NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Almirall:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Eczema Outreach Support
   b. National Eczema Society
   c. British Association of Dermatologists

4. **Expert personal perspectives** from:
   a. Prof. Richard Weller – Clinical expert, nominated by Almirall
   b. Mr. Stephen Pugh – Patient expert, nominated by National Eczema Society

5. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre

6. **External Assessment Group response to factual accuracy check of EAR**

7. **Company additional evidence on key issue**

8. **EAG response to company additional evidence on key issue**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Document B

Company evidence submission

Revised May 2024

File name	Version	Contains confidential information	Date
ID4025_Lebrikizumab_Almirall_ Doc B (Nov2023)_REVISED_16.5.24 [CON]	**FINAL**	**Yes**	**16.5.24**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

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In this template any information that should be provided in an appendix is listed in a box.

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Abbreviations

Acronym	Definition
AAD	American Academy of Dermatology
AD	Atopic dermatitis
AE	Adverse event
AST	Aspartate transferase
AZA	Azathioprine
BMI	Body mass index
BSA	Body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CsA	Ciclosporin A
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
FLG	Filaggrin
HRQoL	Health-related quality of life
IGA	Investigators Global Assessment
IL-13	Interleukin-13
ILC2	Type 2 innate lymphoid cells
ITT	Intention to treat
JAK	Janus kinase
LEB or Leb or Lebri	Lebrikizumab
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
MCMC-MI	Markov Chain Monte Carlo multiple imputation
mITT	Modified intention to treat
MMF	Mycophenolate mofetil
MMRM	Mixed models for repeated measures
MTA	Multiple technology appraisal
MTX	Methotrexate
NRI	Non-responder imputation
PBO	Placebo
POEM	Patient Oriented Eczema Measure

PROMIS	Patient-Reported Outcomes Measurement Information System
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SAE	Serious adverse event
SF-36	Short Form 36
SF-6D	Short Form 6 dimensions
SmPC	Summary of product characteristics
STAT	Signal Transducer and Activator of Transcription
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
TEAE	Treatment emergent adverse event

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication: the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy.

Table 1 describes the decision problem.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and over with moderate to severe atopic dermatitis who are candidates for systemic therapy	Same as scope	-
Intervention	Lebrikizumab (brand name: Ebglyss)	Same as scope	-
Comparator(s)	People for whom systemic therapy is suitable and have not previously received a systemic therapy: • 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	Same as scope (and in line with the appraisals for other currently-available second-line systemics) 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	Consideration of this sub-population reflects the anticipated positioning of lebrikizumab in the UK treatment pathway
Outcomes	The outcome measures to be considered include: • measures of disease severity	The outcome measures in the clinical effectiveness section include: • measures of disease severity	Clinical experts have stated that disease free period, maintenance of remission, time to relapse and

	• 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	• measures of symptom control • rescue therapy use • TCS-free days • treatment discontinuation • adverse effects of treatment, • health-related quality of life	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 MTA
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Same as scope	-
Subgroups to be considered	Not specified	-	-
Special considerations	Not specified	The use of lebrikizumab is not expected to raise any equality	-

including issues related to equity or equality		issues. However, it is important to note that assessment of AD in 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.	

B.1.2 Description of the technology being evaluated

Table 2 gives an overview of lebrikizumab. Please refer to Appendix C for the draft Summary of Product Characteristics (SmPC). At the time of submission, the UK Public Assessment Report was not available.

Table 2: Technology being evaluated

UK approved name and brand name	Lebrikizumab [brand name: Ebglyss®]
Mechanism of action	IL-13 is the key cytokine in the skin of people with atopic dermatitis. Its levels are significantly elevated and it drives skin barrier dysfunction, inflammation, itch and skin thickening. Lebrikizumab is a monoclonal antibody that selectively binds to IL-13 with high affinity and a slow off-rate, specifically preventing the formation of the IL-13Rα1/IL-4Rα heterodimer complex and subsequent signalling, and thereby inhibiting the biological effects of IL-13. Lebrikizumab does not prevent binding to the IL-13 receptor alpha 2 (IL-13R α2 or 'decoy' receptor), which allows internalisation of IL-13 into the cell.
Marketing authorisation/CE mark status	Lebrikizumab does not currently have a UK marketing authorisation. EMA CHMP positive opinion was received on 14th September 2023 (4) and EMA marketing authorisation is expected in November 2023. In the UK, a marketing authorisation application was made to MHRA in [redacted] (reliant on EMA CHMP positive opinion), and MHRA approval is expected in [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication for lebrikizumab is ***"for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy"***. Contraindications included in the draft SmPC: • Hypersensitivity to lebrikizumab or the following excipients: L-histidine; acetic acid, glacial (E260); sucrose; polysorbate 20 (E432); water for injection
Method of administration and dosage	**Administration** Lebrikizumab is administered by subcutaneous injection. Patients may self-inject, or the patient's caregiver may administer the injection (if their healthcare professional deems this appropriate).

	Injections should be given into the thigh or abdomen (except for 5 cm around the navel). If the caregiver administers the injection, it can also be given in the upper arm. It is recommended to rotate the injection site with each injection. **Dose** The recommended dose for adults and adolescents weighing ≥40 kg is 500 mg (given as two 250 mg injections) at Week 0 and Week 2, followed by 250 mg every other week (Q2W) up to Week 16. Consideration should be given to stopping treatment in patients who do not respond after 16 weeks. Some patients with initial partial response may further improve with continued treatment every other week up to Week 24. Once clinical response is achieved, the recommended maintenance dose is 250 mg every four weeks (Q4W). Lebrikizumab can be administered as monotherapy or in combination with TCS or TCI. **Special populations** No dose adjustment is required for elderly patients (aged ≥65 years), for patients with renal or hepatic impairment, or for body weight. The safety and efficacy of lebrikizumab in adolescents weighing less than 40 kg has not been established. A study is currently underway in children aged 6 months to <12 years.
Additional tests or investigations	No additional tests or investigations are required for patients treated with lebrikizumab
List price and average cost of a course of treatment	Lebrikizumab list price: £2,271.26 (pack of 2) (ex VAT) No limit on duration of treatment. Approximately 71 units over 5 years of treatment (for patients who achieve response at 16 weeks)
Patient access scheme (if applicable)	A simple discount PAS has been submitted to NHS England to provide lebrikizumab at a [redacted]% discount resulting in a net price of [redacted] (pack of 2 prefilled pens or prefilled syringes).

