not recommended for treating moderate to severe atopic dermatitis in young people 12 years and over denies adolescents access to a treatment that may provide significant relief from the chronic condition. Finding a treatment that works for severe eczema is a process of trial and error, so choice of treatment is very important. Families endure many years of trying different treatments including steroids, moisturisers, creams and bandages, light therapy and	Comment noted. The recommendation section has been updated in the FAD.

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			immunosuppressants, but if none of this works, they are reaching the end of the line for treatments which can be very stressful. Having more options at this stage would make a huge difference to adolescents who feel they are running out of options. Finding a treatment that works can be life changing for adolescents, significantly improving their physical and mental health, and their life chances.	
45.	Consultee	Eczema Outreach Support (EOS)	EOS are concerned that a delay in making abrocitinib and upadacitinib available as an option to adolescents with severe eczema may lead to avoidable suffering for young people struggling to manage the physical and mental impact of the condition.	Comment noted. The recommendation section has been updated in the FAD.

Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis

EAG response to ACD

May 2022

Source of funding

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1 Introduction

The first appraisal committee meeting (ACM) to discuss abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis took place in March 2022 and the committee concluded that none of the drugs could be recommended within their marketing authorisations as the results from the clinical and cost-effectiveness analyses are highly uncertain. In the appraisal consultation document (ACD), the committee requested further analyses that represented its preferred assumptions. The additional analyses requested by the committee are as follows:

- Data from the adult population to generalise to the adolescent population;
- A fixed effect model for the network meta-analysis (NMA);
- A pooled cost-effectiveness estimate for each of the treatment options that have high and low doses;
- Additional utility values scenarios based on degree of change observed in the trials, health-state specific values rather than treatment-specific utility values and utility values used in TA534;
- Analysis that represents best supportive care (BSC) treatment waning over time and sensitivity around the modelled time horizon.

In the following sections of this document, the EAG explores and discusses the requested committee analyses and, where appropriate, provides revised clinical and cost-effectiveness results. All cost-effectiveness results presented in this report are based on list prices. For cost-effectiveness results inclusive of confidential patient access scheme (PAS) discounts, please refer to the confidential appendix to this report.

2 Revised clinical effectiveness analyses

The clinical experts at the appraisal committee meeting (ACM) explained that abrocitinib, tralokinumab and upadacitinib are all likely to be offered alongside topical corticosteroids (TCS) in clinical practice. The committee therefore agreed to focus on the evidence for 'combination therapy' as the most relevant evidence for decision-making. Only the combination therapy analyses have therefore been updated and presented in this report.

The clinical experts at the ACM also explained that the current treatment pathways for adults and adolescents with atopic dermatitis are similar. The committee considered that because of the likely similarity between adolescents and adults, the results of the combination therapy analysis for adults who had previously received systemic immunotherapy would likely be generalisable to the adolescent population. An updated separate analysis for the adolescent population is therefore not provided. The ERG explored the possibility of incorporating adolescent data in the updated analyses for the first line and second line populations. However, the data requested by the EAG and provided by the companies at the clarification stage for the adolescent population for abrocitinib and upadacitinib were not separated by line of therapy. The adolescent data could therefore not be included in the updated analyses.

Data for the trial JADE DARE,[1] comparing abrocitinib and dupilumab, both in combination with TCS were not available in time for inclusion in the original EAG report but have been included in this updated analysis.

The committee considered that the small number of trials for each treatment arm of the analyses may be inflating the heterogeneity in the network when analysed using a random effects model. It concluded it would like to consider the results of the fixed effects analysis, which may reduce the uncertainty and also may plausibly affect the point estimates of the results used in the deterministic base case analysis. Results are therefore provided both using a fixed effect model and using a random effects model, with the latter using an informed prior for the between-trial heterogeneity.

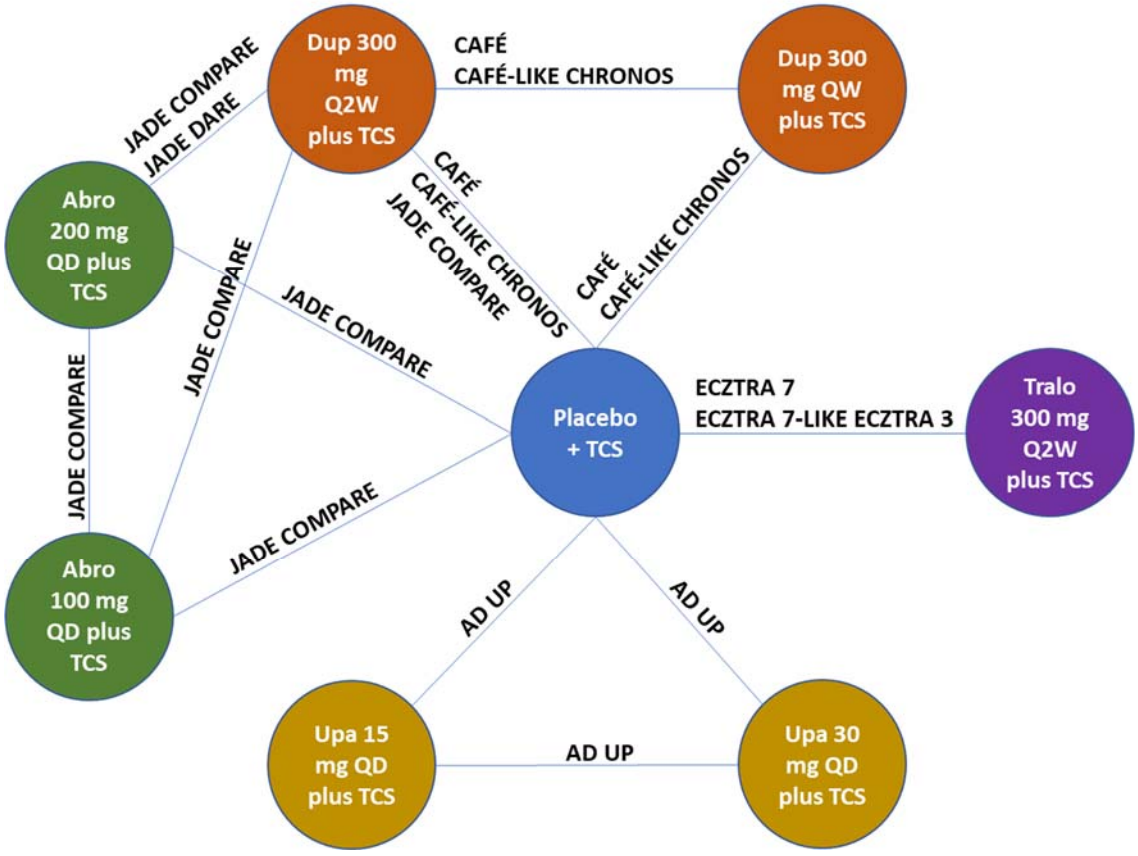
2.1 Second line - patients who have failed on CsA

The updated analysis of the NMA in the second-line setting is focused on the composite outcome. Baricitinib, for which data are only available for EASI 75, is therefore not included as a comparator in the updated NMA. As in the original analysis for the NMA of interventions used in combination with

TCS in the second-line setting, *post hoc* subgroups were used for all studies apart from the dupilumab trial CAFÉ[2] and the tralokinumab study ECZTRA 7.[3] However, the data for dupilumab were informed by the pooled results of CAFÉ and the relevant *post hoc* subgroup data from CHRONOS[4] presented in TA534.[5] The pooled data have been considered as a single study. The updated analysis for the combination therapy NMA is based on using all observed data, regardless of rescue medication use, to determine response.

The network of trials contributing to the NMA of combination therapies on EASI 50 + ΔDLQI ≥4 in the second line adult population is presented in Figure 1. This network includes two head-to-head trials of an active intervention versus the comparator dupilumab (JADE COMPARE[6] and JADE DARE[1]). This is likely to produce different results to a "star shaped" network that relies only on indirect comparisons.

Figure 1. Network plot second line adult population, combination therapy, EASI 50 + ΔDLQI ≥4



Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Tralo, tralokinumab; Upa, upadacitinib.

The fixed effect and random effects models were similar in terms of goodness of model fit (similar DIC) and residual deviance (Table 3). As would be expected, the models produced very similar point estimates but the random effects model resulted in wider 95% credible intervals (CrIs).

Table 1. Summary of NMA model characteristics

Characteristic	Random effects	Fixed effect
Deviance information criterion	96.14	95.3
Total residual deviance	15.4	16.2
Number of data points	16	16

The fixed effect analysis shows that treatment with abrocitinib, dupilumab, tralokinumab or upadacitinib lead to a statistically significant improvement in EASI 50 + ΔDLQI ≥4 compared with placebo (Table 2**Error! Not a valid bookmark self-reference.**), in agreement with findings from pair-wise meta-analyses. Using a random effects model, the 95% CrIs were wider and although treatment with any of the interventions was favoured over placebo, the results for tralokinumab did not reach statistical significance.

When compared with dupilumab, there were no comparisons that reached statistical significance using the random effects model. With the fixed effect model the results were statistically significant for upadacitinib 30 mg, in favour of upadacitinib [redacted], and for tralokinumab, in favour of dupilumab [redacted]. The OR of upadacitinib 15 mg, abrocitinib 100mg and 200 mg were closer to 1, favouring dupilumab for both of the lower doses and favouring abrocitinib for the higher dose.

