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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Karen Pickett critically appraised the clinical effectiveness systematic review, indirect treatment comparisons, drafted the report, project managed the review and is the project guarantor; Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review, and drafted the report; Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Alexander Scott critically appraised the indirect treatment comparisons, and drafted the report.

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LIST OF ABBREVIATIONS

AD	Atopic dermatitis
AE	Adverse event
AIC	Academic in confidence
ANCOVA	Analysis of covariance
A&E	Accident and emergency
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDLQI	Children's Dermatology Life Quality Index
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Database of Systematic Reviews
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CsA	Ciclosporin A
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DSU	Decision Support Unit
EAG	External Assessment Group
EASI	Eczema Area and Severity Index
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
FAS	Full analysis set
GP	General practitioner
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment

ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IGA	Investigator's Global Assessment
IPD	Individual patient level data
ITT	Intent to treat
JAK	Janus kinase
MAIC	Matching-adjusted indirect comparison
MCMC-MI	Markov Chain Monte Carlo Multiple Imputation
mITT	Modified intent to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
ONS	Office of National Statistics
OWSA	One way sensitivity analysis
PAS	Patient Access Scheme
PGA	Patient Global Assessment
PICOD	Population, intervention, comparator, outcome, design
POEM	Patient Oriented Eczema Measure
PO-SCORAD	Patient-Oriented Scoring for Atopic Dermatitis
PROMIS	Patient-reported Outcomes Measurement Information System
PROs	Patient-reported outcome measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Q2W	Every two weeks
Q4W	Every four weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCORAD	Scoring Atopic Dermatitis

SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TCS	Topical corticosteroid
TCI	Topical calcineurin inhibitors
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UK	United Kingdom
US	United States
WTP	Willingness-to-pay threshold
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

In this report, we refer to systemic treatments for people with moderate-to-severe atopic dermatitis for whom systemic therapy is suitable and who have not received a prior systemic therapy as 'first-line systemic therapies'. We use the term 'second-line systemic therapies' to refer to systemic treatments for people whose condition has not responded to at least one prior systemic therapy or in whom these are not suitable.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID	Summary of issue	Report sections
1	Generalisability of the populations of the lebrikizumab and NMA trials to the population of patients who will receive lebrikizumab in clinical practice	2.3, 3.2.1, 3.3 and 3.7
2	Use of Eczema Area and Severity Index (EASI) 75 to calculate the NMA odds ratios that inform response at week 16	4.2.6.1
3	Use of the average of the conditional discontinuation rates for weeks 16 to 52 from all treatments to inform response at week 52	4.2.6.2
4	Conditional discontinuation rate of lebrikizumab combination therapy for weeks 16 to 52	4.2.6.2
5	Use of the average of the conditional discontinuation rates to inform long-term discontinuation in the model (from week 52 onwards)	4.2.6.3
6	Use of treatment-specific utility values (active treatment versus best supportive care)	4.2.7.2

ID	Summary of issue	Report sections
7	Ambiguity in the CS about the population in whom the company are positioning lebrikizumab	2.2.3, 2.3 and 4.2.3

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the estimates for conditional discontinuation rates between week 16 and week 52, the estimates for long-term discontinuation from week 52 onwards and the health state utility estimates (section 1.7).

1.2 Overview of key model outcomes

NICE technology appraisals assess how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Following their response to the clarification questions, the company updated their economic model. The company's updated base case deterministic cost-effectiveness results are shown in Table 2 with a confidential PAS discount applied for lebrikizumab. The results are for lebrikizumab and the comparators in combination with topical corticosteroids, rather than monotherapy. Lebrikizumab dominates baricitinib and tralokinumab as it is less costly and more effective. Abrocitinib, upadacitinib and dupilumab have higher QALYs than lebrikizumab but the ICERs for these treatments vs lebrikizumab are greater than £300,000 per QALY. These results do not reflect the price of the comparator treatments to the NHS as these treatments have a confidential discount. The results with all discounts included are shown in an EAG addendum.

Table 2 Company's updated base-case results for combination therapy with PAS discount for lebrikizumab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Pairwise NMB vs. Comparator
Lebrikizumab	[redacted]	[redacted]				
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	£568,504
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£366,436	£366,436
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1,408,755

Results shown for combination therapy: all treatments include topical corticosteroids
Source: Reproduced from Clarification response document Table 30.
Ext dominated, extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

The modelling assumptions that have the greatest effect on the ICER are the conditional discontinuation rates between week 16 and week 52 and long-term discontinuation rates from week 52 until death.

1.3 The decision problem: summary of the EAG's key issues

The EAG have not identified any key issues in relation to the company's decision problem.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Generalisability of the populations of the lebrikizumab and NMA trials to the population of patients who will receive lebrikizumab in clinical practice

Report section	2.3, 3.2.1, 3.3 and 3.7
Description of issue and why the EAG has identified it as important	The company appear to be positioning lebrikizumab treatment in a population of patients in whom conventional, first-line systemic therapies have been inadequately effective, not tolerated or contraindicated. Our clinical expert agreed with this positioning. The company use treatment response rate odds ratios from an NMA to calculate response rates for both lebrikizumab and the second-line systemic therapy comparators in their economic model. The lebrikizumab and other studies eligible for the NMA included a range of patients; for example, those who were systemic therapy-naïve, or those who had had an inadequate response to topical therapies, or those who had previously failed on or were unsuitable for systemic treatment. Only one lebrikizumab trial (ADvantage) explicitly included patients who had failed on or who were unsuitable for a first-line systemic therapy, specifically ciclosporin A. We understand from our clinical expert that off-label methotrexate is the most commonly used first-line systemic therapy in practice, followed by ciclosporin A in a smaller proportion of patients. There is no evidence in the CS for lebrikizumab use in a population who have failed on or are unsuitable for methotrexate. So overall the company use some data to inform response rates that do not fully match the population of interest.
What alternative approach has the EAG suggested?	We acknowledge that this is the nature of the lebrikizumab and other randomised controlled trials (RCTs) available for conducting an NMA. We also suggest that the ADvantage trial results may be of some generalisability to patients who have previously failed on methotrexate. We do not suggest an alternative approach.
What is the expected effect on the cost-effectiveness estimates?	Clinical expert advice to the EAG is that, on average, people who fail on methotrexate or ciclosporin A are likely to respond less well to lebrikizumab and other novel systemic therapies than patients naïve to systemic therapies. We suggest the inclusion of people naïve to systemic treatment in some of the studies could potentially impact on the response rates used in the economic model, although we do

	not expect this to have an important impact on the model conclusions as this issue affects data for both lebrikizumab and the comparators.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion about whether or not the evidence included in the CS and used in the NMA for lebrikizumab, including the ADvantage trial, and the comparators is generalisable to the patients expected to receive lebrikizumab treatment in practice, if it is approved.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 2 Use of EASI 75 to calculate the NMA odds ratios that inform treatment response at week 16.

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	In the absence of data available for the EASI 50 + DLQI ≥4 improvement treatment response measure for the comparators, the company used the EASI 75 odds ratios, obtained from the NMA, to calculate the base case treatment response at week 16 for all treatments (including lebrikizumab). The company argue that the proportions of patients achieving EASI 75 were the most similar to the proportions of patients achieving the composite endpoint in the lebrikizumab trials. EASI 50 + DLQI ≥4 improvement was the preferred endpoint to inform response at week 16 in previous NICE appraisals (TA534, TA681 and TA814). The NICE committee for TA814 considered that EASI 75 may not capture all meaningful improvements among patients with atopic dermatitis receiving second-line systemic therapies. Clinical expert advice to the EAG is that fewer patients are likely to achieve EASI 75 compared to EASI 50 + DLQI ≥4 improvement.
What alternative approach has the EAG suggested?	We do not suggest an alternative approach as the data on EASI 50 + DLQI ≥4 is redacted for comparators in previous NICE appraisal documentation. We acknowledge the limitations of using EASI 75, but we consider that it is a reasonable approach in the absence of better data. For completeness, we tested the use of EASI 50 in a scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	It is unknown how similar the EASI 75 and the EASI 50 + DLQI ≥4 outcomes are for the comparators. Therefore, it is difficult to predict the effect of using EASI 50 + DLQI ≥4 improvement rather than EASI 75 in the model base case. Using EASI 50 instead of EASI 75 leads to a small reduction in the ICER of dupilumab, upadacitinib and abrocitinib vs lebrikizumab. Lebrikizumab continues to dominate baricitinib and tralokinumab.
What additional evidence or analyses	Further clinical expert opinion on the plausibility of using EASI 75 as a proxy for EASI 50 + DLQI ≥4 improvement in

might help to resolve this key issue?	patients with atopic dermatitis who are candidates for second-line systemic therapies would be helpful.

Issue 3 Use of the average of the conditional discontinuation rates for weeks 16 to 52 from all treatments to inform treatment response at week 52.

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	The company used the average of the conditional discontinuation rates from all treatments to inform treatment response at week 52 and did not explain the rationale behind this assumption. In TA814, individual conditional discontinuation rates for each treatment were used and accepted by the NICE committee. Moreover, using the individual discontinuation rates has a potentially large effect on the ICER.
What alternative approach has the EAG suggested?	The EAG prefers to use the individual conditional discontinuation rates for each treatment for weeks 16 to 52, as previously done in TA814. The individual conditional discontinuation rate for lebrikizumab is specifically discussed in the next key issue.
What is the expected effect on the cost-effectiveness estimates?	Using the individual conditional discontinuation rates for each treatment leads to a reduction in the ICER of dupilumab, upadacitinib, abrocitinib and tralokinumab vs lebrikizumab. Lebrikizumab continues to dominate baricitinib. (Table 3).
What additional evidence or analyses might help to resolve this key issue?	Clarification from the company on why they have used an average conditional discontinuation rate of all treatments. Further clarification on how the conditional discontinuation rates for each treatment were derived from their respective trials. Clinical advice on the plausibility of different treatments having the same discontinuation rate at week 52.

Issue 4 Conditional discontinuation rate for lebrikizumab combination therapy for weeks 16 to 52.

Report section	4.2.6.2
Description of issue and why the EAG has identified it as important	In response to clarification question B7(a), the company explained how the individual conditional discontinuation rate was derived for lebrikizumab and informed the EAG of an updated value for lebrikizumab. The EAG incorporated this as part of the EAG corrections to the company's model, as it was not included in the company's updated model. The EAG notes that the lebrikizumab discontinuation rate is [redacted] than the corresponding values for the comparators for combination therapy. The reason for this is unclear but we suspect that it could be related to how the rates were derived from each trial and may not reflect the true relative effect of lebrikizumab versus the comparators.

What alternative approach has the EAG suggested?	As we were not able to confirm the reason for the large difference in the conditional discontinuation for lebrikizumab for combination therapy versus the other treatments, we use the company's updated value in our EAG base case but explore the impact of using the following conditional discontinuation rates in scenario analyses: (1) the conditional discontinuation rate based on a response defined as achieving EASI 75. (2) the conditional discontinuation rate from monotherapy trials for lebrikizumab based on a response defined as achieving EASI 50 + DLQI ≥4 improvement (3) the weighted average of the monotherapy and combination therapy conditional discontinuation rates for lebrikizumab based on a response defined as achieving EASI 50 + DLQI ≥4 improvement (4) the average of the conditional discontinuation rates for the subset of biologic treatments (i.e., lebrikizumab, tralokinumab and dupilumab)
What is the expected effect on the cost-effectiveness estimates?	Using the alternative discontinuation rates above have a minimal impact on the company base case. However, for the EAG base case, there is an increase in the ICER for all treatments vs lebrikizumab (Table 48). Lebrikizumab continues to dominate baricitinib.
What additional evidence or analyses might help to resolve this key issue?	Further clarification on how the conditional discontinuation rates for each treatment were derived from their respective trials. Further clinical advice on the plausibility of the individual rates.

Issue 5 Use of the average treatment conditional discontinuation rate for long-term discontinuation (from week 52 onwards)

Report section	4.2.6.3
Description of issue and why the EAG has identified it as important	The company assumed that the long-term discontinuation, used from week 52 onwards in the model, is the mean 36-week conditional discontinuation rate converted to an annual rate and used for all treatments. The clinical expert advising the EAG did not consider that using the same long-term discontinuation rate for all treatments is reflective of clinical practice as, in their opinion, JAK inhibitors would have a worse safety profile than biologics.
What alternative approach has the EAG suggested?	We apply a drug class approach in our EAG base case where an average of the annual discontinuation rates of biologics is applied to lebrikizumab, dupilumab and tralokinumab and an average of the annual discontinuation rates of JAK inhibitors is applied to baricitinib, abrocitinib and upadacitinib.
What is the expected effect on the cost-effectiveness estimates?	Using a drug class approach leads to a reduction in the ICER for upadacitinib and abrocitinib vs lebrikizumab and an increase in the ICER for dupilumab vs lebrikizumab (Table 3). Lebrikizumab continues to dominate baricitinib and tralokinumab.

What additional evidence or analyses might help to resolve this key issue?	Further clinical advice on the expected long-term discontinuation rates for the drugs being compared.

Issue 6 Use of treatment-specific utility values (active treatment versus best supportive care)

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The company used treatment-specific utilities in their base case, i.e. utility values conditional on response but also different for active treatment and best supportive care (BSC). In TA814, the committee considered that not using treatment-specific utility values was a better approach. As part of the response to clarification question B11, the company added an option to the model where overall health state utilities (baseline, response and non-response) could be selected.
What alternative approach has the EAG suggested?	We prefer to use the overall health state utilities (baseline, response and non-response) rather than treatment-specific utilities (active treatment versus BSC) in our EAG base case, as preferred by the NICE committee in TA814. We also note that for the health state utilities, the company's overall health state utilities for response and non-response do not appear plausible. We changed the utility values for response and non-response provided by the company. We calculated the utility values for response and non-response as the weighted average of the utility values from the lebrikizumab and placebo arms used in the company's base case. In the EAG's base case, we use the following utilities: • Baseline: [redacted] • Response: [redacted] • Non-response: [redacted]
What is the expected effect on the cost-effectiveness estimates?	Using overall health state utilities leads to an increase in the ICER for dupilumab, upadacitinib and abrocitinib vs lebrikizumab (Table 3). Lebrikizumab continues to dominate baricitinib and tralokinumab.
What additional evidence or analyses might help to resolve this key issue?	Further discussion on which approach is the most appropriate.

1.6 Other issues: summary of the EAG's view

Issue 7 Ambiguity in the CS about the population in whom the company are positioning lebrikizumab

Report section	2.2.3, 2.3 and 4.2.3
Description of issue and why the EAG has identified it as important	We believe the company are positioning lebrikizumab treatment in a population of patients in whom conventional, first-line systemic therapies (that is, azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) have been inadequately effective, not tolerated or contraindicated, in line with other second-line systemic therapies approved by NICE. However, there is some ambiguity about this in the CS, as the company state in their decision problem that they consider a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised, as they state this *"reflects the anticipated positioning of lebrikizumab in the UK treatment pathway"* (CS Table 1). The company's meaning here is unclear, but could be taken to mean that they are positioning lebrikizumab specifically in people who have had an inadequate response to or who are unsuitable for ciclosporin A. It could alternatively mean that the company are arguing that evidence from the ciclosporin A population reflects the wider population of patients who have failed on or are unsuitable for first-line systemic therapies.
What alternative approach has the EAG suggested?	The EAG's clinical expert expects lebrikizumab to be used among people who have an inadequate response to, inability to tolerate or contraindication to first-line systemic therapies (the most commonly used of which is methotrexate, followed by ciclosporin A). The company's economic model focuses on people who have failed on or are unsuitable for systemic therapies, so we do not suggest an alternative approach, but further clarification about the population in whom the company is positioning lebrikizumab (that is, patients who have failed on or are unsuitable for any of the first-line systemic therapies, or specifically ciclosporin A) would be beneficial for resolving the noted ambiguity.
What is the expected effect on the cost-effectiveness estimates?	None.
What additional evidence or analyses might help to resolve this key issue?	Confirmation from the company about the population in whom they are positioning lebrikizumab treatment.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG's critique of the company's model (discussed in section 5.2.4), we have identified the following key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Response at week 52**: we use the individual treatment-specific conditional discontinuation rates, rather than taking an average across all treatments.
- **Long-term discontinuation rate**: we use the average discontinuation rate by drug class, rather than taking an average across all treatments. For JAK inhibitors, we use the average of the baricitinib, abrocitinib and upadacitinib 52-week rates. For biologics, we use the average of lebrikizumab, dupilumab and tralokinumab 52-week rates.
- **Utility values**: we use the health state utilities, i.e. utilities for response and non-response only, rather than using different utility values for active treatments and BSC. We use the weighted average of the treatment-specific utilities for the active treatment and BSC for responders ([redacted]) and non-responders ([redacted]).

Table 3 shows the cumulative cost-effectiveness results for combination therapy when applying the EAG's preferred model assumptions to the company's corrected base case and when using the PAS discount for lebrikizumab and the list price for the comparator treatments. Results are shown for the comparators vs lebrikizumab, as they are more expensive than lebrikizumab.

The incremental cost-effectiveness results are shown in Table 4 and Table 5. For the EAG base case, lebrikizumab continues to dominate baricitinib. The ICERs of dupilumab, upadacitinib, abrocitinib and tralokinumab versus lebrikizumab are greater than £400,000 per QALY.

The change that has the most significant impact on the cost-effectiveness results is using the treatment-specific conditional discontinuation rates.

Table 3 Cumulative cost effectiveness results for combination therapy of the EAG's preferred model assumptions with PAS discount for lebrikizumab only, pairwise against lebrikizumab

Preferred assumption	Treatment	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
Company base-case with EAG corrections (section 5.2.3)	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib			Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£592,286
	Tralokinumab			Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	£379,263
	Dupilumab	[redacted]	[redacted]	£1,454,408
	Lebrikizumab	[redacted]	[redacted]	

Preferred assumption	Treatment	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
+Response at week 52: use individual treatment-specific conditional discontinuation rates	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£243,136
	Tralokinumab			£432,622
	Upadacitinib			£240,316
	Dupilumab			£381,367
+Long-term discontinuation rate: use average rate by drug class for 52 weeks	Lebrikizumab			
	Baricitinib			Lebrikizumab dominates
	Abrocitinib			£487,484
	Tralokinumab			£455,851
	Upadacitinib			£356,511
	Dupilumab			£396,023
+Use overall health state utilities. Utility for responders ([redacted]) and non-responders ([redacted]).	Lebrikizumab			
	Baricitinib			Lebrikizumab dominates
	Abrocitinib			£629,041
	Tralokinumab			£443,379
	Upadacitinib			£514,899
	Dupilumab			£461,012
EAG base case (including the assumptions above)	Lebrikizumab			
	Baricitinib			Lebrikizumab dominates
	Abrocitinib			£629,041
	Tralokinumab			£443,379
	Upadacitinib			£514,899
	Dupilumab			£461,012

Results shown for combination therapy: all treatments include topical corticosteroids
EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-years.

Table 4 EAG incremental base case results for combination therapy with PAS discount for lebrikizumab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	ICER vs lebrikizumab (£/QALY)
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]		
Baricitinib					Dominated	Lebrikizumab dominates
Abrocitinib					Ext dominated	£629,041
Tralokinumab					Ext dominated	£514,899
Upadacitinib					£443,379	£443,379
Dupilumab					£503,428	£461,012

Results shown for combination therapy: all treatments include topical corticosteroids.
Ext dominated, extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Modelling errors identified and corrected by the EAG are described in section 5.2.3. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Almirall on the clinical effectiveness and cost effectiveness of lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over. It identifies the strengths and weaknesses of the CS. A clinical expert was consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 23rd November 2023. A response from the company via NICE was received by the EAG on 7th December 2023 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The company provide an overview of atopic dermatitis in CS sections B.1.3.1 (overview), B.1.3.2 (epidemiology), B.1.3.3 (pathophysiology) and B.1.3.4 (Burden of atopic dermatitis). In this report we concentrate on moderate to severe atopic dermatitis because people with this severity of the disease are the focus of this appraisal.

2.2.1 Background information on moderate to severe atopic dermatitis

Atopic dermatitis (also known as atopic eczema) is a chronic relapsing inflammatory skin condition that is currently uncurable which affects children and adults. The condition is characterised by dry, flaky and inflamed skin which is intensely itchy. Disease flare ups (transient exacerbations) are a common feature of atopic dermatitis. Clinical expert advice to the EAG is that the severity of atopic dermatitis is commonly assessed in clinical practice based on the clinical judgement of the treating physician, but many clinicians have adopted severity scoring into routine NHS clinical care monitoring, using measures such as the Patient Oriented Eczema Measure (POEM) and Eczema Area and Severity Index (EASI). Our clinical expert stated that most clinics will solely use the POEM, but tertiary clinics in particular will also use the EASI.

Evidence from the clinical trial setting has historically used a variety of clinical scales and patient reported outcome measures (many of which are unvalidated) to assess disease severity and this made comparisons between different trials difficult.[1] The Harmonising Outcomes for Eczema (HOME) initiative, founded in 2008, recommends the EASI to assess the severity of atopic dermatitis and it was reported in 2014 that the EASI would be used in

all future atopic dermatitis trials.[2] Other measures, such as the Investigator Global Assessment (IGA; there are multiple versions most of which are not validated[3-5]) and the Scoring Atopic Dermatitis (SCORAD) index are also used in the clinical trial setting to classify disease.[6] The use of these scales to classify atopic dermatitis as moderate or severe is summarised in Table 5.

Table 5 Severity scales to classify moderate and severe atopic dermatitis

Severity scale	Moderate atopic dermatitis	Severe atopic dermatitis	Total range of score
EASI[7]	6.0 to 22.9	23.0 to 72	0-72
IGA[3]	3	4	0-4 or 0-5
SCORAD[7]	29-48.9	49.0 to 103	0-103

Source: Table created by the EAG using information from the cited references.
EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; SCORAD, Scoring Atopic Dermatitis.

The company summarise the epidemiology of atopic dermatitis in CS section B.1.3.2, noting that there are wide variations in the estimation of atopic dermatitis prevalence because of methodological and reporting differences between studies. We have summarised the information identified by the company relevant to the prevalence of moderate-to-severe atopic dermatitis in Table 6.

Table 6 Summary of data on the prevalence of moderate-to-severe atopic dermatitis in the UK

Methodology	Definition of moderate and severe	Prevalence of atopic dermatitis
Analysis of data for adults from the UK Clinical Practice Research datalink (CPRD) database 2015 to 2019.[8]	Referral to a specialist (either a dermatologist or an immunopathologist) or prescription for topical calcineurin inhibitors, phototherapy or systemic treatments [a]	2.4% (active AD [b]) Moderate-to-severe AD ranged from 7.5% to 8.3% of those with active AD in the 5 years analysed.
Cross-sectional survey of UK adults (n=10,001, with n=256 contributing severity data).[9]	PO-SCORAD: moderate 25-49, severe ≥50. POEM: moderate 8-16, severe >16 PGA: self reported moderate or severe	2.5% (95% CI 2.2% to 2.8%) Moderate AD: 49%-56% depending on the assessment scale.

Methodology	Definition of moderate and severe	Prevalence of atopic dermatitis
		Severe AD:4%-12% depending on the assessment scale.
Cohort study analysing UK data from the Health Improvement Network database, from 1994 to 2013.[10]	Moderate: earliest of i) second potent topical steroid within a year or ii) first calcineurin inhibitor treatment Severe: earliest of i) first systemic treatment for AD (i.e. ciclosporin, azathioprine, mycophenolate or methotrexate) or ii) first phototherapy or iii) first referral to secondary care.	Children 0-17 years: 18.3% Moderate AD: 5.6% Severe AD: 1.9% Adults 18-74 years: 7.7% Moderate AD: 20.1% Severe AD: 2.7%

Source: Table created by the EAG using information cited in the CS, supplemented with information sourced from Kleyn et al. 2023,[8] Barbarot et al. (2018)[9] and Chan et al. (2021)[10]
AD, atopic dermatitis; PGA, Patient Global Assessment; POEM, Patient Oriented Eczema Measure; PO-SCORAD, Patient-Oriented Scoring for Atopic Dermatitis.
[a] These included methotrexate/methotrexate sodium, azathioprine, mycophenolate mofetil/mycophenolate sodium, ciclosporin and dupilumab but not oral glucocorticoids
[b] The numbers of UK adult patients in the dataset with active atopic dermatitis ranged from 72,013 to 121,176 per year during the five years studied.

2.2.2 Background information on lebrikizumab

The company's description of lebrikizumab is provided in CS section B.1.2. Lebrikizumab, brand name Ebglyss®, is a monoclonal antibody. It selectively binds to IL-13, the key cytokine in the skin of people with atopic dermatitis, thereby inhibiting the biological effects of IL-13 that drive the skin barrier dysfunction, inflammation, itch and skin thickening signs and symptoms of atopic dermatitis.

Marketing authorisation was granted in the European Union on 16th November 2023 and MHRA approval was received on 19th December 2023.

The lebrikizumab SmPC recommends an initial dose of 500 mg (administered via two 250 mg injections) at both week 0 and 2 of treatment, followed by 250 mg administered every other week until week 16. The SmPC suggests that some patients with initial partial response may further improve with continued treatment every other week up to week 24. When clinical response has been achieved, the SmPC states that the recommended maintenance dose of lebrikizumab is 250 mg every four weeks.

Lebrikizumab is administered by subcutaneous injection into the thigh or abdomen which can either be administered by the patient (self-injection) or by their caregiver if deemed appropriate by the treating physician. Caregivers can also give the injection in the upper arm of the patient. Rotating the injection site with each injection is recommended.

2.2.3 The position of lebrikizumab in the treatment pathway

The SmPC states that lebrikizumab is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy. This is in line with the population defined in the scope of this appraisal.

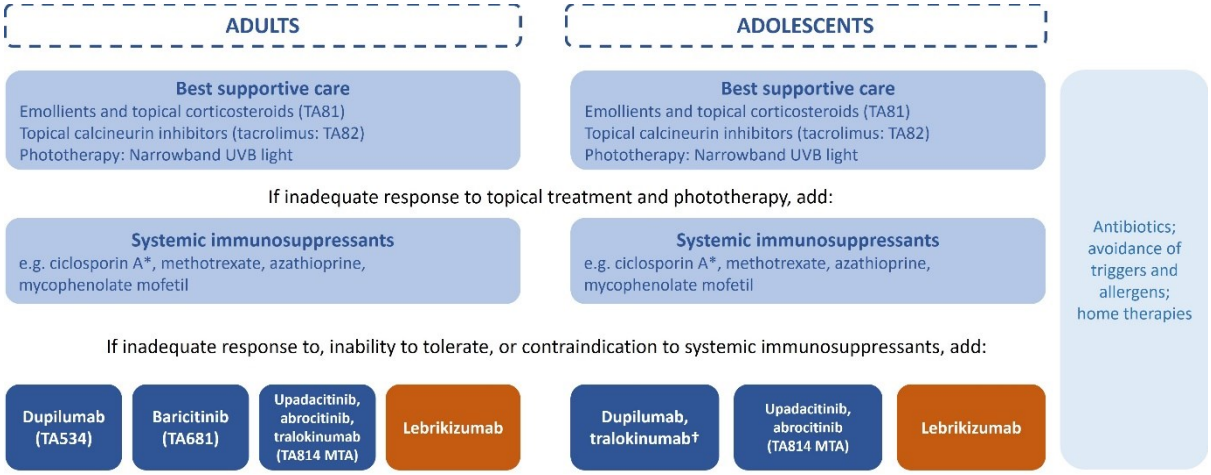
The CS describes the clinical pathway of care in CS section B.1.3.5 with the anticipated position of lebrikizumab shown in CS Figure 2 which we have reproduced below as Figure 1.

The treatment pathway begins with best supportive care (BSC) which is the same for adults and adolescents. The BSC treatment options are topical therapies and phototherapy. Lebrikizumab would not be used at this point in the treatment pathway.

When there is an inadequate response to the topical therapy options and phototherapy the next step in the treatment pathway is to move to a systemic immunosuppressant (plus emollients and topical corticosteroid [TCS]/topical calcineurin inhibitors [TCI]). The first line systemic immunosuppressants include ciclosporin A, methotrexate, azathioprine and mycophenolate mofetil. Of these, ciclosporin A is the only licensed first-line treatment in the UK. During TA814[6] (abrocitinib, tralokinumab or upadacitinib for treating moderate-to-severe atopic dermatitis) the committee heard that many clinicians now prefer to consider methotrexate first (used off-label) as, even though ciclosporin is licensed, toxicity concerns mean ciclosporin is used for only short periods. Additionally, we received clinical advice that the majority of patients receive off-label methotrexate as a first line systemic immunosuppressant in the UK, with ciclosporin A being the next most common option. Some patients with particularly severe disease may be started on ciclosporin A but subsequently transition to methotrexate. Azathioprine and mycophenolate mofetil are very rarely used in the UK. Although the lebrikizumab marketing authorisation would allow for lebrikizumab to be used at this point in the treatment pathway, this is not where the company have positioned lebrikizumab and consequently the first-line systemic therapies are not included as comparators in the CS (see section 2.3 for more discussion about this).

If there is an inadequate response to first-line systemic immunosuppressants (or they cannot be tolerated or are contraindicated) the next step in the treatment pathway is a second-line

systemic treatment, either a biologic (dupilumab or tralokinumab) or a Janus kinase (JAK) inhibitor (abrocitinib, upadacitinib or baricitinib). The treatment options at this level differ slightly between adults and adolescents because baricitinib is an option for adults but not adolescents. The company have positioned lebrikizumab at this point in the treatment pathway.



*Ciclosporin A is the only systemic immunosuppressant licensed for use in AD (NB only approved for severe AD). The rest are used off-label.
†Dupilumab and tralokinumab are commissioned by NHS England for adolescents.
NICE TA81: Frequency of application of topical corticosteroids for atopic eczema[11]
NICE TA82: Tacrolimus and pimecrolimus for atopic eczema[12]
NICE TA534: Dupilumab for treating moderate to severe atopic dermatitis[13]
NICE TA681: Baricitinib for treating moderate to severe atopic dermatitis[14]
NICE TA814: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis[6]

Figure 1 The anticipated position of lebrikizumab in the clinical pathway of care for moderate-to-severe atopic dermatitis.

Source: Reproduction of CS Figure 2

As discussed in more detail in the next section of this report (EAG report section 2.3), while the company appear to be positioning lebrikizumab among people who have failed on or are unsuitable for any of the first-line systemic therapies used in clinical practice, the company's decision problem includes consideration of a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised. The company state that this sub-population reflects the *"anticipated positioning of lebrikizumab in the UK treatment pathway"* (CS Table 1).

The experts advising the EAG that conducted the MTA for NICE TA814 stated that systemic therapies are usually given concomitantly with topical corticosteroids in clinical practice. Additionally, it was noted in the dupilumab and baricitinib appraisals (TA534 and TA681, respectively)[13,14] that both these drugs were likely to be offered with TCS too. Our clinical expert similarly advised us that they expect lebrikizumab to be used in combination with topical corticosteroids. This is discussed further in section 3.2.1.1.

In line with the EAG MTA report for the NICE TA814 appraisal,[15] in this report, and as mentioned in the Executive Summary above, we refer to treatment for people for whom systemic therapy is suitable and who have not received a prior systemic therapy as 'first-line systemic therapies' (i.e. the positioning of ciclosporin A, methotrexate, azathioprine and/or mycophenolate mofetil in the care pathway). We use the term 'second-line systemic therapies' to refer to treatment for people whose condition has not responded to at least one prior systemic therapy or in whom these are not suitable (i.e., the positioning of abrocitinib, tralokinumab, upadacitinib, dupilumab and/or baricitinib in the clinical pathway).

EAG comment

The company have provided an accurate overview of atopic dermatitis and highlight the difficulty of comparing prevalence estimates for atopic dermatitis because of methodological and reporting differences between studies. The company have described lebrikizumab's mode of action and indicated where they are positioning lebrikizumab within the treatment pathway for patients with moderate-to-severe atopic dermatitis but there is some ambiguity in the CS about the population who would receive lebrikizumab (patients in whom conventional first-line systemic therapies have been inadequately effective, not tolerated or contraindicated or specifically a sub-population of those patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised). Our clinical expert agreed with the company's proposed positioning of lebrikizumab as a second-line systemic therapy.

2.3 Critique of the company's definition of the decision problem

Table 7 summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this. The company's decision problem largely reflects the NICE scope, with some deviations in terms of the comparators and outcomes. The main deviation is that the company has not included the first-line immunosuppressive therapies specified in the NICE scope as comparators (i.e. azathioprine, ciclosporin, methotrexate and mycophenolate mofetil), but we view this as reasonable given the company and our clinical expert's anticipated positioning of lebrikizumab as a second-line therapy in the clinical pathway (see 2.2.3 for further details).

In the CS, the company focus on comparing lebrikizumab to the second-line systemic therapies abrocitinib, tralokinumab, upadacitinib, dupilumab and baricitinib. Of these, the clinical expert advising us considered upadacitinib, abrocitinib and dupilumab to be the most relevant comparators for lebrikizumab in treating adolescents and adults, based on the drugs' efficacy. In terms of treatment sequencing the expert advised us that dupilumab is usually used after methotrexate and ciclosporin A in clinical practice. After this, a JAK-inhibitor will typically be used. As noted in the company's depiction of the clinical pathway in CS Figure 2, dupilumab and tralokinumab are commissioned by NHS England for the treatment of adolescents, but are recommended by NICE for use in adults only.[6,13]

As outlined in Table 7 and as stated in section 2.2.3, in their decision problem and CS, the company considers a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised, as this *"reflects the anticipated positioning of lebrikizumab in the UK treatment pathway"* (CS Table 1). The company provided no further rationale in the CS for the focus on this population or why the population reflects the expected positioning of lebrikizumab. The EAG asked the company to clarify this in clarification question A2. The company responded that ciclosporin A is the only first-line treatment licensed in the UK, and that one of the lebrikizumab trials was conducted in this population, as were trials of other second-line systemic therapies (clarification response A2). Our clinical expert advised us that, in the UK, clinicians do not have to adhere to licensing. As outlined in section 2.2.3, our expert advised us that the majority of patients receive methotrexate, with ciclosporin A being the next most commonly used treatment. We also note that in the committee discussion for TA814 it was commented that many clinicians prefer to use methotrexate first, as there are toxicity concerns associated with ciclosporin A and so it is only used for short periods of time.[6] The expert advising us did not believe that the company's focus on solely the ciclosporin A sub-population was justified. Our expert said it would be more relevant to focus on patients who have received either methotrexate or

ciclosporin A. The EAG is therefore of the opinion that a more relevant population to clinical practice in England in which to assess the clinical efficacy of lebrikizumab as a second-line treatment would be people who have not responded to either ciclosporin A or methotrexate, or in whom these therapies are unsuitable. The ciclosporin A sub-population is only part of the population of patients who will potentially receive lebrikizumab. The population of interest in the company's economic model, however, is people for whom systemic therapies have been inadequately effective, not tolerated or contraindicated.