Key: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; IL-13, interleukin-13; MHRA, Medicines and Healthcare Products Regulatory Agency; SmPC, Summary of Product Characteristics; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

B.1.3 Health condition and position of the technology in the treatment pathway

Key points

- AD is a chronic, intensely itchy, inflammatory skin condition that affects people of all ages
- The clinical presentation of AD is heterogeneous and varies with age (5-7)
- The pathophysiology of AD is multifactorial, resulting from a complex interaction between genetic risk factors, skin barrier dysfunction, immune dysregulation and an altered skin microbiome
- IL-13 is the key cytokine in the skin of patients with AD, and drives skin barrier dysfunction, inflammation, itch and skin thickening. It correlates with disease severity and chronicity, and is present in both lesional and non-lesional skin (8-13)
- Itch is one of the main symptoms of AD and the most bothersome for patients, impacting many aspects of their lives (14-17)
- The impact of AD goes beyond the physical symptoms; it can also affect patients' mental health, causing anxiety and depression (17, 18)
- Increasing disease severity is associated with worse HRQoL in AD (18-22)
- Systemic therapy is necessary when AD is no longer controlled sufficiently with appropriate topical treatments and phototherapy. However:
    - Dupilumab and tralokinumab are associated with variable response (1, 23, 24)
    - JAK inhibitors require safety monitoring and their use is limited to patients at low risk of developing serious side effects (such as cardiovascular conditions, blood clots, cancer and serious infections) (25, 26)

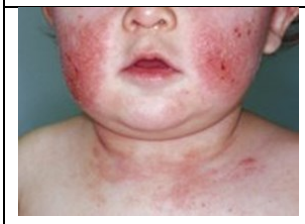
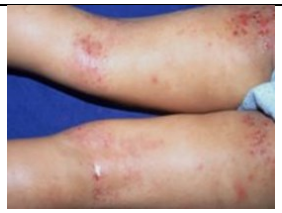
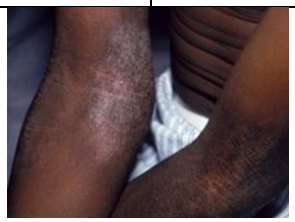
- Evidence suggests that many patients with moderate-to-severe AD may not be receiving the level of treatment they need (20, 27)
- Up to three-quarters of patients with moderate-to-severe AD say their treatment expectations are only partially met or not met at all (28)
- There is a need for an alternative treatment that offers both short- and long-term disease control without safety trade-offs
- The anticipated position of lebrikizumab (a selective IL-13 inhibitor) in the treatment pathway is as a second line systemic treatment for moderate-to-severe AD (i.e. after the condition has not responded to at least 1 first line systemic treatment, or unsuitability for first line systemic treatment).

B.1.3.1. Overview of atopic dermatitis

Atopic dermatitis (AD; also known as atopic eczema) is a chronic inflammatory skin condition characterised by dry, itchy, flaky skin. It is an episodic condition in which patients experience flares (transient exacerbations of the inflammatory skin lesions) followed by periods of relative improvement. Flares can occur several times per month and may be triggered by a variety of factors, including irritants, allergens and hormones (29).

AD can develop at any age, but presents most commonly in infancy: approximately 85% presents by the age of 5 years and 70% remits by adolescence (30). Only 2-8% of patients present in adulthood (30). AD can present in three different phases: acute, sub-acute and chronic (31). Acute AD is associated with weeping, crusting skin lesions, whereas patients with sub-acute AD have dry, scaly, red lesions. Lichenification (skin thickening) caused by repeated scratching is a feature of chronic AD. Skin lesions typically show an age-related distribution (Table 3).

Table 3: Age-related presentation of AD

Infancy **3 months to 2 years**	**Childhood** **2 to 12 years**	**Adolescence/adults** **>12 up to 60 years**	**Elderly** **>60 years**
			
Typically localised to face, scalp and exterior aspects of the arms and legs	Lesions tend to shift location and often involve flexures of the elbows, knees, wrists and ankles	Lesions are frequently localised to face, neck and flexural sites	Lesions are extensive with a strong itch component
Lesions are characterised by redness, raised bumps, blisters, oozing, formation of crusts and areas of damage caused by scratching	Generally, lesions becomes drier with skin thickening, raised bumps and areas of damage caused by scratching	In adults, AD can also affect the hands	Sometimes flexural areas are spared

Source: Bieber et al (2017) (5); Thomsen (2014) (6); Lyons et al (2015) (7)

B.1.3.2. Epidemiology

It is important to note that methodological and reporting differences between studies has led to wide variations in the estimation of AD prevalence; this is reflected in the data reported in this section. In addition, epidemiological data are more readily available for children than for adults.

UK

An analysis of data from the UK Clinical Practice Research datalink (CPRD) database showed that between 2015 and 2019, 2.4% of adults in the UK had active AD (32). In this cohort of patients with active AD, 7.5% to 8.3% had moderate to severe AD during this 5-year period. Moderate-to-severe AD was defined as either referral to a specialist (dermatologist or immunopathologist) or a prescription for TCIs, phototherapy or systemic treatments (including methotrexate, azathioprine, mycophenolate mofetil/mycophenoate sodium, ciclosporin and dupilumab, but excluding oral glucocorticoids). The proportion of patients with moderate to severe

AD in this analysis is in line with the figures used in the NICE TA814 Resource Impact Report (33).

In an international, cross-sectional study, Barbarot et al reported a point prevalence of AD for adults in the UK of 2.5% (27). In this study, between a half and two-thirds of patients rated their AD as moderate or severe (depending on the assessment scale used).

In a cohort study of over 9 million individuals who were registered in the Health Improvement Network (a database of electronic records from general practices across the UK, 1994 - 2013), physician-diagnosed AD was 18.3% in children and adolescents (0 - 17 years), 7.7% in adults aged 18 – 74 years and 11.6% in those aged 75 to 99 years of age (34). Abuabara et al (2019) also analysed data from the Health Improvement Network and found the lifetime cumulative prevalence of AD to be 9.9% (35).

England

de Lusignan et al (2021) used data from more than 3.85 million people in the Royal College of General Practitioners Research and Surveillance Centre's Primary Care Research Database to estimate the incidence and prevalence of AD in England (36). Table 4 shows the data for adolescents and adults. Having decreased throughout childhood, the incidence of AD plateaued during adolescence up to age 18. In adults, incidence was relatively stable from ages 18 to 49, after which there was a steady increase. AD was more common in females in all adolescent and adult age groups, except for adults aged over 70.

Table 4: Incidence and prevalence of AD in adolescents and adults in England

Age, years	Incidence rate, per 100-person years (95% CI)	Prevalence, % (95% CI)*
12	0.57 (0.54, 0.61)	7.0 (6.7, 7.3)
13	0.48 (0.45, 0.51)	6.4 (6.2, 6.7)
14	0.49 (0.46, 0.52)	6.4 (6.2, 6.7)
15	0.50 (0.48, 0.53)	6.2 (5.9, 6.5)

Age, years	Incidence rate, per 100-person years (95% CI)	Prevalence, % (95% CI)*
16	0.48 (0.45, 0.51)	6.0 (5.7, 6.3)
17	0.50 (0.47, 0.53)	6.2 (5.9, 6.4)
18-29	0.36 (0.36, 0.37)	3.9 (3.8, 4.0)
30-39	0.36 (0.36, 0.37)	2.8 (2.8, 2.9)
40-49	0.35 (0.34, 0.35)	3.0 (2.9, 3.0)
50-59	0.40 (0.39, 0.41)	3.5 (3.4, 3.5)
60-69	0.55 (0.54, 0.56)	4.9 (4.8, 5.0)
70-79	0.69 (0.68, 0.70)	6.8 (6.7, 6.9)
80+	0.79 (0.78, 0.81)	9.9 (9.7, 10.0)