Table 2. Estimates of effect (EASI 50 + ΔDLQI ≥4) of second line systemic treatments in combination with TCS at 16 weeks, generated by NMA and pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)	
		Fixed effect	Random effects
Treatments versus placebo + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	7.05 (4.22 to 11.77)	[redacted]	[redacted]
Dup 300 mg QW + TCS	6.60 (4.09 to 10.66)	[redacted]	[redacted]
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]

Treatments versus Dup 300 mg every 2 weeks + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Tralokinumab + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]
Treatment doses versus each other			
Abro 200 mg QD + TCS vs Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS vs Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

2.2 First line – patients who are naïve to systemic therapy

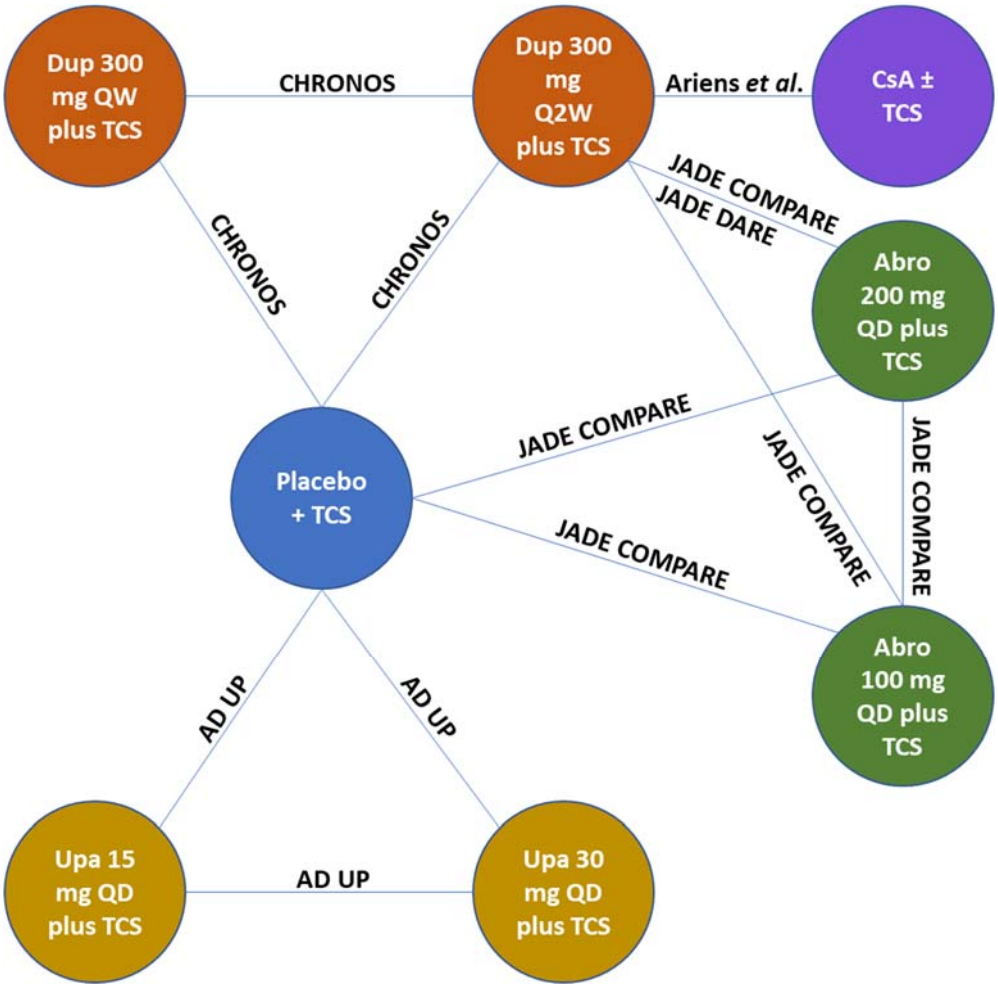
Upadacitinib was originally the only one of the interventions assessed in this MTA that was proposed as a first-line systemic therapy for adults having inadequate response to topical treatments. However, the company for abrocitinib has put forward a request for abrocitinib to be assessed as a treatment option in the first-line setting. The analysis has therefore been updated incorporating the relevant data for abrocitinib. The network of studies informing the analysis is otherwise unchanged and the data informing the comparator, CsA, is still based on Ariens *et al*.[7] which provides the results of a regression analysis of patient level data for patients treated with dupilumab in the placebo controlled RCT CHRONOS and patients treated with CsA in daily practice at the Department of Dermatology and Allergology, University Medical Center (UMC) Utrecht, the Netherlands. Data for EASI 50 + ΔDLQI ≥4 were not available from Ariens *et al*. and so EASI 75 became the primary outcome for this population.

The analysis focused on the *post hoc* subgroup of patients in the upadacitinib trial AD UP and the abrocitinib trials JADE COMPARE and JADE DARE, for whom the trial intervention was their first-line systemic therapy. Of the CsA-treated patients in Ariens *et al*., 70% had no history of previous treatment with oral immunosuppressive drugs, though outcome data for this specific subgroup were not available and this cohort was therefore compared with the full population of the CHRONOS trial treated with dupilumab. Of the dupilumab treated patients in CHRONOS, 41% had previously received systemic immunosuppressants to treat AD. The difference in prior systemic therapy introduces clinical heterogeneity into the analysis, which is likely to favour upadacitinib and abrocitinib over CsA because those with prior treatment are likely to be more severe at baseline.

The data from Ariens *et al*. (CsA versus dupilumab) and from CHRONOS (dupilumab versus placebo), were analysed as two separate studies.

The network of trials contributing to the NMA in the first-line population is presented in Figure 2.

Figure 2. Network plot first-line adult population, combination therapy, EASI 75



Abbreviations: CsA, cyclosporine A; Dup, dupilumab; OD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Upa, upadacitinib. For the NMA in the first line adult population, the random and fixed effect models for the primary analysis and the sensitivity analyses were similar in terms of goodness of model fit (Table 3), but the residual deviance for the random effects model was closer to the number of unconstrained data points than the fixed effect model.

Table 3. Summary of NMA model characteristics

Characteristic	Random effects	Fixed effect
Deviance information criterion	101.7	102.3

Total residual deviance	14.4	16.5
Number of data points	14	14

The results of the NMA, presented in Table 4, show that abrocitinib, upadacitinib, dupilumab and CsA are all more effective than placebo, i.e., leading to more responders (patients achieving EASI 75). The difference versus placebo was statistically significant for abrocitinib (both doses), upadacitinib (both doses) and dupilumab, but not for CsA, irrespective of the use of fixed or random effects model. Results from the NMA were in agreement with findings from pair-wise meta-analyses, in which all interventions analysed were found to be statistically significantly more effective than placebo.

Both doses of upadacitinib were shown to be more effective than CsA, with a larger OR for upadacitinib 30 mg than for upadacitinib 15 mg. The point estimates were similar for the fixed and random effects models and the results were statistically significant except for the lower upadacitinib dose using the random effects model. Both doses of abrocitinib were also shown to be more effective than CsA, with a dose dependent response. However, only using the fixed effect model for the comparison of abrocitinib 200 mg were the results statistically significant.

Table 4. Estimates of effect (EASI 75) of first line systemic treatments in combination with TCS at 16 weeks, generated by NMA and pair-wise meta-analysis

Comparison	Pair-wise meta-analysis OR (95% CI)	NMA OR (95% CrI)	
		Fixed effect	Random effects
Treatments versus placebo + TCS			
Abro 200 mg QD + TCS	[redacted]	[redacted]	[redacted]
Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Dup 300 mg Q2W + TCS	5.82 (3.56 to 9.52)	[redacted]	[redacted]
Dup 300 mg QW + TCS	5.07 (3.62 to 7.11)	[redacted]	[redacted]
CsA + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]
Treatments versus CsA + TCS			
Abro 200 mg QD + TCS	NA	[redacted]	[redacted]
Abro 100 mg QD + TCS	NA	[redacted]	[redacted]
Upa 30 mg QD + TCS	NA	[redacted]	[redacted]
Upa 15 mg QD + TCS	NA	[redacted]	[redacted]
Treatment doses versus each other			

Abro 200 mg QD + TCS vs Abro 100 mg QD + TCS	[redacted]	[redacted]	[redacted]
Upa 30 mg QD + TCS vs Upa 15 mg QD + TCS	[redacted]	[redacted]	[redacted]

Abbreviations: Abro, abrocitinib; CI, confidence interval; CrI, credible interval; Dup, dupilumab; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

The limitations of these analyses are the same as in the original EAG report.

The evidence informing the NMAs are primarily derived from *post hoc* subgroups, which introduces bias and uncertainty around the results generated by the NMAs, and is a considerable limitation that impacts on the robustness and confidence in the estimates of effect for clinical effectiveness. Methodological heterogeneity between the trials in the networks is also likely to have contributed to the uncertainty in the results.

For the analysis of first-line systemic treatment, no randomised controlled trial (RCT) was identified to inform the effectiveness of CsA. Thus, results for the comparison with upadacitinib and abrocitinib in the first-line setting are derived from observational data, which is associated with the bias inherent in observational studies and the results should be interpreted with caution. In addition, the data for upadacitinib and abrocitinib were for the subgroup of patients who were naïve to systemic therapy. However, the population informing the comparator, CsA, was not limited to those who were naïve to systemic therapy. It is unclear how this difference in the populations may affect the results of the analysis and the generalisability of the results to the systemic naïve patients in clinical practice.

The EAG considers it important to note that the sample sizes informing the NMAs equate to a small proportion of the overall trial populations from which the subgroups are created, particularly for the second line population and, in particular, for abrocitinib. The effect of small sample size on the results of the NMA is apparent in the wide 95% CrIs, irrespective of the use of fixed or random effects model, which indicate considerable uncertainty around the true estimate of comparative effectiveness.

3 Revised cost-effectiveness analyses

3.1 Treatment effectiveness

As mentioned in Section 2, the first-line network meta-analysis (NMA) was revised to include abrocitinib 100 mg and 200 mg as interventions, and the second-line NMA was revised to include the abrocitinib trial JADE DARE. For the Evidence Assessment Group (EAG) base case, both NMAs used a random effects model, consistent with the model type in the EAG report. However, to address committee concerns that a fixed effects model could also be appropriate, the EAG ran a scenario analysis in the economic model exploring the results of the NMA using the fixed effects model.

Table 5 presents the baseline Week 16 treatment response by population used in the economic model. The baseline Week 16 treatment response was converted into log-odds to be applied to the log-odds ratios from the NMA (representing treatment versus placebo) to estimate baseline-adjusted log-odds for each treatment. The baseline-adjusted log-odds for each treatment were then exponentiated and transformed to calculate the probability of patients responding to treatment at Week 16. Table 6 presents the updated Week 16 treatment response probabilities for each population and model type. The results of the fixed effects and random effects model are comparable, thus the EAG maintains the used of the random effects model in the updated base case. However, results of the scenario analysis using response probabilities based on the fixed effects model are presented in Section 4.2.

Table 5. Baseline BSC treatment response at Week 16 used in the economic model

Population	Baseline response	Source
First-line systemic treatment (combination therapy) - EASI 75	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16
Second-line systemic treatment (combination therapy) - EASI 50 +DLQI ≥4	[redacted]	AD UP – [redacted] patients responded to placebo at Week 16

Abbreviations: BSC, best supportive care; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index

Table 6. Week 16 treatment response probabilities

Intervention	Fixed effects (scenario)	Random effects (updated base case)
First-line systemic treatment (combination therapy) - EASI 75		
CsA	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]

Second-line systemic treatment (combination therapy) - EASI 50 +DLQI ≥4		
Abrocitinib - 100 mg	[redacted]	[redacted]
Abrocitinib - 200 mg	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]
Upadacitinib - 15 mg	[redacted]	[redacted]
Upadacitinib - 30 mg	[redacted]	[redacted]

Abbreviations: CsA, ciclosporin; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; N/A, not available

3.2 Health state utilities

In the ACD, the committee considered that the treatment-specific utilities used in the MTA model introduced unnecessary complexity in the model and instead preferred the use of health-state utilities, including a single baseline utility for each population. The committee suggested a single synthesis of the utility evidence linked via the common comparator of placebo, similar to the NMA approach used for the effectiveness data. However, the EQ-5D data were not provided in the same format by all the companies and an NMA was therefore not possible.