The outcomes stated to be of interest in the company's decision problem match those specified in the NICE scope, with the exceptions stated by the company in Table 7. The expert advising us did not agree with the company's focus on rescue therapy use, TCS-free days and treatment discontinuation instead of the NICE scope-specified outcomes of disease free period, maintenance of remission, time to relapse and prevention of relapse. The expert stated that there have now been trials that have assessed disease relapse, which is a highly relevant outcome in a waxing and waning disease such as atopic dermatitis. For example, this has been defined as returning to 50% of baseline score on the EASI disease severity measure. The expert said that disease free period is also a relevant outcome. This can be measured with an instrument such as the AD Control Test or assessing if patients reach an IGA of 0. The company use the rescue therapy and treatment discontinuation outcomes in the economic model, using conditional discontinuation (i.e. the all-cause discontinuation rate) to model longer-term treatment responses, which aligns with the approach taken in the MTA for TA814 (CS section B.3.3.3). While the outcomes in the company's decision problem partially deviate from those in the NICE scope, we do not consider this a key issue.

We note that in NICE TA814 a composite endpoint of a disease severity and a quality of life measure – EASI 50 plus an improvement in Dermatology Life Quality Index (DLQI) score of at least four (referred to hereafter in this report as 'EASI 50 + DLQI ≥4') – was considered the most relevant endpoint for decision making and for defining treatment response.[6] The company have provided results for this outcome in the CS from the lebrikizumab trials in CS section B.2.7.2, CS Appendix F, and clarification response A24. The company, however, uses a different response measure – EASI 75 (a 75% reduction from baseline in EASI; hereafter referred to as 'EASI 75' in this report) – to calculate response rates for both lebrikizumab and the comparators in their economic model due to data availability for the comparators (CS section B.3.3.2). We discuss this further in sections 3.2.3 and 4.2.6).

The company has not differentiated between the adolescent and adult populations in their decision problem and NICE did not specify that any subgroup analyses by age were of interest in the scope. We consider it is reasonable for the company to have not differentiated between the adolescent and adult populations, as our clinical expert advised us that they would expect the efficacy and safety of lebrikizumab and the second-line systemic therapy comparators to be generally similar between adults and adolescents.

Table 7 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People 12 years and over with moderate to severe atopic dermatitis who are candidates for systemic therapy.	Same as scope	-	The population is in line with the NICE scope. The company more specifically state in CS section B.1.1 that the submission covers lebrikizumab's full marketing authorisation indication, which is: "the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy" (EMA, 2023, page 2).[16] This is appropriate.
Intervention	Lebrikizumab	Same as scope	-	The intervention is as per the NICE scope. Additionally, we note that the lebrikizumab SmPC states that lebrikizumab can be used in combination with topical corticosteroids or without these. Use of topical calcineurin inhibitors is also permitted in the SmPC, for problem areas only.[16] As stated in section 2.2.3, based on clinical expert advice, we expect lebrikizumab to be used in combination with TCS in clinical practice.
Comparators	People for whom systemic therapy is suitable and have not previously received a systemic therapy:	Same as scope (and in line with the appraisals for other currently-available second-line systemics)	Consideration of this sub-population reflects the anticipated positioning of lebrikizumab in the UK treatment pathway	The company's selected comparators reflects the anticipated position of lebrikizumab in practice as a second-line systemic therapy. The company include all second-line systemic

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	• Immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) People whose condition has not responded to at least 1 other systemic therapy, or these are not suitable: • Abrocitinib • Tralokinumab • Upadacitinib • Dupilumab • Baricitinib	Note that the submission will include consideration of a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised		therapies in the scope but no first-line therapies. The EAG considers this reasonable. Regarding the ciclosporin A sub-population, as discussed above in this section, it would have been more relevant to clinical practice to focus on patients who have had an inadequate response to either methotrexate or ciclosporin A or in whom these treatments are unsuitable.
Outcomes	The outcome measures to be considered include: • measures of disease severity • measures of symptom control • disease free period/maintenance of remission • time to relapse/prevention of relapse • adverse effects of treatment • health-related quality of life.	The outcome measures in the clinical effectiveness section include: • measures of disease severity • measures of symptom control • rescue therapy use • TCS-free days • treatment discontinuation • adverse effects of treatment, • health-related quality of life	Clinical experts have stated that disease free period, maintenance of remission, time to relapse and prevention of relapse are not commonly used in clinical practice for AD and are not defined in AD. The submission therefore includes rescue therapy use, TCS-free days and treatment discontinuation, which is consistent with the TA914 [a] MTA	As discussed above in this section, the outcomes selected by the company do not fully match those in the NICE scope. The clinical expert advising the EAG did not agree with the company's rationale and focus on rescue therapy use, TCS-free days and treatment discontinuation instead of the NICE scope-specified outcomes.
Economic analysis	The reference case stipulates the following requirements for cost-	Same as scope	-	The company's cost-utility analysis adheres to the NICE reference case (see section 4.2.1). CS Table 2 states

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	effectiveness analyses: costs assessed as cost per quality-adjusted life year (QALY), adequate time horizon, NHS and Personal Social Services perspective, commercial arrangements and managed access taken into account and availability and cost of biosimilar and generic products taken into account. (NICE scope wording abridged by EAG here for brevity.)			that a simple PAS discount has been submitted to NHS England for lebrikizumab. The lebrikizumab PAS price is applied in the economic evaluation (see section 5.1).
Subgroups	None specified	-	-	No subgroups were specified to be of interest in the NICE scope. As stated above, the company give consideration in the CS to a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised. Other planned and post-hoc subgroup analyses of the lebrikizumab trials' data are provided in the CS (CS sections B.2.7.1 and B.2.7.2, and CS Appendix E), which include analyses by age (adolescents 12 to <18 years, and adults ≥18 years).
Special considerations including issues related	None specified	The use of lebrikizumab is not expected to raise any equality issues. However, it is important to note that assessment of AD in	-	The EAG note the equity and equality considerations raised in NICE TA814,[6] and which have been highlighted by the company in this table. In TA814, the committee noted

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
to equity or equality		patients with skin of colour can be challenging. NICE recommends that when assessing response to treatment, healthcare professionals should take into account how skin of colour may affect the EASI score and make any appropriate adjustments (1-3). NICE also recommends that healthcare professionals should take into account any physical, psychological, sensory or learning disabilities, or communication difficulties that may affect patients' responses to the DLQI.		that in people with brown or black skin, the EASI measure of disease severity may underestimate the severity of the person's condition. The EAG and the EAG's expert have not identified any other equity or equality considerations.

Source: Partly reproduced from CS Table 1.
AD, atopic dermatitis; CS, company submission; DLQI, Dermatology Life Quality Index; EAG, External Assessment Group; EASI, Eczema Area and Severity Index; EMA, European Medicines Agency; IGA, Investigators Global Assessment; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PAS, Patient Access Scheme; SmPC, Summary of Product Characteristics; TA, technology appraisal; TCS, topical corticosteroid; UK, United Kingdom
[a] The EAG assumes that this is an error and that the company is referring to TA814.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company describes their systematic literature review (SLR) of the clinical effectiveness and safety of lebrikizumab and relevant comparators for the treatment of adult patients with moderate-to-severe atopic dermatitis in CS Appendix D. This SLR also informed the company's network meta-analysis (NMA) and matching-adjusted treatment comparison (MAIC). The EAG's appraisal of the company's systematic review methods is summarised in Appendix 1. We believe the review is comprehensive and matches the decision problem. Although the searches were around six months old when the CS was received by the EAG, we believe there is a low risk that relevant randomised controlled trials (RCTs) have been missed.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

From the SLR, supplemented with data-on-file clinical study reports (CSRs) for three studies of lebrikizumab (CS Appendix D, section D.1.1), the company identified and included four phase III, placebo-controlled, RCTs of lebrikizumab in the CS (CS section B.2.2):

- **ADvocate 1**: NCT04146363
- **ADvocate 2**: NCT04178967
- **ADhere**: NCT04250337
- **ADvantage**: NCT05149313

The company also included an open-label long-term extension study (**ADjoin,** NCT04392154), which includes patients previously enrolled in ADvocate 1 and 2 and ADhere, as well as other studies.

A further three placebo-controlled lebrikizumab RCTs were identified for inclusion in the company's NMA (CS Appendix D, Table 91) [**J2T-DM-KGAF** (NCT03443024[17]), **ADhere-J** (NCT04760314) and **ADopt-VA** (NCT04626297)], with an additional two trials mentioned in the safety section of the CS and included in a published integrated safety analysis[18] [**ARBAN** (NCT02465606)[19] and **TREBLE** (NCT023402340]. The CS also mentions a phase 3 open-label, single-arm trial of lebrikizumab conducted in adolescents aged ≥12 to <18 years (weighing ≥40 kilograms), **ADore** (NCT04250350).[20] We provide more information about these trials in Appendix 2. We believe it is reasonable that these studies have not

been considered in detail in the CS. The ADore trial provides evidence for adolescents, but the lebrikizumab RCTs included in the CS recruited both adults and adolescents and thus provide evidence for the younger age group.

No head-to-head trials of lebrikizumab versus the comparator therapies were identified (CS section B.2.2). The company therefore carried out indirect treatment comparisons (ITCs), in the form of an NMA and MAIC, to compare the efficacy of lebrikizumab with the second-line systemic therapy comparators (CS sections B.2.8 and B.2.9) (see sections 3.3 and 3.4 of this report for a critique of the NMA and MAIC).

The ADvocate 1 and 2, ADhere, and ADjoin trials were sponsored by Dermira Inc. (a wholly-owned subsidiary of Eli Lilly).[21-23] The ADvantage trial was funded by Almirall S.A.[24]

[redacted], while Lilly has exclusive rights for the development and commercialisation of lebrikizumab outside of Europe, including in the United States.[23]

Data from both the ADvocate trials and the ADhere trial have been published in journal articles.[18,21,22,25] Results from the ADvantage and ADjoin trials have only been presented at conferences.[23,26,27] The company supplied copies of these publications and presentations with the CS, along with the CSRs for all five trials.[24,28-31] A combination of data from the publications and the CSRs are used in the CS.

CS section B.2.2 states that efficacy and safety data presented from the ADvantage study in the CS are from an interim analysis with a data cut-off date of 18th April 2023. The last participant completed this study on 5th October 2023 and a clinical study report is planned for April 2024 (response to clarification question A7). Results from an interim analysis of the ADjoin trial are also presented in the CS, but the data cut-off date for this analysis is not provided in Document B of the CS. In response to clarification question A8, the company stated that the ADjoin efficacy and safety results provided in the CS (presented in CS sections B.2.6.4 and B.2.10.5, respectively) were from an analysis with a cut-off date of 18th April 2023. The ADjoin study is expected to complete in September 2024 with final results expected Q3 2024 (response to clarification question A8).

Treatment response, treatment discontinuation, adverse events and HRQoL data from the lebrikizumab RCTs are used to inform the company's CS economic model (CS section B.3.3). Rescue therapy use in the trials is used to inform flare rates (that is, this outcome is used as a proxy for flare rates) in the model (CS section B.3.3.8).

3.2.1.1 Study characteristics

Of the five key lebrikizumab trials the company includes in the CS, ADvocate 1 and 2 are described as 'monotherapy' trials whereas ADhere and ADvantage are described as 'combination therapy' trials (e.g. CS Table 39). In the latter two trials lebrikizumab was used in combination with TCS. The remaining study – the ADjoin study – was a long-term extension study, which included participants from the ADvocate 1 and 2 and ADhere parent studies, as well as other lebrikizumab studies (CS section B.2.3.1). Concomitant use of TCS appeared to be permitted in ADjoin (see section 3.2.1.1.4 for details).

We understand from our clinical expert that in clinical practice, when patients are in receipt of systemic therapies, they remain on a repeat prescription for TCS and can use them as needed. As noted in section 2.3, our expert expected lebrikizumab to be used in combination with TCS in clinical practice. Similarly, in NICE TA814, clinical experts explained to the committee that abrocitinib, tralokinumab and upadacitinib were likely to be used alongside TCS in practice. The committee did not consider that the monotherapy trials represented how the treatments would be used in practice and concluded that the combination therapy evidence was most relevant to decision-making.[6] In the lebrikizumab CS economic model base case, the company assumes that all patients will receive combination therapy (CS section B.3.3.2 and CS Table 89). Given that trials of combination therapy are likely to form the most relevant evidence for how lebrikizumab will be used in practice, in presenting the characteristics of the lebrikizumab studies here, we have focused on these trials. We provide a briefer overview of the monotherapy trials. First, we provide an overview of how atopic dermatitis and severe-to-moderate atopic dermatitis was defined in the participant eligibility criteria of the key lebrikizumab trials.

3.2.1.1.1 How atopic dermatitis and moderate-to-severe disease was defined in the trials

To be eligible for the ADvocate 1 and 2 trials and the ADhere trial, participants needed to have a diagnosis of chronic atopic dermatitis defined by the American Academy of Dermatology (AAD) Consensus Criteria (CS, Table 6; no reference is provided in the CS for the criteria), and in the ADvantage trial this was defined by the Hanifin and Rajka Criteria[32] (CS, Table 7; reference provided in response to clarification question A15). We asked the company in clarification question A15 how reflective each of these sets of criteria are of those used to diagnose chronic atopic dermatitis in clinical practice in England. In their response (clarification response A15), the company stated that the Hanifin-Rajka criteria are one of the earliest and most recognised criteria and are considered the gold standard for diagnosing atopic dermatitis. They stated AAD Consensus Criteria are a version of the

Hanifin and Rajka Criteria, and that both sets of criteria are reflective of those used in clinical practice for diagnosing atopic dermatitis. The EAG's clinical expert confirmed that use of these sets of criteria is appropriate.

In the two lebrikizumab monotherapy trials, ADvocate 1 and 2, and in the combination therapy trials, ADhere and ADvantage, moderate-to-severe atopic dermatitis was defined as having all of the following at baseline:

- EASI of 16 or more
- IGA score of 3 or more
- BSA of 10% or more

The clinical expert advising us stated that this definition appears to be reasonable. It is derived from the dupilumab trials, and the concept of 'moderate-to-severe atopic dermatitis' comes from those trials. Use of this definition means that trials in atopic dermatitis have similar inclusion criteria. The expert noted that in clinical practice, BSA is not worked out, and an EASI score of 16 or more is on the more severe side of atopic dermatitis. He noted that not many people with more moderate disease would fall within this definition.

3.2.1.1.2 Monotherapy trials: ADvocate 1 and 2

Table 52 in Appendix 3 provides an overview of the characteristics of the ADvocate 1 and 2 monotherapy studies. Both trials had exactly the same design (CS section B.2.3.1). They were 52-week, placebo-controlled trials, with a 16-week induction phase and a 36-week maintenance phase, in adults and adolescents (aged 12 to <18 years and weighing ≥40 kg; as per the SmPC[16]) with moderate-to-severe atopic dermatitis who were candidates for systemic therapy. Responders to induction treatment were re-randomised to maintenance treatment. Participants received the SmPC-indicated dose of lebrikizumab as induction treatment. One of the two lebrikizumab maintenance doses used in the trials matched that indicated in the SmPC (see Table 52). The trials both had two disease severity primary outcomes: 1) percentage of participants achieving EASI 75 at Week 16, and 2) percentage of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to Week 16.

The EAG notes that participation in the ADvocate 1 and 2 trials did not appear to be limited to people whose condition has not responded to at least one systemic therapy or in whom such treatment is not suitable (CS Table 6). Therefore, the trials' populations may not fully reflect the patient population in whom the company is positioning lebrikizumab treatment

(see 2.2.3). As previously stated, monotherapy trials are unlikely to represent how lebrikizumab will be used in practice.

3.2.1.1.3 Combination therapy trials: ADhere and ADvantage

We summarise the characteristics of the ADhere and ADvantage combination therapy studies in Table 8. Unlike the two monotherapy trials which had exactly the same design, the two combination therapy trials differ in several aspects, most notably the included participants.

In line with the lebrikizumab SmPC indication, both the ADhere and ADvantage trials included adults or adolescents (aged 12 to <18 years and weighing ≥40 kg) with moderate-to-severe atopic dermatitis who were candidates for systemic therapy. As with ADvocate 1 and 2 (see section 3.2.1.1.2 of this report), the EAG notes the participant eligibility criteria listed in the CS for ADhere (CS Table 6) did not limit participation to participants who had previously not responded to at least one systemic therapy or in whom other systemic therapies were not suitable. Therefore, again, the trial population may not fully reflect the population expected to receive lebrikizumab in clinical practice.

In contrast to ADhere, the ADvantage trial specifically focuses on a sub-population of participants in whom ciclosporin A was not medically advisable or whose disease was previously not adequately controlled on ciclosporin A (CS section B.2.3.1). Thus, the ADvantage trial provides data for the ciclosporin A sub-population specified in the company's decision problem (CS Table 1 and see section 2.3). It is the only lebrikizumab trial that corresponds to the patient population in whom lebrikizumab is expected to be used in practice (based on clinical expert advice to us; see section 2.3); that is, patients who have failed on or are unsuitable for first-line systemic therapies.

Additionally, in relation to the ciclosporin A sub-group, in the CS, the company provides a post-hoc sub-group analysis of efficacy results from participants in ADhere who had previously been exposed to ciclosporin A (CS section B.2.7.2), but it is unclear whether or not these participants had just previously received ciclosporin A rather than had had an inadequate response to it.

The RCTs also differ in their design. ADhere was a 16-week trial and participants who completed it could choose to enrol in the ADjoin long-term extension study. ADvantage was a 52-week trial with a 16-week induction period and a 36-week maintenance period. No participants from ADvantage entered the ADjoin long-term extension study. In ADvantage after the induction period, all participants, regardless of whether or not they had been

randomised to lebrikizumab or placebo, entered the maintenance treatment period, where all participants received the same dose of lebrikizumab treatment (CS section B.2.3.1), i.e., there was no maintenance comparator arm. Both trials were placebo-controlled during the induction treatment periods.

The CS presents ADvantage results only for the 16-week induction period from an interim analysis dated 18 April 2023 (CS section B.2.2), as maintenance data are not yet available (CS section B.2.2). In response to clarification question A7 the company said that they anticipate that the findings from the maintenance phase will *"read out"* (clarification response A7) on 4th January 2024. They stated that the CSR is planned for April 2024.

Both the ADhere and ADvantage trials used the SmPC-indicated induction treatment dose of lebrikizumab.[16] The lebrikizumab maintenance dose used in the ADvantage trial up to week 52, however, does not match that specified in the SmPC.[16] Therefore, when the maintenance data are available from this trial, the trial will not provide evidence in relation to the SmPC-indicated maintenance dose. We note participants based in Germany, had the option to take part in an additional extension period to the study in which they were due to receive [redacted] (CS section B.2.3.1 and ADvantage CSR, page 25[24]). The company stated in clarification response A14 that the study was extended only in Germany due to the resources available.

Slightly different approaches to the use of concomitant TCS were taken in the ADhere and ADvantage trials. In ADhere, participants could reduce, cease or resume TCS as needed (CS section B.2.3), and our expert confirmed that this reflects how TCS are used alongside systemic treatments in clinical practice. In the ADvantage trial, all participants received mid-potency TCS during the induction period up to week 16, until skin lesions were clear or almost clear (low potency TCS were permitted to be used on sensitive areas). Then participants switched to low-potency TCS for seven days, after which they ceased to use them (CS section B.2.3.1). If lesions re-occurred, then participants had to resume mid- to low-potency TCS. (See footnote 'd' in Table 8 for a description of use of TCS during the maintenance period). Our clinical expert advised us that this use of TCS is less reflective of clinical practice, which would mean that less well-controlled disease would potentially be more likely, as a lower potency treatment was used.

[redacted] [24,30]

A primary outcome in both the ADhere and ADvantage trials was EASI 75 at week 16. The ADhere trial additionally measured the percentage of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to week 16 as a primary outcome.

Table 8 ADhere and ADvantage combination therapy studies' designs and characteristics

Study characteristics	ADhere	Advantage
Study design and length	A 16-week, double-blind, placebo-controlled, phase 3 RCT, consisting of a 16-week treatment period. Participants who completed the study could enter the ADjoin LTE. Those who did not join the LTE or complete the study had a follow-up visit around 12 weeks after their last dose of study medication.	A 52-week, double-blind, placebo-controlled, phase 3 RCT, with a 16-week induction and a 36-week maintenance period. After completion of the week 16 visit, participants received lebrikizumab 250 mg Q2W. [a] If participants did not achieve an EASI 50 response for two consecutive visits between weeks 24 and 48, they had to discontinue from the study. Only week-16 data are presented in the CS, from an interim analysis. The company state maintenance data are not yet available.
Study locations	Canada, Germany, Poland, US. No UK centres or participants (clarification response A10)	Austria, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, UK (four UK centres, recruiting 10 participants; clarification response A11)
Population	Adults and adolescents with moderate-to-severe AD	Adults and adolescents with moderate-to-severe AD who are not adequately controlled with CsA or for whom CsA is not medically advisable.
Intervention	Induction: • **Lebrikizumab 250 mg Q2W + TCS (participants received a loading dose of lebrikizumab 500mg at weeks 0 and 2)** [b] Maintenance:	Induction: • **Lebrikizumab 250 mg Q2W + TCS (participants received a loading dose of lebrikizumab 500mg at weeks 0 and 2)** [c] Maintenance:

Study characteristics	ADhere	Advantage
	• No maintenance period.	• Lebrikizumab 250 mg Q2W + TCS
Comparator	• Placebo Q2W + TCS [b]	Induction • Placebo Q2W + TCS [c] Maintenance: • None (all participants received lebrikizumab during the maintenance period)
Sample size	N randomised: 211 (lebrikizumab + TCS: n = 145; placebo + TCS: n = 66)	N randomised: 331 (lebrikizumab + TCS: n = 220; placebo + TCS: n = 111)
Key eligibility criteria	• Adult or adolescent (aged 12 to <18 years and weighing ≥40 kg) • Diagnosis of chronic AD (AAD Consensus Criteria) for ≥1 year before screening • Candidate for systemic therapy • No treatment with dupilumab within the last eight weeks [d]	• Adult or adolescent (aged 12 to <18 years and weighing ≥40 kg) • Diagnosis of chronic AD (Hanifin and Rajka Criteria) that had been present for ≥1 year before screening • No previous CsA exposure and not a candidate for it as it is not medically advisable, or previously discontinued CsA (due to intolerance, unacceptable toxicity, dose or duration needed outside of prescribing information, or inadequate response)
Primary outcome	Co-primary endpoints: • Percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI) at week 16 • Percentage of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to week 16	• Percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI) at week 16
Other outcomes	• Measures of symptom control • Adverse effects of treatment • Health-related quality of life	• Measures of symptom control • Adverse effects of treatment

Source: Partly reproduced from CS Tables 5, 6 and 7, CS sections B.2.2 and B.2.3.1 and clarification responses A10, A11 and A12.
Bold text shows the lebrikizumab doses that match the posology specified in the lebrikizumab SmPC.
AAD, American Academy of Dermatology; AD, atopic dermatitis; CS, company submission; CsA, ciclosporin A; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; LTE, long-term extension study; Q2W, every 2 weeks; RCT, randomised controlled trial; TCS, topical corticosteroids; UK, United Kingdom; US, United States
[a] Participants who had received induction placebo received the 500 mg loading dose of lebrikizumab at weeks 16 and 18. The study was open-label from week 20 onwards (CS section B.2.3.1).

[b] Participants could reduce, cease or resume TCS use as needed (CS section B.2.3). TCI use on sensitive areas was also permitted (CS Table 6).
[c] All participants received mid-potency TCS up to week 16, until skin lesions were clear or almost clear. Then participants switched to low-potency TCS for seven days, after which they ceased to use them. TCI or high-potency TCS were classed as rescue medication. Low-potency TCS could be used on sensitive areas (CS section B.2.3.1). Between weeks 16 and 52, TCS could be used at the Investigator's discretion (CS Table 7).
[d] Participants were not eligible for trial if had had previous treatment with dupilumab in the last eight weeks (clarification response A12, Table 13), as this has a similar mechanism of action to lebrikizumab and these participants were excluded to avoid prior exposure to dupilumab affecting the results of the studies (clarification response A12).

3.2.1.1.4 Long-term extension study: ADjoin

We provide an overview of the characteristics of the ADjoin study in Table 9. ADjoin is an ongoing 100-week, long-term follow-up extension study which includes adults and adolescents with moderate-to-severe atopic dermatitis, who had completed ADvocate 1 and 2, ADhere, ADore or ADopt-VA, or, in the US only, people who have otherwise met the study inclusion criteria (recruited to enable collection of additional safety data; clarification response A16). Participants from ADvocate 1 and 2 continued their maintenance dose from that study. Responders to induction therapy in ADhere were re-randomised to either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W. Non-responders received lebrikizumab 250 mg Q2W. During ADjoin, participants from ADvocate 1 and 2 and ADhere were permitted to use TCS (CS section B.2.3.1). It is unclear in Document B of the CS whether participants from the other parent studies were permitted to do so.

The primary outcome in ADjoin was the percentage of participants discontinued from treatment due to adverse events (CS Table 8). The trial also included measures of symptom control (CS Table 8). As stated in section 3.2.1, interim results are presented in the CS from ADjoin. Efficacy outcomes are presented in the CS up to 104 weeks of lebrikizumab treatment (CS section B.2.6.4). Long-term results are presented separately for participants from the monotherapy parent studies ADvocate 1 and 2, and the combination therapy parent study ADhere (CS section B.2.6.4). During the long-term extension period for the ADhere parent study, between 14 and 25 patients treated with the lebrikizumab 250 mg Q4W dosing regime (i.e. the SmPC-indicated maintenance dose) had data available up to week 104, depending on the outcome, according to CS Figures 27, 28 and 29. There are therefore limited long-term follow-up data available in the CS for the SmPC-indicated maintenance dose of lebrikizumab in the combination therapy context. Long-term data are presented for the SmPC-indicated dose from the monotherapy ADvocate 1 and 2 trials up to 104 weeks, with data available for 55 and 80 participants at week 104, depending on the outcome, according to CS Figures 27, 28 and 29, which offers further insight into the potential

maintenance of disease response over time with lebrikizumab. The company stated in clarification response A8 that ADjoin is expected to complete in September 2024, with the final results expected in Q3 2024.

Table 9 ADjoin study design and characteristics

Study characteristics	Details
Study design and length	100-week long-term extension study; see 'Population' row for which lebrikizumab studies participants needed to have completed to be eligible for this study.
Study locations	Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, US. No UK centres (clarification response A10).
Population	Adults and adolescents with moderate-to-severe atopic dermatitis who had completed the ADvocate 1 or 2, ADhere, ADore [a] or ADopt-VA studies, or, in the US only, who had otherwise met the study inclusion criteria.
Intervention [b c]	• **Lebrikizumab 250 mg Q4W** (blinded) [d] • Lebrikizumab 250 mg Q2W (blinded) [d] • Lebrikizumab 250 mg Q2W (open-label) • Lebrikizumab open label 250 mg Q2W (US only; additional safety data)
Comparator	• None
Sample size	[redacted] participants, of whom [redacted] were enrolled from ADvocate 1 and 2, from ADhere, and 149 from ADore (ADore data from clarification response A17). No ADopt-VA participants were included in the interim CSR analysis – the company states that this was due to the ADopt-VA trial still being ongoing at the time of the ADjoin interim analysis (clarification response A17).
Key eligibility criteria	• Participation in one of the stated parent studies (see 'Population' row of this table)
Primary outcome	• Percentage of participants discontinued from study treatment because of adverse events through the last treatment visit
Other outcomes	• Measures of symptom control

Source: Partly reproduced from CS Tables 5 and 8, CS section B.2.3.1 and clarification responses A16 and A17.
Bold text shows the lebrikizumab dose that matches the posology specified in the lebrikizumab SmPC.
CSR, clinical study report; Q2W, every 2 weeks; Q4W, every 4 weeks; UK, United Kingdom; US, United States
[a] A phase 3, open-label, single arm trial in adolescents (NCT04250350).[20]
[b] Participants received the same treatment regimen as they did in the parent study (CS Figure 6). Participants joining from the ADvocate 1 and 2 trials continued their maintenance period dosing regimen (CS section B.2.3.1). Participants enrolling from ADhere who had achieved EASI 75 by week 16 were randomised to either lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W when joining ADhere. If participants had not achieved an EASI response by week 16, they then received lebrikizumab 250 mg Q2W in ADjoin.
[c] Participants from the ADhere trial could cease or continue TCS, as needed (CS section B.2.3.1 and CS Table 8). Participants from the ADvocate 1 and 2 trials were permitted to use TCS intermittently (CS Table 8). Short-term use of systemic treatments for atopic dermatitis was permitted and discussed on a case-by-case basis (CS Table 8).
[d] Some participants were in receipt of a loading dose of lebrikizumab at baseline and week 2 (CS Figure 6).

3.2.1.1.5 Other lebrikizumab RCTs

As stated in section 3.2.1, the company identified and included another three placebo-controlled lebrikizumab RCTs: J2T-DM-KGAF, ADhere-J and ADopt-VA, all of which were included in their NMA. We provide an overview of the characteristics of these studies in Appendix 2 and then next consider the trials as part of our NMA critique (section 3.4).

In their clarification response A6, the company provided information on an additional study evaluating the safety and efficacy of lebrikizumab, ADhope (NCT05990725), which is due to start soon, and which is anticipated to complete in May 2025. We also note that the CS mentions that a phase 3 single-arm study – ADmirable (NCT05372419) – is currently in progress that assesses lebrikizumab in a population of adults and adolescents with skin of colour (results expected in Q4 2024) (CS section B.2.12). Another trial of lebrikizumab, called ADapt (NCT05369403), of its efficacy in adults and adolescents who were previously treated with dupilumab is also ongoing (results are expected in October 2024) (CS Table 53).

3.2.1.2 Patients' baseline characteristics

The company summarised participant baseline characteristics from the ADvocate 1 and 2, ADhere, ADvantage and ADjoin trials in CS section B.2.3.3 (in CS Tables 10, 11 and 12, respectively). The characteristics presented from the ADjoin LTE were for responders to lebrikizumab at 16 weeks in the parent studies (ADvocate 1 & 2 combined and ADhere), due to data availability (CS section B.2.3.3). The company provided race and ethnicity baseline characteristics for the participants in the ADjoin LTE in response to EAG clarification question A18.

3.2.1.2.1 Balance of baseline characteristics within the key lebrikizumab trials

Baseline characteristics of the participants in the ADvocate 1 and 2, ADhere and ADvantage trials were well-balanced across the trial arms within the studies, with the exceptions that in ADvocate 1:

- There were proportionally more Asian participants in the placebo than lebrikizumab 250mg Q2W arm (22.0% versus 13.8%) (CS Table 10).
- Proportionally more participants had previously received a systemic treatment in the placebo than lebrikizumab 250mg Q2W arm (60.3% versus 50.9%) (CS Table 10).

It is unclear whether these differences might impact on outcomes.

3.2.1.2.2 Balance of baseline characteristics between the key lebrikizumab trials

The majority of the participants in the ADvocate 1 and 2, ADhere and ADvantage trials were adults (aged ≥18 years). The proportions of adolescents (aged 12-18 years) included across the trials' arms ranged from 10.7% to 22.1%, with proportionally more adolescent participants in the ADhere trial (around 20%) than in the ADvocate 1 and 2 trials (around 12%) (CS Table 10) or the ADvantage trial (also around 12%, CS Table 11). This difference was reflected in the proportions of adolescent participants from each of these parent studies in the ADjoin LTE (CS Table 12). The EAG does not believe that the heterogeneity between the trials in the proportion of adolescents included would impact the studies' results, as the clinical expert advising us expected that the efficacy of lebrikizumab would generally be similar in adults and adolescents.

Weight marginally differed between participants in ADvantage compared to those in ADvocate 1 and 2 and ADhere, with participants in ADvantage generally of a lower weight (CS Tables 10 and 11). Lower weight was also seen in the ADjoin trial participants who were 16 week trial responders compared to the baseline characteristics of the parent studies of ADvocate 1 and 2 and ADhere. Clinical expert advice to the EAG is that the lower the average weight, the higher the efficacy is likely to be from a standard dosing regimen (i.e. one that is not dosed by body weight).

There was some variation between the ADvocate 1 and 2, ADhere and ADvantage trials in the proportions of White, Black and Asian participants (CS Tables 10 and 11). In the ADvocate 1 and 2 and ADhere trials, between 58.2% and 69.3% of the participants in each trial arm were White. In contrast, around 94% of the participants in each trial arm in the ADvantage trial were White, with only [redacted] Black and [redacted] Asian participants included. It is unclear how these differences may impact on outcomes. Clinical expert advice to the EAG is that findings within the literature on systemic treatment response in people with skin of colour are conflicting. Proportions of White patients in ADjoin (responders from the ADvocate and ADhere parent trials) ranged from [redacted] to [redacted] across the arms presented in Table 14 in clarification response A18.

In ADvocate 1 and 2 and ADhere, between 45.5% and 60.3% of participants across the trial arms had previously received systemic therapies for atopic dermatitis (CS Table 10). The trials therefore included some people who were naïve to systemic treatment. CS section B.3.3.2 states that [redacted] of the participants in the pooled ADvocate trials had previously received CsA, azathioprine, methotrexate, MMF, JAK-inhibitors or biologics. Around [redacted] had received CsA. In ADvantage, [redacted] of the participants in each arm had previously

received ciclosporin A ([redacted] in the placebo arm, and [redacted] in the lebrikizumab arm (CS Table 11). Around 17% in both trial arms had previously received dupilumab.

Regarding the representativeness of the lebrikizumab trials of patients treated in the NHS, clinical expert advice to the EAG is that due to the enrolment of patients naïve to systemic treatment, the trials do not fully reflect NHS clinical practice. However, the expert was of the opinion that inclusion of a relatively high number of patients treated with ciclosporin A was a strength of the ADvantage trial.