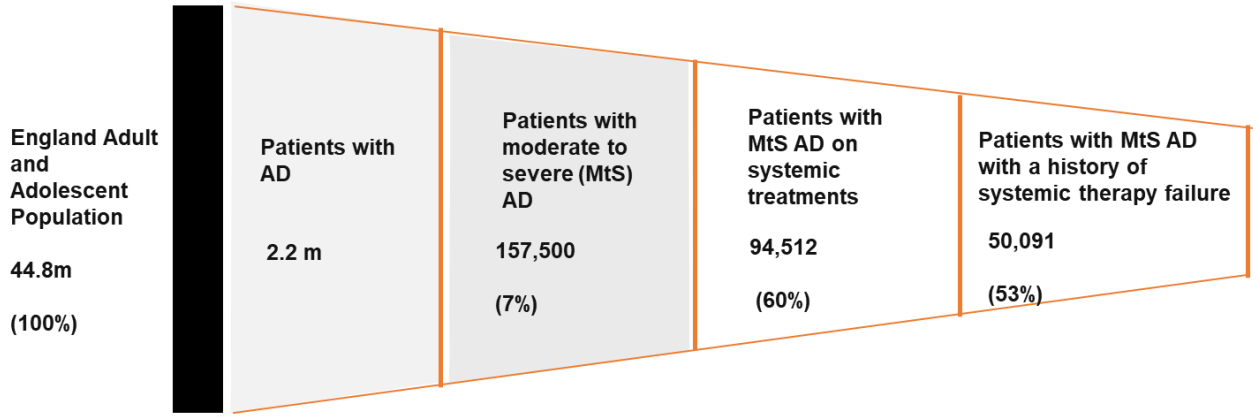
*Derived using data from 2018
Key: CI, confidence interval
Source: de Lusignan et al (2021) (supplementary information) (37)

Both incidence and prevalence of AD were highest in North-West England. Urban settings and a lower socioeconomic status was associated with a greater incidence of AD.

AD was more common in people of Asian, black and mixed ethnicity than in those from white ethnic groups. This is consistent with data from the US (38) and may be due to genetic, skin barrier, immune and environmental differences between people of different ethnicities.

In 2022, the National Institute for Health and Care Excellence (NICE) carried out a multiple technology appraisal (MTA) on abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis (TA814) (3). The resource impact report for TA814 included a prediction of the number of adults and adolescents who will have moderate to severe AD in England in 2026/7 (Figure 1) (33).

Figure 1 Predicted number of adults and adolescents in England with moderate-to-severe AD in 2026/27



Key: AD, atopic dermatitis; MtS, moderate to severe
Source: TA814 resource impact report (33)

B.1.3.3. Pathophysiology

The pathophysiology of AD is multifactorial and involves a complex interplay between skin barrier dysfunction, immune dysregulation and an altered skin microbiome.

In the skin of people with AD, synthesis of structural proteins is reduced and the lipid composition is significantly altered, causing disruption to the skin barrier. This leads to increased water loss (causing dehydration), and makes it easier for irritants, allergens and pathogens to penetrate and stimulate an immune response. The skin barrier can also be damaged by scratching in an attempt to relieve the persistent itch that is a dominant feature of AD. Subsequent penetration of allergens and irritants causes further inflammation and irritation, resulting in more itch and further scratching. This is known as the itch-scratch cycle.

Genetic factors, most notably mutations in the *FLG* gene that codes for filaggrin (a protein expressed by skin cells that is involved in formation of the outermost layer of the skin), have been implicated in skin barrier dysfunction. The risk of AD is increased 3- to 5-fold in individuals with loss-of-function *FLG* mutations (39) and patients with these mutations typically suffer from severe and persistent forms of the disease (40). Unique *FLG* mutations have been identified in East Asian and black AD populations that are not present in white Europeans with AD (41, 42); this may be one reason for the increased risk of AD in people of Asian and black ethnicity.

However, not everyone with AD has *FLG* mutations and not everyone with *FLG* mutations will develop AD (43), suggesting the involvement of other factors in skin barrier dysfunction.

Patients with AD have an altered skin microbiome, with increased levels of *Staphylococcus aureus* and decreased bacterial diversity. *S. aureus* has been shown to cause skin barrier disruption (by inducing skin cell death) and direct type-2 immune activation (44).

Skin inflammation occurs as a result of an abnormal type-2 immune response, characterised by inappropriate activation of type 2 helper T (T_H2) cells and type 2 innate lymphoid cells that results in increased expression of serum IgE and the inflammatory cytokines IL-4, IL-5 and IL-13.

There is considerable evidence that IL-13 is the key cytokine in the skin of patients with AD (8). It has been implicated in inflammation, skin barrier dysfunction, skin thickening and itch (9, 10). Levels of IL-13 are elevated in both lesional and non-lesional skin of people with AD (compared with healthy controls) and correlate with AD severity and chronicity (11-13). IL-13 exerts its effects by binding to IL-13 receptor α1 (Il-13Rα1). This binding favours recruitment of IL-4Rα, resulting in Janus kinase (JAK) 1 activation and phosphorylation of STAT6, a transcription factor that promotes T_H2 differentiation and immunoglobulin class switching to IgE (45).

At present, it is not clear whether skin barrier dysfunction causes the abnormal immune response (the ‘outside-in theory’) or is a result of it (the ‘inside-out’ theory) (46).

B.1.3.4. Burden of AD

Itch is the dominant symptom of AD and results in a significant burden for patients. A study by Falissard et al (2020) found that “itch” was the word most frequently used by patients to describe their condition (14). Patients with moderate-to-severe AD linked itch to “pain”, “uncomfortable”, “tired” and “skin”, suggesting that its impact can be more than just physical (14). Relief of itch is an important treatment goal for patients. In an international survey of adults with AD (n = 688) and parents of

children with AD (n = 423), 95.4% of respondents rated itch as being ‘quite important’ or ‘very important’ when deciding whether a treatment is working (15). Similarly, in a German study of 1,619 adults with AD, the most common treatment goals were to ‘be free of itch’ and ‘to get better skin quickly’ (16).

Patients with AD also report sleep disturbance. In a study that included 172 adults with AD, 87% said their condition negatively affected their ability to sleep (47). There is a link between sleep disturbance and itch. In a German cross-sectional study of 1,678 adult patients (≥ 18 years) with AD, 26.6% reported that they experience sleeplessness “often” or “every night” due to severe itching (17). The prospective, observational EUROSTAD study in 308 adults from 10 European countries (including the UK) who had moderate-to-severe AD and who started or switched systemic therapy found a significant correlation between sleep scores and itch scores ($r = 0.40$; $P < 0.0001$) (48). The prevalence of sleep difficulties increases with increasing disease severity (Luger 2022) and impaired sleep is significantly correlated with poor health-related quality of life (HRQoL) in AD (49).

As well as the physical burden of itch and fatigue caused by disturbed sleep, patients with AD report mental health issues, including anxiety and depression. In a cross-sectional study of 1,678 adult German patients, 73.1% said they believe emotional factors and/or stress to be a reason for itching or worsening of their symptoms (17). Data from the 2017 National Health and Wellness Survey for France, Germany, Italy, Spain and the UK revealed that anxiety and depression were significantly more common in adults with AD than in those without ($P<0.0001$) and increased with increasing disease severity (18).

HRQoL decreases as AD severity increases in both adolescents (19) and adults (18, 20-22). Adults with AD have reported worse HRQoL than those with other chronic skin conditions (vitiligo, psoriasis and rosacea) (50). A systematic literature review found that the HRQoL burden of moderate-to-severe AD is similar to or greater than other chronic conditions, including vision disorders, hepatitis and some types of cancer (51).