In line with using the AD UP upadacitinib trial data for baseline characteristics in the adult first- and second-line model, the EAG extracted overall health-state utilities values (HSUVs) based on data from AD UP from the company's response to clarification questions (Table 7). The HSUVs were implemented in the EAG model for all treatments, irrespective of drug class and for BSC. Results of the HSUV scenario are presented in Section 0 as well as results using utility values from TA534 as requested by the committee in the ACD. As a reminder, the TA534 values for baseline, Week 16 responder and BSC were 0.663, 0.898 and 0.797, respectively.

Table 7. Health state utility values

Health state	Utility value (standard error)	Source
First-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial
Second-line population (combination therapy) - EASI 50 + DLQI ≥4		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial

Second-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 responder	[redacted]	Data supplied AbbVie - AD UP trial
Week 16 non-responder	[redacted]	Data supplied AbbVie - AD UP trial
Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index.		

3.3 Best supportive care waning

In the ACD, the committee considered that assumptions in the BSC health state have a large impact on the cost-effectiveness results and in particular the treatment effect for patients on BSC may wane over time. The committee recognised that in clinical practice people would receive further treatments as part of a sequence before going on to BSC. However, the committee acknowledged that no clinical data on sequential effectiveness exist, and treatment sequences offered would vary substantially in clinical practice. As such, the committee requested a scenario analysis exploring BSC waning based on the assumptions accepted in TA534. Table 8 presents the proportion of patients losing quality of life benefits over time considered plausible by the committee in TA534.

Table 8. TA534 best supportive care waning assumptions

Year	Proportion of patients who return to baseline utility
2	57%
3	82%
4	92%
5+	97%

In TA534, the BSC waning proportions were used to calculate a weighted average utility value for the health state comprised of the average utility for BSC and baseline utility from CHRONOS. In TA534, from Year 5 onwards, 97% patients in the BSC arm accrued the baseline utility. In line with TA534, the EAG implemented the BSC waning proportions to adjust down the BSC health state utility value over time. For example, in Year 2, 57% of BSC patients returned to baseline utility and 43% retained the benefits of BSC (weighted average utility of responder and non-responder to BSC). By Year 5, 97% of BSC patients have returned to baseline utility. Table 9 presents the BSC utility values used in the BSC waning scenario.

In the ACD, the committee recommended exploring tunnel states to implement BSC waning, but due a paucity of time, the EAG were unable to adapt the model to include this. Nonetheless, the scenario explored by the EAG is consistent with TA534 and TA681. The results of this scenario are presented

in Section 0. In addition to the BSC waning, the EAG explored a reduced time horizon of 5 years, also presented in Section 0.

Table 9. Best supportive care health state utility values

Category	Utility value	Source/ Assumptions
First-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Weighted average of responder and non-responder utility values	[redacted]	Data supplied AbbVie - AD UP trial. Responders to BSC = [redacted]. Responder utility value = [redacted] and non-responder utility value = [redacted].
Second-line population (combination therapy) - EASI 50 + DLQI ≥4		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Weighted average	[redacted]	Data supplied AbbVie - AD UP trial. Responders to BSC = [redacted]. Responder utility value = [redacted] and non-responder utility value = [redacted].
Second-line population (combination therapy) - EASI 75		
Baseline	[redacted]	Data supplied AbbVie - AD UP trial
Weighted average	[redacted]	Data supplied AbbVie - AD UP trial. Responders to BSC = [redacted]. Responder utility value = [redacted] and non-responder utility value = [redacted].

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index.

3.4 Dose pooling

Abrocitinib and upadacitinib are both available in high and low doses. In the ACD, the committee considered that in clinical practice, the decision to start patients on a particular treatment would be driven by the overall effectiveness of a drug rather than the effectiveness of individual doses. However, the EAG notes that trials for abrocitinib and upadacitinib randomised patients to high and low dose and these were considered separately in the NMA and the economic model. Nonetheless, the committee requested that a scenario is explored where the results of the high and low doses are pooled, using a proportional weighting of each treatments' expected dose distribution in clinical practice. The EAG consulted its clinical experts who advised that dosing decisions depend on the treating clinician, and these decisions vary hugely; some clinicians may have significant concerns regarding JAK2 side effects and therefore start and maintain treatment on a lower dose, whereas other clinicians may prefer to start treatment for a patient with severe disease on a higher dose. For these reasons, the EAG's clinical experts were unable to provide the expected dose distribution in clinical practice. Thus, to provide committee with a pooled cost-effectiveness estimate for each of the treatment options that have high and low dose, the EAG has assumed a 50:50 low-/high- dose

distribution, in the absence of robust data. The results of the dosing pooling scenario are presented in Section 4.2.

4 Updated cost-effectiveness results

4.1 Updated base case results

In response to the appraisal consultation document (ACD), the economic analysis was revised so that the first-line network meta-analysis (NMA) (combination therapy – EASI 75) included abrocitinib 100 mg and 200 mg as comparators, and the second-line NMA (combination therapy – EASI 50 + DLQI ≥4) included data for abrocitinib from JADE DARE. Revised deterministic results are presented in Section 4.1.1 and revised probabilistic results are presented in Section 0.

The Evidence Assessment Group (EAG) cautions the interpretation of the cost-effectiveness results presented in this report as they are based on list prices for abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib which all have confidential patient access scheme (PAS) discounts in place. As such, the cost-effectiveness results presented in the confidential appendix, which includes applicable PAS discounts for these treatments, are more relevant for decision-making.

4.1.1 Deterministic results

Updated list price incremental cost-effectiveness ratios (ICERs) are presented in Table 10 for the first-line population (combination therapy – EASI 75) and Table 11 for the second-line population (combination therapy – EASI 50 + DLQI ≥4). The EAG notes that incremental QALYs were relatively small and incremental costs were relatively large for each treatment in each population resulting in highly sensitive ICERs.

As noted in Section 2, the EAG's analyses considering baricitinib as a comparator (combination therapy - EASI 75) have not been updated and therefore the results in Table 12 are reproduced from the EAG report. As noted in the EAG report, data were not available for baricitinib using the EASI 50 + DLQI ≥ 4 response definition, and so it was not included in the base case analysis and results using EASI 75 were presented as a scenario. Additionally, there was uncertainty around whether baricitinib 4 mg can be considered a high dose JAK inhibitor (a 2 mg dose is available but not recommended for treatment of atopic dermatitis). Additionally, both doses of abrocitinib and upadacitinib are more effective than baricitinib 4 mg. As such, Table 12 includes two scenarios for the baricitinib analyses using either high dose or low dose JAK inhibitors utility values.

Table 10. Updated deterministic base case results: adults first-line systemic treatment, combination therapy – EASI 75 (list prices)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg+ TCS (4)	CsA + TCS (5)	Incremental value			
						(1-5)	(2-5)	(3-5)	(4-5)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-					£91,156	£79,392	£79,969	£146,465

Abbreviations: Abro, abrocitinib; CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NMA, network meta-analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids; upa, upadacitinib.

Table 11. Updated deterministic base case results: adults & adolescents second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list prices)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-						£169,480*	Dominant	£181,649*	£130,198	£220,333*

Abbreviations: Abro, abrocitinib; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; Dup, dupilumab; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 12. Deterministic base case results vs baricitinib: adults second-line systemic treatment, combination therapy - EASI 75 – (list prices)

Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Bar 4 mg + TCS (6)	Incremental value				
							(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
High dose JAKi utilities for baricitinib											

Total costs	[redacted]										
QALYs	[redacted]										
ICER	-						Dominated	£81,431	Dominated	£187,893	£551,116
Low dose JAKi utilities for baricitinib											
Total costs	[redacted]										
QALYs	[redacted]										
ICER	-						£183,004	£62,242	£138,506	£144,557	£117,828

Abbreviations: Abro, abrocitinib; Bar, baricitinib; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Bar + TCS)

4.1.2 Probabilistic results

List price probabilistic ICERs based on 1,000 iterations are presented in

Table 13 for the first-line population (combination therapy – EASI 75) and Table 15 for the second-line population (combination therapy – EASI 50 + DLQI ≥4). For details on the location of the iterations on the cost-effectiveness plane, see Table 14 for the first-line population and

Table 16 for the second-line population. Probabilistic ICERs considering baricitinib as a comparator (combination therapy - EASI 75) have not been provided as these are scenario analyses, consistent with the EAG report.

It should be noted that for each population and intervention, PSA were run separately due to the structure of the model and therefore the sampling from parameter distributions for the comparator provide slightly different mean estimates for each pairwise comparison. However, total costs and QALYs for the

comparator are similar for the PSA results. Additionally, the EAG notes that incremental QALYs were relatively small and incremental costs were relatively large for each treatment in each population resulting in the sensitive ICERs.

Table 13. Updated probabilistic base case results: adults first-line systemic treatment, combination therapy – EASI 75 – (list prices)

Comparison	Total		Incremental		ICER		Probability intervention is cost-effective at the WTP threshold	
	Costs	QALYs	Costs	QALYs	PSA	Deterministic	£20,000	£30,000
CsA + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£76,111	£79,969	0%	7%
CsA + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£144,898	£146,465	0%	0%
CsA + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Abrocitinib 100 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£88,718	£91,156	0%	3%
CsA + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Abrocitinib 200 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£82,104	£79,392	0%	5%

Abbreviations: CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids; WTP, willingness-to-pay.

Table 14. Location of PSA simulations on the CE plane: Adult first-line systemic treatment population, combination therapy – EASI 75 (list prices)

Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Upadacitinib 15 mg + TCS vs CsA + TCS	84%	0%	0%	16%
Upadacitinib 30 mg + TCS vs CsA + TCS	82%	0%	0%	18%

Abrocitinib 100 mg + TCS vs CsA + TCS	82%	0%	0%	18%
Abrocitinib 200 mg + TCS vs CsA + TCS	82%	0%	0%	18%

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west; TCS, topical corticosteroids.

Table 15. Updated probabilistic base case results: adults & adolescents second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list prices)

Comparison	Total		Incremental		ICER		Probability intervention is cost-effective at the WTP threshold	
	Costs	QALYs	Costs	QALYs	PSA	Deterministic	£20,000	£30,000
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Abrocitinib 100 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£194,978*	£169,480*	98%	93%
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Abrocitinib 200 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant	91%	86%
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Upadacitinib 15 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£188,608*	£181,649*	99%	93%
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Upadacitinib 30 mg + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£119,330	£130,198	21%	27%
Dupilumab + TCS	[redacted]	[redacted]	-	-	-	-	-	-
Tralokinumab + TCS	[redacted]	[redacted]	[redacted]	[redacted]	£236,522*	£220,333*	99%	99%

Abbreviations: EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids; WTP, willingness-to-pay.