EAG comment on included studies

Of the five key trials of lebrikizumab included in the CS, only ADvantage explicitly included participants who had previously failed on or were unsuitable for first-line systemic therapies, specifically ciclosporin A. The other trials included a mixture of participants who were either systemic therapy-naïve or -experienced, and thus are not fully representative of the patients in the NHS who receive second-line therapies. There is no explicit evidence in the CS regarding the efficacy of lebrikizumab in people who previously failed on or who were unsuitable for methotrexate. Clinical expert advice to the EAG is that ciclosporin A is generally more efficacious than methotrexate, and they would therefore expect that most people who do not respond to ciclosporin A would also not respond to methotrexate. Given this, the EAG suggests that the ADvantage trial population and results may be of some generalisability to patients who have previously failed on methotrexate. Limited long-term follow-up data are available on the maintenance of treatment response among participants treated with lebrikizumab combination therapy, making the results uncertain, although more long-term follow-up data are available for lebrikizumab monotherapy, which provides a further indication of maintenance of response with lebrikizumab. No long-term follow-up data is available in the CS specifically for people who failed on or were unsuitable for ciclosporin A.

3.2.2 Risk of bias assessment

CS Table 17 provides a summary of the company quality assessments for the key lebrikizumab studies with the full assessments provided in CS Appendix D.1.3 Tables 100 to 103. These assessments were all conducted using the NICE recommended CRD checklist for RCTs[33] which is an appropriate tool for the ADvocate 1 and 2, ADhere and ADvantage RCTs but may not be wholly appropriate for the long-term ADjoin extension study, in which

the responders to induction therapy from ADhere were re-randomised to maintenance treatment, the participants from ADvocate 1 and 2 continued within their previously randomised maintenance groups or escape arm treatment and other participants could enter from other studies or elsewhere.

We have conducted our own critique of the lebrikizumab studies using the published paper for ADvocate 1 and 2,[21] and CSRs[24,28-31] and included an interpretation of the risk of bias because the company did not comment on this in their own assessments. Additionally, we have assessed the ADjoin study using the criteria in Bowers et al. (2012) aimed at judging the quality of open-label extension studies, although we acknowledge that some blinding was maintained in ADjoin so this was not a fully open-label study. The full risk of bias assessments are available in Appendix 4. We summarise our findings, paying particular attention to points where our view diverges from that of the company, below.

For most items of the risk of bias assessment for the monotherapy ADvocate 1 and 2 RCTs we agreed with the company's judgements. The assessments where we disagreed were i) that we judged that it was unclear whether the groups were similar at the outset of the studies in terms of prognostic factors due to differences between arms of ADvocate 1 in the use of systemic treatments and the proportion of the Asian participants and we therefore rated this aspect as having an unclear risk of bias and ii) although intention-to-treat (ADvocate 1) or modified intention-to-treat (ADvocate 2) analyses were conducted the assumption that patients who received topical rescue therapy were non-responders may not reflect clinical practice so we also rated this aspect as having an unclear risk of bias. All other aspects were rated as having a low risk of bias.

For combination therapy ADhere RCT we agreed with the company's judgements and gave a rating of a low risk of bias for all the aspects of the assessment except the final point where although we agree that analyses were conducted using a modified intention-to-treat population, we noted that patients who received topical rescue therapy were considered non-responders and this may not reflect clinical practice. Consequently, we rated this aspect as having an unclear risk of bias.

There was less information available to the EAG when assessing the risk of bias for the ADvantage RCT (combination therapy in the failed CsA or CsA not medically advisable population) because this has not been fully published yet. We could not find a description of the method of randomisation or the concealment of allocation and therefore judged these two aspects to be at unclear risk of bias because we do not know if appropriate methods have been used. We also note that whilst the first 16 weeks of the trial was double-blind and

therefore at low risk of bias, the trial is open-label from week 20 onwards and which led to our judgement of high-risk of bias for this portion of the trial. Finally, in common with the other key RCTs patients who received topical rescue therapy were considered non-responders and this may not reflect clinical practice. Consequently, we rated this aspect as having an unclear risk of bias. All other aspects of the assessment were rated as having a low risk of bias.

As the ADjoin long-term extension study has not been fully published yet we could not find a description of the method of randomisation or the concealment of allocation and therefore judged these two aspects to be at unclear risk of bias for the ADhere participants who were randomised into this study. We also noted an unclear risk of bias arising from a difference in the prognostic factor of [redacted] which differed between the two re-randomised arms of ADhere that entered ADjoin. For all other aspects of the ADjoin assessment we gave a rating of a low risk of bias. We also used the criteria from Bowers et al.[34] which raised a concern about what the rate of sample slippage might be in relation to the numbers randomized in the preceding RCTs. Due to the multiple RCTs feeding into the ADjoin study and the CS focus on only three of these we were unable to determine with any certainty what the sample slippage may have been.

3.2.3 Outcomes assessment

Outcomes are defined in CS section B.2.3.2 Table 9. Here we focus on the key efficacy outcomes from the combination therapy trials relevant to the company decision problem and those that inform the economic model, as summarised in Table 10. Most of these outcomes were also reported by the monotherapy trials. The outcomes are briefly explained in the sections below.

Table 10 Summary of the outcomes presented in this EAG report

Decision problem outcome	Outcome type and summary	Location in EAG report [a]
Measures of disease severity	Primary outcomes: • Percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI) at week 16. (Note, EASI 75 was used to calculate response rates for both lebrikizumab and the second-line systemic therapy comparators in the company's economic model and, as an option, could be used in its own right in the model; CS section B.3.3.2 and see section 4.2.6 of this report) (Co-primary endpoint for ADvocate 1 & 2 monotherapy and ADhere combination therapy RCTs; primary endpoint for	Section 3.2.6.1

Decision problem outcome	Outcome type and summary	Location in EAG report [a]
	ADvantage RCT combination therapy in failed CsA treatment or CsA not medically advised population) • Percentage of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to week 16 (Co-primary endpoint for ADvocate 1 & 2 monotherapy and ADhere combination therapy RCTs, secondary endpoint for ADvantage RCT)	Section 3.2.6.2
	Secondary trial outcomes (options to use in economic model): EASI 50; EASI 90	Section 3.2.6.4
Measure of disease severity & HRQoL	EASI 50 + DLQI ≥4 at week 16 (this composite outcome from the ADhere and ADvantage trials informs placebo response rates in an economic model scenario analysis)	Section 3.2.6.2
Measures of symptom control	Secondary outcomes: Itch numerical rating scale, sleep-loss scale, and skin pain numerical rating scale.	Section 3.2.6.7
Rescue therapy use	Secondary outcome (used in economic model to inform flare rates)	Section 3.2.6.6
TCS-free days	Secondary outcome (not used in economic model)	Section 3.2.6.5
Treatment discontinuation	Discontinuation due to adverse events is reported. Conditional discontinuation (used in economic model) is not reported among the trial results.	Sections 3.2.7 and 4.2.6
Adverse effects of treatment	Adverse events (used in economic model)	Section 3.2.7
HRQoL	EQ-5D-5L (mapped to EQ-5D-3L for use in the economic model), DLQI, POEM, PROMIS, CDLQI and SCORAD	Section 3.2.6.8

Source: Source: Table created by the EAG
CDLQI, Children's Dermatology Life Quality Index; CsA, ciclosporin A; DLQI, dermatology quality of life index; EAG, External Assessment Group; EASI, Eczema Area and Severity Index; EQ-5D-3L, European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels; EQ-5D-5L, European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; HRQoL, Health-related quality of life; IGA, Investigators Global Assessment; POEM, Patient Oriented Eczema Measure; PROMIS, Patient-Reported Outcomes Measurement Information System; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid.
[a] for combination therapy trials. Only the monotherapy trials results for EASI 75, composite outcome EASI 50 + DLQI ≥4 and a post-hoc analysis by prior ciclosporin A use are summarised in this report in section 3.2.5.

3.2.3.1 Efficacy outcome(s)

The EASI measure is part of the core outcome set recommended by the Harmonising Outcome Measures of Eczema (HOME) initiative[1] and is widely used in clinical trials of AD. It measures four clinical signs of disease at four body regions to generate a score ranging

from zero to 72. A higher score represents a higher disease burden. The EASI 50, EASI 75 and EASI 90 outcomes represent the proportion of patients who have achieved a 50%, 75% or 90% improvement respectively in EASI score from baseline. The EASI 75 at week 16 was a co-primary outcome or the primary outcome in all four of the company's key RCTs and was an outcome assessed in the company's NMA (see section 3.3). The EASI 75 NMA odds ratios are used to calculate the probability of response for lebrikizumab and the active comparators in the economic model. Pooled results for the composite outcome of the EASI 50 and the DLQI ≥4 at week 16 from the placebo arms of the ADhere and ADvantage trials inform the baseline response in a scenario analysis of the economic model. This composite outcome has been used in previous NICE appraisals of treatment for moderate-to-severe atopic dermatitis and, as stated in section 2.3, was considered the most relevant for decision making.[13,14] Section 4.2.6 of this report provides a detailed description of treatment effectiveness parameters in the economic model.

The Investigator's global assessment (IGA) is an additional tool to assess the overall severity of AD. There are multiple versions of the IGA,[5] most are not validated[3,4] and most measure the severity of four clinical features using scale ranging from 4- to 7-points. The IGA used in the company's RCTs was a 5-point scale from zero (clear skin) to four (severe disease). The proportion of patients achieving an Investigator's global assessment score of zero (clear skin) or 1 (almost clear skin) with a ≥2-point improvement from baseline at week 16 was a co-primary outcome in three of the four company's key RCTs (ADvocate 1 & 2 and ADhere) and was a secondary outcome in the fourth RCT (ADvantage). This outcome is not used in the economic model.

Three measures of symptom control were used in one of more of the company's key RCTs. The itch numerical rating scale and the sleep-loss scale are both described in CS section B.2.3.2 Table 9. The skin pain numerical rating scale is an 11-point scale from zero representing no pain to 10 representing the worst pain imaginable. None of these measures contributed data to the economic model.

Rescue therapy was reported as use of any rescue medication, as well as being reported separately in the CS for topical rescue therapy and systemic rescue therapy for the ADvocate and ADhere trials (CS Table 33). Rescue therapy use in ADvantage is reported in the CSR. Rescue therapy rates were used as a proxy for flare rates in the economic model.

TCS-free days (i.e. percentage of days when a participant did not use TCS) are reported (CS section B.2.6.1) but this outcome was not used in the economic model.

Treatment discontinuation data informs the conditional discontinuation rate that is applied in the economic model to estimate the probability of week 16 responders transitioning to long-term maintenance treatment at week 52 (CS section B.3.3.3).

3.2.3.2 HRQoL and other patient reported outcomes

In this report we focus on the EQ-5D-5L because this contributes data to the health economic model. We also briefly describe the DLQI, the Children's version of the DLQI (the CDLQI) and the three other patient reported outcome measures for which data is presented in the CS: the Patient-Oriented Eczema Measure (POEM), the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety and Depression short forms and the Scoring Atopic Dermatitis index (SCORAD).

The EQ-5D-5L is a standardised measure of health status consisting of two components: i) a visual analogue scale (VAS) from zero to 100 on which the trial participant rates their own health state between the extremes of 'best imaginable health' and 'worst imaginable health' and ii) a descriptive system capturing each of five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a five point scale (no problems to extreme problems). The descriptive system produces a health state profile that can be converted into a single index value ranging from 1 (full health) to zero (dead).[35] The EQ-5D data from ADvocate 1 and 2 (monotherapy) and from ADhere (combination therapy) were mapped to the EQ-5D-3L to generate response-associated utility values for the lebrikizumab and BSC modelled populations in the economic model (CS section B.3.4.1). Further details can be found in section 4.2.7.2 of this report.

The DLQI can be completed by people aged over 16 years old (CS Table 9). Patients rate the impact of atopic dermatitis for 10 items and score each of these from zero (impact 'Not at all') to three (impact 'Very much') and scores are summed to generate a total DLQI score that can range from zero to 30. The minimal clinically important difference is considered to be a 4-point change from the baseline value (CS Table 9). As noted above, the composite outcome of EASI 50 and an improvement in DLQI of at least 4-points was previous NICE committees' preferred outcome measure for assessing response to treatment in moderate-to-severe atopic dermatitis. However, due to data availability, the company do not use this outcome in their economic model in this appraisal (see section 4.2.6).

For children up to 16 years there is a children's version of the DLQI, the CDLQI. The questions are similar but with some alterations to make the questions more pertinent to children (e.g. asking about the impact of atopic dermatitis on school/holidays and on teasing

/bullying). The scoring is the same as for the DLQI (CS Table 9). Data from the CDLQI do not contribute to the economic model.

None of the final three other patient reported outcome measures for which data is presented in the CS (POEM, PROMIS and SCORAD) contribute data to the economic model. POEM measures seven aspects of atopic dermatitis (skin dryness; itching; flaking; cracking; sleep loss; bleeding; weeping) with each aspect scored from zero ('No days') to four ('Every day') giving a score range from zero to 28 with higher scores indicating worse HRQoL (CS Table 9). The PROMIS Anxiety and Depression short forms assess symptoms of anxiety and depression and scores each option from one (almost never) to five (almost always). Sum of the raw scores is converted to a T-score using a conversion table with higher T-scores indicating greater anxiety and depression (CS Table 9). The SCORAD index assesses the extent and intensity of atopic dermatitis using three components; A, B and C which are used in a formula to calculate the index:
A - a surface involvement score that ranges from zero to 100;
B - an intensity score that grades six items from none (0) to severe (3) so the maximum score for intensity is 18;
C - a subjective assessment for itch and for sleeplessness, both of which are scored from zero (no itch or no sleeplessness) to 10 (worst imaginable itch or worst imaginable sleeplessness). Maximum possible score is 20 (i.e. 10 for itch and 10 for sleeplessness). The index, which has a maximum of 103, is calculated using the formula:[36]

$$\frac{A}{5} + \frac{7B}{2} + C$$

3.2.3.3 Safety outcomes

All the key lebrikizumab RCTs included in the CS (the monotherapy RCTs ADvocate 1 and ADvocate 2 and the combination therapy RCTs ADhere and ADvantage) and the long-term extension study ADjoin reported treatment emergent adverse events (graded by severity), serious adverse events, deaths and adverse events leading to treatment discontinuation.

Conjunctivitis was one adverse event considered of special interest because a greater likelihood for conjunctivitis in atopic dermatitis has been observed with other drugs, such as dupilumab and tralokinumab, used to treat atopic dermatitis (CS section B.2.10.1). The CS also reports other treatment emergent adverse events of clinical interest, including infections and injection site reactions.

The safety outcomes for combination therapy that inform the economic model are taken from the ADhere study. The adverse events included are injection site reaction, allergic

conjunctivitis, infectious conjunctivitis, oral herpes, upper respiratory tract infection and acne. The ADhere trial rescue therapy rates were used as a proxy for flare rates in the combination therapy economic model (CS section B.3.3.8). ADhere trial discontinuation rates for patients who responded to treatment at week 16 but withdrew from treatment between week 16 and week 52 were used to obtain conditional discontinuation rates that were used in the model. These model inputs are described in more detail in section 4.2.6 of this report.

EAG comment on outcomes assessment

The company has included outcomes for efficacy, HRQoL and safety that are relevant and clinically meaningful. The outcomes that inform the economic model are relevant, however the composite EASI 50 and the DLQI ≥4 at week 16 outcome, considered the most relevant for decision making in previous NICE appraisals of atopic dermatitis, is not used in the company's base case for the reasons discussed in 4.2.6.1.

3.2.4 Statistical methods of the included studies

The statistical methods of the ADvocate 1 and 2, ADhere and ADvantage RCTs are summarised in Table 11 below. We have not conducted a detailed assessment of the statistical method for the long-term extension study ADjoin. As stated in CS section B.2.4.3 the data presented in the CS from ADjoin are for lebrikizumab week 16 responders who rolled over from ADvocate 1 and 2 or ADhere. All analyses in ADjoin used observed data, collected regardless of rescue medication use. The response rates reported from ADjoin are described as descriptive in the CS.

Table 11 Summary of statistical methods of the included studies

ADvocate 1	ADvocate 2	ADhere	ADvantage
Analysis populations			
Induction ITT population: defined as all randomised participants, regardless of whether they received study medication or completed the trial. Maintenance primary population: all participants who responded to treatment with lebrikizumab during induction and were re-randomised to one of three arms in the maintenance period.	Induction Modified ITT population: Excluded 18 participants from one study site because some or all did not have moderate-severe AD. Modified maintenance primary population: [redacted]	Induction: Modified ITT population: excluded 17 participants from one study site (stated in CSR to be [redacted]). Maintenance: not applicable, no maintenance period.	Induction FAS population: all randomised participants who received at least one dose of study medication. Maintenance population not included in CS as data not yet available.
Safety population: all randomised participants who received at least	Modified safety population: [redacted]		Safety analysis set (SAF): all randomised participants who received at least one dose of lebrikizumab or placebo.

ADvocate 1	ADvocate 2	ADhere	ADvantage
one dose of lebrikizumab or placebo.			
EAG comment: ADvocate 1: True ITT population and only one participant missing from the lebrikizumab arm of the safety population. ADvocate 2: the 18 patients excluded because they may not have met the trial entry criteria represent 4% of the 445 enrolled (ITT) population. The EAG agrees with the company's rationale for excluding these participants. One participant is missing from the placebo arm of the modified safety population. ADhere: the 17 excluded patients represent 7.5% of the 228 enrolled (ITT) population. The EAG agrees with the company's rationale for excluding these participants. No participants missing from the modified safety population. ADvantage: The CSR (page 6) confirms [redacted]. CS section B.2.10.4 suggests no participants were missing from the safety analysis set.			
Sample size calculations			
Based on results from a phase 2b trial an estimated sample size of 96 in the lebrikizumab arm and 48 in the placebo group for each of the ADvocate studies was estimated to have more than 95% power to detect a statistically significant difference in the outcome of IGA score of 0 or 1 with a reduction of ≥2 points from baseline at week 16. Sample size was increased to approximately 400 in total (2:1 lebrikizumab:placebo) for each trial to ensure sufficient responders for the maintenance portion of the trials.	To give >95% power to detect superiority of lebrikizumab over placebo (based on assumed IGA 1, 0 and EASI 75 response rates) the estimated sample size needed was 150 in the lebrikizumab group and 75 in the placebo group.	To give >95% power to detect a statistically significant difference of 25% in the proportion of participants achieving EASI 75 at week 16 the estimated sample size needed was 208 in the lebrikizumab arm and 104 in the placebo arm.	

<table>
<tr><th>ADvocate 1</th><th>ADvocate 2</th><th>ADhere</th><th>ADvantage</th></tr>
<tr><td colspan="4">EAG comment:
ADvocate 1&2: Trials sufficiently powered for a primary outcome as the calculated sample size was exceeded in each trial (424 participants enrolled in ADvocate 1 and 445 enrolled in ADvocate 2)
ADhere: although sample size was exceeded at randomisation (n=228) the exclusion of 17 participants means the mITT population is 211 participants (i.e. 14 participants under the planned sample size).
ADvantage: Trial sufficiently powered for the primary outcome as the planned sample size exceeded (randomised n=220 in lebrikizumab arm and n=111 in placebo arm).</td></tr>
<tr><td colspan="4">Methods to account for multiplicity</td></tr>
<tr><td colspan="3">Graphical multiple-testing schemes were prespecified in the statistical analysis plan (SAP) for all primary and major secondary endpoints for the induction period (CS B.2.4.3, ADvocate CSRs sections 5.1.2, ADhere SAP section 6.6) .
A hierarchical testing procedure was also prespecified in the ADvocate SAPs for the major secondary endpoints in the Maintenance blinded period. A table in section 2 of the ADvocate CSRs lists the primary and key/major secondary endpoints that were adjusted for multiplicity and a separate table lists other secondary endpoints that were not adjusted for multiplicity.</td><td>[redacted] (CS section B.2.4.3).</td></tr>
<tr><td colspan="4">EAG comment:
ADvocate 1&2 and ADhere: Appropriate procedures were prespecified and used during the analysis of trial data to prevent statistically significant effects being detected by chance.
ADvantage: As the analysis of the secondary outcomes did not include any control for multiplicity it is possible that statistically significant effects could have been detected by chance. The EAG notes that the ADvantage CSR footnotes to Table 16 states that “[redacted]” which we agree with.</td></tr>
<tr><td colspan="4">Analysis of outcomes</td></tr>
</table>

<table>
<tr><th>ADvocate 1</th><th>ADvocate 2</th><th>ADhere</th><th>ADvantage</th></tr>
<tr><td colspan="3">Categorical outcomes: Cochran-Mantel-Haenzel test. Induction period analyses adjusted for region, age group and baseline disease severity. ADvocate maintenance period analysis adjusted for region.
Continuous outcomes: analysis of covariance (ANCOVA). Induction period analysis adjusted for region, age group and baseline disease severity, trial group and baseline value. ADvocate maintenance period analysis adjusted for region.
Pooled analyses of ADvocate maintenance period data were additionally adjusted for study.</td><td>Primary outcome: Cochran-Mantel-Haenzel test adjusted for country, age (adult/adolescent), prior dupilumab use and baseline disease severity.
Other outcomes were reported in the CSR to have been analysed using [redacted]
(ADvantage CSR, section 9.7).</td></tr>
<tr><td colspan="4">EAG comment:
ADvocate 1&2 and ADhere: Analyses for the induction period were adjusted for stratification factors. Analyses of ADvocate 1&2 for the maintenance period were conducted separately for lebrikizumab arm responders (the maintenance primary population/modified maintenance primary population) and placebo arm responders (the maintenance secondary population).
[redacted]. Analytical methods appear appropriate.
ADvantage: Analyses were adjusted for stratification factors and country. Analytical methods for the primary and other outcomes appear appropriate.</td></tr>
<tr><td colspan="4">Handling of missing data</td></tr>
<tr><td colspan="4">How missing data were handled varied according to the estimand being evaluated.</td></tr>
</table>

ADvocate 1	ADvocate 2	ADhere	ADvantage
Induction period, primary estimand (CS Table 14): participants who received rescue medication or discontinued treatment due to lack of efficacy were considered as non-responders. For other missing data Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) was used to impute missing data. Induction period, supportive estimands: [redacted] ADvocate 1 & 2 maintenance period, primary estimand (CS Table 15): participants who received systemic rescue medication, discontinued treatment due to lack of efficacy or transferred to the escape arm were considered non-responders. If participants used topical rescue medication or discontinued treatment for any reason other than lack of efficacy data were considered missing and imputed using MCMC-MI. ADvocate 1 & 2 maintenance period, supportive estimand: [redacted]			Induction period, primary estimand (CS Table 16): a composite strategy is described with values set to baseline when participants had used rescue or prohibited medication or discontinued due to lack of efficacy, whereas for discontinuation due to other reasons values were set to missing (hypothetical strategy). For all other missing data MCMC-MI was used to impute missing values. Induction period, supportive primary estimand and secondary estimands: non-responder imputation used. Induction period, continuous other secondary supportive estimands MMRM used.
EAG comment: In the analyses for the induction period of the ADvocate 1 and 2 and the ADhere trials, participants who received topical or systemic rescue medication were considered non-responders. In ADvantage values were set to baseline which would also be considered non-response. When censoring rules were discussed during the appraisal of baricitinib (TA681[14]) clinical advice was that topical rescue medication would be used concomitantly with baricitinib so therefore data should not be censored after the initiation of topical rescue therapy with TCS.			

ADvocate 1	ADvocate 2	ADhere	ADvantage
Sensitivity and post-hoc analyses			
The CSRs indicate that [redacted] but this is not mentioned in the CS. The EAG has been unable to find [redacted] in the CSRs. Post-hoc subgroup analyses (CS section B.2.7.2) on subgroups of ADvocate 1 and 2 and ADhere participants previously exposed to CsA were conducted for four outcomes, including EASI 75. A post-hoc subgroup analysis was also conducted for ADhere participants previously exposed to dupilumab for one outcome. Post hoc analysis was also conducted for the EASI 50 + DLQI ≥4-point improvement composite outcome at weeks 16 and 52 for the adult and adolescent subgroups.			The CSR indicates that [redacted]. The EAG has identified [redacted] in the CSR.
EAG comment: There is evidence in the CSRs [redacted] but we were not able to find [redacted].			

Source: Table created by the EAG using information from the CS supplemented with information from the CSRs and SAPs for ADvocate 1,[28,37] ADvocate 2[29,38] and ADhere[30,39] and the CSR for ADvantage.[24]
AD, atopic dermatitis; ANCOVA, analysis of covariance; CSR, clinical study report; EAG, External Assessment Group; FAS, Full analysis set; ITT, intention to treat; SAF, safety analysis set; SAP, statistical analysis plan

EAG comment on study statistical methods

Sufficient details are provided either in the CS or in the clinical study reports on most of the statistical methods used, which were standard methods. The EAG are satisfied that the approaches taken by the company are generally appropriate with the exception that the participants who received topical treatments as rescue medication were considered as non-responders. This was considered inappropriate during the appraisal of baricitinib by the EAG (TA681[14]) because clinical advice was that topical rescue medication would be used concomitantly with baricitinib. Clinical advice to us was that topical corticosteroids of low, medium, high and ultra-high potency could all potentially be used concomitantly with lebrikizumab in clinical practice when a disease flare occurs. Although there is evidence in the CSRs [redacted]. All the included studies were adequately powered.

3.2.5 Efficacy results of the monotherapy trials (ADvocate 1 and ADvocate 2)

The CS presents efficacy and safety data for the ADvocate 1 and ADvocate 2 trials in CS section B.2.6.1, with some results provided from a pooled analysis of both trials. In these two trials lebrikizumab was administered as a monotherapy but our clinical expert expects that lebrikizumab will be used in combination with topical steroids in NHS practice. Furthermore, in NICE TA814[6] the committee concluded that combination therapy evidence was most relevant to decision making.[6] Consequently, we focus mainly on the results from the combination therapy trials but include results here for EASI 75, the composite endpoint and the post-hoc subgroup analysis by prior ciclosporin A exposure. The full results from the monotherapy trials can be found in CS sections B.2.6.1 and B.2.6.4.

3.2.5.1 EASI 75

The percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI score) at week 16 was a co-primary outcome for both of the ADvocate RCTs. In both ADvocate trials the EASI 75 response rate at week 16 was statistically significantly higher in the lebrikizumab arm than in the placebo arm (Table 12). The difference between the lebrikizumab arm and placebo arm in both trials was higher than in the combination therapy trials (see Table 15), despite a lower proportion of the lebrikizumab monotherapy patients achieving EASI 75, because the placebo response rate was also much lower (less than 20%) than in the ADhere and ADvantage combination therapy trials where the placebo +TCS response rate was over 40% (see section 3.2.6.1 for further discussion of this).

Table 12 EASI 75 response at week 16

	ADvocate 1 [a]		ADvocate 2 [b]	
	Lebrikizumab monotherapy N=283	**Placebo N=141**	**Lebrikizumab monotherapy N=281**	**Placebo N=146**
% of participants	58.8	16.2	52.1	18.1
Difference (95% CI)	42.0 (33.3 to 50.6)		33.3 (24.4 to 42.2)	
P value	<0.001		<0.001	

Source: Partly reproduced from CS Table 18. Missing data were imputed using MCMC-MI
CI, confidence interval; EASI, Eczema Area and Severity Index, MCMC-MI, Markov Chain Monte Carlo multiple imputation
[a] ITT population
[b] mITT population

CS Figure 7 shows the EASI 75 responses for ADvocate 1 and 2 over time up to week 16 in the lefthand and middle panels for analyses with missing data either imputed using Markov Chain Monte Carlo multiple imputation or using non-responder imputation. In ADvocate 1, [redacted].

CS Figure 8 shows the EASI 75 outcome for a pooled population of ADvocate 1 and 2 participants who achieved an EASI 75 response at week 16 and were re-randomised to placebo, lebrikizumab 250mg every 4 weeks or lebrikizumab 250mg every 2 weeks. Participants who received either of the lebrikizumab maintenance doses had a similar EASI 75 maintenance of response at week 52 (lebrikizumab 250mg every 4 weeks 82% versus lebrikizumab 250mg every 2 weeks 78%) whereas the EASI 75 maintenance of response at week 52 was lower at 66% for the group of lebrikizumab 16-week responders re-randomised to placebo maintenance.

Participants who completed either of the ADvocate RCTs could enrol in the ADjoin long-term extension study. The top panel of CS Figure 27 shows that EASI 75 rates for participants who received either of the lebrikizumab maintenance doses were maintained during the ADjoin long-term extension from week 52 to week 104.

3.2.5.2 Post-hoc composite outcome EASI 50 and (c)DLQI ≥4-point improvement from baseline at week 16

For those participants who had a baseline DLQI≥4 in the pooled ADvocate 1 and ADvocate 2 populations a post-hoc analysis was conducted (separately for adults and adolescents) on the composite outcome of EASI 50 + DLQI ≥4-point improvement (or EASI 50 + cDLQI ≥4-point improvement for adolescents) at week 16.

In response to clarification question A24 the company provided more detailed results than are provided in CS section B.2.7.2 and these are reproduced below in Table 13.

In the pooled ADvocate 1 and 2 trial population almost [redacted] of the adult participants in the lebrikizumab monotherapy arm achieved the composite endpoint in comparison to [redacted] of the placebo arm participants (Table 13). The result for the adolescent subgroup is [redacted] to that of the adults.

Table 13 Post-hoc composite outcome EASI 50 and (c)DLQI ≥4-point improvement from baseline at week 16

	ADvocate 1 and 2 pooled (mITT population)	
	Lebrikizumab monotherapy **Adults n=497** **Adolescents n= 67**	**Placebo** **Adults n= 252** **Adolescents n= 35**
Adults (≥ 18 years old)		
n/N (%) of participants [a]	[redacted]	[redacted]
Adolescents (>12 to <18 years old)[b]		
n/N (%) of participants [a]	[redacted]	[redacted]

Source: Partly reproduced from company response to clarification question A24, Table 20.
[a] Analyses restricted to patients with a (c)DLQI score ≥4-points at baseline.
[b] In the trials adolescents aged 16 to 18 years old should have completed the DLQI; however, some completed the CDLQI. The company report adolescents who completed the CDLQI only.

3.2.5.3 Post-hoc analysis by prior ciclosporin A exposure

In the ADvocate 1 and 2 pooled population post-hoc analyses were conducted for participants who had previously been exposed to ciclosporin (n=[redacted] who received lebrikizumab Q2W and n=[redacted] who received placebo). For the four outcomes analysed (EASI 75, IGA 0,1, NRS itch ≥4-point improvement and EASI 90 at week 16) the proportion of participants achieving these endpoints at week 16 was [redacted] in the CsA prior use subgroup than in the overall ADvocate population. Results for EASI 75 are shown in Table 14.

Table 14 EASI 75 post-hoc sub-group analysis by prior ciclosporin use

	Ciclosporin previous exposure		Overall ADvocate population	
	Lebrikizumab N=[redacted]	Placebo N=[redacted]	Lebrikizumab N=[redacted]	Placebo N=[redacted]
% of participants	[redacted]	[redacted]	[redacted]	[redacted]
Risk difference	[redacted]		[redacted]	

Source: Compiled by EAG from information presented in Almirall 2023 ADvocate post-hoc analyses pt.2 PowerPoint file[40]

3.2.6 Efficacy results of the combination therapy trials (ADhere and ADvantage)

The trials of combination therapy (lebrikizumab plus TCS) presented in the CS represent two different patient groups. The ADhere RCT included participants with moderate-to-severe atopic dermatitis who were candidates for systematic therapy whereas the ADvantage RCT included participants with moderate-to-severe atopic dermatitis who had failed CsA or for whom CsA was not medically advisable. Neither patient group fully aligns with the patient population included in the cost-effectiveness analysis (adults and adolescents with moderate-to-severe atopic dermatitis for whom systemic therapies have been inadequately effective, not tolerated or contraindicated). The ADhere RCT participants are a wider group than included in the cost-effectiveness analysis whereas the ADvantage RCT participants are a subgroup of the population included in the cost-effectiveness analysis. In this section we focus on the primary outcome of each RCT and the outcomes that were important for the economic model.

3.2.6.1 EASI 75

The percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI score) at week 16 was a co-primary outcome for the ADhere RCT and the primary outcome of the ADvantage RCT. In both the ADhere and ADvantage RCTs the EASI 75 response at week 16 was significantly higher in the lebrikizumab plus TCS arm than in the placebo plus TCS arm (Table 15). In both RCTs over 40% of participants in the placebo plus TCS arm achieved an EASI 75 response. For ADhere, the company state that this was to be expected because participants could use TCS at their discretion, including triamcinolone which is considered a high-potency TCS in some countries and which, depending on the treated area has the potential to be absorbed and available systemically. The company do not comment on the high placebo + TCS response in the ADvantage RCT but the EAG notes that participants were required to use a mid-potency TCS (unclear if this would have included triamcinolone as for ADhere) up to 16 weeks, switching to a low-potency TCS for

seven days when lesions were under control. If medically necessary high potency TCS or systemic treatments could be used (which were considered rescue medication).

Table 15 EASI 75 response at week 16

	ADhere (candidates for systemic therapy)[a]		**ADvantage (failed CsA or CsA not medically advisable)[b]**	
	Lebrikizumab+TCS N=145	**Placebo+TCS N=66**	**Lebrikizumab+TCS N=220**	**Placebo+TCS N=111**
% of participants	69.5	42.2	68.4	40.8
Difference (95% CI)	26.4 (12.1 to 40.8)		[redacted]	
P value	<0.001		<0.001	

Source: Partly reproduced from CS Table 18 and CS Table 35
CI, confidence interval; CsA, ciclosporin A; EASI, Eczema Area and Severity Index, MCMC-MI, Markov Chain Monte Carlo multiple imputation; TCS, topical corticosteroid.
[a] mITT population, missing data were imputed using MCMC-MI
[b] FAS population, missing data were imputed using MCMC-MI

CS Figure 7 shows the EASI 75 responses for ADhere over time up to week 16 in the far righthand panel and CS Figure 24 shows EASI 75 responses over time for ADvantage. In ADhere [redacted]. In ADvantage, the company state a statistically significant difference between the trial arms was observed from week 8 with the median time to an EASI 75 response of [redacted] days for lebrikizumab + TCS-treated participants compared to [redacted] days for the placebo + TCS participants.