Parents and carers of adolescents with AD report that their child's AD has an impact on family life, which increases with increasing disease severity (52). Burden on families was reported to be higher when one or both parents also has AD (19).

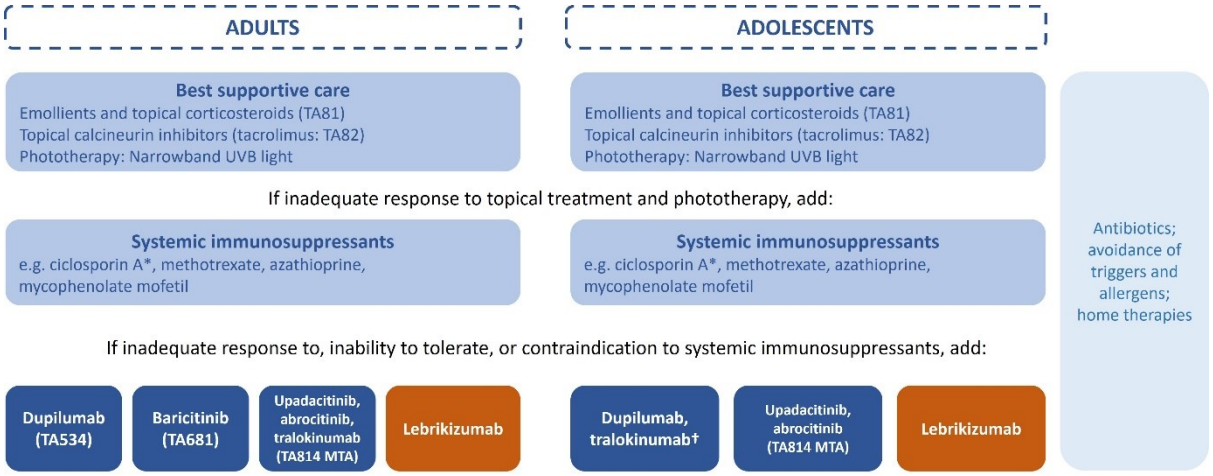
AD also places a considerable burden on society, as it can result in missed work/education days (absenteeism) and reduced work/educational productivity (presenteeism) (53). A study of 1,189 adults with AD across 9 European countries (including the UK) found that 57% had missed 1 to 5 days, 26% had missed 6 to 10 days, and 13% had missed 11 or more days at work because of their AD during the previous year (54). Another study that included 548 adults with AD from France, Germany and the UK found that the effect of AD on work impairment increased with increasing disease severity: those with mild AD reported a mean of 1.9 hours per week of potential work productivity lost, compared with 9.8 hours for those with moderate AD and 23.6 hours for those with severe AD (55). Carers are also affected; in a survey that included parents and caregivers of 1,070 adolescents with AD across Europe, the average number of hours spent on care in the last week ranged from 3.6 for carers of adolescents with mild AD to 13.5 for carers of those with severe AD (52). The average number of days missed from work in the last month was 1.1 for carers of adolescents with mild AD, 2.9 for carers of those with moderate AD and 4.5 for carers of those with severe AD (52).

The impact of AD on patients' work lives has financial consequences both for the economy and for patients themselves (56). A recent study based on 2017 data found that the cost to society of absenteeism and presenteeism in adult patients with moderate-to-severe AD is between £6,741 and £14,166 per patient per year (57). Patients have reported a financial burden because they have not always received paid sick leave, or have had to take unpaid leave for hospital appointments (56).

B.1.3.5. Clinical pathway of care

The aims of AD treatment are to reduce skin inflammation and itching, restore skin barrier function and improve quality of life. The current typical treatment pathway for moderate-to-severe AD and the anticipated position of lebrikizumab within it is shown in Figure 2.

Figure 2: The anticipated position of lebrikizumab in the clinical pathway of care for moderate-to-severe AD



*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 (58)
NICE TA82: Tacrolimus and pimecrolimus for atopic eczema (59)
NICE TA534: Dupilumab for treating moderate to severe atopic dermatitis (1)
NICE TA681: Baricitinib for treating moderate to severe atopic dermatitis (2)
NICE TA814: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (3)

Emollients are the foundation of treatment and are used to hydrate and repair the skin. If symptoms persist after correct use of emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are introduced. TCS are effective for short-term or intermittent long-term treatment. However, continuous long-term use of TCS is not recommended because of the risk of local and systemic side effects, including skin atrophy, dyspigmentation and hypertension. If TCS and TCI do not adequately control the disease, phototherapy can be used, although access to this is variable across the UK.

If AD is not sufficiently controlled with appropriate topical treatments and phototherapy, systemic therapy is introduced. First-line systemic therapy includes the immunosuppressants ciclosporin A (CsA), methotrexate (MTX), azathioprine (AZA) and mycophenolate mofetil (MMF). Of these, only CsA is licensed in the UK (for treatment of severe AD only); the others are used off-label.

The biologic dupilumab was recommended by NICE in 2018 for adults with moderate-to-severe AD who have failed treatment with at least one systemic immunosuppressive therapy, or who cannot tolerate or have a contraindication to

systemic immunosuppressants (TA534) (1). NICE has not appraised dupilumab for adolescent patients owing to the positive guidance for adults, and states that treatment will be commissioned for patients aged <18 years where specific commissioning conditions within a NICE Technology Appraisal or NHS England and Improvement policy are met (60). A second biologic, tralokinumab, was appraised as part of a multiple technology appraisal and was recommended in 2022 for adults with moderate-to-severe AD who have failed treatment with at least one systemic immunosuppressant, or are not suitable for systemic immunosuppressants (TA814) (3). Tralokinumab has not been appraised by NICE for use in adolescents.

In 2021, NICE recommended the Janus kinase (JAK) inhibitor, baricitinib, for adults with moderate-to-severe AD who have failed treatment with at least one systemic immunosuppressant, or are not suitable for systemic immunosuppressant therapy (TA681) (2). Baricitinib is not licensed for use in adolescents in the UK. Two other JAK inhibitors, abrocitinib and upadacitinib, were appraised as part of a multiple technology appraisal and were recommended in 2022 for adults and adolescents with moderate-to-severe AD who have failed treatment with at least one systemic immunosuppressant, or are not suitable for systemic immunosuppressant therapy (TA814) (3).

Limitations of current systemic therapies for moderate-to-severe AD

Systemic immunosuppressants are associated with safety concerns. Patients taking CsA must be frequently monitored for potential side effects, including hypertension, nephrotoxicity and infection. Treatment with CsA should be short-term (<1 year) (61, 62). MTX, AZA and MMF are associated with a range of side effects, including hepatotoxicity, malignancy and gastrointestinal intolerance.

Some patients receiving dupilumab have little or no improvement after 16 weeks of treatment and are considered primary non-responders. Others are either partial responders (i.e. have some improvement in symptoms but do not reach their treatment goal after 16 weeks) or secondary failures (i.e. achieve therapeutic endpoint with subsequent loss of efficacy) (23). In the UK economic model for dupilumab, it was assumed that 2% of the benefit would be lost in Year 2, 5% in

Year 3, 7% in Year 4, and 8% in Year 5 and beyond (1). In a UK multiple technology appraisal of biologics and JAK inhibitors in AD (TA814), it was assumed that 2-3% of patients on tralokinumab would lose treatment response up to Year 4, with 1% losing response each year from Year 5 (24).