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

Table 16. Location of PSA simulations on the CE plane: adults & adolescents second-line systemic treatment, combination therapy – EASI 50 + DLQI ≥4 (list prices)

Comparison	NE quadrant	SE quadrant, dominant	SW quadrant	NW quadrant, dominated
Abrocitinib 100 mg + TCS vs dupilumab + TCS	0%	32%	68%	0%
Abrocitinib 200 mg + TCS vs dupilumab + TCS	1%	57%	42%	0%
Upadacitinib 15 mg + TCS vs dupilumab + TCS	0%	32%	68%	0%
Upadacitinib 30 mg + TCS vs dupilumab + TCS	55%	5%	6%	34%
Tralokinumab + TCS vs dupilumab + TCS	1%	28%	71%	0%

Abbreviations: CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NE, north-east; NW, north-west; PSA, probabilistic analysis; QALY, quality-adjusted life year; SE, south-east; SW, south-west; TCS, topical corticosteroids.

4.2 Scenario analyses

The additional analyses requested by the committee in the ACD were as follows:

- A fixed effect model for the NMA (see Section 2 and 3.1);
- Additional utility values scenarios based on health-state specific values rather than treatment-specific utility values and utility values used in TA534 (see Section 3.2);
- Analysis that represents BSC treatment waning over time and sensitivity around the modelled time horizon (see Section 3.3); and
- A pooled cost-effectiveness estimate for each of the treatment options that have high and low doses (see Section 3.4);

Results exploring these scenarios are presented in Table 17 for the first-line population (combination therapy – EASI 75) and Table 18 for the second-line population (combination therapy – EASI 50 + DLQI ≥4).

Across both populations, using a fixed effects model for the NMA had a negligible impact on the results.

The dose pooling scenario (a 50:50 share for low-/high- dose, respectively) had an impact on the magnitude of the ICERs in the first line population (all base case ICERs and pooled ICERs occupied the north-east quadrant). In the second-line population, the base case ICERs for the low dose option and high dose option occupied different quadrant on the cost-effectiveness plane. As such, the dose pooling scenario changed the direction of the results for one dose. For abrocitinib in the second-line population, a south-west quadrant base case ICER (low dose) and dominant base case ICER (high dose) produced a south-west ICER when pooled. For upadacitinib in the second-line population, a south-west quadrant base case ICER (low dose) and north-east base case ICER (high dose) produced a south-west ICER when pooled.

When the EAG explored health-state specific values rather than treatment-specific utility values, the incremental QALYs reduced in every comparison and population (except tralokinumab vs dupilumab at second-line), which had a substantial impact on the results. Health-state specific values from AD-UP upadacitinib trial data and TA534 produced similar ICERs. In the first-line population, heath-state specific values had an impact on the magnitude of the ICERs but not the direction of the results (the north-east quadrant ICERs increased substantially in favour of CsA). In the second-line population,

the ICER for abrocitinib 200 mg vs dupilumab switched from a dominant ICER to a south-west quadrant ICER. For abrocitinib 100 mg and upadacitinib 15 mg vs dupilumab in the second-line population, the south-west quadrant ICERs increased but still favoured the intervention. For upadacitinib 30 mg in the second-line population, the north-east quadrant ICER increased but still favoured dupilumab. As for tralokinumab in the second-line population, the ICERs produced using health-state specific values from AD-UP upadacitinib trial data favoured tralokinumab while values from TA534 favoured dupilumab, however, both scenarios had a relatively small impact on the results.

When the EAG explored BSC treatment waning as per TA534, the incremental QALYs increased in every comparison which utilised a lifetime time horizon and this had a substantial impact on the results. In the first-line population, assuming BSC treatment waning as per TA534 had an impact on the magnitude of the ICERs but not the direction of the results (the north-east quadrant ICERs reduced substantially in favour of the interventions). In the second-line population, the ICER for abrocitinib 200 mg vs dupilumab switched from a dominant ICER to a south-west quadrant ICER using a lifetime horizon. For upadacitinib 30 mg in the second-line population, the ICER switched from a north-east quadrant ICER to a dominated ICER using a lifetime horizon. For abrocitinib 100 mg, upadacitinib 15 mg and tralokinumab vs dupilumab in the second-line population, the south-west quadrant ICERs reduced in favour of dupilumab using a lifetime horizon. Combining the BSC treatment waning scenario with a reduction in time horizon (from lifetime to 5 years) had an impact on the magnitude of the ICERs in the both populations (in favour of CsA in the first-line population and in favour of dupilumab in the second-line population), but not the direction of the results.

The EAG also combined individual scenarios to present committee with the impact on the ICER for combined assumptions, presented in Table 17 to Table 19.

Table 17. Scenario analysis deterministic results: adults first-line systemic treatment, combination therapy – EASI 75 – (list prices)

	Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg+ TCS (4)	CsA + TCS (5)	Incremental value			
							(1-5)	(2-5)	(3-5)	(4-5)
0	**Updated base case (random effects NMA)**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£91,156	£79,392	£79,969	£146,465
1	**Fixed effects NMA**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£90,854	£79,383	£80,213	£146,689
2	**Dose pooling: 50/50 for low-/high-dose, respectively**									
	Total costs	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	
	QALYs	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	
	ICER	-					£83,876		£125,596	
3	**Non-treatment specific utility values: obtained from upadacitinib trials**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£130,911	£119,336	£114,845	£220,153
4	**Non-treatment specific utility values: obtained from TA534**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£136,119	£124,082	£119,414	£228,910
5	**BSC treatment waning as per TA534: lifetime horizon**									

	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£28,164	£30,922	£26,151	£59,232
6	**BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£50,608	£44,207	£44,898	£82,086
7	**Combined scenario 3+6: Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£53,227	£49,831	£47,357	£92,789
8	**Combined scenario 4+6: Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-					£62,670	£59,666	£55,933	£111,382
9	**Combined scenario 2+3+6: Dose pooling: 50/50 for low-/high-dose, respectively + Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
	ICER	-					£51,160	£74,801		
10	**Combined scenario 2+4+6: Dose pooling: 50/50 for low-/high dose, respectively + Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
	ICER	-					£60,752	£89,345		

Abbreviations: Abro, abrocitinib; CsA, ciclosporin; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; NMA, network meta-analysis; QALY, quality-adjusted life year; TCS, topical corticosteroids; upa, upadacitinib.

*Utility values and total QALYs vary according to whether the intervention is high dose or low dose. Total QALYs for CsA + TCS based on a high dose or low dose intervention are as follows: updated base case, 14.76 or 14.77; scenario E, 11.25 or 11.58; scenario F, 3.19 or 3.26, respectively.

Table 18. Scenario analysis deterministic results: adults & adolescents second-line systemic treatment, combination therapy - EASI 50 + DLQI ≥4 – (list prices)

	Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Dup + TCS (6)	Incremental value				
								(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
0	**Updated base case (random effects NMA)**											
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-						£169,480*	Dominant	£181,649*	£130,198	£220,333*
1	**Fixed effects NMA**											
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER							£169,430*	Dominant	£181,689*	£130,444	£218,400*
2	**Dose pooling: 50/50 for low-/high- dose, respectively**											
	Total costs	[redacted]		[redacted]		-	[redacted]	[redacted]		[redacted]		-
	QALYs	[redacted]		[redacted]		-	[redacted]	[redacted]		[redacted]		-
	ICER	-						£594,420*		£335,422*		-
3	**Non-treatment specific utility values: obtained from upadacitinib trials**											
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER							£273,134*	£1,325,902*	£288,558*	£2,360,388	£229,425*

4	**Non-treatment specific utility values: obtained from TA534**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£244,803*	£1,188,371*	£258,627*	£2,115,553	-£205,627*
5	**BSC treatment waning as per TA534: lifetime horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£27,120*	£68,120*	£29,198*	Dominated	£93,859*
6	**BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£61,330*	Dominant	£68,192*	£157,790	£107,862*
7	**Combined scenario 3+6: Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£130,136*	Dominant	£141,621*	£330,651	£90,584*
8	**Combined scenario 4+6: Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£164,400*	Dominant	£178,771*	£392,800	£111,085*
9	**Combined scenario 2+3+6: Dose pooling: 50/50 for low-/high-dose, respectively + Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]		-						-		
	QALYs	[redacted]		-						-		

	ICER	-				£225,285*	£46,193*	-
10	**Combined scenario 2+4+6: Dose pooling: 50/50 for low-/high-dose, respectively + Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**							
	Total costs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-
	QALYs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	-
	ICER	-				£256,041*	£57,742*	-

Abbreviations: Abro, abrocitinib; CQ, clarification question; CS, company submission; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; Dup, dupilumab; ICER, incremental cost-effectiveness ratio; mg, milligram; NA, not applicable; NMA, network meta-analysis; Q2W, twice weekly; Q4W, every 4 weeks; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib

*This is a south west quadrant ICER, where the intervention is cost-effective if the ICER is above the WTP threshold (the intervention is less expensive and less effective than Dup + TCS)

For the analyses considering baricitinib as a comparator (combination therapy - EASI 75) the EAG has provided a succinct number of scenarios to reduce the number of scenarios using either high dose or low dose JAK inhibitors utility values. As such, the BSC treatment waning scenario is considered on top of health-state specific values rather than treatment-specific utility values. Results of the EAG's scenario analyses are presented in Table 19.

Table 19. Deterministic base case results vs baricitinib: adults second-line systemic treatment, combination therapy - EASI 75 – (list prices)

	Results per patient	Abro 100 mg + TCS (1)	Abro 200 mg + TCS (2)	Upa 15 mg + TCS (3)	Upa 30 mg + TCS (4)	Tralo + TCS (5)	Bar 4 mg + TCS (6)	Incremental value				
								(1-6)	(2-6)	(3-6)	(4-6)	(5-6)
0a	**High dose JAKi utilities for baricitinib**											
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	-						Dominated	£81,431	Dominated	£187,893	£551,116
0b	**Low dose JAKi utilities for baricitinib**											
	Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ICER	-						£183,004	£62,242	£138,506	£144,557	£117,828
1	**Non-treatment specific utility values: obtained from upadacitinib trials**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£154,268	£138,876	£116,757	£320,441	£243,501
2	**Non-treatment specific utility values: obtained from TA534**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£131,703	£118,563	£99,679	£273,571	£207,884
3	**Combined scenario: Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: lifetime time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£50,504	£42,644	£38,294	£98,566	£68,029
4	**Combined scenario: Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: lifetime time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£64,051	£54,888	£48,545	£126,818	£89,375
5	**Combined scenario: Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										
	ICER	-						£57,060	£48,178	£41,284	£126,261	£107,252
6	**Combined scenario: Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**											
	Total costs	[redacted]										
	QALYs	[redacted]										

	ICER	-				£70,965	£60,733	£51,320	£159,068	£141,911
7	**Combined scenario: Dose pooling: 50/50 for low-/high- dose, respectively + Non-treatment specific utility values: obtained from upadacitinib trials + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	QALYs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	ICER	-				£50,995	£100,863			-
8	**Combined scenario: Dose pooling: 50/50 for low-/high- dose, respectively + Non-treatment specific utility values: obtained from TA534 + BSC treatment waning as per TA534: 5-year time horizon**									
	Total costs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	QALYs	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	ICER	-				£64,994	£127,506			-

Abbreviations: Abro, abrocitinib; Bar, baricitinib; EASI, Eczema Area and Severity Index; ICER, incremental cost-effectiveness ratio; mg, milligram; QALY, quality-adjusted life year; TCS, topical corticosteroids; Tralo, tralokinumab; Upa, upadacitinib.