Participants who completed the ADhere study could enrol in the ADjoin long-term extension study. CS Figure 9 shows that, among the 29 participants who achieved an EASI 75 response at week 16 in ADhere and then received the recommended maintenance dose of lebrikizumab (250 mg every four weeks) in ADjoin, 81.2% retained their EASI 75 response after a total of 56 weeks on treatment. An interim analysis of ADjoin assessing efficacy outcomes up to 104 weeks in total of lebrikizumab treatment is presented in CS section B.2.6.4. The bottom panel of CS Figure 27 shows that by week 104 there are data for 25 of the 29 participants receiving the recommended maintenance dose of lebrikizumab and

96.0% of these participants retained their EASI 75 response. Long-term (week 52) data for participants from the ADvantage RCT are not yet available (clarification response A7).

3.2.6.2 Post-hoc composite outcome: EASI 50 and (c)DLQI ≥4-point improvement from baseline at week 16

The composite outcome of EASI50 and DLQI ≥4-point improvement was NICE's favoured way of measuring treatment response in previous NICE appraisals (TA534,[13] TA681[14] and TA814[6]).

A post-hoc analysis for the adult and adolescent subgroups of ADhere was conducted for those participants who had a baseline DLQI≥4 on the composite outcome of EASI 50 + DLQI ≥4-point improvement (or EASI 50 + cDLQI ≥4-point improvement for adolescents) at week 16. In the economic model patients achieving this outcome (calculated in the model base case using EASI 75 odds ratios from the NMA, rather than direct trial data for the composite outcome) at week 16 continue to receive treatment (those that do not achieve this outcome discontinue treatment and receive BSC) (see section 4.2.6.1). We report these composite outcome results here to allow the reader to compare them with the EASI 75 response rates reported above.

In response to clarification question A24 the company provided more detailed results than are provided in CS section B.2.7.2. As can be observed from Table 16, there are some missing data (e.g. number of adults randomised to the lebrikizumab+TCS arm of ADhere was 113, results available for [redacted]) and it is unclear to the EAG whether this is because all the missing participants had a baseline DLQI that was less than four and therefore could not be included in the analysis or if data are missing for additional reasons. Quantity of missing data for adults is similar for the ADhere and ADvantage RCTs ([redacted]). The number of adolescent participants is much smaller so the impact of a missing individual is greater ([redacted]).

In both the ADhere and ADvantage trials approximately [redacted] of the adult participants in the lebrikizumab+TCS arm achieved the composite endpoint in comparison to [redacted] of the placebo+TCS treated participants. The result for the adolescent subgroup in the ADhere study was [redacted] to that of the adults. In the ADvantage study the difference between the arms [redacted]. The adolescent subgroup analysis results should be interpreted with caution due to the small number of participants in each of the trials' arms.

Table 16 Post-hoc composite outcome EASI 50 and (c)DLQI ≥4-point improvement from baseline at week 16

	ADhere (candidates for systemic therapy)[a]		ADvantage (failed CsA or CsA not medically advisable)[b]	
	Lebrikizumab+TCS Adults n=113 Adolescents n=32	Placebo+TCS Adults n= 52 Adolescents n= 14	Lebrikizumab+TCS Adults n= 194 Adolescents n= 26	Placebo+TCS Adults n= 98 Adolescents n= 13
Adults (≥ 18 years old)				
n/N (%) of participants [c]	[redacted]	[redacted]	[redacted]	[redacted]
Adolescents (>12 to <18 years old)[d]				
n/N (%) of participants [c]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from company response to clarification question A24, Table 20.
CsA, ciclosporin A; TCS, topical corticosteroid.
[a] mITT population
[b] FAS population
[c] Analyses restricted to patients with a (c)DLQI score ≥4-points at baseline.
[d] In the trials adolescents aged 16 to 18 years old should have completed the DLQI; however, some completed the CDLQI. The company report adolescents who completed the CDLQI only.

3.2.6.3 IGA (0,1) with a ≥2-point improvement from baseline

The percentage of participants achieving an IGA score of zero or one (corresponding to clear or almost clear skin in atopic dermatitis respectively) with a ≥2-point improvement from baseline at week 16 was a co-primary outcome for the ADhere RCT and a key secondary outcome of the ADvantage RCT. The economic model has the functionality to use IGA (0,1) as a response criterion but this is not considered in the company's scenario analyses (CS section B.3.9.3).

In ADhere there was a [redacted] difference in the percentage of lebrikizumab+TCS versus placebo+TCS participants who achieved an IGA score of zero or one with a ≥2-point improvement from baseline ([redacted]) (Table 17). The percentages of patients achieving this outcome in the two trial arms of the ADvantage trial were consistent with those observed in ADhere with a difference between trial arms of 17.80 (7.03 to 28.57).

Although a p-value is reported for ADvantage there was no control for multiplicity for secondary outcomes in this trial (as we have discussed in this report, section 3.2.4).

Table 17 IGA 0 or 1 with a ≥2-point improvement from baseline at week 16

	ADhere (candidates for systemic therapy)[a]		**ADvantage (failed CsA or CsA not medically advisable)[b]**	
	Lebrikizumab+TCS N=145	**Placebo+TCS N=66**	**Lebrikizumab+TCS N=220**	**Placebo+TCS N=111**
% of participants	41.2	22.1	42.0	24.5
Difference (95% CI)	18.3 (5.1 to 31.5)		[redacted]	
P value	[redacted]		<0.01	

Source: Partly reproduced from CS Table 19 and CS Table 36.
CI, confidence interval; CsA, ciclosporin A; IGA, Investigators Global Assessment; MCMC-MI, Markov Chain Monte Carlo multiple imputation; TCS, topical corticosteroid.
[a] mITT population, missing data were imputed using MCMC-MI
[b] FAS population, missing data were imputed using MCMC-MI

CS Figure 10 shows the percentage of participants achieving an IGA score of zero or one with a ≥2-point improvement over time up to week 16 in the far righthand panel for ADhere and CS Figure 25 shows the IGA outcome over time for ADvantage.

In ADhere [redacted]. In ADvantage, the CS states that a statistically significant difference between the trial arms was observed from week 4. The difference appeared to be maintained over time, with a statistically significant difference observed at week 16 (but note, as stated above, there was no control for multiplicity of testing secondary outcomes in this trial).

Participants who completed ADhere could enrol in the ADjoin long-term extension study. CS Figure 12 provides the IGA (0,1) maintenance rates for 16 participants who were responders in ADhere and who then received the recommended maintenance dose of lebrikizumab (250 mg every four weeks). At 56 weeks of treatment 86.8% of these 16 participants had

maintained their IGA response, although the EAG notes that this proportion had dropped to approximately 70% at week 44 of treatment. CS Figure 28 (bottom panel) from the interim analysis of ADjoin shows that at week 104 there are data for 14 of the 16 participants receiving the recommended maintenance dose of lebrikizumab and 78.6% of these participants retained their IGA (0,1) response. Long-term data for participants from the ADvantage RCT are not yet available (clarification response A7).

3.2.6.4 Other EASI outcomes

The percentage of participants achieving either EASI 90 or EASI 50 responses at week 16 were secondary outcomes in the ADhere and ADvantage RCTs. The economic model has the functionality to use EASI 90 or EASI 50 as a response criterion although neither are considered in the company's scenario analyses (CS section B.3.9.3). We do, though, use EASI 50 in one of our scenario analyses (see section 6.2.1).

In both ADhere and ADvantage significantly more participants in the lebrikizumab+TCS trial arm achieved EASI 90 than in the placebo+TCS trial arm (Table 18). [redacted] CS Figure 13 (right-hand panel) shows [redacted].

Among the ADhere responders in the ADjoin LTE, the interim analysis of those on the recommended maintenance dose of lebrikizumab (n=29 participants) shows that at 56 weeks of treatment 62.2% had an EASI 90 response (CS Figure 15) and the EASI 90 response rates continued to be maintained or improved to week 104 (CS Figure 29, lower panel). Maintenance period data for ADvantage are not available (clarification response A7).

Table 18 EASI 90 and EASI 50 responses at week 16

	ADhere (candidates for systemic therapy)[a]		**ADvantage (failed CsA or CsA not medically advisable)[b]**	
	Lebrikizumab+TCS N=145	**Placebo+TCS N=66**	**Lebrikizumab+TCS N=220**	**Placebo+TCS N=111**
EASI 90				
% of participants	41.2	21.7	42.9	20.8
Difference (95% CI)	18.9 (6.1 to 31.7)		Not reported	

	ADhere (candidates for systemic therapy)[a]		ADvantage (failed CsA or CsA not medically advisable)[b]	
	Lebrikizumab+TCS N=145	Placebo+TCS N=66	Lebrikizumab+TCS N=220	Placebo+TCS N=111
P value	<0.01		<0.001	
EASI 50				
% of participants	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted][c]	

Source: Partly reproduced from CS Table 20 and CS Table 37. Data for EASI 50 in ADhere comes from the ADhere CSR. The EASI 50 difference for ADvantage comes from the ADvantage CSR.
CI, confidence interval; CsA, ciclosporin A; EASI, Eczema Area and Severity Index, MCMC-MI, Markov Chain Monte Carlo multiple imputation; TCS, topical corticosteroid.
[a] mITT population, missing data for EASI 90 were imputed using MCMC-MI, [redacted].
[b] FAS population, CS Table 37 does not indicate how missing data were handled and it is not clear to the EAG in the CSR which approach to missing data was taken (the SAP is not included with the ADvantage CSR and the EAG has not been able to find it in the public domain).
[c] [redacted]

3.2.6.5 TCS-free days

Participants in the ADhere study reported days where they did not use TCS or topical calcineurin inhibitor (CS section B.2.6.1). Although the lebrikizumab + TCS treated participants had a numerically greater mean percentage of TCS/topical calcineurin inhibitor-free days than the placebo group at week 16, the difference was not statistically significant (Table 19). The CS does not report TCS-free days for the ADvantage study.

Table 19 Proportion of TCS/TCI-free days at week 16

	ADhere (candidates for systemic therapy)	
	Lebrikizumab+TCS N=145	Placebo+TCS N=66
Proportion of TCS/TCI-free days at week 16 LSM (SE), N of patients with non-missing values	31.2 (3.5), N=131	23.9 (4.8), N=53
Least squares mean difference (SE), 95% CI, p-value	7.3 (5.1), 95% CI -2.8 to 17.4, p=0.155	

Source: Table compiled from information in the CS and Simpson 2023[22]

CI, confidence interval; TCS, topical corticosteroid.

3.2.6.6 Rescue therapy use

The use of rescue therapy in the ADhere trial was lower among participants in the lebrikizumab+TCS arm than for participants in the placebo+TCS arm through week 16 (Table 20). [redacted] proportions of participants received rescue medication in each arm in the ADvantage trial (Table 20).

Table 20 Rescue therapy use through week 16

	ADhere (candidates for systemic therapy)[a]		ADvantage (failed CsA or CsA not medically advisable)[b]	
	Lebrikizumab+TCS N=145	Placebo+TCS N=66	Lebrikizumab+TCS N=[redacted]	Placebo+TCS N=[redacted]
Use of any rescue medication, n (%)	6 (4.1)	7 (10.6)	[redacted]	[redacted]
Topical [c]	2 (1.4)	3 (4.5)	[redacted]	[redacted]
Systemic [d]	5 (3.4)	5 (7.6)	[redacted]	[redacted]

Source: Part reproduction of CS Table 33 with ADvantage data from CSR.[24]
TCS, topical corticosteroid.
[a] mITT population
[b] [redacted]
[c] high-potency TCS only for ADhere; [redacted] for ADvantage
[d] Systemic corticosteroids, immunosuppressants, biologics and phototherapy/photochemotherapy for ADhere; [redacted]

3.2.6.7 Other outcomes

The CS also reports on the outcomes of itch (for ADhere in CS section B.2.6.1, Table 22, CS Figure 17, CS Table 23 and CS Figure 19; for ADvantage in CS section B.2.6.3 and CS Figure 26), skin pain (for ADvantage only in CS section B.2.6.3 as this was the first lebrikizumab study to collect data on skin pain) and sleep-loss (for ADhere in CS section B.2.6.1, Table 24 and Figure 20; not reported in the CS for ADvantage although this outcome is available in the interim CSR the company provided). Here we briefly summarise the results from the CS for comparisons between the lebrikizumab+TCS and placebo+TCS arms, for full results please refer to the CS. In both the ADhere and ADvantage trials among participants who had itch NRS ≥4 at baseline statistically significant treatment differences for the outcome of achieving a ≥4-point improvement at week 16 were observed in favour of

lebrikizumab+TCS. In ADvantage among participants who had skin pain NRS ≥4 at baseline a higher proportion of lebrikizumab + TCS-treated participants achieved a ≥4-point improvement from baseline compared to the placebo + TCS group at week 16 ([redacted]). In ADhere among participants who reported a sleep-loss scale score ≥2 at baseline, an improvement of at least 2 points was reported by a significantly greater proportion of lebrikizumab+TCS treated participants than placebo+TCS participants.

3.2.6.8 HRQoL outcomes

We focus on DLQI and EQ-5D-5L HRQoL outcomes in this section. The DLQI ≥4-point improvement from baseline at week 16 outcome is included in the composite outcome of EASI 50 + DLQI ≥ 4, preferred by the NICE committee for measuring treatment response in TA814.[6] The EQ-5D-5L data collected in the ADhere RCT at week 16 was mapped to the EQ-5D-3L to provide response-associated utility values which were used in the economic model (further details are provided in section 4.2.7.2). We also include the cDLQI outcome in this section (this does not contribute data to the economic model).

3.2.6.8.1 DLQI

Among the ADhere participants who reported a DLQI total score of ≥4 at baseline, the percentage of participants having at least a 4-point improvement from baseline in the lebrikizumab+TCS trial arm was statistically significantly greater than in the placebo trial arm (difference 17.2, 95% CI 0.1 to 34.3, p=[redacted]) (Table 21). For the ADvantage trial the CS does not state how many participants had a DLQI total score of ≥4 at baseline. Table 21 shows there was a [redacted] in the ADvantage trial compared to the ADhere trial ([redacted] in ADvantage versus 58.7% in ADhere) and consequently no difference was observed between the trial arms ([redacted] even though the proportion of participants in the lebrikizumab+TCS arm of the ADvantage study was [redacted] to that of the ADhere study ([redacted] in ADvantage versus 77.4% in ADhere).

Table 21 DLQI ≥4-point improvement from baseline at week 16

	ADhere (candidates for systemic therapy)[a]		ADvantage (failed CsA or CsA not medically advisable)[b]	
	Lebrikizumab+TCS N=105	Placebo+TCS N=48	Lebrikizumab+TCS N=not reported	Placebo+TCS N=not reported
% of participants	77.4	58.7	[redacted]	[redacted]
Difference (95% CI)	17.2 (0.1 to 34.3)		[redacted]	
P value	[redacted]		[redacted][c]	

Source: Partly reproduced from CS Table 25 supplemented with text from CS section B.2.6.3.
CI, confidence interval; CsA, ciclosporin A; MCMC-MI, Markov Chain Monte Carlo multiple imputation; TCS, topical corticosteroid.
[a] mITT population, missing data were imputed using MCMC-MI
[b] FAS population, text in the CS describing this outcome does not indicate how missing data were handled and it is not clear to the EAG in the CSR which approach to missing data was taken (the SAP is not included with the ADvantage CSR and the EAG has not been able to find it in the public domain).
[c] P value considered nominal because multiplicity not controlled for

CS Figure 21, right hand panel shows the percentage of participants with a ≥4-point improvement in DLQI from baseline at ADhere study visits from baseline to week 16.

[redacted] The CS states that in ADvantage larger DLQI score reductions in the lebrikizumab+TCS trial arm were observed compared to the placebo+TCS trial arm from week 4 continuing to week 16. Additionally, the CS notes that the impact of atopic dermatitis on quality of life (QoL) was decreased almost to none (mean DLQI [redacted]) after 16 weeks of treatment in the lebrikizumab+TCS trial arm whereas a moderate effect of atopic dermatitis on QoL remained in the placebo+TCS trial arm (mean DLQI [redacted]).

No longer term data on DLQI are presented in the CS.

3.2.6.8.2 CDLQI

The CS presents results for the CDLQI from 39 adolescent participants in the ADvantage RCT but does not present CDLQI results from the ADhere RCT (CS B.2.6.3). No difference

between the ADvantage RCT groups was observed at week 16, but as the CS notes, the number of participants included in the analysis was small.

3.2.6.8.3 EQ-5D-5L

EQ-5D-5L was measured in the ADhere trial but not in the ADvantage trial. The ADhere trial EQ-5D-5L health state index data at week 16 were mapped to UK EQ-5D-3L values for use in the economic model (see section 4.2.7.2).

As summarised in Table 22, ADhere trial participants in the lebrikizumab+TCS group had a greater improvement in their EQ-5D-5L VAS scores at week 16 than those in the placebo+TCS group [redacted]. A statistically significant improvement in the EQ-5D-5L Health State Index Score was observed at week 16 in the lebrikizumab+TCS group in comparison to the placebo+TCS group (p<0.001).

Table 22 Change in EQ-5D-5L from baseline at week 16

	ADhere (candidates for systemic therapy)[a]	
	Lebrikizumab+TCS N=143	**Placebo+TCS N=65**
Change from baseline in EQ-5D-5L VAS scores at week 16		
LS mean (SE) % change	10.1 (1.8)	6.5 (2.4)
LS mean difference (SE)	3.6 (2.4)	
P value	[redacted]	
Change from baseline in EQ-5D-5L Health State Index (UK) scores at week 16		
LS mean (SE) % change	0.15 (0.02)	0.05 (0.03)
LS mean difference (SE)	0.1 (0.03)	
P value	<0.001	

Source: Partly reproduced from CS Table 30 and CS Table 31.
CI, confidence interval; CsA, ciclosporin A; LOCF, last observation carried forward; TCS, topical corticosteroid.
[a] mITT population, missing data were imputed using LOCF. Company response to clarification question A23 confirms the number of patients with missing data was small (Lebrikizumab+TCS [redacted], placebo+TCS [redacted]).

3.2.6.8.4 Other patient-reported outcomes

In the ADhere trial at week 16 participants in the lebrikizumab+TCS arm had a statistically greater reduction (improvement) in POEM scores than placebo arm participants. There were

[redacted] in change in anxiety and depression from baseline between the lebrikizumab+TCS and placebo+TCS treated adult participants.

Results were reported for POEM and SCORAD from the ADvantage trial in the CS. For both of these measures, larger reductions (improvements) from baseline occurred among lebrikizumab+TCS treated participants than among the placebo+TCS participants. [redacted]

3.2.6.9 Analyses by prior ciclosporin A exposure or prior dupilumab exposure

In ADhere analyses by prior ciclosporin A or dupilumab exposure were conducted post hoc. [redacted] patients had previously been exposed to ciclosporin A. Due to [redacted].

Among the ciclosporin-A exposed subgroup, the proportions who achieved IGA 0,1, NRS ≥4-point improvement and EASI 90 were [redacted] than they were for the overall ADhere population. A [redacted] proportion of lebrikizumab patients in the prior ciclosporin A subgroup achieved EASI 75 than in the overall ADhere lebrikizumab trial arm but for placebo arm participants the proportion achieving EASI 75 was [redacted] in the prior ciclosporin A subgroup than in the overall ADhere placebo trial arm (Table 23).

A similar post-hoc analysis was reported for the [redacted] patients in ADhere previously exposed to dupilumab [redacted]. The proportion of participants who achieved EASI 75 was [redacted] for the lebrikizumab+TCS treated patients in the prior dupilumab subgroup than for those who received placebo+TCS and the proportions were [redacted] to the overall ADhere population. CS Appendix E Table 107 also provides proportions of patients achieving EASI 75 at week 16 using non-responder imputation which results in [redacted] proportions ([redacted]% instead of [redacted]% for the lebrikizumab+TCS dupilumab-exposed group and [redacted]% instead of [redacted]% for the placebo+TCS dupilumab exposed group).

Table 23 ADhere post-hoc sub-group analyses for EASI 75 by prior ciclosporin or prior dupilumab use

	Ciclosporin previous exposure		Dupilumab previous exposure		Overall ADhere population	
	LEB+TCS N=[redacted]	PBO+TCS N=[redacted]	LEB+TCS N=[redacted]	PBO+TCS N=[redacted]	LEB+TCS N=145	PBO+TCS N=66
% of participants	[redacted]	[redacted]	[redacted][a]	[redacted][a]	69.5	42.2
Risk difference	[redacted]		[redacted]		26.4%	

Source: Compiled by EAG from information presented in CS section B.2.7.2, CS Table 18, CS Appendix E Figure 57 and Almirall 2023 ADvocate post-hoc analyses pt.1 and pt.2 PowerPoint files[40]
PBO, placebo; TCS, topical corticosteroid.
[a] [redacted]

In ADvantage, the subgroup analyses by previous exposure to dupilumab were pre-planned but, due to the small sample size, the results should be interpreted cautiously. The CS presents results for three outcomes up to week 16: EASI 75, IGA (0,1) and 2-point improvement from baseline, itch NRS ≥4-point improvement from baseline and states that in general the results were [redacted] for the dupilumab-exposed and dupilumab-naïve participants. We present the results for EASI 75 in Table 24.

Table 24 ADvantage sub-group analyses for EASI 75 by prior dupilumab use

	Dupilumab exposed		Dupilumab-naïve		Overall ADvantage population	
EASI 75 up to week 16	LEB+TCS N=[redacted]	PBO+TCS N=[redacted]	LEB+TCS N=[redacted]	PBO+TCS N=[redacted]	LEB+TCS N=220	PBO+TCS N=111
% of participants	[redacted]	[redacted]	[redacted]	[redacted]	68.4%	40.8%
Treatment effect (95% CI), p-value	[redacted][a]		[redacted][a]		[redacted][b] p-value <0.001	

Source: Compiled by EAG from information presented in CS section B.2.7.2, CS Table 35 and CS Appendix E Table 106

CI, confidence interval; NA, not applicable (assumed as not defined in CS Appendix E Table 106); TCS, topical corticosteroid.
[a] Common risk difference vs placebo
[b] Difference

3.2.6.10 Subgroup analyses

The company report the results of pre-planned subgroup analyses from ADhere in CS Appendix E Figure 55. Results are shown for four outcomes (IGA 0,1; Pruritus NRS ≥4-point improvement; EASI 75 and EASI 90). The chief finding highlighted by the company was that for EASI 75 and EASI 90 when the results were separated by sex, males had a greater risk difference compared with the overall study population whereas females had a lower risk difference for both these outcomes than the overall study population. Differences by sex were not noticeable for the IGA (0,1) and itch NRS ≥4-point improvement outcomes. One other finding (differences by geographic region for [redacted]) involved a subgroup with a small proportion of participants so making a reliable conclusion would be difficult.

3.2.7 Safety outcomes

Adverse events associated with use of lebrikizumab for treating moderate-to-severe atopic dermatitis are reported in CS section B.2.10. The company reports:

- Adverse events experienced in the 16-week induction phase from the ADvocate 1, ADvocate 2 (lebrikizumab monotherapy) and ADhere (combination therapy) pivotal trials (CS section B.2.10.1).
- Adverse events experienced in the maintenance period (weeks 16 to 52) from the ADvocate 1 and 2 trials (CS section B.2.10.2).
- Results of an integrated analysis of safety data by Stein Gold et al. (2023)[18] from eight lebrikizumab trials [ADvocate 1 and 2, ADhere, ADore, ADjoin, ARBAN, J2T-DM-KGAF (NCT03443024) and TREBLE] (CS section B.2.10.3). Results of an analysis of safety in the placebo-controlled induction period (phase 2b dose-ranging study, ADvocate 1 and 2 and ADhere trials only) and an analysis of the long-term safety of lebrikizumab (all eight trials) are presented.
- Adverse events data from the 16-week induction period of the ADvantage trial (combination therapy in the failed CsA or CsA not medically advisable population) (CS section B.2.10.4).
- Longer-term safety data from the ongoing ADjoin LTE, specifically from an interim analysis of 267 patients with up to 104 weeks of treatment who had responded to

lebrikizumab at week 16 in the ADvocate 1 and 2 or ADhere trials (CS sections B.2.10.5).

3.2.7.1 Summary of adverse events experienced in the induction treatment period (baseline to week 16)

Between baseline and week 16, across the monotherapy ADvocate 1 and 2, and combination therapy ADhere and ADvantage trials, between 43.4% and 61.8% of participants treated with lebrikizumab experienced any treatment-emergent adverse event, compared to between 34.8% and 66.2% of participants treated with placebo (CS Tables 42 and 48). Adverse events were generally classed as mild or moderate, with a minority of participants experiencing a severe treatment-emergent adverse event (CS Tables 42 and 48). The highest rate of treatment-emergent adverse events occurred in the lebrikizumab 250 mg Q2W + TCS arm of the ADvantage trial (61.8%) (CS Table 48). Also in this trial, [redacted] of the participants in the lebrikizumab 250 mg Q2W + TCS arm had treatment-emergent adverse events considered to be related to treatment, while [redacted] of participants treated with placebo + TCS had the same (CS Table 48). Treatment-emergent adverse events considered related to the treatment (by the investigator) are reported in the ADvocate 1 and ADvocate 2 trials' CSRs.[28,29] In ADvocate 1, [redacted] of lebrikizumab-treated participants had a treatment-emergent adverse event considered to be treatment-related compared to [redacted] treated with placebo. In ADvocate 2, these rates were [redacted] and [redacted] for lebrikizumab and placebo, respectively. The integrated treatment analysis of placebo-controlled trials (ADvocate 1 and 2, ADhere) found that the proportions of participants treated with either lebrikizumab (n=783) or placebo (n=404) who experienced at least one treatment-emergent adverse event were 49.2% and 53.1%, respectively (CS section B.2.10.3).

Table 25 shows common adverse events reported by ≥5% of participants in any lebrikizumab arm in any of the monotherapy and combination therapy trials, using data from the safety section of the CS (CS section B.2.10). As stated in section 3.2.3.3, CS section B.2.10.1 notes that conjunctivitis is an adverse event of special interest associated with lebrikizumab. As can be seen in Table 25, proportionally more participants treated with lebrikizumab than with placebo reported conjunctivitis [redacted] across the trials and in the integrated safety analysis. We understand from our clinical expert that conjunctivitis can often be managed with lubricating eye drops, with or without antihistamine eye drops. Sometimes corticosteroid or ciclosporin A eye drops need to be added, but this is done under the guidance of an ophthalmologist. Rates of the other commonly reported AEs were similar across the trials and within the integrated safety analysis between the lebrikizumab and placebo arms, except for exacerbation of atopic dermatitis in the

monotherapy trials (ADvocate 1 & 2) which was experienced by proportionally more participants receiving placebo than receiving lebrikizumab.

CS Table 45 shows the results from the ADvocate 1 and 2 and ADhere trials for other treatment-emergent adverse events of special interest and CS Table 51 shows the results for adverse events of special interest for the ADvantage trial. Rates of eosinophilia were generally [redacted] in lebrikizumab-treated than placebo-treated patients (ADvocate 1: 0.4% of participants treated with lebrikizumab 250 mg Q2W versus 2.1% treated with placebo; ADvocate 2: 1.1% versus none, respectively; ADhere: 0.7% of participants treated with lebrikizumab 250 mg Q2W + TCS versus none treated with placebo + TCS; ADvantage: [redacted] versus [redacted], respectively). Injection site reactions (another adverse event of special interest) were [redacted] in the lebrikizumab 250 mg Q2W (with or without TCS) than placebo (with or without TCS) arms in the ADvocate 2, ADhere and ADvantage trials (ADvocate 2: 2.1% versus 0.7%; ADhere: 2.8% versus 1.5%; ADvantage: [redacted] versus [redacted]) and in the integrated safety analysis (adjusted percentages: 0.6% versus 0.3%).

Between 0.7% and 2.1% of participants treated with either lebrikizumab monotherapy or combination therapy had a serious adverse event, compared to between 0.7% and 2.8% of participants treated with placebo in these trials (CS Tables 42 and 48). Of the 11 serious adverse events reported in the lebrikizumab arms of the monotherapy trials, [redacted] were considered to be [redacted] lebrikizumab ([redacted] and [redacted]). The [redacted] adverse event led to study discontinuation. In the combination therapy trials, none of the serious adverse events reported across the arms were considered to be related to the study treatment (CS sections B.2.10.1 and B.2.10.4).

Across both the monotherapy and combined therapy studies, there was one death, which occurred in the placebo arm of ADvocate 2 (CS Tables 42 and 48). This appeared to be due to a myocardial infarction serious adverse event (CS section B.2.10.1).

In the monotherapy and combination therapy trials, the proportion of lebrikizumab 250 mg Q2W-treated participants who had an adverse event that led to treatment discontinuation ranged between 1.1% and 3.2%, compared to none and 2.8% of placebo-treated patients (CS Table 42). In the ADvantage combination therapy trial of the ciclosporin A failed or not medically advisable population, there were 0.9% treatment discontinuations due to a treatment-emergent adverse event in the lebrikizumab 250 mg Q2W + TCS arm and 1.8% in the placebo + TCS arm (CS Table 48).

3.2.7.2 Summary of adverse events experienced in the maintenance treatment period (weeks 16 to 52) and in the long-term

Safety data for the maintenance period (weeks 16 to 52) is presented in the CS from the ADvocate 1 and 2 monotherapy trials, with the data pooled from these trials (CS section B.2.10.2). Rates of any treatment-emergent adverse event in the placebo and lebrikizumab trial arms were similar (placebo: 50.0%; lebrikizumab 250 mg Q4W: 51.7%; and lebrikizumab 250 mg Q2W: 49.6%; CS Table 46). Two participants in each of the lebrikizumab arms had serious adverse events compared with one from the placebo arm. There were no deaths.

Long-term safety data (for up to 104 weeks) is presented from an interim analysis of ADjoin, separately for participants joining from the ADvocate and ADhere trials (after week 52 and week 16 of these studies, respectively) in CS section B.2.10.5. The proportions of participants who experienced at least one treatment-emergent adverse event ranged from 58.6% to 68.3% across all of the trials' arms (CS Table 52). Rates of serious adverse events were higher in the participants from the two ADhere trial lebrikizumab arms (5.3% in the 250 mg Q2W arm and 6.9% in the 250 mg Q4W arm) than in the ADvocate 1 and 2 trials arms (2.4% in the 250 mg Q2W arm and 3.0% in the 250 mg Q2W arms). There was one death, which occurred in the ADjoin lebrikizumab 250 mg Q2W arm. The death was reported to be from natural causes and was considered to be unrelated to the study treatment.

Table 25 Treatment-emergent adverse events in the induction period reported by ≥5% of participants in any lebrikizumab arm of the ADvocate 1 and 2, ADhere and ADvantage trials, presented alongside associated rates from the integrated safety analysis (ADvocate 1&2, ADhere)

Adverse event	n (%) of participants								n (adjusted % [a]) of participants	
	ADvocate 1		ADvocate 2		ADhere		Advantage		Integrated safety analysis	
	LEB 250 Q2W (N = 282)	PBO (N = 141)	LEB 250 Q2W (N = 281)	PBO (N = 145)	LEB 250 Q2W + TCS (N = 145)	PBO + TCS (N = 66)	LEB 250 Q2W + TCS (n = 220)	PBO + TCS (n = 111)	LEB 250 mg Q2W (N = 783)	Placebo (N = 404)
Conjunctivitis	21 (7.4)	4 (2.8)	21 (7.5)	3 (2.1)	7 (4.8)	0	25 (11.4)	2 (1.8)	51 (6.5)	7 (1.8)
Allergic conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	18 (8.2)	3 (2.7)	14 (1.8)	3 (0.7)
Exacerbation of AD	17 (6.0)	30 (21.3)	29 (10.3)	39 (26.9)	3 (2.1)	3 (4.5)	[redacted]	[redacted]	NR	NR
Nasopharyngitis	11 (3.9)	4 (2.8)	14 (5.0)	3 (2.1)	3 (2.1)	4 (6.1)	28 (12.7)	14 (12.6)	34 (4.4)	13 (3.2)
Headache	9 (3.2)	2 (1.4)	14 (5.0)	6 (4.1)	7 (4.8)	1 (1.5)	6 (2.7)	6 (5.4)	34 (4.4)	12 (2.9)
Oral herpes	NR	NR	NR	NR	NR	NR	11 (5.0)	3 (2.7)	15 (1.9)	9 (2.3)
Infection	61 (21.6)	28 (19.9)	65 (23.1)	30 (20.7)	24 (16.6)	9 (13.6)	NR	NR	NR	NR

Source: Table partly reproduced from CS Tables 43, 44, 45, 47, 49 and 51
LEB, lebrikizumab; NR, not reported in safety section of CS (CS section B.2.10.5); PBO, placebo; Q2W, every 2 weeks
[a] Study-size adjusted

3.2.8 Pairwise meta-analysis of intervention studies

Pairwise meta-analyses were not conducted (CS section B.2.8).

3.3 Critique of studies included in the indirect comparisons (ITCs)

3.3.1 Rationale for ITCs

As no head-to-head trials comparing lebrikizumab with the comparators were available, the company conducted NMAs to compare the efficacy of lebrikizumab to that of dupilumab, tralokinumab, baricitinib, abrocitinib and upadacitinib (CS sections B.2.8 and B.2.9.1), i.e. all the second-line comparators stated to be of interest in the NICE scope. The EAG agrees with the company's rationale for carrying out NMAs. The company also carried out a MAIC that compared the efficacy and safety of lebrikizumab monotherapy versus dupilumab monotherapy at week 52 (CS section B.2.9.2). The company did not provide a rationale for focusing on only dupilumab in the MAIC. We asked the company to clarify this in clarification question A28. In response, the company stated dupilumab was chosen as it is the most commonly used second-line systemic treatment (clarification response A28). As the results of the MAIC are not used in the company's economic model and as it only includes one of the comparators of interest in this appraisal and examines monotherapy rather than combination therapy, we only provide limited information about it and a limited critique of it here (see section 3.3.3).

3.3.2 NMA

3.3.2.1 Overview of the methodology of the NMA

The methodology used to carry out the NMA is described in CS section B.2.9 and CS Appendix D, section D.1.1. The company also provided a confidential, full technical report of the NMA, with the CS[41] (linked data files were missing from this, but these were provided by the company in response to the EAG's request for these in clarification question A25). Separate NMAs were carried out comparing the efficacy of lebrikizumab with that of the comparator treatments for when the drugs were used either as monotherapy or in combination with TCS. The outcomes of interest were:

- [redacted].