In clinical practice, conjunctivitis has been reported by up to 65% and paradoxical head/neck dermatitis/facial erythema by up to 10% of patients receiving dupilumab (63, 64). Such adverse events are burdensome for patients as they may require additional physician visits and treatment. Head/neck dermatitis/facial erythema can be distressing for patients owing to its visibility and may lead to early discontinuation from treatment.

JAK inhibitors are associated with an increased risk of infection, cancer, major adverse cardiovascular events (MACE) and thrombosis (65-67). Clinical experts consulted in the development of this submission have indicated that due to JAK inhibitor safety concerns, biologics are often considered before JAK inhibitor use. Indeed, it was noted by clinical experts that JAK inhibitors are not being used in the age 65 and older population so they would not be a relevant comparator to lebrikizumab (and biologics) in older patients. In early 2023, the EMA recommended measures to minimise the risk of these serious JAK inhibitor side effects (25), which were also adopted by the MHRA (26):

- Unless there are no suitable alternatives, avoid prescribing JAK inhibitors in patients with the following risk factors:
    - Aged ≥65 years
    - Current or past long-time smoker
    - Other risk factors for cardiovascular disease or malignancy
- Use caution if prescribing in patients with risk factors for venous thromboembolism (VTE), other than those listed above
- Where applicable, use a lower dose in patients with risk factors
- Carry out periodic skin examinations to check for signs of skin cancer
- Inform patients of these risks and the key signs and symptoms that may warrant urgent medical attention.

Unmet need

There is evidence that many patients with moderate-to-severe AD may not be receiving the level of treatment they require. A global web-based survey by Barbarot et al. included 249 adults with AD in the UK (27). Of these, just 80% reported that they were receiving treatment. A retrospective study that included 289 patients with moderate-to-severe AD in the UK found that, whilst most were treated with topical therapies, use of systemic treatments was low (only 18% received conventional systemic treatment regimens) (20). More than half of the UK patients surveyed (59%) had uncontrolled (i.e. changeable or deteriorating) disease and 40% said they were currently experiencing a flare, indicating a need for better ongoing disease control (20). In addition, studies carried out in Sweden, Germany and Denmark suggest that the level of persistence with conventional systemic therapies is low (68-70).

In a global survey of 1,988 adults with moderate-to-severe AD (including from the UK), 75% said their treatment expectations were only partially met or not met at all (28). Treatments used were topical therapies (69.7%), systemic therapies (28.1%) and biologics (2.3%).

Together, the limitations of current therapies and the undertreatment of adults and adolescents with moderate-to-severe AD highlight the need for an alternative treatment that provides long-term disease control without safety trade-offs.

Place of lebrikizumab in therapy for moderate-to-severe AD

The anticipated position of lebrikizumab in the treatment pathway is as a second line systemic treatment for moderate-to-severe AD (i.e. after the condition has not responded to at least 1 systemic immunosuppressant, or these are not suitable) (Figure 2).

B.1.4 Equality considerations

The use of lebrikizumab is not expected to raise any equality issues. However, it is important to note that assessment of AD in patients with skin of colour can be challenging. For example, erythema can be more difficult to detect in darker skin types, as it often appears grey or dark brown in colour (71). 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). Lebrikizumab is currently being assessed in adults and adolescents with moderate-to-severe AD and skin of colour (ADmirable study; NCT05372419). The study is expected to complete in August 2024.

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.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify clinical evidence relevant to the decision problem described in Section B.1.1. Full details are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

There are no RCTs that compare lebrikizumab with other active treatments for AD. Relevant evidence for the clinical effectiveness of lebrikizumab comes from four Phase 3 placebo-controlled trials (ADvocate 1, ADvocate 2, ADhere and ADvantage) and an open-label long-term extension study (ADjoin) (Table 5). The ADvocate studies and ADhere are the pivotal studies for lebrikizumab. The ADvantage study was carried out in a population of patients who were not adequately controlled with ciclosporin A (CsA) or for whom CsA was not medically advisable; this study is included in the submission because the patient population reflects the expected positioning of lebrikizumab in the UK. ADjoin is an ongoing extension study that includes patients who were previously enrolled in ADvocate 1 & 2 and ADhere; this study is included in the submission as it provides longer-term discontinuation data for ADhere that are used in the economic model.

Table 5: Clinical effectiveness evidence: ADvocate 1 & 2, ADhere, ADvantage, ADjoin

Study	ADvocate 1 (NCT04146363) ADvocate 2 (NCT04178967)	ADhere (NCT04250337)	ADvantage[a] (NCT05149313)	ADjoin (NCT04392154)
Study design	Randomised, double-blind, placebo-controlled, parallel group studies 52 weeks: 16-week induction phase; 36-week maintenance phase	Randomised, double-blind, placebo-controlled, parallel group study 16 week induction phase	Randomised, double-blind, placebo-controlled, parallel group studies 52 weeks: 16-week induction phase; 36-week maintenance phase	Long-term extension study 100 weeks
Population	Adults and adolescents with moderate-to-severe AD	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	Adults and adolescents with moderate-to-severe AD who completed one of the following lebrikizumab studies: • ADvocate 1 • ADvocate 2 • ADhere • ADore • ADopt-VA or who otherwise met the inclusion criteria (US only)
Intervention(s)	Induction: Lebrikizumab 250 mg Q2W[b] Maintenance: Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q4W	Lebrikizumab 250 mg Q2W[b] + TCS	Induction: Lebrikizumab 250 mg Q2W[b] + TCS Maintenance: Lebrikizumab 250 mg Q2W + TCS	Lebrikizumab 250 mg Q4W Lebrikizumab 250 mg Q2W ± TCS Open-label or blinded, depending on the participant's enrolment route

Study	ADvocate 1 (NCT04146363) ADvocate 2 (NCT04178967)	ADhere (NCT04250337)	ADvantage[a] (NCT05149313)	ADjoin (NCT04392154)
Comparator(s)	Induction: Placebo Q2W Maintenance: Placebo (lebrikizumab withdrawal)	Placebo Q2W + TCS	Induction Placebo Q2W + TCS Maintenance: None	N/A
Indicate if study supports application for marketing authorisation	Yes	Yes	No	Yes[c]
Indicate if study used in the economic model	Yes	Yes	Yes	Yes
Rationale if study not used in model	N/A	N/A	N/A	N/A
Reported outcomes specified in the decision problem	Trial outcomes include: • **[Disease severity / symptom control]** Primary endpoints: W16 IGA (0,1) with ≥2-point reduction from BL and W16 % EASI 75 • **[Disease severity / symptom control]:** Secondary endpoints include: W16 EASI 50 and DLQI	Trial outcomes include: • **[Disease severity / symptom control]** Primary endpoints: W16 IGA (0,1) with ≥2-point reduction from BL and W16 % EASI 75 • **[Disease severity / symptom control]:** Secondary endpoints: EASI 50, DLQI • **[Disease free period / maintenance of**	Trial outcomes include: • **[Disease severity / symptom control]** Primary endpoint: W16 % EASI 75 • **[Disease severity / symptom control]:** Secondary endpoints: W16 IGA (0,1) ≥2-point reduction from BL, EASI 50, EASI 90, DLQI	Trial outcomes include: • **[Disease severity / symptom control]** EASI 75, IGA (0,1), itch NRS, EASI 50, EASI 90, • **[Disease free period / maintenance of remission]** Treatment discontinuation • **Adverse events** Primary endpoint: % of participants who