5 References

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	This document outlines AbbVie's perspective on the ACD. AbbVie welcome the Committee's conclusions which were broadly positive for upadacitinib. However, AbbVie were disappointed to learn that the Committee issued an appraisal consultation, bearing in mind the recent positive Scottish Medicines Consortium (SMC) decision for upadacitinib for people over 12 years with moderate to severe atopic dermatitis. Unfortunately, AbbVie did not receive the updated External Assessment Group (EAG) model by 4th May 2022. Therefore, AbbVie adapted the original EAG model to address issues in the ACD, using the second-line, combination treatment effectiveness inputs for both adults and adolescents. While the ACD focussed on specific modelling assumptions, it is important to highlight to the Committee that upadacitinib has been studied in a head-to-head study against dupilumab. The effectiveness of upadacitinib 30 mg monotherapy compared to dupilumab monotherapy was established in the Heads UP trial. At 16 weeks, patients aged over 18 years with moderate to severe atopic dermatitis achieved an EASI 75 improvement of 71% (247/348) in the upadacitinib arm and 61.1% (210/344) in the dupilumab arm (mean adjusted difference: 10 %, 95% confidence interval (CI) for difference 2.9 to 17.0, p=0.006), which supports the conclusions of the fixed effects and random effects network meta-analysis that upadacitinib 30 mg is more effective than dupilumab 300 mg. To address the Committee's key concern regarding counter-intuitive results (issue 4 and 5), AbbVie thoroughly queried interactions between clinical and cost-effectiveness, the inputs for conditional discontinuation, best supportive care (BSC)

	and health state utility values (HSUV). The combination of data inputs applied in the initial EAG model including baseline HSUV utilities, responder HSUV and conditional discontinuation produces a scenario where interactions between the inputs lead to counter-intuitive results. Once the model is updated with common baseline utilities and responder utilities rather than treatment arm-specific utilities, the direction of the cost-effectiveness results follows the clinical effectiveness. While applying responder utilities improves the intuitiveness of the model outputs, it does have its own limitations. Given that conditional discontinuation is currently derived as naïve rates from each trial without adjustment for potential differences, expanding the assumption of responder-derived values to also cover conditional discontinuation represents a consistent approach and removes a source of bias where the evidence-base for treatment differences remains unclear. Therefore, AbbVie carried out a scenario whereby discontinuation rates were based on TA534 (3.7%) or AD UP ([redacted]) across all agents. The inputs for BSC HSUV (high or low), baseline HSUV and conditional discontinuation (AD UP or TA534) influence the ICERs and are interactive between each other. If it is assumed that conditional discontinuation is treatment-specific rather than responder-specific, this further complicates the issue as different treatments benefit from BSC at different time-points depending on which effectiveness and conditional discontinuation rates are applied in the cost-effectiveness model (CEM). However, the direction of results is consistent with expected clinical effectiveness results if disease specific responder values are applied rather than treatment-specific values. AbbVie agrees with the Committee's preference for a common HSUV baseline value (Section 3.20), where it is assumed that randomisation to placebo or active treatment do not impact on baseline HSUV. AbbVie believe that applying the upadacitinib clinical trial data from AD UP and dupilumab clinical trial data from

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	TA534 for HSUV are reasonable options, since this reflects the available evidence for responders. However, due consideration for the results of Heads UP is appropriate as additional benefit is likely to be conferred on patients with response per EASI 90 or EASI 100 criteria. The Committee recognised the burden of disease of atopic dermatitis and the need for alternative treatments. Combining these scenarios yields cost-effectiveness results for upadacitinib that represent good use of NHS resource and will enable people with atopic dermatitis who have failed least one conventional systemic immunosuppressant, such as ciclosporin, to benefit from a clinically effective agent.
1	**Response to Appraisal Consultation Document** Although the Committee were unable to come to a decision after the first Committee meeting, the discussion at the Committee meeting was broadly positive: • Recognition of the burden of disease of atopic dermatitis (Section 3.1) and the need for alternative treatments (Section 3.1, 3.3). • Adult evidence is generalisable for adolescents (Section 3.12). In the meeting, one of the clinical advisors pointed out that equal access for adolescents and adults is important. • Abrocitinib, tralokinumab and upadacitinib are clinically effective vs placebo (Section 3.10). The network meta-analysis with dupilumab or baricitinib is appropriate for decision-making (Section 3.13) and the fixed effects results (AbbVie original choice) may be more appropriate than the random effects (EAG choice) (Section 3.15). • The structure of the economic model is appropriate for decision-making (Section 3.17). • Combination therapy as base case (Section 3.5), with AD UP providing evidence for upadacitinib (Section 3.8).

	• EASI 50 + Dermatology Life Quality Index (DLQI) 4 is the most relevant endpoint for decision-making (Section 3.11). **Scenario analyses to existing model** Unfortunately, AbbVie did not receive the updated EAG model by 4th May 2022 and had to adapt the existing EAG model to address issues in the ACD, using the second-line, combination treatment effectiveness inputs for both adults and adolescents. AbbVie further requests that cost-effectiveness results presented by the EAG include the PAS prices that [redacted] to the NHS: • Upadacitinib 15 mg: [redacted] • Upadacitinib 30 mg: [redacted] The issues are addressed as per the bullet points for additional analysis requested by the Committee on page 22 of the ACD.
2	***Issues 4 and 5: Counter-intuitive results in the model vs clinical response*** **Discontinuation as a model driver** As discussed in the summary, the model ceases to produce counter-intuitive results (i.e., decreasing effectiveness improves cost-effectiveness) when data inputs for HSUV and conditional discontinuation are assumed to be for responders rather than being treatment-specific. The Committee has requested analyses which assess disease health state utilities, it is important to note the limitations with this approach (see Alternative active

treatment utility values). To avoid biasing the results without robust evidence, the Committee should also consider disease-specific conditional discontinuation rates, as was the case in TA681 (baricitinib appraisal in moderate-severe AD).

Responder conditional discontinuation rates

In the previous EAG base case, the conditional discontinuation rates were [redacted] for upadacitinib 15 mg, [redacted] for upadacitinib 30 mg (both from AD UP) and 3.7% for dupilumab from TA534 (dupilumab appraisal in moderate to severe AD).

As conditional discontinuation is currently derived from each trial without adjustment for differences, expanding the assumption of responder-derived values to also cover conditional discontinuation is consistent and removes a potential bias where the evidence-base for differences remains unclear. Therefore, AbbVie carried out a scenario whereby discontinuation rates were based on TA534 (3.7% across all agents), together with a scenario using AD UP-derived value of [redacted] across all agents.

More recent clinical trials, such as AD UP, were conducted at a time when treatment choice in clinical practice and the clinical trial setting had drastically improved. Clinical expert opinion suggests that availability of alternative treatments is likely to influence patient discontinuation. Therefore, extending the assumption of responder values for HSUV to also cover conditional discontinuation from AD UP is a reasonable assumption when considering disease specific utilities. Patients with a response to treatment were assumed to have similar risk of discontinuing treatment, and the AD UP conditional discontinuation rates were pooled ([redacted]) and this rate applied across all treatments.

In summary, both doses of upadacitinib remained cost-effective compared to dupilumab, when a consistent discontinuation rate was used across all treatments.

Utility values for BSC

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	The ACD stated that utility values for the BSC health state are highly uncertain and have a large impact on the cost-effectiveness results (Section 3.21). Utility values for the BSC health state were derived using a weighted average of the utility values for responders and non-responders at week 16. The current base case BSC utility for the second-line adult combination population is [redacted], based on the average of responders and non-responders to placebo in the AD UP trial (see Table 45 of the MTA report). AbbVie has explored the issue by varying the BSC HSUV higher and lower than [redacted] as follows: • TA534 generalised BSC non-responders (0.7732): week 16 non-responder utility for BSC from TA534 (Higher BSC HSUV). • TA534 baseline combination (0.663): baseline utility from TA534 for combination treatment to model complete treatment effect waning for BSC (Lower BSC HSUV). For upadacitinib 15 mg, ICERs are in the SW quadrant, while cost-effective, ICER decrease with a lower BSC HSUV due to higher proportion of patients in BSC. For upadacitinib 30 mg, ICERs remain in the NE quadrant. A low BSC HSUV results in marginally improved ICERs (lower NE quadrant ICERs) as more patients are on modelled on BSC for dupilumab. **Alternative active treatment utility values** The Committee suggested that treatment-specific utility values are uncertain and alternative utility value scenarios should be explored (Section 3.20). The Committee suggested that alternative utility values could be based on degree of change observed in the trials, HSUV rather than treatment-specific utility values, and

utility values used in TA534.

AbbVie has carried out scenarios based on the following:

- Common baseline and responder utilities based on TA534 (baseline utility = 0.663; responder utility = 0.8979).
- Common baseline utility based on AD UP ([redacted]), made up of an average of current high and low dose JAK inhibitor utilities for second-line combination population ([redacted]) and responder utilities for active treatment based on combined AD UP results for both doses from upadacitinib applied to all responders on upadacitinib or dupilumab. Notably, this should be considered a conservative analysis for upadacitinib 30 mg vs dupilumab due to the positive results for upadacitinib vs dupilumab in the Heads UP trial.

While using upadacitinib clinical trial data from AD UP is an appropriate approach given that it is a recent high quality clinical trial and considered representative of clinical practice, using disease-specific responder utilities has the limitation of not considering the impact of clinical effectiveness improvements on quality of life.

Applying disease-specific responder conditional discontinuation rates as an appropriate extension to this scenario further establishes that upadacitinib 15 mg and upadacitinib 30 mg represent a cost-effective use of NHS resources.

Shorter time horizon for consideration

Applying a time horizon of 5 or 10 years has significant limitations. Atopic dermatitis is a chronic condition, and as suggested by NICE methods and previous precedent, a life-time horizon is most appropriate, therefore the base case considered a life-time time horizon (100 years).