The composite EASI 50 + DLQI ≥4 outcome, which was preferred by the NICE committee in TA814[6] for defining treatment response in moderate-to-severe atopic dermatitis and reflects how treatment response is assessed in clinical practice (see section 2.3), [redacted]. We received clinical expert advice that this outcome is more relevant to clinical practice than the EASI 75 outcome. CS section B.3.3.2 states that it was not possible to conduct an NMA using the composite outcome, as data are not published for the comparator trials, with the relevant results being redacted in previous NICE appraisals. It is unclear from the text in the CS whether or not data for this outcome are publicly available for the comparators in publications other than the previous appraisals' documentation. Clinical expert advice to the EAG is that trials do not usually measure the composite outcome. The EAG therefore expect it is unlikely that sufficient data for the composite outcome would be available to inform an NMA.

NMAs were not conducted to assess the efficacy of maintenance treatment (this is assessed for dupilumab only in the MAIC). In the CS economic model, conditional discontinuation data (the all-cause treatment cessation rate among week 16 responders to induction treatment who then withdrew from treatment at week 52) are used to model treatment response at week 52 (CS section B.3.3.3). The company state that this is in accordance with how this was modelled in TA814 and TA681 (CS section B.3.3.3). For our critique of the use of conditional discontinuation in the model, see section 4.2.6.3.

In our critique of the NMA here, we focus on the combination therapy NMA of EASI 75 as combination therapy is more relevant to clinical practice than monotherapy and the EASI 75 outcome is used to calculate treatment response rates in the economic model base case.

3.3.2.2 Identification, selection and feasibility assessment of studies for NMA

The NMA included studies identified in the company's systematic literature review (CS section B.2.9.1). Details of the methodology of the review are provided in CS Appendix D, section D.1.1 and we have critically appraised this in section 3.1 of this report. Key points we note about the study eligibility criteria for the SLR in relation to the ITCs are:

- The patient population was people with moderate-to-severe atopic dermatitis, so study inclusion was not specifically limited to trials of people who had had an inadequate response to, inability to tolerate or contraindication to the first-line immunosuppressant therapies. Therefore, the study eligibility criteria do not fully reflect the expected positioning of lebrikizumab in the treatment pathway or the company's decision problem.

- Studies reporting on the composite EASI 50 + DLQI ≥4 measure were eligible for inclusion in the SLR, but, as described in section 3.3.2.1, this was not one of the four listed outcomes of interest for the NMA.

The SLR identified 72 studies that met the eligibility criteria (CS Appendix D, section D.1.1). The EAG note that the PRISMA flowchart in CS Figure 43 states that 74 studies were included in the review. The reason for this discrepancy is unclear. The company state that after completing the SLR, three unpublished lebrikizumab studies were also identified for consideration for inclusion in the review (CS Appendix D, section D.1.1, and CS Appendix D, Figure 44). The company note in the full NMA technical report[41] that [redacted].

The 72 studies identified from the SLR, plus the unpublished lebrikizumab studies, were further assessed for inclusion the NMAs (CS Appendix D, section D.1.1), [redacted].[41] Reasons for excluding studies from further consideration are provided in CS Appendix D, section D.1.1. As [redacted],[41] studies that did not report on a dose approved for atopic dermatitis were excluded (CS Appendix D, section D.1.1). The EAG agrees that this is appropriate. Similarly, we agree with the exclusion of extension studies, studies with a non-randomised induction period and those not reporting outcomes of interest (CS Appendix D, section D.1.1). However, it should be noted, as stated above and in section 3.3.2.1, that the [redacted] (CS section B.2.9.1) which could have theoretically led to studies reporting data on this outcome being excluded. The company also excluded studies that were not placebo-controlled to *"remove bias arising from absence of a placebo control arm"* (CS Appendix D, section D.1.1). Two studies were excluded for this reason (CS Appendix D, Figure 44 and Table 92):

- HEADS-UP (monotherapy study of upadacitinib versus dupilumab)
- JADE DARE (combination therapy study of abrocitinib + TCS versus dupilumab + TCS)

The EAG asked the company to clarify the rationale for this decision in clarification question A27 and asked the company to provide an NMA with these studies included. The company responded that other published NMAs have excluded head-to-head trials, that including studies with a common comparator reduced bias arising from an absence of a placebo arm and that non-placebo-controlled trials cannot be included in a baseline-adjusted NMA that was carried out (clarification response A27). We note that the NMA conducted by Silverberg et al. (2023),[42] that the company cite in clarification response A27 as an NMA that excluded head-to-head trials, did not exclude such trials. They were permitted in the study eligibility criteria, but none were found for inclusion in the NMA. We provide our opinion on whether or not the HEADS-UP and JADE DARE studies could have been incorporated into the NMA in section 3.4.2 and 3.4.4.

After further assessment of the study eligibility for the NMA, 38 studies were included; 22 were monotherapy trials and 16 were combination therapy trials (CS Appendix D, Figure 44). The studies included in the combination therapy NMAs are shown in Table 26, along with the interventions(s) and comparator(s) they evaluated.

Table 26 RCTs included in the combination therapy NMAs

RCT	Intervention(s) and comparator(s) evaluated						
	Lebrikizumab	Dupilumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib	Placebo
AD Up						X	X
ADhere-J	X						X
ADhere	X						X
ADopt-VA	X						X
ADvantage	X						X
BREEZE-AD4					X		X
BREEZE-AD7					X		X
ECZTRA 3			X				X
ECZTRA 7			X				X
ECZTRA 8			X				X
I4V-MC-JAHG					X		X
JADE COMPARE		X		X			X

RCT	Intervention(s) and comparator(s) evaluated						
	Lebrikizumab	Dupilumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib	Placebo
JADE TEEN				X			X
LIBERTY AD CAFÉ		X					X
LIBERTY AD CHRONOS		X					X
Rising Up						X	X

Source: Table partly reproduced from CS Appendix D, Table 93.
'X' shows the intervention(s) and comparator(s) evaluated in a study.

The EAG did not have any concerns about the searches for the systematic literature review (see section 3.1), so we believe the likelihood that relevant studies were missed is low.

All combination therapy trials identified in the TA814 MTA[15] were included in the lebrikizumab CS NMA, except for a trial called D2213C00001 of tralokinumab combination therapy versus placebo + TCS,[43] but we note that the MTA report stated that participants did not receive a loading dose of tralokinumab in this study (MTA report, Table 94), so we consider it reasonable that this study is not included in the present CS NMA (i.e. the dosing regimen used is not as per the SmPC posology).

3.3.2.3 Similarity and clinical heterogeneity assessment

[redacted][41] The clinical expert advising the EAG considered the company's statement of treatment effect modifiers and prognostic factors to be adequate. As stated in section 3.2.1.2, he noted that there are conflicting results in the literature regarding the impact of skin colour and race on treatment efficacy.

Information about the characteristics of the studies included in the NMA is provided in CS Appendix D, section D.1.1 (specifically, Tables 94, 95 and 96) and in section 3.5.1 of the full NMA report.[41] In the CS, the company narratively summarise the findings regarding heterogeneity in the combination therapy NMA in CS section B.2.9.2. The full NMA report also [redacted].

3.3.2.3.1 Heterogeneity assessment – study designs, populations and methodology

3.3.2.3.1.1 Study designs

The study design characteristics of the combination therapy included trials were similar, with most of the trials being phase 3, double-blind, multinational, placebo-controlled RCTs (CS Appendix D, Table 94). Three trials were carried out solely in Japan (ADhere-J, ECZTRA 8 and Rising Up) and one in the United States (ADopt-VA). The inclusion of the trials carried out in Japan may be a source of heterogeneity in the NMA. It was noted in the TA681 baricitinib EAG report[46] that a greater response was observed in patients based in Europe compared to those in non-European countries or Japan. It was speculated that this may be due to differences in clinical practice and baseline atopic dermatitis severity. The report notes that in practice in Japan, high potency TCS are favoured, whilst in Europe use of these is generally limited. Use of high potency TCS rescue therapy by trial participants led to them being censored and non-responder imputation was used for censored participants in the analyses. The higher level of censoring due to high potency TCS rescue therapy use in trials conducted in Japan would potentially result in lower response rates being found. In TA814,[47] the EAG identified ECZTRA 8 as an ongoing trial located in Japan and raised concerns that including the trial in an NMA could increase heterogeneity and uncertainty. Given these previously raised concerns, a sensitivity analysis removing the trials conducted in Japan may have been beneficial in the lebrikizumab CS to explore the impact of these RCTs on the results.

There was variability across the trials in their duration, with this ranging from 12 to 260 weeks. CS Appendix D, Table 94, shows that all of the combination therapy trials, except one (JADE TEEN) were of at least 16 weeks' duration. The full NMA report states that [redacted] (full NMA report, section 3.1[41]). Although not clearly stated in either the CS or full NMA report, the EAG assumes that the week 12 data from JADE TEEN were used in the combination therapy NMA. The EAG considers this approach acceptable.

CS Appendix D, Table 94, shows that there was cross-over in only three of the combination therapy trials; in these studies cross-over occurred at week 16. Given that the NMAs were focused on outcomes at week 16, there is not a heterogeneity issue to consider in relation to cross-over (e.g. differences in study designs regarding whether or not participants were re-randomised).

3.3.2.3.1.2 Study populations

Limited information is provided about the previous treatment(s) received by participants in the combination therapy studies included in the NMA, or the studies' participant eligibility criteria in relation to previous treatment. The full NMA report[41] states that [redacted]. The EAG suggests that additional ITCs comparing lebrikizumab with baricitinib, tralokinumab and dupilumab could have been conducted using these studies to explore efficacy in this subgroup, even if data for all the comparators were not available. It is otherwise unclear how many of the other studies included people whose condition had not previously responded to a systemic therapy or in whom systemic therapies are not suitable (i.e. the position in the clinical pathway in which lebrikizumab is expected to be and the second-line therapy comparators are used in practice; see sections 2.2.3 and 2.3).

Table 4 in the TA814 MTA EAG report[15] outlines the populations of participants included in their systematic review of clinical effectiveness and provides information on previous inadequate response to therapy. All but one of the comparator studies included in the lebrikizumab CS combination therapy NMA were included in the TA814 review (the missing one is ECZTRA 8, which, as mentioned above, was identified as an ongoing study at that time). Table 4 of the TA814 EAG report indicates that of the comparator studies included in the lebrikizumab CS combination therapy NMA:

- Five included participants who had had an inadequate response to either topical or systemic therapies (JADE TEEN, JADE COMPARE, BREEZE-AD7, I4V-MC-JAHG and LIBERTY AD CHRONOS)
- One included participants who had had an inadequate response to topical therapies (ECZTRA 3)
- One included participants who had had an inadequate response to topical therapies or in whom these were medically inadvisable (RISING UP)

- Two included participants with a documented inadequate response to topical treatments and who either had not previously been exposed to ciclosporin A and not currently a candidate for this treatment or who had previously had an inadequate response to it (ECZTRA 7, and LIBERTY AD CAFÉ)
- One included participants with a history of inadequate response to topical therapy and a history of intolerance to, contraindication to or inadequate response to ciclosporin A (BREEZE-AD4)
- For one it is just stated that participants had moderate-to-severe atopic dermatitis (AD UP)

Additionally, we note that the ECZTRA 8 trial (not included in the TA814 MTA) included participants with a recent history of inadequate response to topical medication.[48]The populations of the lebrikizumab studies included in the NMA are outlined in section 3.2.1 of this report. Overall, given the population descriptions available for most of the studies, there was heterogeneity in the study populations. Not all of the trials included people who were unsuitable for or who had had an inadequate response to systemic therapies (i.e. where lebrikizumab is expected to be and the comparators are positioned in the clinical pathway). We acknowledge that this is the nature of the evidence available for carrying out an NMA. Our clinical expert advised us that among people who have failed previously on ciclosporin A or methotrexate, a reduced response may be expected in comparison to that found in the RCTs.

3.3.2.3.1.3 Study treatment – TCS and rescue therapy use

[redacted] We understand from our clinical expert that patients in practice do not use TCS in as regulated a way as in some clinical trials, and this may explain the large placebo response rates seen in some atopic dermatitis trials. It was also noted in the TA814 MTA EAG report[15] that use of and the potency of rescue therapy TCS might impact on treatment and placebo response rates. In the lebrikizumab CS,
b[redacted] For our critique of the statistical methods used in the NMA, see section 3.4.

The company have not commented in the CS nor full NMA report[41] on potential heterogeneity between the trials included in the NMA in rescue therapy use and how this was handled in the trials (e.g. whether there were different censoring rules for those receiving rescue therapy across the trials). It is therefore unclear if there were differences in how this intercurrent event was handled in the trials and the analyses of the endpoints used in the NMA which may have impacted on response rates. In TA814,[15] the EAG used all data available from the trials, regardless of rescue medication use, in the primary analysis, as clinical experts indicated that including rescue medication use more closely reflects what happens in clinical practice. In TA814, a sensitivity analysis was planned where participants requiring rescue therapy were considered non-responders. The MTA concludes that generally there were only small differences in findings between the main and sensitivity analyses for majority of comparisons undertaken, with some disparity in findings. We suggest that a similar sensitivity analysis would have been desirable in the lebrikizumab CS NMA, if required results were available from the relevant trials.

3.3.2.3.1.4 Study outcomes

EASI 75 is a standardised treatment response outcome measure, so the EAG has no concerns about heterogeneity in how the outcome of interest was defined across the studies.

3.3.2.3.1.5 Heterogeneity assessment – participants' baseline characteristics

The company presents the baseline characteristics of the participants included in the combination therapy NMA in CS Appendix D, Table 96, and we focus on these here rather than the monotherapy baseline characteristics. A summary of the heterogeneity assessment is provided in the full NMA report in section 3.5.7[41] and in CS section B.2.9.2. The EAG agrees with the company that mean age of the participants in the combination therapy trials at baseline was relatively homogeneous [ranging from 33.8 (SD 12.5) to 39.1 (SD 15.2)], except in one outlying study that included adolescents only (JADE TEEN), in which mean age was 14.9 (SD 1.8) (CS section B.2.9.2 and CS Appendix D, Table 96). There was heterogeneity in the race of the participants included in the trials, with the proportions classified as White ranging from none to 98.2% (CS Appendix D, Table 96). There was also variability in gender, with proportions of male participants ranging from 44.9% to 77.6% (CS Appendix D, Table 96). As stated above, in the full NMA report, [redacted].[41]

In the full NMA report, [redacted][41] Weight, where reported, was relatively well-balanced

across the trials, both in terms of mean weight and BMI (CS Appendix D, Table 96), although was higher in the ADopt-VA trial than the other trials. We note that, in general, [redacted] data sourced from full NMA report, Figure 22). Generally, participants in the lebrikizumab trials also had lower mean EASI and SCORAD scores (CS Appendix D, Table 96). Together, these results indicate that the severity of disease experienced by the participants in the lebrikizumab trials was generally lower than in the other trials included in the NMA. [redacted][41] For our critique of the statistical methods used in the NMA, see section 3.4.

3.3.3 MAIC

The methodology used to carry out the MAIC is described in CS section B.2.9 and CS Appendix D, section D.1.1. In the MAIC, individual patient data were used from the ADvocate 1 and 2 trials for lebrikizumab. For dupilumab, aggregate data from one trial (SOLO-CONTINUE) were used. The purpose of the SOLO-CONTINUE trial was to assess the efficacy and safety of various dupilumab maintenance treatment regimens after response to induction treatment.[49] It is unclear from the information provided in the CS how the SOLO-CONTINUE study was identified and selected for use in the MAIC.

In the MAIC, re-weighting was applied to individual patient data from the ADvocate trials to match the data to the prognostic factors and effect modifiers in SOLO-CONTINUE (CS section B.2.9.2).

Outcomes of interest in the company's MAIC included EASI 75, IGA 0,1, overall adverse events and discontinuations due to adverse events at week 52.

3.3.4 Risk of bias assessment for studies included in the ITCs (NMA and MAIC)

CS Appendix D, section D.1.1, states that the studies included in the NMA were critically appraised using the Cochrane risk of bias assessment tool. It is unclear if the original version of this tool[45] or the more recent version – the risk of bias 2.0 tool – was used.[50] From the risk of bias domains presented in CS Appendix D, Figure 49, it appears to the EAG that the original tool may have been used. Both tools are appropriate methods for assessing risk of bias in RCTs, but, in the EAG's opinion, it is more appropriate to use the 2.0 version. Conference abstracts were not used as sources of data for the assessment, due to insufficient information, and the EAG considers this acceptable. Based on the company's

assessment presented in CS Appendix D, Figure 49, we agree with the company that few of the studies were judged by the company to have ratings of a high risk of bias across the domains assessed. Most were considered by the company to be of a low risk of bias, with some judgements of unclear information across the risk of bias domains, particularly in relation to complete outcome data (attrition bias), and random sequence generation and allocation concealment (selection bias). We have summarised the TA814 MTA[15] authors' risk of bias assessments for the corresponding studies included in the lebrikizumab CS in Appendix 5. The studies were also mostly rated as being of a low risk of bias. Some concerns were noted about the I4V-MC-JAHG, JADE TEEN and Rising Up trials.

It is unclear from the information provided in CS Appendix D, section D.1.1, if the SOLO-CONTINUE study included in the MAIC was critically appraised.

EAG comment on the studies included in the ITC

We overall consider that studies were appropriately identified and selected for inclusion in the NMA, but some of the studies' populations do not fully reflect the populations that would receive second-line systemic therapies in clinical practice and where lebrikizumab is expected to be used (i.e. people with an inadequate response to or who were unsuitable for first-line systemic therapies). We acknowledge that this is the nature of the evidence available for conducting the NMA. We consider it unlikely that an NMA of the composite EASI 50 + DLQI ≥4 outcome could have been conducted.

The extent of heterogeneity between the trials included in the NMA in how rescue therapy use was handled in the individual trial analyses is unclear and presents an area of uncertainty.

[redacted] Analyses were adjusted for baseline disease severity and placebo response rates (see section 3.4), taking into account these sources of heterogeneity. A sensitivity analysis excluding trials conducted in Japan may have been beneficial. A further uncertainty associated with the NMA is the exclusion of two head-to-head trials and the potential impact of this on the results (see section 3.4 for further discussion about this).

3.4 Critique of the indirect treatment comparisons

As described in 3.3.2.1, the company conducted a series of NMAs in the monotherapy and combination therapy settings. Comparators to lebrikizumab were tralokinumab, dupilumab, and the JAK inhibitors. Population matching techniques were also employed to compare lebrikizumab to dupilumab monotherapy using longer-term data.

3.4.1 Data inputs to the NMA

The NMA included 22 studies in the monotherapy analysis, and 16 in the combination therapy analysis. The endpoints analysed up to 16 weeks are described in section 3.3.2.1. Data for abrocitinib improvement in pruritus used 12-week rather than 16-week data. Our expert confirmed this difference was acceptable. An NMA was precluded at 52 weeks due to the placebo arms being incomparable post week 16 (responders to active treatment in the 16-week studies were subsequently re-randomised).

As described in section 3.3.3, population matching was conducted using pooled individual patient data from ADVOCATE 1 & 2 matched to SOLO-CONTINUE. Both MAIC and simulated treatment comparisons (STC) techniques were used. The week 52 endpoints analysed are outlined in section 3.3.3.

3.4.2 Statistical methods for the NMA

Fixed effects and random effects models were conducted for the NMA with and without baseline risk adjustment. This is appropriate given the differences in placebo response observed among the included trials. Meta-regression models were also conducted as a secondary analysis on the EASI response and IGA 0/1 response endpoints, adjusting for disease severity as defined by baseline EASI score and IGA score ≥4 score, respectively.

The NMA models used a probit link for the multinomial function for categorical EASI (50, 75, 90) response, and a logit link function for binary outcomes (IGA0/1 and pruritis). All models were correctly specified, following NICE Technical Support Document (TSD) 2.[51] Informative priors from Turner[52] were used for the random effects standard deviation given the lack of treatment comparisons to reliably estimate this parameter (CS Appendix D, page 54).

[redacted] As noted below head-to-head studies which would have added additional loops to the network were excluded from the analysis.

The company excluded two head-to-head studies (HEADS UP, JADE DARE) from the NMA. As described in section 3.3.2.2, HEADS UP compared upadacitinib versus dupilumab as monotherapy, and JADE DARE compared abrocitinib versus dupilumab as combination therapy. In clarification response A27, the company stated that "*non-placebo trials cannot be included in the baseline-adjusted NMA (which requires placebo)*" and "*it is not technically possible for us to provide an NMA that includes the non-placebo-controlled studies*". However, our view is that the methods described in Achana 2013[54] could have been applied using the exchangeability assumption to assume that treatment arms are missing at random. Furthermore, consideration was not given to adding these head-to-head studies to the unadjusted models as a scenario analysis in the company NMA.

OpenBUGS code for the NMA was provided in clarification response A26. The EAG confirms the models had been implemented correctly.

3.4.2.1 Choice between random effects and fixed-effect model

Best fit model for the NMA was determined by [redacted]. Focusing on EASI 75 for combination therapy which was used in the economic model, the company's preferred model was the random effects (RE) baseline risk adjusted (Table 19, NMA technical report[41]). [redacted].

The meta-regression model adjusting for disease severity had a higher DIC than the baseline risk adjusted model and thus did not improve fit and the coefficient on baseline EASI response was not statistically significantly different from no effect (Table 42, NMA technical report[41]).

[redacted]

3.4.3 Statistical methods for the MAIC

Population matching comprised both unanchored MAICs and STCs. Age, sex, white vs non-white, BSA at week 16, and EASI at week 16 were adjusted for in the population matching. Sensitivity analyses used IGA, DLQI, or POEM in place of EASI response.

Prognostic factors / treatment effect modifiers were identified through a targeted literature search, and subgroup analysis of the SOLO-CONTINUE-like subset of the ADvocate

dataset. This is a reasonable approach, however, the prognostic factors / treatment effect modifiers from Thom 2022[55] were based on mild-to-moderate atopic dermatitis patients. Our expert also queried this approach if data on prognostic factors for the moderate-to-severe population are available. It is noteworthy that Thom reported different prognostic factors for IGA 0/1 response at 4 weeks compared to 52 weeks, whilst neither 16 weeks nor the other endpoints were considered. In their own analysis, Thom and colleagues matched on age, proportion male, proportion Caucasian, percentage body surface area, ISGA/ IGA score, proportion receiving prior TCI, and proportion receiving prior TCS. However, our clinical expert agreed the list of prognostic and treatment effect modifiers was reasonable, and did not identify any missing factors.

[redacted]

(Figure 1, MAIC/STC technical report[56]). [redacted] (Section 5.1, MAIC/STC technical report). Matching appeared to work reasonably well with matching factors being similar post-match (Table 3, MAIC/STC technical report[56]).

3.4.4 Summary of EAG critique of the ITCs

We summarise our critique of the ITCs in the CS as follows:

- The company ITCs were described and conducted appropriately.
- Only the EASI 75 results from the NMA were included in the economic model, as a proxy for the composite EASI 50 and DLQI ≥4 outcome, and therefore our critique has focused on this outcome.
- The exclusion of the HEADS UP and JADE DARE head-to-head trials from NMA introduces uncertainty. These should have been included in the unadjusted NMA or in a baseline risk model.
- Choice of best fit model was appropriate [redacted]. Differences in EASI 75 between best fit model and alternative models with similar fit[redacted].
- The population matching analysis was comprehensive and included appropriate known prognostic factors and treatment effect modifiers.

3.5 Results from the indirect treatment comparisons

3.5.1 Results of the NMA

CS Table 40 summarises the results of the NMAs using coloured table cells to show where lebrikizumab was statistically significantly superior or inferior to the comparator treatments, and where there was numerical evidence in favour of lebrikizumab compared to the comparators or the comparators compared to lebrikizumab on four outcomes, including EASI response (but not EASI 75). Numerical results from the NMA are not presented in this table or elsewhere in the CS, but are available in the full NMA report and its accompanying files.[41] We summarise the RE baseline risk-adjusted combination therapy NMA results in Table 27, specifically for the outcome of the proportion of participants achieving EASI 75, as this was the only NMA outcome that was used to inform the company's economic model. As stated in section 2.3, in the economic model, EASI 75 odds ratios were used to calculate response rates for both lebrikizumab and the comparator treatments (CS section B.3.3.2). The odds ratios from the [redacted] model were available in an Excel file provided by the company.

The first column in Table 27 shows the results that were used to calculate response rates in the company's economic model. This shows that [redacted] Table 27 also shows odds ratios for achieving EASI 75 with lebrikizumab 250 mg Q2W + TCS versus the other active combination therapies. [redacted]

Table 27 Summary of the NMA EASI 75 at week 16 results from the [redacted] model

Treatments	Active treatments + TCS vs. PBO + TCS OR (95% CrI) [a]	LEBRI + TCS vs. other active treatments + TCS or PBO + TCS OR (95% CrI)
Lebrikizumab 250 mg Q2W + TCS	[redacted]	-

Treatments	Active treatments + TCS vs. PBO + TCS OR (95% CrI) [a]	LEBRI + TCS vs. other active treatments + TCS or PBO + TCS OR (95% CrI)
Dupilumab 300 mg Q2W + TCS	[redacted]	[redacted]
Baricitinib 2 mg QD + TCS	[redacted]	[redacted]
Baricitinib 4 mg QD + TCS	[redacted]	[redacted]
Abrocitinib 100 mg QD + TCS	[redacted]	[redacted]
Abrocitinib 200 mg QD + TCS	[redacted]	[redacted]
Tralokinumab 300 mg Q2W + TCS	[redacted]	[redacted]
Upadacitinib 15 mg QD + TCS	[redacted]	[redacted]
Upadacitinib 30 mg QD + TCS	[redacted]	[redacted]
Placebo + TCS	-	[redacted]

Source: Excel file accompanying the full NMA report.[41]
CrI, credible interval; LEBRI, lebrikizumab; OR, odds ratio; PBO, placebo; Q2W, once every two weeks, QD, once a day
[a] These results are used to calculate response rates for both lebrikizumab and the comparator treatments in the company's economic model

3.5.2 Results of the MAIC

Results of the MAIC are provided in CS section B.2.9.2 for all the outcomes analysed. We focus on just the results for the EASI 75 outcome here. There were no statistically significant differences in the effectiveness of lebrikizumab compared to dupilumab in EASI 75 response at week 52.

3.6 Conclusions on the clinical effectiveness evidence

The company's decision problem adequately matches the NICE scope. It is reasonable that the company have focused on the second-line, rather than first-line, systemic therapies as comparators, as this reflects the expected positioning of lebrikizumab in the clinical pathway.

The company's key evidence comes from four RCTs and a long-term extension study. The four RCTs provide evidence for the use of lebrikizumab as:

- a monotherapy in patients who were candidates for systemic therapy (ADvocate 1 and 2; total randomised N = 851, with 564 participants in the lebrikizumab arms and 287 in the placebo arms),
- combination therapy in patients who were candidates for systemic therapy (ADhere; total randomised N = 211, with 145 participants in the lebrikizumab + TCS arm and 66 in the placebo arm), and,
- combination therapy in patients who have previously not responded to ciclosporin A or in whom this treatment is not suitable (ADvantage: N randomised: 331, with 220 in the lebrikizumab + TCS arm and 111 in the placebo + TCS arm).

The monotherapy trials do not represent how lebrikizumab would be used in clinical practice, and neither of the two combination therapy trials fully reflect the population in which lebrikizumab is expected to be positioned in clinical practice. Additionally, clinical expert advice to the EAG was that while the definition of moderate-to-severe atopic dermatitis used in the lebrikizumab trials was reasonable, it would not capture many people with more moderate disease.

There is also an issue with the potential generalisability of the patient populations in the comparator trials included, along with the lebrikizumab trials, in the NMA, to the patients seen in clinical practice who may receive lebrikizumab and other second-line systemic therapies. The comparator studies eligible for the NMA included a range of patients; for example, those who had had an inadequate response to topical therapies, or those who had previously failed on or were unsuitable for systemic treatment. We do not expect this, however, to have an important impact on the economic model conclusions as this affects both the lebrikizumab and the comparator trials in the NMA.

The lebrikizumab combination therapy trials, ADhere and ADvantage, found that a statistically significant greater proportion of participants treated with lebrikizumab 250 mg Q2W + TCS achieved EASI 75 compared to those treated with placebo + TCS at week 16. The results for the week 16 EASI 50 + cDLQI ≥4 composite outcome, which was the NICE committee's favoured measure of treatment response in previous appraisals, [redacted], in terms of the proportions of participants in each arm achieving the outcome, [redacted]. Statistically significant improvements in HRQoL, as measured by the DLQI and EQ-5D-5L Health State Index, favouring lebrikizumab 250 mg

+ TCS over placebo + TCS were observed in ADhere at week 16. [redacted] (EQ-5D was not measured in ADvantage). Statistically significant improvements in itch in both combination therapy trials, and sleep-loss due to itch were also found with lebrikizumab 250 mg + TCS compared to placebo + TCS at the end of induction therapy. We note that participants requiring [redacted] rescue medication[24,30] were treated as non-responders in the primary analyses of EASI 75 in the combination therapy trials. We do not agree that this was appropriate for participants receiving topical rescue treatments.

The limited long-term data available for lebrikizumab 250 mg Q4W combination therapy indicates that EASI 75 response is generally maintained over time up to 104 weeks, but small numbers of participants were included in the analyses leading to some uncertainty. However, the results are in line with those from the monotherapy trials that included more participants, providing more confidence in the results.

Rates of induction treatment-emergent adverse events [redacted] were higher with lebrikizumab than placebo treatment (with or without TCS) [redacted]. Adverse events were generally classed as mild or moderate and the incidence of specific adverse events was generally similar between the trial arms, but a higher proportion of participants treated with lebrikizumab (with or without TCS) experienced conjunctivitis.

The company's ITCs were conducted appropriately and the best fit choice of model was appropriate. There were some uncertainties associated with the NMA, including: the impact of not including two head-to-head trials, unexplored potential heterogeneity in rescue therapy use and handling of this in the analyses across the trials, and the impact of including trials conducted in Japan. The NMA found [redacted] EASI 50 + DLQI ≥4 composite outcome were not undertaken, but this appears to have been unavoidable.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company reports their economic search strategy in CS section B.3.1 and CS Appendix G. They conducted searches for published economic evaluations for adolescents and adults with moderate-to-severe atopic dermatitis for the period 2014 to 13 January 2023. CS Appendix G Table 113 presents the inclusion and exclusion criteria.

The company literature searches to identify relevant economic evaluations are based on the search strategy used in TA814 with additional terms for lebrikizumab and methotrexate and expanded to include non-English publications (CS Appendix G). TA814 is a recent (2022) NICE Multiple Technology Assessment for the same condition (atopic dermatitis) carried out by an independent External Assessment Group (BMJ-TAG). The search strategies used an adapted version of the Canadian Agency for Drugs and Technologies in Health (CADTH) search filter for economic evaluations; therefore, we find it appropriate to use the same strategy. The searches were performed in a relevant range of databases and websites for the period 2014 to 13 January 2023, and they were about ten months old at the time of submission. Of the identified and reported studies in the company's search, we agree that the NICE appraisals are the most pertinent to the current model as they assess all the treatments being compared with lebrikizumab and have been discussed and accepted by previous appraisals' NICE committees. We are not aware of any additional cost-effectiveness studies that have been missed by the company.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The EAG's critique is focused on lebrikizumab and the comparators when they are used in combination with TCS, as monotherapy is not considered reflective of clinical practice. Unless otherwise stated, all data and results shown are for combination therapy. For further details, please see section 4.2.4.

Twenty-two studies were identified and summarised in CS Table 54. Three out of the 22 studies were previous NICE technology appraisals: TA534 assessing dupilumab[13], TA681 assessing baricitinib[14] and TA814 assessing abrocitinib, tralokinumab and upadacitinib[6]. These were the economic studies that informed the current cost-effectiveness model, particularly the recent TA814. In TA814, a hybrid model was developed (short-term decision tree and a long-term Markov model) to assess the cost-effectiveness of abrocitinib, tralokinumab and upadacitinib compared to systemic immunosuppressants (including first-

line ciclosporin A and second-line dupilumab and baricitinib) for treating moderate-to-severe atopic dermatitis. None of the 22 studies identified assessed the cost-effectiveness of lebrikizumab.

4.2.1 NICE reference case checklist

The company's economic model fulfils the requirements of NICE's reference case (Table 28).

Table 28 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, maximum age 100 years
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, EQ-5D-5L data from ADvocate 1&2 trials (for monotherapy) and from ADhere (for combination therapy)

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes, EQ-5D-5L data was mapped to the UK 3L value set using the Hernández-Alava et al. 2020 method[57]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes, lebrikizumab does not meet the criteria for the NICE severity modifier (CS B.3.6)
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

Source: EAG assessment based on the company submission
CS, company submission; EAG, Evidence Review Group; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PSS, Personal Social Services; QALY, quality adjusted life-year; UK, United Kingdom.

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company developed a de novo cost-effectiveness model, which is described in CS section B.3.2.2. The model parameters are presented in CS sections B.3.3 to B.3.5, the base case inputs in CS Appendix M and the model assumptions in CS section B.3.7.2. The company developed a hybrid model closely aligned to the model of the recent TA814,[6] comprising a short-term decision tree (one year) to capture the induction treatment phase followed by a long-term Markov model (lifetime) with an annual cycle length, for which a half cycle correction was applied – see Figure 2 and Figure 3, respectively. In the model:

- All patients enter the decision tree and start treatment with lebrikizumab or a comparator.

- At week 16, response to treatment is assessed, informed by the proportion of patients that achieve the EASI 50 + DLQI ≥4. The responders remain on treatment and the non-responders discontinue treatment and receive BSC.
- Patients on BSC are divided into responders and non-responders to capture the potential improvement and worsening of symptoms expected at this stage. Response to BSC is informed by week 16 placebo response data. This approach was used and accepted in previous NICE appraisals, including TA814.[6]
- At week 52, the responders to active treatment enter the Markov model in the "initial treatment" phase and remain on treatment, while the non-responders to active treatment enter the Markov model in the "subsequent treatment" phase and receive BSC. The response at week 52 is based on conditional discontinuation data as follows:.
  - Week 52 responders are the patients who sustained response between week 16 and week 52.
  - Week 52 non-responders are the patients who responded at week 16 but discontinued treatment (due to lack of response or other discontinuation reasons) between week 16 and week 52.
- At week 52, all patients receiving BSC (responders and non-responders) enter the Markov model in the "subsequent treatment" phase and remain on BSC thereafter.
- The Markov model comprises the following health states: response, partial response and non-response under the initial treatment phase, response, partial response and non-response under the subsequent treatment phase and death.
  - Partial response is not considered in the model base case due to lack of data to inform the proportion of partial responders for all comparators.
- In each annual cycle, patients receiving active treatment may remain in the "initial treatment" response health state or move to the "subsequent treatment" health state and start treatment with BSC. This is driven by loss of response (treatment waning) or all-cause treatment discontinuation.
- In each cycle of the Markov model, patients that do not respond or discontinue active treatment are split into BSC responders and non-responders, based on the week 16 placebo response rate. The EAG notes that patients do not transition between "subsequent treatment" response and non-response health states.
- All patients can move to the death health state at any point in time. This is informed by the general population mortality rates as it is not expected that patients with atopic dermatitis have a higher risk of death than the general population.