Study	ADvocate 1 (NCT04146363) ADvocate 2 (NCT04178967)	ADhere (NCT04250337)	ADvantage[a] (NCT05149313)	ADjoin (NCT04392154)
	CFB W16; W52 maintenance EASI 75 • **[Disease free period / maintenance of remission]** Treatment discontinuation • **Adverse events** • **Health-related quality of life (EQ-5D-5L).**	**remission]** Treatment discontinuation • **Adverse events** • **Health-related quality of life (EQ-5D-5L).**		discontinue because of AEs
All other reported outcomes	• Secondary endpoints: ≥4-point improvement from BL in pruritus NRS, EASI 90, sleep loss	• Secondary endpoints: ≥4-point improvement from BL in pruritus NRS, EASI 90, sleep loss	• Secondary endpoints: ≥4-point improvement from BL in pruritus NRS, BSA, SCORAD, POEM	• BSA, sleep-loss, POEM

[a]Data presented in this submission are for the induction period only; data for the maintenance period are not yet available. [b]A loading dose of lebrikizumab 500 mg was administered at Week 0 and Week 2. [c]Only 1-year data from patients originating from the Adhere study were used in the MAA
Key: AD, atopic dermatitis; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids

Efficacy and safety data from the ADvocate studies have been published in the New England Journal of Medicine (72) and the British Journal of Dermatology (73). Safety data have also been used in an integrated analysis published in the American Journal of Clinical Dermatology (74). Data used in this submission have been taken from the publications and, where necessary, from the lebrikizumab pivotal trial clinical study reports (75, 76).

Efficacy and safety data from ADhere have been published in JAMA Dermatology (77). Safety data have also been used in an integrated analysis published in the American Journal of Clinical Dermatology (74). Data used in this submission have been taken from these publication and, where necessary, from the clinical study report (78).

Efficacy and safety data from the ADvantage study have been presented at the 2023 European Academy of Dermatology ad Venereology Congress (79). Data used in this submission are taken from the presentation given at this congress and from the clinical study report (80). The data presented are from an interim analysis (data cut-off 18 April 2023) conducted when all patients had either completed the 16-week induction period or discontinued from the study prior to Week 16. Maintenance period data are not yet available.

Efficacy and safety data from interim analyses of ADjoin have been presented at the 2023 World Congress of Dermatology (81) and the 2023 Fall Clinical Dermatology Conference (82). Data used in this submission are taken from the presentations given at these congresses and an interim clinical study report (83).

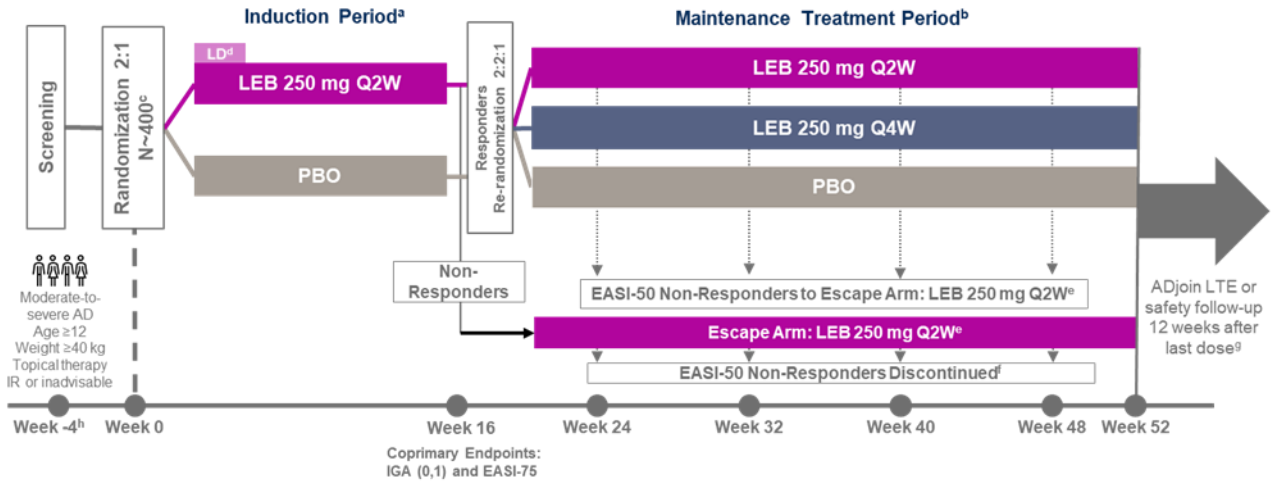
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Trial design and methodology

ADvocate 1 and 2 (lebrikizumab monotherapy studies)

ADvocate 1 and ADvocate 2 were randomised, double-blind, placebo-controlled studies to evaluate the efficacy and safety of lebrikizumab as monotherapy in adults and adolescents with moderate-to-severe AD. The studies had identical designs (Figure 3).

Figure 3: ADvocate 1 and 2 study designs



[a]Use of topical/systemic treatments for AD was prohibited. [b]Use of intermittent topical rescue medications for AD was permitted. Responders who received PBO during induction and who were re-randomized to LEB received a LD of either 500 mg given at W16 or 500 mg given at W16 and W18. [c]N = 424 in ADvocate 1 and 427 in ADvocate 2 with moderate-to-severe AD. [d]500 mg LD at Week 0 and Week 2. [e]Maintenance of response assessed by EASI-50 at Weeks 24, 32, 40, and 48. Patients receiving systemic rescue medication were required to washout for 5 half-lives prior to initiating treatment in the Escape Arm. [f]Participants who were eligible for the Escape Arm at Week 16 received blinded LD at Week 16 and Week 18, based on their prior treatment assignment. [g]Patients completing ADvocate 1/2 could enter the long-term extension ADjoin; otherwise they attended a safety follow-up 12 weeks after their last dose. [h]≤30-day screening period.
Key: AD, atopic dermatitis; EASI-50, 50% improvement in Eczema Area and Severity Index; EASI-75, 75% improvement in Eczema Area and Severity Index; LD, loading dose; LEB, lebrikizumab; LTE, long-term extension; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks

The studies consisted of a 16-week induction period followed by a 36-week maintenance period. At entry to the induction period, participants were randomised 2:1 to lebrikizumab 250 mg Q2W or placebo Q2W (note that participants received a 500 mg loading dose at Week 0 and Week 2). Randomisation was stratified by geographic region (US *vs.* European Union *vs.* Rest of the World), age group (adolescents *vs.* adult) and disease severity (IGA score of 3 *vs.* 4).

Participants who had responded to treatment at Week 16 (i.e. achieved 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 rescue medication use) were re-randomised 2:2:1 to either lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W or placebo Q2W. Those who did not respond to treatment by Week 16, or who received rescue therapy between baseline and Week 16, were assigned to an 'escape arm' and received open-label lebrikizumab Q2W through Week 52.