AbbVie modelled a 5-year and 10-year time horizon as scenarios to reflect [redacted]. These shorter time horizons reflect

	that patients may switch to another active agent, rather than remain on BSC. Reducing the time horizon in this way results in upadacitinib remaining cost-effective vs dupilumab.
3	***Issue 1: Adult results generalisable to adolescent population*** Section 3.12 concluded that the results of the 'combination therapy' analysis for adults who had tried systemic immunotherapy would likely be generalisable to the adolescent population. A scenario analysis was carried out running the adolescent baseline characteristics in the adult model (second-line combination data). Results from the original adolescent model showed that upadacitinib 15 mg was dominant vs dupilumab. The scenario showed that upadacitinib 15 mg remained cost-effective with ICERs in the SW quadrant. Due to the preference of adolescents, the results based on adolescent clinical trial participants should not be ignored for decision making.
4	***Issue 2 – Fixed effect network meta-analysis*** Section 3.15 states that random effect models with uninformed priors may not be appropriate because of the small number of trials for each treatment arm. The Committee concluded it would like to consider the results of the fixed effects analysis, which may reduce the width of the credibility intervals and also may plausibly affect the point estimates of the results used in the deterministic base case analysis. This is shown in Table 1 below, which is taken from the Appendices submitted by AbbVie in our initial Single Technology Appraisal submission (Table 49). We acknowledge that the use of a random effects model is often preferred in a Bayesian indirect comparison, as it allows for between-studies heterogeneity in the

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	estimates of treatment effect. However, where there is a single data source for the treatment, as is the case for many treatments in this analysis, this benefit is negated. Furthermore, in the situation where single studies feed into the analysis, a random effects model will yield zero-estimates for type I error, probably reflecting unchanged non-informative priors[2,3]. This effect results in the lack of face validity seen in the random effects model, which yielded an estimate of 95% CI that substantially exceeded the 95% CI seen in the source study. Results from the random and fixed effects models are similar, in particular the point estimates. The credible intervals are wider for the random effects model. However, this is a function of small numbers of studies feeding into the analyses causing the posterior of between trial standard deviation to be sensitive to the prior[4]. The vague prior therefore results in posteriors which allow for unrealistically high levels of heterogeneity. Consequently, in this situation the fixed effects model is the appropriate network meta-analysis model for base case analysis due to the low number of trials used to estimate between study variability.

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

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Table 1: Combination therapy adult systemic-exposed, all observed – model results summary: estimates, fit statistics and SUCRA values

Treatment	EASI 50 + DLQI ≥4		EASI 75		EASI 50	
	Fixed effects	Random effects	Fixed effects	Random effects	Fixed effects	Random effects
	Median log-odds estimate (95% CrI) vs placebo					
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean log-odds estimate (SD) vs placebo					
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	SUCRA					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab 300 mg Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Fit statistics					
Between trial SD [mean (SD)]	N/A	2.449 (0.124, 4.876)	N/A	1.561 (0.100, 4.728)	N/A	1.121 (0.042, 4.649)
D_{res} (mean)	5.13	5.13	8.51	7.11	6.21	6.89
p_D	5.13	5.13	6.01	7.00	6.21	6.89
DIC	10.25	10.26	14.53	14.12	12.42	13.79

CrI: Credible Interval, DIC: Deviance Information Criterion, DLQI: Dermatology Life Quality Index, DRES: Posterior mean of the residual deviance, EASI: Eczema Area and Severity Index, N/A: Not Available, pD: Effective Number of Parameters, Q2W: Every 2 Weeks, SD: Standard Deviation, SUCRA: Surface Under the Cumulative Ranking Curve

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

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1	LEO Pharma would like to highlight the frustrations with the process that tralokinumab has been through over the last 12 months. The justification for using a hybrid Multiple Technology Appraisal (MTA) was to increase the speed of decision making and reduce the workload for NICE due to capacity reasons. Regrettably, this has not been the case and a standard Single Technology Appraisal (STA) would have been more timely and would also have given clarity and reduced the workload for all parties. LEO Pharma consider it imperative that further delays, which could adversely impact treatment access for patients with Atopic Dermatitis, are avoided.
2	The hybrid MTA has been an 'off process' approach with no published documentation or project plan for companies to follow. All companies find themselves in the position of having to comment at the ACD stage on a model that has been deemed inappropriate for decision making by the NICE committee members. A crucial aspect seems to be the External Assessment Group (EAG) model's lack of consistency with the models used in the previous dupilumab appraisal (TA534); the unsuitability of the EAG model has limited LEO Pharma's ability to proactively input into this process.
3	The economic model submitted as part of LEO Pharma's STA included assumptions that were more in line with previous STAs (TA534) and LEO Pharma believe that the revised EAG model should have greater consistency with the models used as the basis for decision making in these previous appraisals.
4	LEO Pharma agree with the recommendation of the committee to explore a long-term utility waning effect in patients treated with BSC. This was an assumption in the tralokinumab STA model and also in previous appraisals such as TA534.
5	Given the potential sources of heterogeneity across the evidence base, as discussed in LEO Pharma's STA submission, we consider the random effects approach to the NMA as more appropriate. Please see Section B.2.9.3 of LEO's STA
6	We note that LEO Pharma will not have sight of the updated EAG model in advance of the next committee meeting and so have no visibility on the final assumptions that will be implemented following the feedback in the ACD.
7	LEO Pharma would like to make the EAG and committee aware of the treatment option of Q4W dosing for tralokinumab. This will be an option in clinical practice based on feedback LEO Pharma has received from leading clinicians in the UK. In addition, Q4W dosing was one of the scenarios run by the EAG in the initial appraisal and we recommend this is revisited for the base case as this will become common practice.

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):	Pfizer Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA

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Name of commentator person completing form:	[redacted]
Comment number	**Comments**
1	**Overarching statement** Abrocitinib received its marketing authorisation (MA) in September 2021, the first MA worldwide. However, prior to the first committee meeting, we were already approximately 4–6 months delayed in terms of the appraisal process given that abrocitinib was re-routed from an STA to MTA process given capacity challenges at NICE. Patients now face a further 2-month delay based on a preliminary negative opinion which we strongly believe could have been avoided. We have been unable within the MTA process to impact the evidence seen by the committee in the meeting, given many of our comments in the EAG consultation period were not addressed, and evidence we submitted in our original STA was not provided for consideration with the first appraisal committee meeting. This is in the context of a successful baricitinib appraisal (TA681) in early 2021 in which the committee made a positive recommendation within one appraisal committee meeting. [redacted] [redacted] The adopted process for appraising abrocitinib is misaligned with NICE's ambition to provide "rapid, robust and responsive" technology evaluation[1] and the recently published Life Sciences Vision for clinically and cost-effective innovations to be rapidly adopted.[2] The lack of efficiency and pragmatism in the NICE process is illustrated by the contrasting approach of the SMC in relation to the appraisal of abrocitinib. [redacted]

[1] NICE strategy 2021 to 2026

[2] Life Sciences Vision (2021)

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	[redacted] Within the comments that follow (5-9) we have provided responses to the specific concerns of the committee identified within the appraisal consultation document (ACD) on page 22. We have highlighted both evidence from our initial STA submission which addresses these concerns and/or adaptations needed to the EAG NMA/model prior to the second appraisal committee meeting. Comments 10-13 relate to other sections of the ACD or the appraisal process thus far. We have sought a meeting with the NICE technical team/EAG on several occasions since the ACD was shared, in order to ensure we can contribute to the work required to ensure the appropriate evidence is provided to the committee during the second appraisal committee meeting. To date (28 April 2022) we have not received a response to this request. Finally, we want to emphasise that abrocitinib was granted a Promising Innovative Medicine (PIM) designation and a positive scientific opinion for Early Access to Medicine Scheme (EAMS) by the MHRA for the treatment of severe AD. This underlines the fact that severe AD is a seriously debilitating condition and that abrocitinib offers major advantages over existing systemic therapies. NICE have not met their commitment to prioritise PIM/EAMS treatments.[3]

[3] NICE (2016) Procedures to support EAMS

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2	[redacted] [redacted] [redacted] [redacted] Clinical outcomes • In JADE COMPARE, EASI (±DLQI) response rates for abrocitinib 100mg and dupilumab are comparable. For several critical response measures (e.g., PP-NRS itch response at Week 2, [redacted] abrocitinib 200mg is statistically significantly better than dupilumab; otherwise no significant differences between these treatments were observed (Abrocitinib submission Document B, Section B.2.6.1 [page 68]). • [redacted] (Abrocitinib submission Document B, Section B.2.9.5 [page 113]). • Results from the NMA (Abrocitinib submission Document B, Section B.2.9.5 [page 113]) also suggests that [redacted] [redacted] [redacted] **Critical request:** [redacted]

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3	**Inaccurate ACM summary** The ACD states on page 3 and 4: *"Standard treatment for moderate to severe atopic dermatitis (eczema) includes topical treatments such as emollients and corticosteroids. If these treatments are not effective, systemic immunosuppressants such as methotrexate and ciclosporin can be added. Dupilumab and baricitinib are used if these systemic treatments are not effective.* *Clinical trial evidence shows that abrocitinib, tralokinumab and upadacitinib all reduce symptoms of atopic dermatitis compared with placebo. They have been indirectly compared with some standard treatments, but the results are highly uncertain.* *The limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a suitable cost- effectiveness estimate for abrocitinib, tralokinumab and upadacitinib. So, they cannot be recommended."* This statement is unacceptably misleading, vague and does not reflect the discussion at the first appraisal committee meeting. The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD was assessed in an extensive clinical trial programme, comprising four pivotal trials (COMPARE, TEEN, MONO-1, and MONO-2). All four trials were randomised, double-blind, and placebo controlled, representing the gold standard for evaluating treatment effectiveness.[4] Importantly, JADE COMPARE evaluated the efficacy and safety of abrocitinib (100 mg and 200 mg) and dupilumab in comparison with placebo. Moreover, JADE DARE was a head-to-head study comparing abrocitinib 200 mg and dupilumab, which is a key comparator relevant to this appraisal. Data are also available for a range of endpoints including those most relevant to decision-making (e.g., EASI-50 and DLQI ≥4) and those most relevant to patients (e.g., PP-NRS) We request that NICE reissue the ACD to clarify specifically the comment related to clinical evidence. It should be clear upfront in the ACD that as per our communication with NICE, the reason for the negative decision was that the committee did not see a model with its preferred assumptions. The paragraph in section 3.23 we believe more accurately reflects the reason for a negative ACM: **"***Because of the issues with the model inputs, the committee did not consider that it had seen analysis that represented its preferred assumptions, so it was unable to assess the cost-effectiveness of the treatments in the appraisal or recommend their use"* **Critical request:** **Re-issue the ACD for this appraisal revisiting the text in page 3 and 4 which is misleadi**
4	**Systemic naïve population** The recommendations from the committee related to the systemic naïve population are unclear. However, as per our request on 16 December 2021, prior to the first appraisal committee meeting, we request that abrocitinib be considered as a first-line systemic for adults and adolescents. We request that the EAG incorporate the data provided previously within the NMA and model prior to the second appraisal committee meeting.
Response to key issues identified in page 22 of the ACD	
5	**Data from the adult population to generalise to the adolescent population (section 3.12)**

[4] Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005;90(8):840-4.