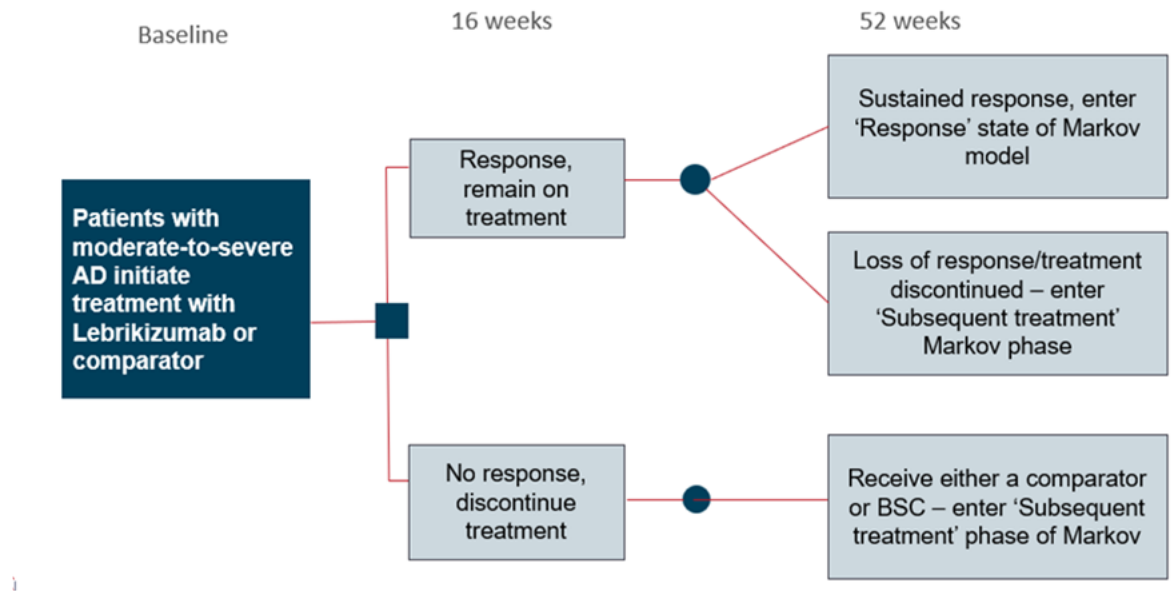


Figure 2 Decision-tree diagram

Source: Reproduced from CS Figure 30.
AD, atopic dermatitis; BSC, best supportive care.

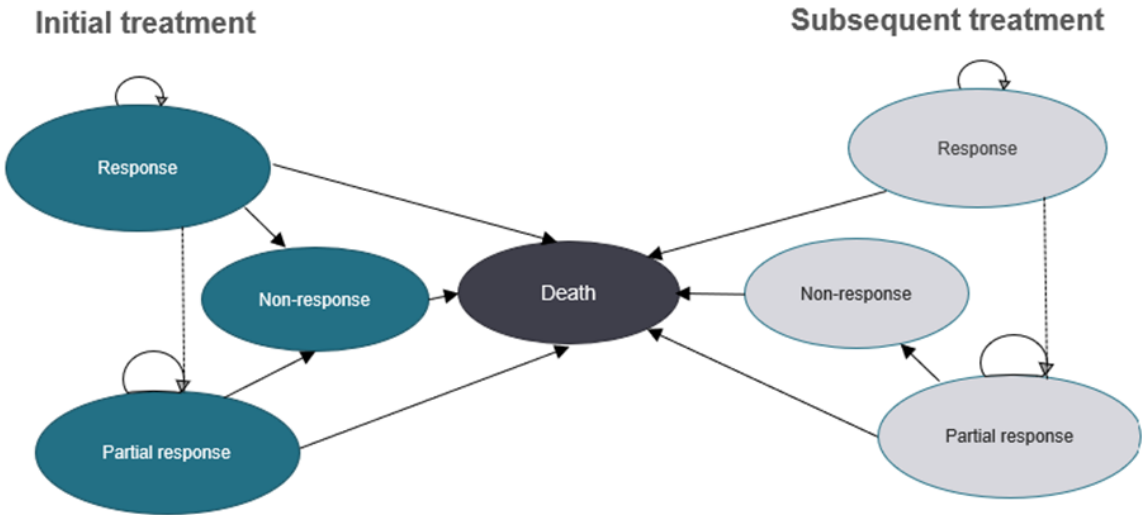


Figure 3 Markov model diagram

Source: Reproduced from CS Figure 31.

4.2.2.2 EAG critique of model assumptions

4.2.2.2.1 Patients who discontinue their initial treatment go on to receive BSC

This assumption is based on the limited data to inform the proportion of patients receiving alternative active treatments as subsequent therapy in practice. This was also an assumption made in TA814, due to the same reason.[6]

We acknowledge the lack of data and the heterogenous responses given by the company's and our consulted experts on subsequent therapy after patients discontinue second-line systemic therapies (see CS Table 80). However, receiving BSC immediately after second-line systemic therapies is not reflective of what occurs in clinical practice. Our clinical expert advised it is very unlikely that a patient would not be receiving treatment at all. Therefore, we explore a scenario analysis where patients are reallocated to receive a basket of treatment options (formed of comparator treatments) after discontinuing combination therapy with lebrikizumab or a comparator treatment (see section 6.1).

EAG comment on model structure

The EAG considers the model structure to be appropriate for this condition given its similarities to the model developed for TA814, which was accepted by the NICE committee. Receiving BSC after discontinuing from second-line systemic therapies does not seem reflective of clinical practice, so we run a scenario analysis where active treatments are offered after discontinuation (section 6.2.1).

4.2.3 Population

The population considered in the company model is described in CS section B.3.2.1 and consists of adults and adolescents (12 years of age and older with a body weight of at least 40 kg) with moderate-to-severe atopic dermatitis for whom systemic therapies have been inadequately effective, not tolerated or contraindicated. The model population is narrower than the population in the NICE scope and SmPC population for lebrikizumab, which includes patients with moderate-to-severe atopic dermatitis who are 12 years of age and older (with a body weight of at least 40 kg) who are candidates for systemic therapy. [58] [16] Moreover, some of the populations included in some of the clinical trials that inform the economic model are broader than the model population, because they include patients naïve to systemic therapies (see sections 3.2.1 and 3.3.2.3). The model population is aligned with the population of other second-line systemic therapies for moderate-to-severe atopic dermatitis recommended by NICE.[6,13,14] The EAG clinical expert agreed that lebrikizumab is not likely to be used as a first-line systemic therapy for moderate-to-severe atopic dermatitis. However, he also said that patients who failed methotrexate or ciclosporin A are likely to respond less well to second-line systemic therapies than patients naïve to systemic therapies.

The current appraisal does not show the model results split by adults and adolescents. The company argues that there is no evidence that the efficacy of lebrikizumab differs between

adults and adolescents. The same was concluded by the committee in TA814 who found the results for adults receiving combination therapy to be generalisable to adolescents and considered that presenting separate results for the adolescents would increase uncertainty around the treatment effect. However, the NHS costs for the paediatric patients were applied to the adolescent subpopulation in the current model.

The baseline characteristics of the model population are presented in CS section B.3.3.1 (CS Table 56). These were taken from the ADvantage trial[24] as the company considers that the ADvantage population (patients with moderate-to-severe atopic dermatitis that was not adequately controlled with ciclosporin or for whom ciclosporin was not medically advisable) is the closest to the population of interest. As stated in section 2.3, the clinical expert advising the EAG informed us that methotrexate is the most widely used first-line systemic therapy in the UK for atopic dermatitis and not ciclosporin A (around two thirds of patients versus one third). Nevertheless, he found the baseline characteristics used in the model reasonably representative of the patients who may receive treatment with lebrikizumab in the clinical practice. Table 29 shows the model inputs for baseline age and gender characteristics.

In the model developed for the TA814 appraisal, the baseline characteristics were taken from the upadacitinib trials (Measure UP 1 and 2 for monotherapy and AD UP for combination therapy) as the clinical experts consulted by the EAG in TA814 considered these trials to appropriately reflect the populations of interest to the MTA model. For validation purposes, Table 29 also shows the pooled baseline characteristics of the overall population (placebo, upadacitinib 15mg and upadacitinib 30mg) in the combination therapy AD UP trial, which shows a mean age equivalent to the current model input, and a slightly lower proportion of females (39% versus 47%).[6] We do not explore a scenario with the baseline characteristics from TA814 as this has a minor impact on the model results.

Table 29 Baseline characteristics of the population

	Model input (ADvantage)	Upadacitinib (AD UP) [a]
Mean age, yrs (SD)	34 (15.24)	34
Female, n (%)	156/331 (47%)	39%

Source: Reproduced from CS Table 56 and Table 9 from AbbVie submission to TA814 appraisal.[6]
SD, standard deviation.
[a] Weighted average of the baseline characteristics of the overall population of the AD UP trial, including patients in the placebo, upadacitinib 15mg and upadacitinib 30mg arms, which we calculated using data from Table 9 of the TA814 AbbVie submission.

EAG comment on model population

The patient population included in the cost-effectiveness analysis aligns with that of previous drugs approved by NICE for the same indication, although it is narrower than the NICE scope, the SmPC population and the populations in the lebrikizumab pivotal trials which included patients both systemic therapy-naïve or -experienced; only ADvantage explicitly included participants who had previously failed on or were unsuitable for first-line systemic therapies, specifically ciclosporin A. The patient baseline characteristics, based on the ADvantage trial population, are reflective of UK clinical practice. Adults and adolescents were deemed to have similar efficacy, which was previously considered appropriate in TA814 and agreed by our clinical expert.

4.2.4 Interventions and comparators

CS sections B.1.2. and B.3.2.3 describe the intervention and comparators. The economic model compares lebrikizumab with dupilumab, tralokinumab, abrocitinib, upadacitinib and baricitinib. Lebrikizumab is administered by subcutaneous injection at the recommended dose of 500mg at week 0 and week 2, followed by 250mg every other week (Q2W) up to week 16 and, for patients who respond, every four weeks (Q4W) after that.

The following assumptions about comparators, based on TA814, were used in the cost-effectiveness model:

- Upadacitinib: 50% of patients receive a dose of 15 mg and the other 50% receive 30mg.
- Abrocitinib: 50% of patients receive a dose of 100 mg and the other 50% receive 200mg.
- Tralokinumab: 90% of patients receive it every 2 weeks (Q2W) and the other 10% receive it every four weeks (Q4W).
- Baricitinib: 100% of patients receive a dose of 4mg and none receive 2mg. Although this is not explicitly stated in the CS, the NMA odds ratio used in the economic model of baricitinib uses the data for patients receiving 4mg only. In addition, TA681 NICE committee considered that the 4mg dose was the licensed dose relevant for most patients.[14]

The model base case assumes that all patients treated with lebrikizumab and the comparators receive combination treatment with TCS (mometasone 0.1% ointment, as used in TA814). Emollients and TCIs are also offered to patients as part of concomitant

medication (see CS section B.3.5.2). The use of TCS and emollients is reduced by 50% for patients who respond to active treatment, compared to baseline and non-responders. The clinical expert advising the EAG agreed that all patients start second-line systemic therapies in combination with topical drugs (not only TCS), and their use tends to decrease when patients respond to the systemic therapies.

Inputs for all treatments assessed as monotherapies are also presented in the CS and their results are shown in a scenario analysis (CS section B.3.9.3). As monotherapy is not reflective of clinical practice, we do not comment on the monotherapy inputs throughout the report.

EAG comment on intervention and comparators

The intervention and comparators in the economic model are broadly consistent with the NICE scope. The model does not include first-line immunosuppressive systemic therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) as comparators. We consider that this is an appropriate reflection of clinical practice in relation to the positioning of lebrikizumab in the care pathway as it is not expected to be used as a first-line systemic therapy for moderate-to-severe atopic dermatitis (see section 4.2.3 above). All patients receive combination therapy with TCS (and several other concomitant medications), which is aligned with clinical practice.

4.2.5 Perspective, time horizon and discounting

The perspective of the analysis is the National Health Service (NHS) and Personal Social Services (PSS) in England and the discounting rate for costs and outcomes is 3.5% per year, all according to the NICE reference case.[59] A lifetime time horizon (up to 100 years old) was applied.

EAG comment on perspective, time horizon and discounting

The company uses the recommended perspective and discounting rates and an appropriate time horizon, which are all in line with NICE guidelines.[59]

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Response at week 16

Response to treatment at week 16 is described in CS section B.3.3.2 and informs the decision of whether a patient continues receiving treatment with a second-line systemic therapy beyond week 16 or discontinues treatment and receives BSC. In the model, this

decision is dependent on achieving the EASI 50 + DLQI ≥4 endpoint at week 16, as preferred by the NICE committee and used in previous NICE appraisals on the basis of clinical experts' opinion.[6,13,14] The economic model includes the option of choosing alternative outcomes to inform response to treatment at week 16: EASI 50 + DLQI ≥4, EASI 50, EASI 75, EASI 90 and IGA 0/1.

The company developed a NMA to estimate the relative treatment effects used in the economic model as no head-to-head trial data are available to compare lebrikizumab with the comparators. The NMA is described in CS section B.2.9 and it is critiqued in the current report in section 3.4 above. Treatment response probabilities at week 16 were calculated by applying the odds ratios obtained from the NMA (representing treatment versus placebo) for each of the treatments to a baseline response rate representative of patients on BSC.

The baseline response rate was based on placebo responses from the clinical studies. For the base case, the company opted to use the upadacitinib AD-UP trial placebo response rates (defined as achieving the EASI 50 + DLQI ≥4 endpoint). These response rates were considered the most generalisable to clinical practice by the EAG in TA814 (based on advice from their clinical experts) and the clinical experts advising the company for the current appraisal were also of this opinion. Table 30 shows the baseline response rates at week 16 applied in the economic model for combination therapy.

The company presented other options for the placebo response rates, based on the lebrikizumab trials, and these are shown in Table 30 below. These are generally based on the subgroup of patients that failed prior systemic therapy, including patients who previously failed ciclosporin A, mycophenolate mofetil, methotrexate, azathioprine, JAK inhibitors and biologics. The company considered this the most relevant subgroup to provide baseline responses as patients in clinical practice now have access to alternative treatment options to immunomodulators, including other biologics and/or JAK inhibitors. The EAG's clinical expert agreed.

Table 30 Baseline response rates at week 16 for combination therapy

Trial	Placebo response (95% CI)	Source
Upadacitinib (Base case)	[redacted]	AD UP trial ([redacted]) [60]; data sourced from TA814 EAG MTA report Table 39

Trial	Placebo response (95% CI)	Source
Lebrikizumab (Scenario analyses)	[redacted]	Pooled data from ADhere and ADvantage prior systemic therapy subgroup
	[redacted]	Pooled data from ADhere prior systemic therapy subgroup and ADvantage FAS
	[redacted]	Pooled data from ADhere prior systemic therapy subgroup and ADvantage prior systemic therapy subgroup, excluding JAKs and biologics

Source: Partly reproduced from Table 23 of the clarification response document.
CI, confidential interval; FAS, full analysis set; JAKs, janus kinase inhibitors.

As discussed in section 3.3.2.1, the company conducted separate NMAs for monotherapy and combination therapy and for each of the outcomes listed above, except EASI 50 + DLQI ≥4. The NMA does not include EASI 50 + DLQI ≥4 as data for this endpoint are not available for all the comparators, and it was also redacted in previous NICE appraisals. The EASI 75 odds ratios from the NMA (RE baseline risk adjusted) for combination therapy were then used to inform the model base-case treatment response at week 16 for all the treatments (lebrikizumab and comparators) (Table 27). The company considered the EASI 75 the next best option after EASI 50 + DLQI ≥4- because it showed the closest relative response rates to the composite endpoint in the lebrikizumab trials. The clinical expert advising the EAG clarified that fewer patients are likely to achieve EASI 75 than EASI 50 + DLQI ≥4. In TA814, the committee considered that EASI 75 alone may not completely capture quality of life and other clinically meaningful improvements.[6] We acknowledge the limitations of using EASI 75 instead of EASI 50 + DLQI ≥4 to inform response at week 16, however it appears to be a reasonable assumption in the absence of data on the EASI 50 + DLQI ≥4 endpoint.

The baseline response (EASI 50 + DLQI ≥4 from placebo at week 16, see Table 30) was converted into odds. The EASI 75 odds ratios from the NMA were applied to the baseline odds to estimate baseline-adjusted odds for each treatment. These were then transformed into the probability of responding to treatment at week 16, shown in CS Table 58 and Table 31 below for combination therapy.

Table 31 Probability of a patient responding to treatment at week 16 for combination therapy

Treatment	Probability (base case)
Lebrikizumab	[redacted]
Dupilumab	78%
Baricitinib	59%
Upadacitinib	85%
Abrocitinib	78%
Tralokinumab	70%

Source: Partly reproduced from CS Table 58.
NMA, network meta-analysis.

4.2.6.2 Response at week 52 (conditional discontinuation rates)

Response to treatment at week 52 is described in CS section B.3.3.3 and informs the decision of whether a patient continues receiving maintenance treatment with a second-line systemic therapy at week 52 or discontinues treatment and receives BSC. It is based on conditional discontinuation data, as previously done in TA814 and TA681.[6,14] This is defined as the all-cause discontinuation rate (including loss of response or intolerance to long-term treatment due to adverse events or any other reasons) for people who responded to treatment at week 16 but withdrew from treatment between week 16 and week 52. Response to treatment at week 16 was assessed by the EASI 50 + DLQI ≥4 endpoint.

For lebrikizumab in combination with TCS, conditional discontinuation data was stated in the CS to have been obtained from the ADhere trial.[40] As part of the clarification response question B7(a), the company clarified that the discontinuation rates were obtained from a post-hoc analysis of patients who achieved the relevant endpoint at week 16 in ADhere and had rolled over into ADjoin. They also updated the conditional discontinuation rates to [redacted] for the EASI 50 + DLQI ≥4 endpoint and [redacted] for the EASI 75 endpoint as they noticed some discrepancies between the patient numbers and what had been implemented in the economic model. For the comparators, conditional discontinuation data was taken from TA814,[15] except for tralokinumab as the data are redacted. Tralokinumab conditional discontinuation data were taken from a study by Silverberg et al. 2021.[61] We note that the definition of responder in the Silverberg et al. 2021 study is having an IGA score of 0/1 or EASI 75 at week 16. Table 32 presents the conditional discontinuation rates for each treatment, i.e., the probability of a patient not responding to treatment at week 52.

Table 32 also shows the average of the conditional discontinuation rates of all treatments, which was applied in the model base case to all treatments for combination therapy. CS Table 59 shows an incorrect mean value of [redacted] compared to the correct mean value of [redacted] calculated in the company model and shown in the table below. The company did not explain the rationale for assuming the same conditional discontinuation rates for all the treatments. The EAG does not consider that this approach is reasonable, and we consider that the individual conditional discontinuation rates should be used for each treatment in the model, as previously assumed in TA814. Moreover, this is an assumption with a significant impact on the model results. Therefore, in the EAG base case, the individual conditional discontinuation rates are used for each treatment (see section 6.2).

Table 32 Probability of a patient discontinuing treatment between week 16 and week 52 for combination therapy (applied in the company's and EAG's base case)

Treatment	Probability (company)	Probability (EAG base case)	Source/assumptions
Lebrikizumab	[redacted]	[redacted]	Discontinuation rate from ADhere, conditional on achieving EASI 50 + DLQI ≥4[40]
Abrocitinib	[redacted]	[redacted]	TA814 report Table 41 (assumed same as upadacitinib)
Baricitinib	[redacted]	[redacted]	TA814 report (assumed same as upadacitinib)
Dupilumab	3.70%	3.70%	TA814 report Table 41
Tralokinumab Q2W	1.45%	1.45%	Figure S2 from ECZTRA 3[61]
Tralokinumab Q4W	4.35%	4.35%	Figure S2 from ECZTRA 3[61]
Tralokinumab	1.74%	1.74%	Weighted average (assuming 90% of patients receiving tralokinumab Q2W and 10% Q4W)
Upadacitinib	[redacted]	[redacted]	TA814 report Table 41
Mean (company base case)	[redacted]	-	Average of all treatments

Source: Partly reproduced from CS Table 59 and Table 24 of the clarification response document.
Q2W, every two weeks; Q4W, every four weeks.

The EAG notes that the conditional discontinuation rate applied to lebrikizumab is [redacted] than the discontinuation rates of the other comparators. The reason for this difference is unclear, although we suspect that it might be more related to how the conditional discontinuation rates were derived from each of the comparator's trials and less related with the true relative effect of lebrikizumab on the discontinuation rates compared to the other second-line systemic therapies. However, it is not possible to confirm this and therefore we use the updated company's input in our EAG base case ([redacted]) and explore several options for the lebrikizumab conditional discontinuation rates as scenario analyses (see Table 33).

In TA814, the conditional discontinuation data of baricitinib and abrocitinib were assumed equal to upadacitinib as they are all JAK inhibitors. However, our clinical expert did not agree with the assumption made in TA814 as baricitinib is less efficacious than the other JAK inhibitors, although its safety profile is similar. Our expert also mentioned that tralokinumab is less effective than the other biologics. [redacted]. For dupilumab and tralokinumab, the EAG in TA814 assumed that the conditional discontinuation data for monotherapy could be used for combination therapy as the type of monoclonal antibody seems to be more relevant for a sustained treatment response than the addition of TCS. The clinical expert advising the EAG in the current appraisal considers that this is a reasonable assumption. Therefore, we explore a scenario analysis where the lebrikizumab conditional discontinuation rate comes from a post-hoc analysis of the monotherapy ADvocate trials (see Table 33).

Table 33 Lebrikizumab conditional discontinuation rates for combination therapy (EAG base case and scenario analyses)

	Conditional discontinuation, n/N (%)	Source and description
Base case	[redacted]	Company's updated conditional discontinuation rate for the EASI 50 + DLQI ≥4 [a] endpoint for combination therapy from a post-hoc analysis of ADhere and ADjoin trials
Scenario analysis 1	[redacted]	Company's updated conditional discontinuation rate for the EASI 75 [b] endpoint for combination

	Conditional discontinuation, n/N (%)	Source and description
		therapy from a post-hoc analysis of ADhere and ADjoin trials
Scenario analysis 2	[redacted]	Conditional discontinuation rate for the EASI 50 + DLQI ≥4 [a] endpoint for monotherapy from a post-hoc analysis of the pooled ADvocate studies
Scenario analysis 3	[redacted]	Pooled conditional discontinuation rate for the EASI 50 + DLQI ≥4 [a] endpoint for monotherapy and combination therapy.
Scenario analysis 4	[redacted]	Average of the conditional discontinuation rates of biologics for lebrikizumab (using base case value), tralokinumab and dupilumab

Q2W, every two weeks; Q4W, every four weeks.
[a] Based on the number of patients who achieve EASI 50 + DLQI ≥4 endpoint at week 16 and then discontinue between week 16 and week 52 due to all-cause discontinuation (including loss of response based on the number of patients that do not achieve the composite endpoint).
[b] Based on the number of patients who achieve EASI 75 endpoint at week 16 and then discontinue between week 16 and week 52 due to all-cause discontinuation (including loss of response based on the number of patients that do not achieve EASI 75).

4.2.6.3 Long-term discontinuation

Long-term discontinuation is described in CS section B.3.3.4 and informs the decision about whether a patient continues receiving maintenance treatment with a second-line systemic therapy from year two onwards or discontinues treatment and receives BSC. Long-term discontinuation data (from year 2 onwards) are not available for any of the treatments being compared in the model. In TA534, TA681 and TA814, long-term discontinuation was assumed to be equal to the conditional discontinuation rate for each individual treatment.[6] Our interpretation of the NICE guidance for TA814 is that this approach was considered to be plausible by the committee.[6]

The company assumed that the long-term discontinuation is the mean 36-week conditional discontinuation rate ([redacted]) converted to an annual rate and equal across treatments. This was considered reasonable by a panel of clinical experts advising the company. In summary, a long-term discontinuation rate of [redacted] per year was applied in the company model for all treatments. The clinical expert advising the EAG considers that assuming an equal discontinuation rate for all drugs may be unreasonable as JAK inhibitors are known to have

a worse safety profile than the biologics. Therefore, we decided to adopt a drug class approach where the average of the annual discontinuation rates of biologics ([redacted]) are applied to lebrikizumab, dupilumab and tralokinumab and an average of the annual discontinuation rates of JAK inhibitors ([redacted]) are applied to baricitinib, abrocitinib and upadacitinib. The EAG considers the drug class approach to be appropriate as the significant differences in the safety profile appear to be related with the drug class, where mode of action and administration of treatment are distinct.

The long-term discontinuation of lebrikizumab and the comparators is a matter of uncertainty in the model and for completeness, we explored a scenario analysis where the individual treatment-specific annual discontinuation rates were used and another scenario where the pooled 36-week rates (conditional discontinuation rates between week 16 and week 52) were applied for each drug class: [redacted] for the biologics and [redacted] for the JAK inhibitors.

4.2.6.4 Treatment waning

Treatment waning is described in CS section B.3.3.5 and refers to the proportion of patients that lose response to treatment over time. The company modelled the same treatment waning assumptions as those accepted in previous NICE appraisals, including TA814[6]: in years 2, 3, 4 and 5 onwards, 2%, 5%, 7% and 8% of patients lose response and discontinue to BSC respectively. Both the company and the EAG in TA814 acknowledged that treatment waning and long-term all-cause treatment discontinuation may overlap since lack of efficacy is included as a reason to withdraw from treatment, but the size of the overlap is unknown. We test the impact of removing treatment waning in a scenario analysis (see section 6.1).

4.2.6.5 Mortality

Mortality is described in CS section B.3.3.6. Age- and gender-adjusted all-cause mortality from the Office of National Statistics (ONS) National Life Tables for England were used to model mortality of patients with atopic dermatitis as the treatment of this condition is not expected to affect people's life expectancy.

4.2.6.6 Adverse events

The adverse events included in the model, described in CS section B.3.3.7, are injection site reaction, allergic conjunctivitis, infectious conjunctivitis, oral herpes, upper respiratory tract infection and acne. In response to clarification question B8(a), the company justified their choice of adverse events to be consistent with those considered in TA814 as lebrikizumab's safety profile is similar to the other biologic drugs for atopic dermatitis. The adverse events included in TA814 were in line with those included in TA534, TA681 and the companies' models and comprised serious adverse events with an incidence of >5% in any treatment

arm.[15] The clinical expert advising us considered that the company has included all relevant serious adverse events.

Adverse event rates for lebrikizumab in combination with TCS were sourced from the ADhere trial,[30] while the rates for the comparators were sourced from TA814.[15] For tralokinumab, the TA814 values are redacted, and the company assumed the same adverse event rates as those for dupilumab. CS Table 60 shows the 16-week adverse event rates applied in the model for each treatment. The 16-week rates were converted to 36-week rates for the maintenance period of the decision tree and then to annual rates for the long-term Markov model.

We queried some of the specific adverse event rates used in the company's model in clarification questions B8(b) to (e). The company updated some of the adverse event rates for tralokinumab in response to clarification question B8(c), by using data from the study of Silverberg et al. 2021.[61] Table 34 shows the updated rates for tralokinumab in combination with TCS. In response to clarification question B8(e), the company also updated the adverse event rate of acne applied to lebrikizumab, reducing from 1.4% to [redacted].

Table 34 Updated 16-week adverse event rates for tralokinumab in combination with TCS

Adverse events	Tralokinumab in combination with TCS
Injection site reaction	6.75%
Allergic conjunctivitis	11.11%
Infectious conjunctivitis	0.00%
Upper respiratory tract infection	7.54%

Source: Partly reproduced from Table 25 of the clarification response document.
TCS, topical corticosteroids.

4.2.6.7 Flares

Flares are described in CS section B.3.3.8 and they are defined as an acute exacerbation of symptoms during treatment for moderate-to-severe atopic dermatitis. In previous NICE appraisals, receiving rescue medication was used and accepted as a proxy for flares when the rate of flares was not available.[13-15] The flare rates for lebrikizumab in combination with TCS were based on the rescue therapy rates from the ADhere trial.[30] For the comparators and BSC, the flare rates were taken from TA814.[15] As data for tralokinumab is redacted in TA814, the flare rates were sourced from the rescue therapy rates in the ECZTRA trials.[61,63] CS Table 61 shows the flare rates observed in the trials and the duration over which flares were observed in the trials. These rates were converted to 16-week, 36-week and annual

rates, as required. Based on the clinical effectiveness data of the second-line systemic therapies showed in the NMA by Drucker et al.,[62] the clinical expert advising the EAG would expect similar flare rates between dupilumab, upadacitinib and abrocitinib (at least at the highest doses) and the flare rates of baricitinib and tralokinumab to be higher than the other drugs.

EAG comment on treatment effectiveness and extrapolation

Based on clinical expert opinion and previous appraisals, we agree that the EASI 50 + DLQI ≥4 endpoint is the most appropriate outcome to inform response at week 16 in the model. However, due to unavailable data on EASI 50 + DLQI ≥4 for the comparators, we consider that EASI 75 is a suitable proxy to be used in the model. The use of placebo responses from AD UP trial to inform the baseline response rate is aligned with the approach taken in TA814. Moreover, the results from the company's scenario analysis using placebo response from the lebrikizumab studies show that this assumption has a low impact on the model conclusions.

Conditional discontinuation rates informed the treatment responses at week 52 and the long-term discontinuation rates used in the model, according to what has been assumed in past NICE appraisals. We consider that treatment-specific discontinuation rates should be used in the model at week 52 and include it in our base case. In a scenario analysis, we use different assumptions for the conditional discontinuation rates of lebrikizumab, baricitinib and tralokinumab as we consider these parameters to be uncertain.

For the long-term discontinuation, we assumed a drug class approach where we applied an average of the annual discontinuation rates of biologics to lebrikizumab, dupilumab and tralokinumab and an average of the JAK inhibitors to the remaining comparators in our base case.

Treatment waning and mortality assumptions as well as adverse event and flare data are plausible.

4.2.7 Health related quality of life

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review of HRQoL studies in patients with moderate-to-severe atopic dermatitis. The methodology is described in CS Appendix H. The search period was 1st January 2014 to 1st December 2022 and the search coding was replicated from TA814. On 7th December 2022, relevant grey literature was searched and multiple databases were manually searched using the term “dermatitis”. Inclusion and exclusion criteria are presented in CS Appendix H Table 120.

The review identified 33 studies that met the inclusion criteria, including 25 publications and eight Health Technology Assessments. From the eight Health Technology Assessments, three are NICE technology appraisals for dupilumab (TA534[13]), baricitinib (TA681[14]) and the MTA for abrocitinib, upadacitinib and tralokinumab (TA814[6]). CS Appendix H Table 121 shows the characteristics of each of the included HRQoL studies.

Although the company uses utility data collected in the lebrikizumab pivotal trials in the model, we provide below a short summary of the HRQoL conclusions in TA814 for reference.[6]

4.2.7.1.1 HRQoL data in TA814

The NICE guidance shows the final committee conclusions on HRQoL data, which were as follows[6]:

- Utility values were appropriately derived from clinical trials: EQ-5D-5L utility data were collected from the key clinical trials and mapped to the EQ-5D-3L using the van Hout crosswalk method.[64]
- Response-based utility values are more appropriate than treatment-specific utility values: the committee preferred a single utility value for baseline and response.
- Utility values for the BSC health state are highly uncertain and have a large impact on the modelled benefit: utility values for BSC were calculated using a weighted average of the utility values for responders and non-responders at week 16. The utility values for BSC non-responders were significantly higher than the baseline utility values.
- BSC waning assumptions are highly uncertain: the committee concluded that using utility waning may oversimplify the quality of life in patients receiving BSC, mainly because of the potential use of further sequential treatments.

4.2.7.2 Study-based health related quality of life

The health-related quality of life data used in the model is described in CS section B.3.4.5. The company base case uses health state utility values collected prospectively from the lebrikizumab ADhere trial. EQ-5D-5L data were collected in ADhere at week 16 and then mapped to UK EQ-5D-3L values using the Hernandez-Alava algorithm.[57]

The regression model selected to generate utilities for the model base case was the "*ADHERE OLS for combination therapy including the treatment arm*response interaction and prior systemic therapy=yes covariate*" (for further details, see CS section B.3.4.1). Responders were defined as having achieved the EASI 50 + DLQI ≥4 endpoint. Prior systemic therapy was defined as having received ciclosporin A, mycophenolate mofetil, methotrexate, azathioprine, JAK inhibitors or biologics.

Utilities were conditional on response and were assumed to be equal across active treatments. The utility for responders or non-responders from the lebrikizumab arm of the ADhere trial at week 16 were allocated to all treatments (lebrikizumab and comparators). The utility for responders or non-responders from the placebo arm of the ADhere trial at week 16 were allocated to patients on BSC. Table 35 shows a summary of the utility values used in the company's base case. The EAG notes that the utility for non-response to active treatment was not used in the economic model.

Table 35 Summary of health state utility values used in the cost-effectiveness model

Health state	Company base case (CI)	Clarification responses (CI)	EAG base case (CI)
Baseline	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]
BSC (weighted average)[a]	[redacted]	[redacted]	[redacted]
BSC responder	[redacted]	[redacted]	[redacted]
BSC non-responder	[redacted]	[redacted]	[redacted]

Source: Partly reproduced from CS Table 65 and Table 27 of the clarification responses document.
BSC, best supportive care; EAG, Evidence Assessment Group; CI confidence interval.
[a] Proportion of responders: 42% (from AD UP trial).