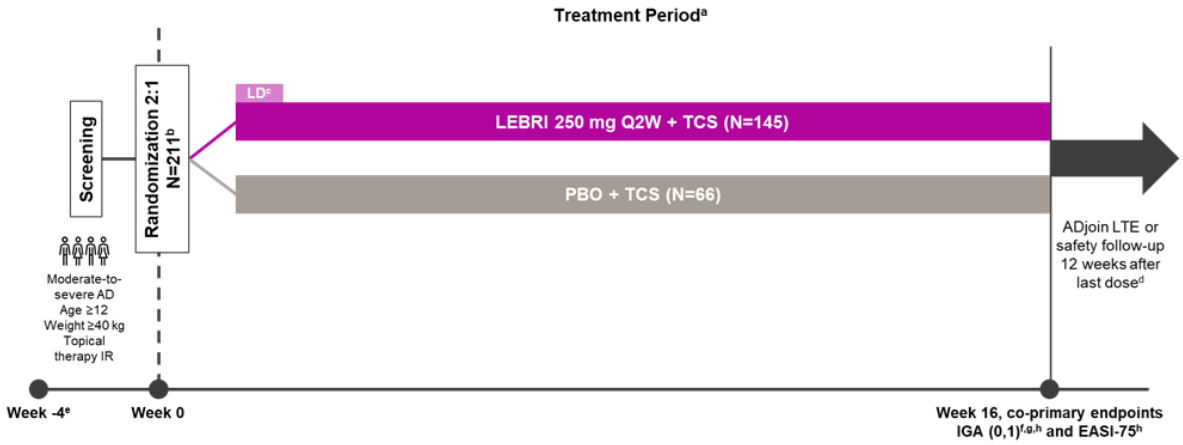
Following re-randomisation, participants who did not maintain EASI 50 at Weeks 24, 32, 40 or 48 were moved to the escape arm and received open-label lebrikizumab Q2W through Week 52. Participants in the escape arm who did not achieve EASI 50 after 8 weeks were discontinued from the study.

Participants who completed either study had the opportunity to enrol in a long-term extension study (ADjoin LTE). Those who did not complete the studies, or chose not to enter ADjoin, had a follow-up visit approximately 12 weeks after their final dose of study medication.

ADhere (lebrikizumab + TCS)

ADhere was a randomised, double-blind, placebo-controlled trial to evaluate the efficacy and efficacy of lebrikizumab when used in combination with TCS in patients with moderate to severe AD (Figure 4).

Figure 4: ADhere study design



[a]Use of TCS was required; could be tapered and stopped then resumed as needed. [b]A total of 211 patients with moderate-to-severe AD. [c]500 mg loading dose at W0 and W2. [d]Patients completing ADhere could enter the long-term extension ADjoin; otherwise they attended a safety follow-up 12 weeks after their last dose. [e]≤30-day screening period. [f]IGA (0,1) with ≥2-point improvement from baseline. [g]FDA primary endpoint. [h]EMA co-primary endpoint.
Key: AD, atopic dermatitis; EASI-50, 50% improvement in Eczema Area and Severity Index; LD, loading dose; LEB, lebrikizumab; LTE, long-term extension; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks

The study consisted of a 16-week treatment period. At entry to the treatment period, participants were randomized 2:1 to lebrikizumab 250 mg Q2W + TCS or placebo Q2W + TCS (with a 500 mg loading dose at Week 0 and Week 2). TCS use could be tapered, stopped and resumed at the participant's discretion. Participants who completed the study had the opportunity to enrol in the ADjoin LTE. Those who did not complete the study, or chose not to enter ADjoin, had a follow-up visit approximately 12 weeks after their final dose of study medication.

Table 6 summarises the methodology of the ADvocate and ADhere studies.

Table 6: Comparative summary of trial methodology: pivotal trials

Trial	ADvocate 1	ADvocate 2	ADhere
Location	International: Australia, Canada, Estonia, France, Latvia, Lithuania, Poland, Republic of Korea, Spain, US	International: Bulgaria, Canada, Germany, Mexico, Singapore, Taiwan, Ukraine	International: Canada, Germany, Poland, US
Trial design	Randomised, double-blind, placebo-controlled, parallel group to evaluate lebrikizumab as monotherapy in adults and adolescents with moderate-to-severe AD 52 weeks: 16-week induction phase; 36-week maintenance phase		Randomised, double-blind, placebo-controlled, parallel group study to evaluate lebrikizumab in combination with TCS in adults and adolescents with moderate-to-severe AD 16 weeks

Eligibility criteria for participants	<u>Key inclusion criteria:</u>
	• Adult or adolescent (aged 12 to <18 years and weighing ≥40 kg)
	• Diagnosis of chronic AD (AAD Consensus Criteria) for ≥1 year before screening
	• Moderate-to-severe AD, 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
	• Candidate for systemic therapy
	
	<u>Key exclusion criteria:</u>
	• Previous enrolment in a lebrikizumab study
	• Previous treatment with dupilumab or tralokinumab
	• Treatment with TCS, calcineurin inhibitors or phosphodiesterase-4 inhibitors in the 7 days before the baseline visit
	• Treatment with immunosuppressants or immunomodulators in the 4 weeks before the baseline visit
	• Treatment with phototherapy or photochemotherapy in the 4 weeks before the baseline visit
			<u>Key inclusion criteria:</u>
			As for ADvocate 1 and 2
			
			<u>Key exclusion criteria:</u>
			As for ADvocate 1 and 2, plus:
			• Having had an important side effect to TCS, such as:
			  ○ intolerance to treatment
			  ○ hypersensitivity reactions
			  ○ significant atrophy
			  ○ systemic effects
			• Treatment with phototherapy or photochemotherapy in the 4 weeks before the baseline visit
			• Treatment with dupilumab in the last 8 weeks

Trial	ADvocate 1	ADvocate 2	ADhere
	• Administration of an investigational drug in the last 8 weeks or within 5 half-lives (whichever is longer) • Treatment with B cell-depleting biologics in the last 6 months or other biologics within the last 16 weeks or 5 half-lives (whichever is longer) • Presence of skin comorbidities that may interfere with study assessments • Uncontrolled chronic disease that may require bursts of oral corticosteroids		
Trial drugs	Induction: Lebrikizumab 250 mg Q2W Placebo Q2W Maintenance: Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q4W Placebo Q2W All study drugs were administered as subcutaneous injections		Lebrikizumab 250 mg Q2W + TCS Placebo Q2W + TCS Lebrikizumab and placebo were administered as subcutaneous injections. TCS was administered as a topical cream
Number of participants (randomised to treatment)	Lebrikizumab (n = 283) Placebo (n = 141)	Lebrikizumab (n = 281) Placebo (n = 146)	Lebrikizumab + TCS (n = 145) Placebo + TCS (n = 66)
Permitted and disallowed concomitant medication	Permitted: • Medicines for other medical conditions (e.g. hypertension, diabetes, acute infection) • Inhaled corticosteroids and bronchodilators for asthma • Systemic antibiotics for acute infection • Non-medicated moisturizers Disallowed: • Medications or therapies for other medical conditions that are known to affect AD (e.g. systemic corticosteroids, MMF, IFN-y, JAK inhibitors, TCI, CsA, AZA, MTX, phototherapy, photochemotherapy, phosphodiesterase-4 inhibitors)		Permitted: As for ADvocate 1 and 2, plus: • TCIs for use on sensitive areas only (e.g. face, neck, intertriginous and genital areas) Disallowed: As for ADvocate 1 and 2, with the exception of TCI (see above)