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	It is appropriate to reflect on the analysis that have been conducted within the adolescent population although we recognise that it is only feasible to conduct a 'monotherapy comparison' versus dupilumab based on EASI75, given the limitations in the evidence available in adolescents available for dupilumab. Therefore, we agree with the approach proposed by the committee to assume that the results from the 'combination therapy' analysis for adults who were previously exposed to a systemic immunotherapy (and based on EASI 50 + DLQI≥4) would be generalisable to the adolescent population. Only the comparison with dupilumab would be relevant given that baricitinib is licensed for adults only.
6	**A fixed effect model for the network meta-analysis (section 3.15 in ACD)** The committee highlighted that they would want to see a fixed effects NMA, given that random effect models with uninformed priors may not be appropriate because of the small number of trials for each treatment arm. We presented fixed effects NMA analyses in our base case within our initial submission and agree with the committee's assessment of the limitations associated with random-effects analysis. However, as also critically highlighted in our original submission, the overall conclusions are largely comparable regardless of approach (fixed or random effects) It is important to ensure that both fixed effects and random effects-are explored in the EAG NMA. Both should be presented to the committee in the next appraisal committee meeting, to ensure that the full complement of evidence is available to ensure rapid decision making and avoid any further delays. **Critical request:** **Present fixed- and random- effects NMAs to the committee to enable rapid decision-ma and avoid further delays**
7	**A pooled cost-effectiveness estimate for each of the treatment options that have high and low doses (section 3.18 in ACD)** In our initial submission (Document B, Section B.3.8.3 [Table 104]) we explored a scenario with a pooled cost-effectiveness estimate for abrocitinib 200 mg and 100 mg doses. An assumption was made that [redacted] of patients would receive abrocitinib 200mg and [redacted] would receive abrocitinib 100mg. [redacted] The wording in the SmPC related to dosing is as follows: *Abrocitinib is to be taken orally with or without food. It is recommended at 200 mg or 100 mg once daily. For most patients, particularly those with severe disease, 200 mg is the recommended starting dose. A dose of 100 mg once daily is the recommended starting dose for patients aged ≥ 65 years, adolescents (12 to 17 years old), and for those who have risk factors for developing an adverse reaction to abrocitinib or those who are less likely to tolerate the adverse reactions. The maximum daily dose is 200 mg.*

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	During treatment, the dose may be decreased or increased based on tolerability and efficacy. Dose reduction can be considered after disease control is achieved in patients receiving 200 mg. Some patients may experience a disease flare after dose reduction. A higher risk of disease flare after dose reduction is associated with history of receiving systemic treatments for atopic dermatitis and extensive disease involving >50% of body surface area (BSA). [redacted] Nonetheless we would ask that the committee have access to Table 104 in our initial submission where this is explored. Further, we would request that the EAG build this scenario into their model to share with the committee ahead of the second appraisal meeting so that all information required for the committee to make a decision in that meeting is available.
8	**Additional utility values scenarios based on degree of change observed in the trials, health-state specific values rather than treatment-specific utility values and utility values used in TA534 (section 3.20 in the ACD)** We agree with the committee's concerns around the utility data incorporated within the EAG model and the clinical plausibility of the inputs. The two key issues are as follows: • **Utility data at baseline:** we agree with the committee that there is no clinical rationale for the EAG's use of different baseline utility values across therapies. Although improvement in utility may differ, a common baseline should be applied in the EAG model. • **Assumptions around utility for responders**: o We agree with the suggestion from the EAG that the utility associated with being a responder may differ by treatment which was also recognised by the NICE committee in the ACD *"it plausible that there may be some differences in utility values based on responses to treatment" (page 19)* o It is logical to expect that responders (defined as EASI 50 + DLQI ≥4) on a treatment providing higher thresholds of response (e.g., EASI90) would have a higher utility score. o We strongly disagreed with the EAGs assumption that the utility associated with being a responder on baricitinib 4mg would be comparable to the higher doses of abrocitinib (200mg) and upadacitinib (30mg), although under the proposals from the NICE committee this assumption would no longer apply which is appropriate given the lack of clinical plausibility. The baricitinib 4mg dose, whilst being the 'higher-dose,' in the arbitrary sense of being the highest marketed dose, has substantially lower efficacy compared with both doses of abrocitinib and upadacitinib (see Pfizer submission Document B, Section B.2.9.6 [Table 47]). The committee's conclusion in the ACD is two-fold: 1. *"To explore treatment-specific response utilities"* by using *"a single baseline value and apply changes in utility based on the degree of change observed in the trials. Ideally, this would include a single synthesis of the utility evidence linked via the common comparator of placebo, similar to the network meta-analysis approach used for the effectiveness data"* 2. "*See analysis that used health-state utility values, in order to more clearly see the effect of using treatment-specific utility values.* The first proposal needs careful consideration & evaluation given the potential heterogeneities between the trials as recognised by the NICE committee (ACD, page 19). An

alternative and more appropriate approach would be to apply a common baseline utility and utility value associated with being a EASI 50 + DLQI ≥4 responder to all treatments, with additional utility benefits applied based on the proportion of patients achieving EASI75 and EASI90 within the trials. The additional utility benefit associated with being a EASI75 or EASI90 responder could be deduced from regression analysis. In our original submission (Abrocitinib submission Document B, Section B.3.4.5 [Table 71]), we presented this analysis, including for DLQI ≥4 response and for different levels of EASI response. The relevant table is copied below. EASI response categories have been defined in a mutually exclusive way, with categories for patients with an EASI-50 response, but not and EASI-75 response, patients with an EASI-75 response but not an EASI-90 response and patients with an EASI-90 response. This analysis demonstrated that higher levels of EASI response are associated with greater improvements in utility. Treatment covariates were also included but were not significant, suggesting that differences in EASI response sufficiently explained variations in utility between treatments.

COMPARE EQ-5D analysis including EASI-75 and EASI-90 response

	Coefficient	Standard error	LCI	UCI
Age	[redacted]	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	[redacted]	[redacted]	[redacted]	[redacted]
DLQI ≥4	[redacted]	[redacted]	[redacted]	[redacted]
EASI-50 to -74	[redacted]	[redacted]	[redacted]	[redacted]
EASI-75 to -89	[redacted]	[redacted]	[redacted]	[redacted]
EASI-90	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DLQI, disease quality of life index; EASI0, Eczema Area and Severity Index; LCI, lower confidence; UCI, upper confidence interval.

Critical request:

- Explore within the model a baseline utility and utility value associated with being EASI 50 + DLQI ≥4 responder to all treatments, with an uplift based on the propo of patients achieving EASI75 and EASI90 within the trials.
- [redacted]

9

Analysis that represents best supportive care treatment waning over time and sensitivity around the modelled time horizon (section 3.21)

While BSC is not a comparator in the EAG model, the utility values for patients ending up on BSC remains an important factor. The EAG model assumed that there is a waning in the utility benefit associated with active treatment and that the response rates seen in clinical trials will not hold in the long-term. However, the model does not include any waning of BSC utility and instead models the BSC as a weighted average of responders and non-responders to BSC, with efficacy taken from the placebo arms of AD UP or MEASURE UP 1 and 2. This is in line with the ERG's preferred approach in TA681, however is at odds with clinical opinion, the approach taken in the company submissions and the committee's preferred assumptions in the baricitinib appraisal (TA681).

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The approach from the EAG produces counterintuitive results as in overestimating the utility values for patients receiving BSC in the long-term, the model overstates the QALY gains for treatments with lower response rates and higher rates of discontinuation.

We were reassured to see that the committee are requesting additional scenarios related to the waning of BSC within the model and we would propose scenario 2 in the below table in the base case, which aligns with the base case in our initial submission.

Clinical opinion provided to the company indicated that the response to BSC seen in clinical trials would be expected to drop off quickly, with one clinician stating that utility for BSC would be more comparable to that of non-responders. Scenario 2 also represents one of the preferred scenarios from the dupilumab appraisal (TA534) based on long-term CHRONOS data.

Waning of utility benefit for BSC in the model, scenarios for consideration

Year	Abrocitinib, dupilumab and baricitinib	BSC – scenario 1	BSC – scenario 2	BSC – scenario 3
2	98%	43%	18%	18%
3	95%	18%	10%	10%
4	93%	8%	6%	10%
5	92%	3%	4%	10%

We also explored additional scenarios for BSC waning in our initial submission.

- Scenario 1 is additional scenario from the dupilumab appraisal based on CHRONOS that was preferred by the committee
- Scenario 3 reflects assumptions that are between the company and ERG base cases in the baricitinib appraisal. In this appraisal in the revised base case the company applied waning assumptions from CHRONOS as per the dupilumab appraisal whereas the ERG preferred no application of treatment waning. The committee commented that the true value was likely somewhere between the company and ERG assumptions. Scenario 3 matches the base case (scenario 2), however there is assumed to be no further waning beyond year 3.

Critical request:

- For the EAG to explore scenarios related to BSC waning including the three scer presented in the above table which represent the two preferred scenarios (1 & 2) the dupilumab appraisal (TA534).
- [redacted]

	Additional comments
10	**Limitations related to the comparison with baricitinib** A broader consideration related to the utility data applied within the EAG model is the absence of reliable baricitinib data, given there was no utility gain associated with being in a maintenance health state (i.e., a responder) based on trial data, as discussed in the final guidance from TA681 (page 17).

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Further, baricitinib discontinuation data (as per the below table) were provided to Pfizer, with permission from Eli Lilly, for inclusion within our initial STA submission for abrocitinib. This data is highly relevant given that discontinuation is a significant driver of the ICER; however, permission has not been given for this data to be used within the ongoing MTA.

Summary of baricitinib discontinuation rates, annual discontinuation week 52 +

NICE baricitinib appraisal TA681[a]		EAG model	
EASI 75	**EASI 50 + DLQI≥50**		**EASI 50 + DLQI≥50**
[redacted]	[redacted]	[redacted]	-

[a]Slide 47 appraisal committee slides; company and ERG alignment

We strongly disagreed with the EAGs initial assumption that the discontinuation associated with baricitinib 4mg would be comparable to the higher doses of abrocitinib (200mg) and upadacitinib (30mg). The baricitinib 4mg dose, whilst being the 'higher-dose,' in the arbitrary sense of being the highest marketed dose, has substantially lower efficacy compared with both doses of abrocitinib and upadacitinib (see Pfizer submission Document B, Section B.2.9.6 [Table 47]).

We appreciate from reading the ACD (section 3.19, page 19) that the EAG also presented to the committee a scenario where baricitinib 4mg was instead assumed to be comparable to the lower doses of abrocitinib (100mg) and upadacitinib (15mg) although the committee's comments on this are unclear.