In the short-term decision tree model, a weighted average of responder and non-responder utilities was applied to the BSC health state. This is in line with the approach taken in TA814.

The company applied a utility waning to the utilities of BSC (both responder and non-responder) due to the placebo effect which is not expected to last. The utilities were assumed to wane to the baseline utility value observed in the lebrikizumab trial. The EAG notes that utility waning has been incorrectly implemented in the economic model. The company base case used the waning data from TA534 sensitivity analysis 1: 82% in year 2, 90% in year 3, 94% in year 4 and 96% thereafter. A scenario analysis based on the waning data from TA534 sensitivity analysis 2 is also mentioned in the CS: 57% in year 2, 82% in year 3, 92% in year 4 and 97% thereafter. In the company model, there was no waning at year 2 and at year 3 all patients were back to baseline utility. Therefore, we correct it as part of the EAG corrections (see section 5.2.3).

In TA814, the committee concluded that the utility waning scenario (also based on TA534 values) was not suitable as it did not appropriately reflect the natural history of the disease and the use of potential further sequential treatments. In scenario analyses, we exclude the utility waning applied to BSC and we note that this does not significantly affect the results (see section 6.1).

According to TA814 (see 4.2.7.1.1 above), the preferred committee assumption was that the use of treatment-specific utility values adds unnecessary complexity to the economic model and the use of a single utility value for each health state. As part of the response to the clarification question B11, the company provided the health state utility values (baseline, response and non-response) based on the overall population of the ADhere trial (lebrikizumab and placebo arms together). However, we would expect that the overall utility for the response health state lies within the interval between [redacted] (BSC response utility) and [redacted] (lebrikizumab response utility), which isn't the case ([redacted]). For consistency with the committee preferences in TA814, we use overall health state utility values in the EAG base case (see Table 35). But these were calculated as the weighted average of utilities from the lebrikizumab and placebo arms used in the company's base case. For this calculation, we considered the number of patients with prior systemic therapy in the lebrikizumab (n=66) and placebo (n=34) arms from the ADhere trial, which was taken from CS Table 10.

4.2.7.3 Adverse event utility decrements

The company included adverse event utility decrements in the model as the health state utilities from the ADhere trial (captured at week 16) are unlikely to capture the impact of treatment-related adverse events which often occur at the start of treatment. This is described in CS section B.3.4.4.

The disutility values were taken from the literature and reported in CS Table 64. It was assumed that all disutilities last for a week, except injection site reaction which was assumed to last 3 days. If the original source did not mention the duration over which the disutility was assumed to occur, then the company assumed an annual value.

EAG comment on HRQoL

The EAG has no concerns with the company's HRQoL searches. The searches are slightly outdated (11 months), but we do not believe this has caused any key HRQoL publications to be missed. The EAG considers that the methods used to derive utilities from the ADhere trial are reasonable. For consistency with the previous appraisal TA814, the EAG consider the use of overall health state utility values to be more appropriate. We conduct a scenario analysis excluding the utility waning of BSC.

4.2.8 Resources and costs

The company's economic SLR was used to identify healthcare resource use studies. The results of the review are shown in CS Appendix I Table 122. Of the studies identified, the NICE TA814 MTA was considered the most relevant. The approach to costing followed by the company in this appraisal is similar to that used in TA814.

4.2.8.1 Drug acquisition

The dosing information for lebrikizumab and the comparator treatments is shown in Table 36 (CS Table 67 and 68). Lebrikizumab is self-administered by subcutaneous injections (250mg). The recommended dosage consists of a loading dose of 500 mg (2 injections) at weeks 0 and 2 and then 250mg every other week (Q2W) up to week 16. At week 16, patients who are not considered to have responded may discontinue treatment whilst responders continue treatment with 250mg given every four weeks (Q4W). The list price for a pack of two 250mg prefilled pens or syringes is £2,271.26, reduced to [redacted] after applying a PAS discount of [redacted].

The dosing schedules for the comparator treatments are shown in Table 36. Upadacitinib, abrocitinib and baricitinib are available as oral treatment, whilst dupilumab and tralokinumab are given as subcutaneous injections. There are two possible doses for upadacitinib, abrocitinib and tralokinumab. For its base case, the company assumes that 50% of patients will have the higher and lower doses for upadacitinib and abrocitinib. For tralokinumab, 90% of patients receive Q2W and 10% Q4W after the induction period. The drug acquisition costs

for the comparators were sourced from the BNF.[65] The costs for the comparator treatments for the induction, maintenance and annual periods are shown in Table 37.

Table 36 Dosing information on lebrikizumab and comparator treatments

Treatment	Strength (mg)	Pack size	Pack cost (list prices)	Cost per unit	Dose
Lebrikizumab	250	2	[redacted]	[redacted]	Loading: 500 mg administered at week 0 and week 2; and 250 mg given Q2W until week 16. 250 mg given Q4W from week 16 onwards
Upadacitinib - 15 mg	15	28	£805.56	£28.77	15 mg once daily
Upadacitinib - 30 mg	30	28	£1,281.54	£45.77	30 mg once daily
Abrocitinib - 100 mg	100	28	£893.76	£31.92	100 mg once daily
Abrocitinib - 200 mg	200	28	£893.76	£31.92	200 mg once daily
Baricitinib	4	28	£805.56	£28.77	4 mg once daily
Dupilumab	300mg/2ml	2	£1,264.89	£632.45	600 mg followed by 300 mg Q2W
Tralokinumab Q2W	150mg/1ml	4	£1,070.00	£267.50	Loading: 600 mg (four 150 mg injections) Maintenance: 300 mg (two 150 mg injections) Q2W
Tralokinumab Q4W	150mg/1ml	4	£1,070.00	£267.50	Loading: 600 mg (four 150 mg injections) Maintenance: 300 mg (two 150 mg injections) Q4W from week 17

Source: Reproduced from CS Table 67 and 68
Q2W, every two weeks; Q4W, every four weeks.

Table 37 Drug costs used in the company model for lebrikizumab and its comparators

Treatment	Cost - induction	Cost - maintenance	Annual cost*
Lebrikizumab	[redacted]	[redacted]	[redacted]
Upadacitinib	£4,174	£9,392	£13,613
Abrocitinib - 100 / 200mg	£3,575	£8,044	£11,659
Baricitinib	£3,222	£7,250	£10,508
Dupilumab	£5,692	£11,384	£16,444
Tralokinumab Q2W / Q4W	£4,815	£9,149	£13,215

Source: Reproduced from CS Table 67 and 69.
Q2W, every two weeks; Q4W, every four weeks.

The EAG notes that there is a discrepancy in how lebrikizumab is costed for the induction period compared to dupilumab and tralokinumab. For dupilumab and tralokinumab, it is assumed that there is no dose in week 16 for the induction period, with doses for week 0-14, in line with the assumption used in TA814. However, for lebrikizumab induction, a dose in week 16 is also included. We consider the dosing for the induction period for lebrikizumab should not include the dose in week 16. We correct this in the company model in section 5.2.3.

There were no drug administration costs used in the model. Baricitinib, upadacitinib and abrocitinib are administered orally and are assumed to incur no administration cost. Based on assumptions from previous appraisals (TA814, TA534 and TA681), patients receive training on how to self-administer subcutaneous injections and thereafter self-administer. The companies who make the subcutaneous injections (including for lebrikizumab) have agreed to provide training to NHS staff on the self-administration of their treatments. Where there would be injections remaining for non-responders, who discontinue treatment at week 16, the cost of any unused (i.e., wasted) syringes are included in the acquisition cost.

4.2.8.2 Concomitant medication

Concomitant medication costs are included for emollient products, mid-potency background TCS and topical calcineurin inhibitors. The company uses the same assumptions with regard to concomitant medication as previously used in TA814 (listed on CS page 167).

The costs of the concomitant medication are shown in CS Table 70. The EAG notes that some of these medications have been costed using BNF,[65] where they are also available on eMIT.[66] These treatments are shown in Table 38 with the eMIT costs. The EAG have used the eMIT prices in the EAG analyses in section 6.

Table 38 Concomitant medication costs included, with costs from eMIT, rather than BNF

Medication	Form	Dose per unit	Price used in CS	eMIT price
Epaderm ointment	Ointment	1000g	£12.89	eMIT: 500g - £3.19
Hydromol	Ointment	500g	£5.50	eMIT: 500g - £3.19
White soft paraffin 50% / Liquid paraffin 50%	Ointment	500g	£4.57	eMIT: £1.90

Source: Partly reproduced from CS Table 70.

We also note that the cost of protopic 0.1% ointment is £27.84 in the BNF, rather than £28.76 as reported in CS Table 70.

4.2.8.3 Health care resource use

Health care resources were based on previous appraisals for atopic dermatitis. These are defined by health state, i.e., stage of treatment (induction vs maintenance), treatment response, treatment received (active treatment vs BSC).

Health care use in the model was informed by TA814 which had in turn been informed by TA534 and TA681. The main resources included are outpatient, GP and A&E visits, hospital admissions, and blood tests. The health care resources are shown in CS Table 73.

The unit costs of the health care resources are shown in CS Table 71 and CS Table 72 for adults and adolescents respectively. The unit costs were taken from the National Schedule of NHS costs 2020/1[67] and Unit Costs of Health and Social Care 2021.[68] Costs in the BSC health state are weighted by the proportion of responders and non-responders to BSC at the week 16 assessment point. The weighted health care resource costs for BSC are shown in CS Table 74.

The EAG notes that the hospitalisation cost for adolescents should be £1,518.41, rather than £2,192 as reported in CS Table 72 or £1,551.92 as used in the economic model. The value used in the model does not include the NHS cost codes for 'Paediatric Skin Disorders with CC Score 4+' in the calculation. The EAG has corrected this in section 5.2.3

4.2.8.4 Adverse event and flare costs

The unit costs for treating adverse events are shown in CS Table 75. The frequency of adverse events is shown in CS Table 60. The adverse event costs were calculated in a

similar way to previous appraisals for atopic dermatitis. The unit costs associated with each adverse event are multiplied by the weekly (short term model) and annual (long-term model) proportion of patients experiencing each AE.

We note that the costs for injection site reaction have been incorrectly calculated and should be £171.93, rather than £124.83. The company acknowledged this error in their clarification response to question B12. However, the correction that was made in response to the clarification was incorrect, as a change was inadvertently made to the infectious conjunctivitis cost. The EAG has corrected these costs in section 5.2.3.

Flare medication acquisition costs are shown in CS Table 76 and the frequency of flares is shown in CS Table 77, which is informed by the prescription of rescue therapy. The total flare costs are calculated by using the cost of the flare medication multiplied by the distributions of flare treatments. We note that some of the medications have been costed using BNF but are also costed as generic medications in eMIT (Table 40). The EAG have used the eMIT prices in the EAG analyses in section 6. In the short-term part of the model, it is assumed that non-responders to systemic treatment incur the flare costs associated with BSC. The EAG considers this is reasonable given this assumption is likely to have an insignificant effect on model results.

Table 39 Flare medication costs included, with costs from eMIT, rather than BNF

Medication	Form	Dose per unit	Price used in CS	eMIT price
Betamethasone valerate	Cream	100g	£5.74	£2.86
Eumovate 0.05% ointment	Ointment	100g	£5.44	£4.09 (clobetasone)
Dermovate 0.05% cream	Cream	100mg	£7.90	£6.84
Prednisolone 5mg (pack of 28 tabs)	Oral tablet	5mg	£0.94	£0.30

Source: Partly reproduced from CS Table 76

EAG comment on resources and costs

The EAG confirms that the approach taken for resources and costs in the company cost effectiveness model is appropriate and follows the approach taken in TA814. The EAG identified some minor errors in the unit costs and note that for some of the concomitant treatments, the source should be from the eMIT, rather than the BNF. We have corrected these in section 5.2.3. The

comparator treatments are associated with confidential discounts and these are shown in the EAG's confidential addendum.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company base-case compares lebrikizumab with baricitinib, abrocitinib, tralokinumab, upadacitinib and dupilumab for atopic dermatitis for combination therapy with a topical corticosteroid. The results use a PAS discount price for lebrikizumab and list prices for the other treatments. The EAG notes that the results reproduced in Table 40 (and the following sections) do not reflect the current costing of the treatments as all of these also have an agreed confidential discount. The results with PAS discounts for all treatments are produced by the EAG in a confidential addendum.

The company made a couple of minor changes to the model following clarification questions:

- The adverse event rates for tralokinumab have been updated, in response to clarification question B8(c),
- The adverse event rate for acne has reduced from 1.4% to [redacted], in response to clarification question B8(e),
- The adverse event cost for infectious conjunctivitis has been altered, in response to clarification question B12). However, the EAG notes that this alteration is incorrect (see section 4.2.8.4).

The cost effectiveness incremental results are shown in clarification response document Table 30 (original results shown in CS Table 81). The results are reproduced in Table 40. Lebrikizumab dominates baricitinib and tralokinumab as it is less costly but also more effective. Abrocitinib, upadacitinib and dupilumab have higher QALYs than lebrikizumab but the ICER for these treatments vs lebrikizumab is greater than £300,000 per QALY

Table 40 Company's base-case results for combination therapy with PAS discount for lebrikizumab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Pairwise NMB vs. LEB
Lebrikizumab	[redacted]	[redacted]				
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	£568,504

Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£366,436	£366,436
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1,408,755

Results shown for combination therapy: all treatments include topical corticosteroids
Source: Reproduced from Clarification response document Table 30.
Ext dominated, extendedly dominated; ICER, incremental cost-effectiveness ratio; LEB, lebrikizumab; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

The CS Table 81 and 82 also shows the results using the net monetary benefit (NMB) which is helpful in certain situations, such as where there is a very small incremental QALY.

5.1.1 Company's deterministic sensitivity analyses

The company considers 279 parameters in their one-way sensitivity analyses (OWSA), according to the company model (Parameters sheet). Variations in input parameters are based on 95% confidence intervals, calculated using the standard error. If the standard error was not reported, the company uses an assumed standard error of 20% of the base case value.

The results for the OWSA are shown in CS Figures 38 to 42 and CS Table 84 to 88 for lebrikizumab vs each of the comparator treatments. The OWSA were presented in terms of NMB, rather than ICER, due to lebrikizumab dominating against some of the comparators and the high ICERs against some of the other comparators, due to the very small differences in QALY. The EAG considers this is a sensible approach. The results show that discontinuation at week 52 is the parameter that has the largest impact on the NMB for lebrikizumab vs comparators. Placebo response at week 16 and the long-term treatment discontinuation rate also has an impact on the results.

5.1.2 Company's scenario analysis

The company conducted five scenario analyses and the results for these are reported in CS Table 89. The CS notes that none of these scenarios had a significant impact on the model results, as they follow a similar pattern to the base-case.

The company provided instructions on how to run the scenario for the source of baseline (placebo) response, in response to clarification question B13. However, the EAG was still unable to replicate this scenario.

5.1.3 Company's probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis using 1000 simulations. The same parameters included in the OWSA were also included in the PSA. The EAG considered that the distributions used in the PSA were appropriate.

The probabilistic results are shown in CS Table 83. The EAG notes that probabilistic results are similar to the deterministic results. A CEAC is shown in CS Figure 37, where lebrikizumab is the treatment with the greatest probability of being the most cost-effective treatment at all WTP thresholds. In addition, the results are shown as scatterplots of lebrikizumab against each of its comparators in CS Figures 32 to 36.

5.2 Model validation and face validity check

5.2.1 Company's model validation

The company's approach to validating their model is described in CS Section B.3.12.1. The CS states that model structure, clinical assumptions and model assumptions were discussed in detail with UK clinical experts. In addition, the model went through internal validation and a quality control check by an external health economist. The EAG notes that CS does not mention the number, location or affiliation of the experts who contributed their opinion, nor include details of the internal model checking so uncertainty remains around the validation completed by the company.

5.2.2 EAG model validation

The EAG conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses
- Checking the individual equations within the model ('white box' checks), including replicating the model.
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks)

We noted some minor discrepancies in the concomitant medication costs and the flare medication costs and these are reported in Table 38 and Table 39.

The EAG found several modelling errors and discrepancies in the company model. These are listed in Table 41. The first issue concerning the discontinuation rate for week 16 to 52, being applied twice in the model, was considered to be an error and was corrected in section 5.2.3. The treatment costs for lebrikizumab for the induction period were calculated, assuming injections given every two weeks up to and including week 16, whereas for dupilumab and tralokinumab, treatment costs were calculated, assuming injections given every two weeks up to but not including week 16. Thus, there was a discrepancy between how the treatment costs were calculated for the induction period. We changed the induction costs for lebrikizumab to be in line with the other treatments, as described in section 5.2.3. The model includes utility waning for patients receiving BSC, however this has not been implemented correctly and thus we correct this.

The final two issues concern discrepancies that are unlikely to materially affect the model results so we have not corrected these issues.

Table 41 List of modelling errors and discrepancies found by the EAG in the company model

Issue	Location in the model	EAG comment	EAG response
16 week – 52 week discontinuation is applied twice in the model.	Decision tree!C135:C141	Model error.	Corrected in section 5.2.3.
Difference in how induction costs for lebrikizumab is calculated compared to dupilumab and tralokinumab for week 16.	Treatment costs!J29:K32	Discrepancy. The number of administrations should be one fewer for lebrikizumab induction and one more for maintenance week 16-52.	Corrected in section 5.2.3.
Utility waning for patients on BSC	Markov Lebrikizumab!BR11:BT75 and comparator sheets	Utility waning has not been implemented correctly.	Corrected in section 5.2.3.

Issue	Location in the model	EAG comment	EAG response
Adverse events / flares in Markov model used for calculations of costs and utilities not using the half cycle correction.	Markov Lebrikizumab!AB11:AO74 and comparator sheets.	For consistency should also use half cycle correction. However, this discrepancy is unlikely to have a material impact on model results.	No action taken.
Annual treatment cost includes costs of TCS but the cost used is for the maintenance period (£47.76) rather than cost for whole year (£68.99).	Markov lebrikizumab!AP8 and comparator sheets.	This discrepancy is unlikely to have a material impact on model results.	No action taken.

EAG, Evidence Assessment Group; TCS, topical corticosteroids.

5.2.2.1 Validation of results against other sources

The company have not validated their cost effectiveness results by comparing with other analyses, e.g. against previous technology appraisals. The EAG notes the difficulty of this task, given the large quantity of redacted data for inputs and results in previous technology appraisals for atopic dermatitis. We have compared the ICERs from the company model against those from TA814 and the results are shown in Table 42. The results appear reasonably similar, except for abrocitinib vs dupilumab, although as stated above it is difficult to gauge how closely the results are due to the large quantity of redacted data (i.e., costs and QALYs).

Table 42 Comparison between ICERs vs dupilumab from TA814 and those in the current model for combination therapy

Comparison	TA814	Current company model
Abrocitinib 100 mg vs dupilumab	£67,274	£943,097
Abrocitinib 200 mg vs dupilumab	£107,901	Dominant
Upadacitinib 15 mg vs dupilumab	£181,963	Dominant

Upadacitinib 30 mg vs dupilumab	£128,561	£95,376
Tralokinumab vs dupilumab	£223,279	£265,048

Source: TA814 and CS Table 54.
ICER, incremental cost-effectiveness ratio.

5.2.3 EAG corrections to the company model

The EAG noted several discrepancies or errors in the company model and produced corrections for the following:

- Week 16-52 discontinuation rate is only applied once in the model (see Table 41).
- Number of injections of lebrikizumab adjusted for the induction and maintenance periods (see Table 41).
- Concomitant and flare medication costs using eMIT costs (Table 38 and Table 39).
- Hospitalisation costs for adolescents (section 4.2.8.3).
- Adverse event costs for injection site reaction and infectious conjunctivitis (section 4.2.8.4).
- Use corrected value for week 16 – 52 conditional discontinuation rate for lebrikizumab ([redacted]).
- Correct implementation of utility waning.

The company base case results with the EAG corrections are shown in Table 43. The corrections only have a minor effect on the model results.

Table 43 Company base case results with EAG corrections for combination therapy with PAS discount for lebrikizumab only

Technology	Cost	QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER vs LEB (£/QALY)
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]		
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	£592,286
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£379,263	£379,263
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	£1,454,408

Results shown for combination therapy: all treatments include topical corticosteroids

EAG, Evidence Assessment Group; Ext dominated, extendedly dominated; ICER, incremental cost-effectiveness ratio; LEB, lebrikizumab; NMB, net monetary benefit; PAS; patient access scheme; QALYs, quality-adjusted life-years.

5.2.4 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 44.

Table 44 EAG observations of the key aspects of the company's economic model.

Parameter	Company base case	EAG comment	EAG base case
Model structure			
Model structure	Decision tree and Markov model in line with TA814	We agree	No change
Subsequent treatment after 2nd line systemic therapies	BSC	This is not representative of UK clinical practice	No change. We test using a basket formed of comparator treatments in a scenario analysis
Population	Section 4.2.3	We agree	No change
Comparators	Section 4.2.4	We agree	No change
Perspective	NHS and PSS	We agree	No change
Time horizon	Lifetime	We agree	No change
Discounting	3.5% for costs and outcomes	We agree	No change
Treatment effectiveness			
Baseline response	Placebo response at week 16 from upadacitinib AD UP trial	We agree	No change
Response at week 16	NMA outputs using EASI 75	Data from the committee-preferred outcome (EASI 50	No change.

Parameter	Company base case	EAG comment	EAG base case
		+ DLQI≥4) is redacted in TA814	We test using NMA outputs using EASI 50 in a scenario analysis.
Response at week 52	Average of conditional discontinuation rates from all treatments	The individual conditional discontinuation rates for each treatment were used to inform treatment response at week 52 in TA814	Use individual conditional discontinuation rates
Lebrikizumab response at week 52	[redacted]	The conditional discontinuation rate applied to lebrikizumab is [redacted] than the rates for the other comparators. The reason behind it is unclear, but we think that it could be related to the way these rates were derived from each trial.	No change. We test the following options in scenario analyses: (1) use EASI 75 value ([redacted]) (2) use monotherapy value ([redacted]) (3) use average between monotherapy and combination therapy value ([redacted]) (4) use average of biologics' values ([redacted])
Baricitinib response at week 52	Same as upadacitinib and abrocitinib	Upadacitinib and abrocitinib show a higher number of responders at week 16 than baricitinib ([redacted] vs. [redacted] vs. [redacted])	No change. We test using the highest discontinuation rate across treatments in a scenario analysis ([redacted]

Parameter	Company base case	EAG comment	EAG base case
Tralokinumab response at week 52	1.74%	According to our clinical expert, tralokinumab was less effective than the other biologics, and therefore it is uncertain whether a lower conditional discontinuation rate versus the other drugs is appropriate.	No change. We test using the highest discontinuation rate across treatments in a scenario analysis ([redacted])
Long-term discontinuation	Average of 36-week discontinuation rates from all treatments converted into 52-week rates	The EAG clinical expert did not consider it reasonable as the safety profile of JAK inhibitors is less favourable than the biologics	For JAK inhibitors, use the average of 52-week baricitinib, abrocitinib and upadacitinib rates. For biologics, use the average of 52-week lebrikizumab, dupilumab and tralokinumab rates We test using the individual rates in a scenario analysis; we test using the 36-week rates in a scenario analysis
Treatment waning	Applied	Treatment waning and all-cause long-term treatment discontinuation may overlap	No change. We test removing treatment waning in a scenario analysis
Mortality	UK Life Tables	We agree	No change
Adverse events	Same as TA814	We agree	No change
Flares	Same as TA814	We agree	No change
Utilities			

Parameter	Company base case	EAG comment	EAG base case
Health state utilities	Treatment-specific utilities (active treatment versus BSC)	According to the committee in TA814, the use of treatment-specific utilities adds unnecessary complexity to the economic model.	Use overall health state utilities
	Overall health state utilities from the regression model Response: [redacted] Non-response: [redacted]	The utilities provided by the company lacks face validity as the utility for the response health state ([redacted]) is much lower than the utilities for both the response of lebrikizumab ([redacted]) and the BSC response ([redacted]).	Use the pooled average of lebrikizumab and placebo treatment-specific utilities. Response: [redacted] Non-response: [redacted]
BSC utilities	Waning effect applied according to TA534 (EAG correction)	In TA814, the committee considered the waning assumption to oversimplify the quality of life of patients on subsequent treatments (potential further sequential treatments)	No change. We test remove the utility waning effect in a scenario analysis
Resource use and costs			
Drug acquisition	Section 4.2.8.1	We agree	No change
Concomitant medication	Section 4.2.8.2	We agree	No change
Healthcare resource use	Section 4.2.8.3	We agree	No change
Adverse event costs	Section 4.2.8.4	We agree	No change

BSC, best supportive care; EAG, Evidence Assessment Group; JAK inhibitors, Janus kinase inhibitors; NHS, National Health Service; NMA, network meta-analysis; PSS, Personal Social Services; UK, United Kingdom.

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

As stated in section 5.1.2, the EAG was unable to replicate the company scenario with an alternative baseline (placebo) response in CS Table 89. We have run this scenario with the company model with EAG corrections and the results are shown in Table 45. Lebrikizumab dominates baricitinib and tralokinumab, i.e. is cheaper and more effective. Dupilumab, upadacitinib and abrocitinib have an ICER greater than £400,000 per QALY compared to lebrikizumab.

Table 45 Scenario analysis results for the company model with EAG corrections for combination therapy with PAS discount for lebrikizumab only, pairwise results vs lebrikizumab

Structural assumption	Scenario	Comparator	Inc. costs (£) vs LEB	Inc. QALYs vs LEB	ICER vs LEB (£/QALY)
Source of baseline (placebo) response. Base case: Upadacitinib studies	Adhere and Advantage 1	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
		Abrocitinib	[redacted]	[redacted]	£725,213
		Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
		Upadacitinib	[redacted]	[redacted]	£461,790
		Dupilumab	[redacted]	[redacted]	£1,825,481

Results shown for combination therapy: all treatments include topical corticosteroids
LEB, lebrikizumab; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; Inc Incremental; PAS, patient access scheme; QALYs, quality-adjusted life-years.

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model discussed in Table 44, we have identified several key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Response at week 52**: we use the individual treatment-specific conditional discontinuation rates, rather taking an average across all treatments.
- **Long-term discontinuation rate**: we use the average discontinuation rate by drug class, rather than taking an average across all treatments. For JAK inhibitors, we use the average of the baricitinib, abrocitinib and upadacitinib 52-week rates. For biologics, we use the average of lebrikizumab, dupilumab and tralokinumab 52-week rates.

- **Utility values:** We use overall health state utilities, i.e. utilities for response and non-response only, rather than using different utility values for active treatment and BSC. We use the weighted average of the treatment-specific utilities for the active treatment and BSC for responders ([redacted]) and non-responders ([redacted]).

Table 46 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the corrected company's base case using the PAS discount for lebrikizumab and list price for the comparator treatments. The results are shown for lebrikizumab compared to each of the comparators. Table 47 shows the incremental results for the EAG's preferred model assumptions. Incorporating all the EAG assumptions, lebrikizumab remains dominant against baricitinib. The ICERs for the other treatments versus lebrikizumab are higher than £400,000 per QALY.

The change that has the most significant impact on the cost-effectiveness results is using the treatment-specific conditional discontinuation rates.

Table 46 Cumulative cost effectiveness results for combination therapy of the EAG's preferred model assumptions with PAS discount for lebrikizumab only, pairwise against lebrikizumab

Preferred assumption	Treatment	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
Company base-case with EAG corrections (section 5.2.3)	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£592,286
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	£379,263
	Dupilumab	[redacted]	[redacted]	£1,454,408
+Response at week 52: use individual treatment-specific conditional discontinuation rates	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£243,136
	Tralokinumab	[redacted]	[redacted]	£432,622
	Upadacitinib	[redacted]	[redacted]	£240,316
	Dupilumab	[redacted]	[redacted]	£381,367
+Long-term discontinuation rate: use average rate by drug class for 52 weeks	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£487,484
	Tralokinumab	[redacted]	[redacted]	£455,851
	Upadacitinib	[redacted]	[redacted]	£356,511

Preferred assumption	Treatment	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
	Dupilumab	[redacted]	[redacted]	£396,023
+Use overall health state utilities. Utility for responders ([redacted]) and non-responders ([redacted]).	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£629,041
	Tralokinumab	[redacted]	[redacted]	£514,899
	Upadacitinib	[redacted]	[redacted]	£443,379
	Dupilumab	[redacted]	[redacted]	£461,012
EAG base case (including the assumptions above)	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£629,041
	Tralokinumab	[redacted]	[redacted]	£514,899
	Upadacitinib	[redacted]	[redacted]	£443,379
	Dupilumab	[redacted]	[redacted]	£461,012

Results shown for combination therapy: all treatments include topical corticosteroids
EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life-years.

Table 47 EAG incremental base case results for combination therapy with PAS discount for lebrikizumab only

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	ICER vs. LEB (£/QALY)
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]		
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Lebrikizumab dominates
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	£629,041
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	Ext dominated	£514,899
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£443,379	£443,379
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£503,428	£461,012

Results shown for combination therapy: all treatments include topical corticosteroids
Ext dominated, extendedly dominated; ICER, incremental cost-effectiveness ratio; LEB, lebrikizumab; NMB, net monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

6.2.1 EAG scenarios

We performed a range of scenario analyses with the EAG base case to analyse the impact of changing some model assumptions on the final cost-effectiveness results. Table 48 below

summarises the results of the scenario analyses on the EAG base case. The following scenarios were conducted:

- Company's scenario analyses (conducted in CS Table 89),
- Use a basket of treatments for subsequent treatment, rather than all patients having BSC following discontinuation of active treatment,
- Use EASI 50 as a basis for 16-week response rates,
- Alternative 16-52 week discontinuation rates for lebrikizumab, baricitinib and tralokinumab,
- Alternative long-term discontinuation rates,
- Removing treatment waning,
- Removing utility waning of BSC.

The results are presented for each of the comparators compared to lebrikizumab. Lebrikizumab is the cheapest treatment (PAS discount applied to lebrikizumab and list price for the comparators). Lebrikizumab dominates the comparators (i.e. is cheaper and more effective) or the ICERs for the comparators vs lebrikizumab are greater than £30,000 per QALY, except for the scenario using the basket of treatments instead of BSC as subsequent treatment.

The results are most sensitive to the scenarios using the basket of treatments for subsequent treatment, using individual treatment specific rates to inform long term discontinuation rates and using the monotherapy value for long term discontinuation for lebrikizumab.

Table 48 EAG scenario analysis results for combination therapy with PAS discount for lebrikizumab only, pairwise results vs lebrikizumab

Scenario	Comparator	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
EAG base case	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£629,041
	Tralokinumab	[redacted]	[redacted]	£514,899
	Upadacitinib	[redacted]	[redacted]	£443,379
	Dupilumab	[redacted]	[redacted]	£461,012
EASI75 used to define response	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	£1,465,886
	Upadacitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Dupilumab	[redacted]	[redacted]	£674,064

Scenario	Comparator	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
Patients have monotherapy treatment	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£109,625
	Dupilumab	[redacted]	[redacted]	£1,156,366
	Upadacitinib	[redacted]	[redacted]	£116,600
50% have monotherapy and 50% combination therapy	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£208,126
	Upadacitinib	[redacted]	[redacted]	£198,332
	Dupilumab	[redacted]	[redacted]	£596,820
Source of baseline (placebo) response: ADhere and Advantage 1	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£767,211
	Tralokinumab	[redacted]	[redacted]	£488,107
	Upadacitinib	[redacted]	[redacted]	£540,320
	Dupilumab	[redacted]	[redacted]	£488,241
Health state utility values from TA681	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£603,222
	Tralokinumab	[redacted]	[redacted]	£449,841
	Upadacitinib	[redacted]	[redacted]	£407,479
	Dupilumab	[redacted]	[redacted]	£404,913
Health state utility values from TA534	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£490,034
	Tralokinumab	[redacted]	[redacted]	£402,606
	Upadacitinib	[redacted]	[redacted]	£347,541
	Dupilumab	[redacted]	[redacted]	£361,294
Utility decrements for adverse events excluded	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£636,808
	Tralokinumab	[redacted]	[redacted]	£499,710
	Upadacitinib	[redacted]	[redacted]	£441,032
	Dupilumab	[redacted]	[redacted]	£449,613
Use basket of treatments for subsequent treatment	Baricitinib	[redacted]	[redacted]	£231,277[a]
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominated
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominated
	Lebrikizumab	[redacted]	[redacted]	
	Upadacitinib	[redacted]	[redacted]	£43,561
	Dupilumab	[redacted]	[redacted]	£65,152
Long-term discontinuation rates: using 36-week rate.	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£503,318
	Tralokinumab	[redacted]	[redacted]	£478,762

Scenario	Comparator	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
	Upadacitinib	[redacted]	[redacted]	£389,399
	Dupilumab	[redacted]	[redacted]	£433,827
Long-term discontinuation rates: using 36-week rate and average across treatments.	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£270,963
	Tralokinumab	[redacted]	[redacted]	£459,092
	Upadacitinib	[redacted]	[redacted]	£269,199
	Dupilumab	[redacted]	[redacted]	£418,626
Long term discontinuation rates: using individual treatment specific rates	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	£107,422
	Abrocitinib	[redacted]	[redacted]	£104,389
	Upadacitinib	[redacted]	[redacted]	£129,280
	Tralokinumab	[redacted]	[redacted]	£92,254
	Dupilumab	[redacted]	[redacted]	£130,415
EASI 50 used to define response	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£973,104
	Upadacitinib	[redacted]	[redacted]	£736,889
	Tralokinumab	[redacted]	[redacted]	£433,663
	Dupilumab	[redacted]	[redacted]	£513,955
Remove treatment waning	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£946,048
	Tralokinumab	[redacted]	[redacted]	£466,150
	Upadacitinib	[redacted]	[redacted]	£497,912
	Dupilumab	[redacted]	[redacted]	£423,999
Lebrikizumab discontinuation rate week 16-52 (1) use EASI 75 value ([redacted])	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	£870,804
	Dupilumab	[redacted]	[redacted]	£579,458
Lebrikizumab discontinuation rate week 16-52 2) use monotherapy value ([redacted])	Baricitinib	[redacted]	[redacted]	£9,112[a]
	Lebrikizumab	[redacted]	[redacted]	
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
	Dupilumab	[redacted]	[redacted]	£1,252,189
Lebrikizumab discontinuation rate week 16-52 (3) use average between monotherapy and	Baricitinib	[redacted]	[redacted]	£3,012[a]
	Lebrikizumab	[redacted]	[redacted]	
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	£12,051,145
	Dupilumab	[redacted]	[redacted]	£877,779

Scenario	Comparator	Total costs	Total QALYs	ICER vs. lebrikizumab (£/QALY)
combination therapy value ([redacted])				
Lebrikizumab discontinuation rate week 16-52 (4) use the average of the biologic values for lebrikizumab, tralokinumab and dupilumab ([redacted])	Baricitinib	[redacted]	[redacted]	£3,134[a]
	Lebrikizumab	[redacted]	[redacted]	
	Abrocitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Upadacitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	£13,740,871
	Dupilumab	[redacted]	[redacted]	£882,093
BARI and TRALO alternative conditional discontinuation rates: highest rate (18.75%)	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£220,597
	Upadacitinib	[redacted]	[redacted]	£247,291
	Dupilumab	[redacted]	[redacted]	£530,904
Remove utility waning of BSC	Lebrikizumab	[redacted]	[redacted]	
	Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
	Abrocitinib	[redacted]	[redacted]	£932,963
	Tralokinumab	[redacted]	[redacted]	£1,066,895
	Upadacitinib	[redacted]	[redacted]	£713,223
	Dupilumab	[redacted]	[redacted]	£883,507

Results shown for combination therapy: all treatments include topical corticosteroids
EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALYs, quality-adjusted life-years.
[a] shows ICER for lebrikizumab vs. comparator

6.3 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of lebrikizumab compared to dupilumab, tralokinumab, abrocitinib, upadacitinib and baricitinib for patients with moderate to severe atopic dermatitis. The EAG considers the structure of the model to be reasonable and appropriate and consistent with previous modelling in NICE technology appraisals. The model uses treatment effectiveness data from the ADhere and ADvantage studies for lebrikizumab. An NMA using EASI 75 (rather than EASI 50 + DLQI ≥4) was conducted to compare response at week 16 between treatments in the company's base case. Conditional treatment discontinuation and long-term discontinuation were assumed to be the same for all treatments (an average across treatments). Treatment-specific utilities were applied for active treatment and BSC. The company's revised base case for combination therapy with a topical corticosteroid shows that lebrikizumab dominates baricitinib and tralokinumab. Abrocitinib, upadacitinib and dupilumab have higher QALYs

than lebrikizumab but the ICER for these treatments vs lebrikizumab is greater than £300,000 per QALY. The company base case includes a PAS discount for lebrikizumab only.

The EAG identified some technical calculation errors in the company's model, but none that have a significant impact on the results. The company made some minor changes to the model inputs in response to clarification questions.

The EAG disagrees with several of the assumptions in the company's model. Our preferred assumptions include:

- Response at week 52: using the individual treatment-specific conditional discontinuation rates, rather than taking an average across all treatments.
- Long-term discontinuation rate: using the average discontinuation rate by drug class, rather than taking an average across all treatments.
- Using overall health state utilities, i.e., utilities for baseline, response and non-response, rather than using different utility values for active treatments and BSC. Using the weighted average of the treatment-specific utilities for the active treatment and BSC for response ([redacted]) and non-response ([redacted]).

Incorporating the EAG preferred assumptions, lebrikizumab remains dominant against baricitinib and the ICERs for the other treatments versus lebrikizumab are higher than £400,000 per QALY. The model results are most sensitive to using the basket of treatments for subsequent treatment, using individual treatment specific rates to inform long term discontinuation rates and using the monotherapy value for long term discontinuation for lebrikizumab.

7 SEVERITY

The 2022 NICE Health Technology Evaluations Manual specifies criteria for QALY weightings for severity based on the proportional and absolute QALY shortfall for the population with the condition, in comparison with the general population with the same age and sex distribution. The company calculated the QALY shortfall for lebrikizumab by using the online tool published by Schneider et al. (2021)[69] The company uses the sex distribution (53% male) and starting age (34 years) from the ADvantage trial. The absolute QALY shortfall for lebrikizumab in the company's original base case was below 12 and the proportional QALY shortfall is less than 85%, so the company did not apply a multiplier for disease severity (CS Table 79). We calculated the absolute and proportional QALY shortfall for the company's revised base case and the same was observed (see Table 49 below).

We also calculated the absolute and proportional QALY shortfall using the EAG base case and obtained similar results to the company's original and revised base case (Table 49), i.e. the thresholds for severity are not met, so we agree that there is not a case for applying a multiplier for disease severity.

Table 49 QALY shortfall analysis

	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportionate QALY shortfall
Company's revised base case				
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case				
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]

Source: Schneider et al.[69]
QALYs, quality-adjusted life-years.

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9 APPENDICES

Appendix 1 EAG critique of systematic review methods

Table 50 summarises the EAG's critique of the methods used in the company systematic review.

Table 50 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	CS appendix D Table 90 provides details of the clinical SLR eligibility criteria. An accurate and broad search, limited to RCT evidence, was conducted.
Were appropriate sources of literature searched?	Yes	The searches covered sufficient databases: • Cochrane CENTRAL and CDSR • Embase (Elsevier) • MEDLINE and MEDLINE-IN-PROCESS (PubMed) Other sources were also searched: • Websites of professional organisations for conference abstracts from the two most recent meetings. • ClinicalTrials.gov and ICTRP for ongoing trials. • HTA websites. • Reference lists of identified systematic reviews and meta-analyses
What time period did the searches span and was this appropriate?	Yes	An initial search and three update searches covered the period from database inception to April 2023 (conferences from 2019). The searches were around 6 months old when the CS was received by the EAG.
Were appropriate search terms used and combined correctly?	Yes	The search strategies for Embase, PubMed, and Cochrane are reported in CS Appendix D.1.1. The database searches combined terms for the patient population and study design (RCTs) (i.e. searches were not limited to any particular interventions).
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Eligibility criteria are provided in CS Appendix D Table 90. For population and comparators these are broader than the decision problem which the EAG view as appropriate because the SLR was also used to identify studies for the NMA. Inclusion was restricted by outcomes of disease response, PROs and drug safety measures. The company's decision problem outcomes of rescue therapy use and TCS-free days were not included among the inclusion criteria but the EAG views it as unlikely that this would have led to the exclusion of any relevant RCTs.

Systematic review components and processes	EAG response	EAG comments
Were study selection criteria applied by two or more reviewers independently?	Unclear	Two reviewers applied study selection criteria in a two-step process (title and abstract screening, full text screening) but it is not clear if they worked independently. Disagreements were resolved by a third researcher.
Was data extraction performed by two or more reviewers independently?	Yes	Although not explicitly stated, it appears that each study underwent data extraction by a single reviewer. A second reviewer independently checked data extractions as part of quality-control procedures.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The lebrikizumab studies were assessed using criteria adapted from "Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)" (CS Appendix D1.3 Table 100 to Table 103). In addition, the Cochrane risk of bias assessment tool (version used not stated) was used to assess risk of bias for all the studies included in the NMA but only a summary of the results is provided (CS Appendix D Figure 49), individual assessments are not provided for each study.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The CS does not state how the risk of bias assessments were conducted.
Is sufficient detail on the individual studies presented?	Yes	CS sections B.2.2 to B.2.7 provide methodological details and results for the key clinical effectiveness evidence from ADvocate 1, ADvocate 2, ADhere, ADvantage and ADjoin with additional information provided in CS Appendices D1.2, D1.3, E and F. The trial CSRs were also provided. In response to clarification question A5 the company provided further details on the ADhere-J and ADopt-VA trials.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	An NMA was undertaken to compare the efficacy of lebrikizumab relative to tralokinumab, dupilumab and the JAK inhibitors baricitinib, abrocitinib and upadacitinib as monotherapy or in combination therapy for four outcomes. A MAIC was undertaken to compare the efficacy and safety of lebrikizumab monotherapy with dupilumab monotherapy. Our critique of the NMA and MAIC methods is provided in section 3.3 of this report.

Source: Table created by the EAG
CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; CS, company submission; CSR,

clinical study report; EAG, External Assessment Group; HTA, health technology assessment; ICTRP, International Clinical Trials Registry Platform; ITC, indirect treatment comparison; JAK, Janus kinase MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PICOD, population, intervention, comparator, outcome, design; PROs, patient-reported outcome measures; RCT, randomised controlled trial; SLR, systematic literature review; TCS, topical corticosteroid.

Appendix 2 Details of other lebrikizumab trials

In the CS, three other placebo-controlled lebrikizumab RCTs were identified for inclusion in the company's NMA in addition to the ADvocate 1 and 2, ADhere, ADvantage and ADjoin clinical trials, but were not otherwise presented in the CS (CS Appendix D, Table 91):

- **J2T-DM-KGAF** (a phase 2b, placebo-controlled, dose-ranging RCT): NCT03443024[17]
- **ADhere-J** (an RCT in Japanese participants): NCT04760314
- **ADopt-VA** (an RCT assessing how lebrikizumab affects immune response to vaccines in adults; the study also assessed outcomes relevant to the NICE scope, such as improvement in disease severity): NCT04626297

In clarification question A5, the EAG queried why the ADhere-J and ADopt-VA trials were included in the NMA, but not listed in CS, Document B, Table 5, as among the relevant, identified clinical effectiveness evidence. In response, the company explained that the ADhere-J and ADopt-VA trials were included in the NMA only, as the NMA was carried out at a global level. The two studies were conducted in Japan and the US, respectively, only. ADhere-J was not part of the evidence base used to support the EMA marketing authorisation, and ADopt-VA was added to the evidence-base for the marketing authorisation part way through the approval process. The company summarised the designs and results of these studies in clarification response A5.

The CS additionally mentions two other trials of lebrikizumab in people with moderate-to-severe atopic dermatitis which were included in the safety section of the CS and in a published integrated safety analysis[18] but not otherwise listed as among the clinical evidence of interest:

- **ARBAN** (a phase 2 open-label RCT): NCT02465606. This study evaluated the safety of lebrikizumab administered with TCS compared to TCS alone (no placebo was used) in adults with persistent, moderate-to-severe atopic dermatitis that was inadequately controlled with TCS.[19]
- **TREBLE** (a phase 2, placebo-controlled RCT): NCT02340234. This study evaluated the efficacy and safety of lebrikizumab combined with TCS in people with persistent, moderate-to-severe atopic dermatitis that was inadequately controlled with TCS compared to placebo plus TCS.[70]

Neither the ARBAN nor TREBLE trials used the SmPC-recommended doses of lebrikizumab.[19,70] We consider it is appropriate that these trials have not received any further consideration in the CS, other than in the safety section.

The CS also mentions a phase 3 open-label, single-arm trial of lebrikizumab conducted in adolescents (aged ≥12 to <18 years weighing ≥40 kilograms), **ADore** (NCT04250350).[20] The company's SLR searches were restricted to RCTs only, so we note that this study would not have been identified as part of the SLR. The ADore trial did not use the SmPC-recommended dose of lebrikizumab, as participants received lebrikizumab every 2 weeks through to week 52. Participants from this study could enter the ADjoin trial. The company confirmed that ADore was the only single-arm trial in their data package (clarification response A6). We consider it is reasonable that this study has not been included in the CS.

The EAG requested copies of the CSRs for the ADhere-J and ADopt-VA trials in clarification question C2, and the company provided these in response.

Overview of the ADhere-J, J2T-DM-KGAF and ADopt-VA trials

An overview of the J2T-DM-KGAF, ADhere-J and ADopt-VA trials is provided in Table 50. To be included in the ADhere-J trial, participants needed to have had an inadequate response to topical medications or to have had treatment failure on systemic therapies (clarification response A5, Table 3). It is unclear which systemic therapies participants had previously failed on, but the study population may to some extent reflect the population in whom lebrikizumab treatment is being positioned. To be included in the J2T-DM-KGAF and ADopt-VA trial, participants had to have had an inadequate response to topical medications or be unsuitable for these (clarification response A5, Table 9). Therefore, the patient populations in J2T-DM-KGAF and ADopt-VA, as with the ADvocate 1 and 2 and ADhere trials, do not fully align with the population our clinical expert expects to receive treatment with lebrikizumab in practice.

Table 51 Overview of the characteristics of the J2T-DM-KGAF, ADhere-J and ADopt-VA trials

	J2T-DM-KGAF (a phase 2b, dose ranging RCT) [71]	ADhere-J (Japan only study)	ADopt-VA (US only study)
Population	Adults ≥18 years, with moderate-to-severe AD	Japanese patients (adults and adolescents) with moderate-to-severe AD	Adults aged 18 to 55 years, with moderate-to-severe AD
Sample size (participants randomised)	280	286	254

Intervention	• Lebrikizumab 125 mg Q4W (250mg LD) [a]
	• Lebrikizumab 250 mg Q4W (500 mg LD) [a]
	• Lebrikizumab 250 mg Q2W (500 mg LD) [a]
		Induction (16 weeks):
		• Lebrikizumab 250mg Q2W (500mg LD at baseline and week 2) + TCS
		• Lebrikizumab 250mg Q4W (500mg LD at baseline) + TCS
		Maintenance (52 weeks): [b]
		• Responders to induction Q2W regimen re-randomised to:
		  • Lebrikizumab 250mg Q2W + TCS
		  • Lebrikizumab 250mg Q4W + TCS
		• Responders to induction Q4W regimen received:
		  • Lebrikizumab 250mg Q4W + TCS
			Induction (16-week study only):
			• Lebrikizumab 250 mg Q2W (500mg LD at baseline and week 2)

Comparator	Matching placebo [a]	Induction (16 weeks): • Placebo + TCS Maintenance (52 weeks): [b] • Responders to placebo received: • Placebo + TCS	Induction (16-week study only): • Placebo
Primary outcome	% change in EASI between baseline and week 16	• % achieving EASI 75 at week 16 • Proportion of participants achieving IGA (0,1) [c] and a reduction of≥2 points from baseline to week 16	Responses to vaccine administration
Other outcomes [d]	Disease severity (e.g. achieving EASI 75); itch	Disease severity (e.g. % change in EASI); itch	Disease severity (e.g. achieving EASI 75); itch; sleep

Source: Table created by the EAG, using information from Guttman-Yassky et al. (2020)[71] and clarification response A5.
AD, atopic dermatitis; CS, company submission; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; LD, loading dose; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids
[a] TCS use was permitted, but for as brief a period as possible
[b] Non-responders entered an 'escape arm' where they received lebrikizumab 250mg Q2W + TCS
[c] The EAG assume this is an error in the company response to clarification question A5 and that the company mean "Proportion of participants achieving IGA (0,1)".
[d] Selected other outcomes measured by the studies are listed here, other outcomes were also measured.

Appendix 3 Design and characteristics of ADvocate 1 and 2

Table 52, shows the design and characteristics of the ADvocate 1 and 2 monotherapy trials.

Table 52 ADvocate 1 and 2 monotherapy studies' designs and characteristics

Study characteristics	Details
Study design and length	A 52-week, double-blind, placebo-controlled, phase III RCT, with a 16-week induction treatment phase and 36-week maintenance treatment phase. Induction period responders [a] were re-randomised to lebrikizumab or placebo maintenance treatment. Induction non-responders or those who used rescue therapy during the induction phase entered an escape arm in which they received open-label lebrikizumab. Re-randomised participants who did not maintain EASI 50 at weeks 32, 40 or 48 entered the escape arm and received open-label lebrikizumab. For participants in the escape arm, if they did not achieve EASI 50 after 8 weeks, they were discontinued from the study. A more detailed overview of the study design is available in CS Figure 3.
Study locations	ADvocate 1: Australia, Canada, Estonia, France, Latvia, Lithuania, Poland, Republic of Korea, Spain, US. ADvocate 2: Bulgaria, Canada, Germany, Mexico, Singapore, Taiwan, Ukraine. No UK centres or participants (clarification response A10).
Population	Adults and adolescents (aged 12 to <18 years) with moderate-to-severe AD.
Intervention [b c]	Induction: • **Lebrikizumab 250 mg Q2W (participants received a loading dose of lebrikizumab 500mg at weeks 0 and 2)** Maintenance: • Lebrikizumab 250 mg Q2W • **Lebrikizumab 250 mg Q4W**
Comparator [b c]	Induction: • Placebo Q2W Maintenance: • Placebo (described by the company as *"lebrikizumab withdrawal"* in CS Table 5 [d])
Sample size	ADvocate 1: N randomised: 424 (lebrikizumab: n = 283; placebo: n = 141) ADvocate 2: N randomised: 427 (lebrikizumab: n = 281; placebo: n = 146)
Key eligibility criteria	• Adult or adolescent (aged 12 to <18 years and weighing ≥40 kg) • Diagnosis of chronic AD (AAD Consensus Criteria) for ≥1 year before screening • Candidate for systemic therapy • No previous treatment with dupilumab or tralokinumab [e]
Primary outcome	Co-primary endpoints:

Study characteristics	Details
	• Percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI) at week 16 • Percentage of participants achieving an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to week 16
Other outcomes	• Measures of symptom control • Adverse effects of treatment • Health-related quality of life

Source: Partly reproduced from CS Tables 5 and 6, CS section B.2.3.1 and clarification response A10.
Bold text shows the lebrikizumab doses that match the posology specified in the lebrikizumab SmPC.
AAD, American Academy of Dermatology; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomised controlled trial; UK, United Kingdom; US, United States
[a] Response to treatment was defined as achieving an IGA score of 0 or 1 with a reduction of ≥2 points from baseline or a 75% reduction in EASI score (EASI 75) without needing to use rescue medication.
[b] Use of topical or systemic treatments for atopic dermatitis was prohibited in the induction phase. Intermittent topical rescue medications were permitted during the maintenance phase.
[c] All study drugs were administered as subcutaneous injections.
[d] In response to clarification question A19, the company elaborated that this arm was labelled *"lebrikizumab withdrawal"*, as the CS focuses on the 'maintenance primary population' from this study; that is, participants who responded to lebrikizumab during induction treatment and who were then re-randomised to one of the maintenance lebrikizumab arms or placebo. The company provided EASI 75 results for the placebo week 16 responders in response to the EAG's request for these data (clarification question and response A20).
[e] Participants were not eligible for trial if had had previous treatment with dupilumab or tralokinumab (CS Table 6), as these drugs have a similar mechanism of action to lebrikizumab and these participants were excluded to avoid prior exposure to these drugs affecting the results of the studies (clarification response A12).

Appendix 4 Risk of bias assessments

The following tables provide the company's and the EAG's risk of bias assessments of the ADvocate 1 and 2, ADhere and ADvantage trials.

Table 53 Company and EAG critical appraisal of the ADvocate 1 & 2[21,28,29] RCTs

Question	Company response	EAG response and interpretation of risk of bias
Was randomisation carried out appropriately?	**Yes.** Randomization was performed with the use of an electronic data-capture system, with stratification according to geographic region (United States vs. European Union vs. the rest of the world), age group (adolescent vs. adult), and disease severity (IGA score of 3 vs. 4)	**Yes**. The electronic data-capture system should have ensured unbiased randomisation to the trial arms and unbiased re-randomisation at week 16. **Low risk of bias.**
Was the concealment of treatment allocation adequate?	**Yes.** Both lebrikizumab and placebo were administered via subcutaneous injection. The induction period was double-blind. To maintain blinding into the maintenance period, all patients received the same number of injections at all visits during the maintenance period using an appropriate combination of active and placebo injections	**Yes**. The electronic data-capture system used should have concealed the forthcoming allocations from clinicians involved in enrolling patients into the trial. **Low risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes.** As described in Section B.2.3, disease characteristics were well balanced between treatment groups at baseline in both studies	**Unclear**. The only differences the EAG observed was for previous use of systemic treatment in ADvocate 1 (placebo arm 60.3%, lebrikizumab arm 50.9%), and that there were proportionally more Asian participants in the placebo than lebrikizumab 250mg Q2W arm (22.0% versus 13.8%) in this trial. The impact these differences could have on the results of the trial is unclear. **Unclear risk of bias.**
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group	**Yes**. The first 16-week period of the trial was double-blind and blinding was maintained after re-

Question	Company response	EAG response and interpretation of risk of bias
	assignments, and blinding integrity was maintained for the duration of both trials	randomisation of responders. The only exception appears to be for patients who were assigned to the Escape Arm either at week 16 or weeks 24, 32, 40, or 48 where they received open label treatment. Patients from the escape arm are not included in the key efficacy analyses. **Low risk of bias.**
Were there any unexpected imbalances in drop-outs between groups?	**No.** In both trials, the number of discontinuations was higher in the placebo groups than in the lebrikizumab groups (14.9% vs. 7.1% in ADvocate 1 and 11.0% vs. 7.8% in ADvocate 2). Reasons for discontinuation in ADvocate 1 included protocol deviation (in 3.5% of the patients in the placebo group and in 2.1% of those in the lebrikizumab group), loss to follow-up (in 0.7% and 1.4%, respectively), and withdrawal by the patient (in 4.3% and 1.1%). Reasons for discontinuation in ADvocate 2 included adverse events (in 2.7% of the patients in the placebo group and in 2.1% of those in the lebrikizumab group), protocol deviation (in none in the placebo group and in 2.1% in the lebrikizumab group), withdrawal by the patient (in 3.4% and 1.4%, respectively), and reasons associated with the coronavirus disease 2019 pandemic (in 0.7% and 1.4%).	**No**. The proportion of discontinuations was higher in the placebo groups than in the lebrikizumab groups. Primarily the difference was due to a greater proportion of withdrawals in the placebo group for the reasons of 'Lack of efficacy' and 'Patient withdrawal' (CS Appendix D.1.2, Figures 50 and 51). It is not unexpected that more patients in the placebo group should have withdrawn for these reasons than in the lebrikizumab group. **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No.** All measured outcomes are reported in the publication and/or the clinical study report.	**No**. CSR reports the outcomes specified. **Low risk of bias.**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate	**Yes.** In ADvocate 1, the efficacy analyses were based on the intention-to-	**Yes**. Intention-to-treat analyses conducted for ADvocate 1 and a modified

Question	Company response	EAG response and interpretation of risk of bias
and were appropriate methods used to account for missing data?	treat population (which included all patients who had undergone randomisation). In ADvocate 2, the efficacy analyses were performed on a modified intention-to-treat population, excluding 18 patients (from a single study site) whose eligibility could not be confirmed). Similarly, safety analyses were carried out on the safety population (all randomised patients who received at least one dose of study medication) in ADvocate 1 and a modified safety population (which excluded the patients from the trial site mentioned above) in ADvocate 2	intention-to-treat conducted for ADvocate 2 (due to the need to exclude 18 patients from one study site who may not have been eligible to take part in the trial). Censoring of patients who received topical rescue therapy may not reflect clinical practice (see section 3.2.4). **Unclear risk of bias.**

Source: Partly reproduced from CS Appendix D1.3, Table 100 supplemented with information from Silverberg et al. 2023[21] and the CSRs for the ADvocate 1 and 2 trials[28,29]
CSR, clinical study report

Table 54 Company and EAG critical appraisal of the ADhere RCT

Question	Company response	EAG response and interpretation of risk of bias
Was randomisation carried out appropriately?	**Yes.** Randomisation was performed with the use of an electronic data-capture system. Randomisation was stratified by geographic region (United States vs. European Union vs. the rest of the world), age group (adolescent vs. adult), and disease severity (IGA score of 3 vs. 4)	**Yes**. The electronic data-capture system should have ensured unbiased randomisation to the trial arms. **Low risk of bias.**
Was the concealment of treatment allocation adequate?	**Yes.** Both lebrikizumab and placebo were administered via subcutaneous injection. The study was double-blind. A medication numbering system was used in labelling the blinded study medication; detail of this were not	**Yes**. The electronic data-capture system used should have concealed the forthcoming allocations from clinicians involved in enrolling patients into the trial. **Low risk of bias.**

Question	Company response	EAG response and interpretation of risk of bias
	available to individuals involved in study conduct	
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes.** As described in Section B.2.3, disease characteristics were well balanced between treatment groups at baseline in both studies	**Yes**. As shown in CS Table 10 the trial arms were balanced in terms of potential prognostic factors (age, proportion female, White race, IGA, % BSA affected). **Low risk of bias.**
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments, and blinding integrity was maintained for the duration of the trial	**Yes**. This was a double-blinded trial. **Low risk of bias.**
Were there any unexpected imbalances in drop-outs between groups?	**No.** The proportion of discontinuations was higher in the placebo + TCS group (12.1%) than in the lebrikizumab + TCS group (7.6%). Reasons for treatment discontinuation included AEs (3/145 [2.1%] in the lebrikizumab + TCS group vs 0/66 in the placebo + TCS group), lack of efficacy (3 [2.1%] vs 1 [1.5%]), withdrawal by patient (3 [2.1%] vs 4 [6.1%]), protocol deviation (2 [1.4%] vs 2 [3.0%]), and physician decision (0 vs 1 [1.5%]).	**No.** The proportion of discontinuation was higher in the placebo +TCS group primarily because of a greater proportion of withdrawals in the placebo group due to 'Withdrawal by subject' (placebo arm 6.1% vs lebrikizumab +TCS arm 2.1%) which would not be unexpected. **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No.** All outcomes measured are reported in the publication and/or the clinical study report	**No**. CSR reports the outcomes specified. **Low risk of bias.**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes.** The efficacy analyses were performed on a modified intention-to-treat population, excluding 17 patients (from a single study site) whose eligibility could not be confirmed. Safety analyses for the treatment period were conducted on all randomized patients who received 1 or more dose of the study drug,	**Yes**. A modified intention-to-treat conducted for ADhere (due to the need to exclude 17 patients from one study site who may not have been eligible to take part in the trial). Censoring of patients who received topical rescue therapy may not reflect clinical practice (see section 3.2.4). **Unclear risk of bias.**

Question	Company response	EAG response and interpretation of risk of bias
	except for the 17 excluded patients mentioned above	

Source: Partly reproduced from CS Appendix D1.3, Table 101 supplemented with information from the ADhere CSR,[30] protocol[72] and statistical analysis plan.[39]
AEs, adverse events; BSA, body surface area; CS, company submission; CSR, clinical study report; IGA, Investigators global assessment; TCS, topical corticosteroid.

Table 55 Company and EAG critical appraisal of the ADvantage RCT

Question	Company response	EAG response and interpretation of risk of bias
Was randomisation carried out appropriately?	**Yes.** Randomisation was stratified by prior use of dupilumab (yes, no), age group (adolescent vs. adult), and disease severity (IGA score of 3 vs. 4)	**Unclear**. The method or system used to carry out randomisation is not described in the CS or CSR (the latter refers the reader to the Study Protocol which was not provided to the EAG). **Unclear risk of bias.**
Was the concealment of treatment allocation adequate?	**Yes.** Both lebrikizumab and placebo were administered via subcutaneous injection. The 16-week induction period was double-blind. To maintain blinding at Weeks 16 and 18, all patients received two injections at Weeks 16 and 18 (either two injections of lebrikizumab or one injection of lebrikizumab and one injection of placebo)	**Unclear**. The method or system used to ensure forthcoming allocations were concealed from those enrolling patients into the trial is not described in the CS or CSR. **Unclear risk of bias.**
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes.** As described in Section B.2.3, disease characteristics were well balanced between treatment groups at baseline in both studies	**Yes**. Prognostic factors appeared well balanced at baseline (CS Table 11). **Low risk of bias.**
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments	**Yes**. The first 16-week phase of the RCT was double-blind. **Low risk of bias** (first 16 weeks) **No.** The maintenance phase (after induction if needed) was open label from week 20. **High risk of bias** (from week 20)

Question	Company response	EAG response and interpretation of risk of bias
Were there any unexpected imbalances in drop-outs between groups?	**No.** [redacted]	**No**. It is not unexpected that more patients in the placebo group should have withdrawn than in the lebrikizumab group. **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No.** All outcomes are reported either in the publication or the clinical study report.	**No**. CSR reports the outcomes specified. **Low risk of bias.**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes.** The efficacy analyses were based on the full analysis set, which included all randomised patients. Safety analyses were conducted on all randomized patients who received 1 or more dose of the study drug	**Yes**. All randomised patients were included in the analysis. Censoring of patients who received topical rescue therapy may not reflect clinical practice (see section 3.2.4). **Unclear risk of bias.**

Source: Partly reproduced from CS Appendix D1.3 Table 102 supplemented with information from the CSR for ADvantage.[24]
CS, company submission; CSR, clinical study report; EAG, External Assessment Group; IGA, Investigators global assessment; RCT, randomised controlled trial; TCS, topical corticosteroid.

Table 56 Company and EAG critical appraisal of the ADjoin extension study

Question	Company response	EAG response and interpretation of risk of bias
Was randomisation carried out appropriately?	**Yes**. Participants enrolling from the ADvantage studies remained on the treatment they were randomised to in the maintenance period of their parent study. Participants enrolling from ADhere were randomised 2:1 to lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W	**Unclear.** The method or system used to carry out randomisation of the ADhere participants who entered this study is not described in the CS or CSR. Not applicable for the ADvocate 1 and 2 participants who had already been re-randomised in the parent studies remained in their randomised groups when entering ADjoin. **Unclear risk of bias** for the ADhere participants entering this study.
Was the concealment of treatment allocation adequate?	**Yes.** Placebo injections were administered to maintain blinding and ensure that all participant received the same number of injections	**Unclear.** The method or system used to ensure concealment of randomised allocations for the ADhere participants who entered this study is not described in the CS or CSR. Not applicable for the ADvocate 1 and 2 participants

Question	Company response	EAG response and interpretation of risk of bias
		who had already been re-randomised in the parent studies. **Unclear risk of bias** for the ADhere participants entering this study.
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes.** As described in Section B.2.3.3, disease characteristics were well balanced between treatment groups at baseline in both studies	**No**. For the prognostic factor of [redacted] the two re-randomised arms of ADhere that entered ADjoin differed ([redacted]). **Unclear risk of bias** for the ADhere participants entering this study.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments	**Yes**. CS section B.2.3.1 states all participants received the same number of injections regardless of their assigned regimen. **Low risk of bias.**
Were there any unexpected imbalances in drop-outs between groups?	**No.** At data cut-off of 6th July 2022, [redacted] participants ([redacted]%) in the lebrikizumab Q4W group and [redacted] ([redacted]%) in the lebrikizumab Q2W group had discontinued treatment	**No**. CS Appendix D1.2 Figure 54 shows participant flow. There is not an unexpected imbalance in drop-outs between groups. **Low risk of bias.**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No.** All the outcomes are reported in the interim CSR	**No**. Expected outcomes are all reported. **Low risk of bias.**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes.** The efficacy analyses were based on a modified intention to treat population: all participant assigned to treatment, regardless of whether they received the treatment, excluding 20 patients (from a single study site) Safety analyses were conducted on a modified safety population: all participant who received at least one dose of lebrikizumab, excluding 20 patients (from a single study site Note that the analyses reported in this submission only include participant who	**Yes**. Results presented for the modified intention-to-treat population and the modified safety population (for week 16 responders who entered ADjoin from the parent studies). Observed analyses using all data collected regardless of rescue medication use were conducted. **Low risk of bias.**

Question	Company response	EAG response and interpretation of risk of bias
	were lebrikizumab responders at Week 16 in their parent study.	

Source: Partly reproduced from CS Appendix D1.3, Table 103 supplemented with information from CS Table 12 and the ADjoin CSR.[31]
CS, company submission; CSR, clinical study report.

Table 57 EAG assessment of ADjoin long-term extension study

Criteria from Bowers et al. 2012[34]	EAG response
Explicitly stated aims, to minimize the possibility of Type I error?	**Yes**. The CS states the aim is to assess the long-term safety and efficacy of lebrikizumab in adults and adolescents with moderate-to-severe atopic dermatitis.
A well-characterized sample representative of the target population in whom the medication will be used?	**Partly**. Those enrolled in ADjoin are drawn from five different parent studies [redacted]. The level of TCS use permitted differed slightly depending on the parent study (CS Table 8).
Outcome assessment is masked to treatment received where possible?	**Yes.** Blinding was maintained by the use of placebo injections (CS section B.2.3.1). [redacted]
A low rate of sample slippage in relation to the numbers randomized in the preceding RCT, but the length of follow-up should be considered in making this assessment?	**Unclear.** Because of the study design (enrolling patients from multiple different sources) and because patients could be entered from an escape arm or as responders it has not been possible to determine sample slippage in relation to numbers randomised in the preceding RCTs.
Objectives, design, conduct, analysis and results are adequately described?	**Partly**. The CS focuses specifically on the ADjoin participants who entered from ADvocate 1, ADvocate 2 and ADhere parent studies as these are most relevant to the appraisal.
Limitations of the specific study design used and its execution should be discussed	ADjoin is an ongoing study with an unusual design as participants have been enrolled from multiple parent studies. Some participants have been randomised into the study whereas other participants have entered from the parent study and remained in their parent study treatment arm.

Source: EAG table
CS, company submission; CSR, clinical study report; RCT, randomised controlled trial; TCS, topical corticosteroid.

Appendix 5 MTA TA814 risk of bias assessments

In Table 58, we have summarised the risk of bias assessments made in the MTA TA814 report[15] for the corresponding studies included in the lebrikizumab appraisal combination therapy NMA.

Table 58 Summary of risk of bias assessments in the TA814 MTA of upadacitinib, abrocitinib and tralokinumab for dermatitis for the studies included in the lebrikizumab appraisal CS NMA

RCT	Overall risk of bias	Risk of bias domains with 'unclear risk of bias' judgement	Risk of bias domains with 'high risk of bias' judgement
AD Up	Low	Selective reporting	None
ADhere-J	Not included in the TA814 SLR		
ADhere	Not included in the TA814 SLR		
ADopt-VA	Not included in the TA814 SLR		
ADvantage	Not included in the TA814 SLR		
BREEZE-AD4	Low	None	None
BREEZE-AD7	Low	None	None
ECZTRA 3	Low	None	None
ECZTRA 7	Low	None	None
ECZTRA 8	Not included in the TA814 SLR		
I4V-MC-JAHG	Some concerns	None	Incomplete outcome data
JADE COMPARE	Low	Sequence generation	None
JADE TEEN	Some concerns	Sequence generation, allocation concealment and selective reporting	None
LIBERTY AD CAFÉ	Low	None	None
LIBERTY AD CHRONOS	Low	None	None
Rising Up	Some concerns	Sequence generation,	None

RCT	Overall risk of bias	Risk of bias domains with 'unclear risk of bias' judgement	Risk of bias domains with 'high risk of bias' judgement
		allocation concealment, incomplete outcome data and selective reporting	

Source: Partly reproduced from Table 5 in the TA814 MTA report.[15]
SLR, systematic literature review