We request that the scenario whereby baricitinib is assumed to be equivalent to the high dose JAKs is not presented to the committee as it is not a plausible scenario. As per the recently published NICE manual:

"*all model parameter values used in base-case, sensitivity, scenario and subgroup analyses should be both clinically plausible and should use methods that are consistent with the data. Results from analyses that do not meet these criteria will not usually be suitable for decision making*[5]*"*

More generally, given the challenges related to utility and discontinuation data for baricitinib we question the reliability of comparisons with baricitinib based on a cost-effectiveness analysis. We would defer the NICE committee to our cost-minimisation analysis in relation to the comparison of abrocitinib versus baricitinib as the economic case is more clearly illustrated.

Critical requests:

- Remove the scenario where baricitinib discontinuation is assumed to be equivale the high doses of abrocitinib (200mg) and upadacitinib (30mg) as this is not clinic plausible and therefore not appropriate for consideration.
- [redacted]

[5] Developing NICE guidelines: the manual paragraph 4.6.27

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11	**Data from JADE DARE** Data from a Phase 3 active-controlled study to assess efficacy of abrocitinib 200mg versus dupilumab 300mg, was requested during the committee meeting. This was shared by us on 17 September 2021 as soon as it was available internally, however it was not incorporated within the NMA/model developed by the EAG even after the consultation period. Given the comments from the committee in the first appraisal meeting we would ask the EAG to incorporate these data within the NMA and modelling. The data from JADE DARE comparing abrocitinib and baricitinib aligns broadly with the narrative from JADE COMPARE as per our initial submission. It is unlikely to change markedly the overall conclusions but add additional weighting to these. **Critical request:** • For the EAG to add JADE DARE into the network for indirect comparisons with baricitinib and dupilumab to ensure that this data is captured prior to the second appraisal committee meeting.
12	**Modelling treatment sequencing (section 3.6)** In our initial submission we presented exploratory analysis looking at treatment sequencing although we highlight several of the limitations associated with the analysis (see Pfizer submission Document B, Section B.3.10). Efficacy data for patients who received their second systemic therapy was assumed as equal to the base-case model data with no adjustment made given that there is no data on sequential effectiveness. We agree with the committee that for that reason cost-effectiveness analysis based on treatment sequencing would be associated with significant uncertainty that is unresolvable.
13	**Minor wording change** • Paragraph 3.4. 'used in inflammatory disorders' is repeated in this paragraph

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eczema Outreach Support (EOS)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Eczema Outreach Support has received funding from the pharmaceutical industry: AbbVie: £10,000 towards charitable activities Pfizer: £30,000 towards charitable activities Leo Pharma: £5,000 towards developing online resources
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	EOS are concerned that the recommendation that abrocitinib and upadacitinib are not recommended for treating moderate to severe atopic dermatitis in young people 12 years and over denies adolescents access to a treatment that may provide significant relief from the chronic condition. Finding a treatment that works for severe eczema is a process of trial and error, so choice of treatment is very important. Families endure many years of trying different treatments including steroids, moisturisers, creams and bandages, light therapy and immunosuppressants, but if none of this works, they are reaching the end of the line for treatments which can be very stressful. Having more options at this stage would make a huge difference to adolescents who feel they are running out of options. Finding a treatment that works can be life changing for adolescents, significantly improving their physical and mental health, and their life chances.
2	EOS are concerned that a delay in making abrocitinib and upadacitinib available as an option to adolescents with severe eczema may lead to avoidable suffering for young people struggling to manage the physical and mental impact of the condition.
3	
4	
5	
6	

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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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 (BAD)]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]

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Name of commentator person completing form:	[redacted] on behalf of the BAD's 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) Has all of the relevant evidence been taken into account?
1	We agree with the committee that all the available evidence was not included in the original document but needs to be considered. This includes data from studies that were not available in the original analysis, e.g. JADE-DARE, AD-UP, RISING-UP.
2	The committee may wish to consider the results of the TREAT trial (ciclosporin vs. methotrexate in adolescents), although we realise these treatments are not currently licensed in adolescents with eczema. The investigators would be happy to share the results confidentially with NICE in a few months' time when they have been accepted for publication. There is also additional published evidence regarding methotrexate in adults which would ideally be considered because methotrexate is the most commonly used first-line treatment for eczema and is much cheaper than ciclosporin or the new drugs
3	Evidence from trial situations is limited because trial data necessarily exclude some patients, e.g. significant mental health difficulties, patients who have not responded to other treatments, patients with very severe disease who it would be unethical to randomise to placebo or who would drop out of the standard run-in period due to disease flares when their current systemic therapy needs to be stopped. Hence, real-world effectiveness data, such as that from the A-STAR registry, are likely to be more representative of the patient populations treated within NHS clinics than cohorts enrolled in trials.
4	There are many patients who have been treated with abrocitinib under the Early Access to Medicines Scheme (EAMS) and with tralokinumab and upadacitinib via free-of-charge (FOC) or nearly FOC schemes from their respective manufacturers. Such patients would have not only failed treatment with at least one conventional systemic but also a novel agent (most likely dupilumab). This shows the need for additional systemic therapies and the companies may have data from enrolment into these schemes that could be additionally used for the NICE technology assessment.
5	It is essential that patients commencing new treatments for eczema are entered into an independent research data platform, such as A-STAR, to allow evidence of comparative

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	effectiveness, safety and treatment effect waning to be taken into account for future appraisals. A-STAR also collects health resource use data that could be used for the health economic evaluation that forms part of the NICE technology assessments.
	2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
6	The summary statement that the drugs in question 'have been indirectly compared with some standard treatments, but the results are highly uncertain' seems disingenuous in the light of overwhelming data showing clinical benefit, including the living NMA (*Drucker et al.*) just published in *JAMA Dermatology*. This NMA has conducted indirect comparisons between the novel systemics using much of the same data as NICE, and demonstrated evidence of efficacy against conventional and other novel drugs, in particular dupilumab., Drucker states, ''*This systematic review with meta-analysis found that compared with dupilumab, abrocitinib, 200 mg daily, and upadacitinib, 30 mg daily, were associated with reductions in EASI scores; upadacitinib, 15 mg daily, was associated with similar reductions, and tralokinumab, 300 mg every other week, and baricitinib, 2 and 4 mg daily, were associated with fewer reductions*''. The uncertainty identified by NICE principally surrounds the meta-analysis approach taken, which essentially favours head-to-head clinical trial data with IMP vs. best supportive care. Unfortunately, such data largely does not exist, and therefore, it seems unreasonable to derive a model that favours it. However, the efficacy of the medications under review against placebo was undoubted and agreed in the report. Indeed, it was a drug vs. placebo technology appraisal model that has been applied for novel AD therapies until now. The uncertainty of effect size due to a circuitous indirect comparison with ciclosporin, risks loss of sensitivity. This results in a negative appraisal which would exclude highly effective treatments from clinical use for our patients. In the single area where head-to-head data is available (albeit not as primary endpoint) abrocitinib vs. dupilumab data, the clinical efficacy of abrocitinib is demonstrated, supporting the argument that the indirect comparison model used in the NMA by Drucker et al. is robust. Another possible reason for difference in analysis results between NICE and Drucker include the categorical/dichotomous outcomes used in the NICE analysis vs. continuous outcomes in Drucker.
7	The cost economic modelling is problematic for several reasons highlighted by the committee in the consultation document. The committee have suggested a number of areas where changes are needed, which we broadly agree with.
8	We are very concerned that different methodology used in the appraisals for novel eczema treatments to date (dupilumab, baricitinib and this one) has led to different

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	conclusions regarding cost effectiveness. For example, the utility value of best supportive care in this model was associated with higher quality of life and lower costs compared with the dupilumab appraisal. The consequence of this is that dupilumab, which was previously recommended, now appears less cost effective. We feel strongly that this needs to be addressed because of the implications for future NICE appraisals of new eczema treatments.
9	It was stated in the ACD document that *"The limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a suitable cost-effectiveness estimate for abrocitinib, tralokinumab and upadacitinib. So, they cannot be recommended."* However, when dupilumab and baricitinib were being appraised by NICE, the evidence available was more limited.
10	'Best supportive care' (BSC) is defined in this model as a single health care state. Costs of BSC are calculated by the weighted average of responders and non-responders at 16 weeks (as guided by the NMA of clinical effectiveness). This is likely to be an underestimate of true costs of BSC (see below). We do not feel it is appropriate to have a single BSC state or that this state should be assumed to be stable for the duration of modelling (5 years). In the current modelling, BSC is associated with high quality of life and low costs. This is incorrect and leads to favouring of ineffective treatments.
11	Patients in BSC are likely to require high-cost, ongoing care, including: i. Ongoing hospital outpatient attendances and investigations. ii. Alternative systemic drugs requiring hospital follow-ups, blood tests, other monitoring and management of drug side effects and toxicity. iii. GP support. iv. Hospital admission for severe uncontrolled disease. v. Mental health input due to impact of severe disease. vi. High social costs due to inability to work, costs of carers and impact on family.
12	Costs of being on different classes of drugs is not considered in the model (apart from the actual drug costs). Conventional systemic drugs and JAK inhibitors require frequent blood tests. Biologics including dupilumab and tralokinumab require minimal blood tests, and less frequent hospital attendances once stable.
	3) Are the recommendations sound and a suitable basis for guidance to the NHS?
13	The BAD does not consider these recommendations, as they stand, to be sound or a suitable basis for guidance to the NHS, for reasons outlined above and below.
14	The most important group of patients who need these drugs are those who have tried all existing treatments for eczema, and none have worked. These patients are desperately in need of new treatments to allow them to return to productive living, as evidenced by the

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	uptake of JAK inhibitors on the EAMS and FOC schemes, where these drugs have proved life-changing for some.
15	There is a need for drugs of different classes to be available because eczema is a long-term disease affecting patients of all ages and with differing co-morbidities and preferences. Clinical judgement will influence treatment choice for individual patients, based on efficacy, adverse effects profile, pre-existing co-morbidities and cost. For this reason, it is not appropriate to dictate a rigid sequence of treatments.
16	Currently, the free of charge schemes run until October 2022, after which patients may not be able to access drugs which are currently working for them
	4) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity.
17	We agree with the committee decision to recommend that adolescents are treated the same as adults to avoid age discrimination.
18	We note that the Scottish Medicines Consortium has approved tralokinumab (https://www.scottishmedicines.org.uk/medicines-advice/tralokinumab-adtralza-full-smc2403/) and upadacitinib (https://www.scottishmedicines.org.uk/medicines-advice/upadacitinib-rinvoq-full-smc2417/), and our understanding is that abrocitinib may be approved shortly. The current recommendation would therefore create a situation where patients in Scotland have access to the medications under assessment, while patients in England might not.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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