Trial	ADvocate 1	ADvocate 2	ADhere
	• Systemic corticosteroids for treatment of AD • Systemic antibiotics for chronic infection • Cannabinoid treatment for AD • Major medical procedures or surgeries		
Primary outcomes (including scoring methods and timings of assessments)	<u>Co-primary endpoints:</u> • 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 used in the economic model/specified in the scope	• Measures of symptom control • Adverse effects of treatment • Health-related quality of life		• Measures of symptom control • Adverse effects of treatment • Health-related quality of life
Pre-planned subgroups	• Age (12 to <18, ≥18 to <65, ≥65 to <75, ≥75 years) • Age (adolescents 12 to <18 years, adults ≥18 years) • Sex • Race (American Indian or Alaskan native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Other, Not reported) • Ethnicity (Hispanic or Latino, not Hispanic or Latino, missing) • Geographic location (US, Europe, Rest of World) • Baseline weight (<60, ≥60 to <100, ≥100 kg) • Baseline BMI (underweight <18.5, normal ≥18.5 to <25, overweight ≥25 to <30, obese ≥30 to <40, extreme obese ≥40 kg/m^2) • Duration since AD onset (0 to <2, 2 to <5, 5 to <10, 10 to <20, ≥20 years) • Baseline IGA score (3, 4) • Baseline itch score (<4, ≥4) • Prior use of systemic treatment (Yes/No)		

Key: AAD, American Academy of Dermatology; AD, atopic dermatitis; AZA, azathioprine; BMI, body mass index; BSA, body surface area; CsA, ciclosporin A; EASI, Eczema Area and Severity Index; IFN, interferon; IGA, Investigators Global Assessment; JAK, Janus kinase; MMF, mycophenolate mofetil; MTX, methotrexate; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; US, United States

ADvantage (lebrikizumab + TCS in patients who failed CsA or for whom CsA is not medically advisable)

ADvantage (NCT05149313) was a 52-week European study in adults and adolescents with moderate-to-severe AD who had failed treatment with CsA or in whom CsA was not medically advisable (80).

The study consisted of a 16-week induction phase followed by a 36-week maintenance period. At entry to the induction period, participants were randomised 2:1 to lebrikizumab 250 mg Q2W or placebo Q2W (note that participants received a 500 mg loading dose at Week 0 and Week 2). Randomisation was stratified by previous dupilumab use, age (adolescent vs adult) and baseline disease severity (IGA score of 3 vs 4).

After completion of the Week 16 visit, participants entered the maintenance period, during which they received lebrikizumab 250 mg Q2W. Those who had received placebo during the induction period received loading doses of 500 mg lebrikizumab at Weeks 16 and 18, blinding was maintained at Weeks 16 and 18. Therefore the study was open-label from Week 20 onwards.

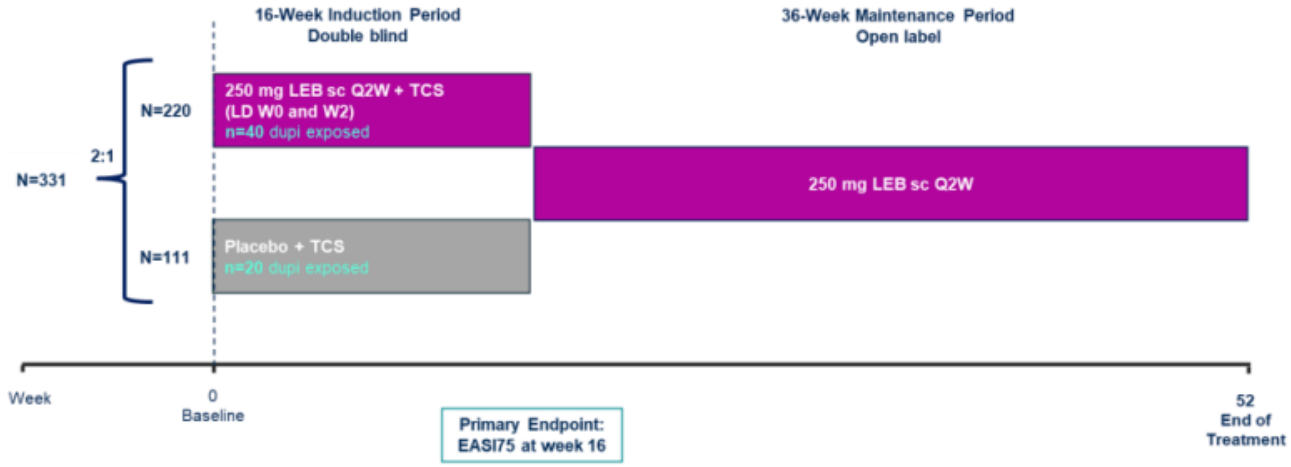
All participants were to receive concomitant mid-potency TCS through Week 16 until lesions were clear or almost clear. Low-potency TCS could be used from the baseline visit instead of mid-potency TCS on sensitive areas. Once lesions were clear or almost clear, participants switched to low-potency TCS for 7 days and then stopped. If lesions reappeared, participants had to resume mid-potency TCS or low-potency TCS. High-potency TCS, TCI or systemic treatments were considered rescue medication. There was a 1-week washout period required for TCS prior to baseline.

Participants who did not achieve EASI 50 for two consecutive visits between Weeks 24 and 48 were discontinued from the study.

Participants in Germany could enter an extension period at the end of the study during which they received lebrikizumab Q4W for a minimum of 6 months.

The study design is shown in Figure 5.

Figure 5: ADvantage study design



Key: EASI = Eczema Area and Severity Index; LD = loading dose; LEB = lebrikizumab; Q2W = every 2 weeks; sc = subcutaneous

Table 7 summarises the methodology of ADvantage.

Table 7: Summary of trial methodology: ADvantage

Trial	ADvantage
Location	Europe: Austria, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, UK
Trial design	Randomised, double-blind, placebo-controlled study to evaluate lebrikizumab in combination with TCS in adults and adolescents with moderate-to-severe AD that are not adequately controlled with CsA or for whom CsA is not medically advised 52 weeks

Eligibility criteria for participants	Key inclusion criteria:
	• 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
	• Moderate-to-severe AD, 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
	• Inadequate response to existing topical medications in the 6 months before screening
	• Either:
	  ○ No previous CsA exposure and not currently a candidate for CsA exposure as it is not medically advisable

Trial	ADvantage
	Or • Previous CsA exposure, but was discontinued because of o intolerance and/or unacceptable toxicity, or o a requirement for CsA at doses or duration beyond that specified in the prescribing information, or an inadequate response <u>Key exclusion criteria:</u> • Previous enrolment in a lebrikizumab study • Previous treatment with IL-4 or IL-14 antagonists (exception: previous treatment with dupilumab was allowed in a subset of participants with a washout of ≥8 weeks before baseline) • Treatment with TCS in the 7 days before the baseline visit • Treatment with TCI, phosphodiesterase-4 inhibitors or cannabinoids in the 2 weeks before the baseline visit • Treatment with immunosuppressants or immunomodulators in the 4 weeks before the baseline visit • Treatment with phototherapy or photochemotherapy in the 4 weeks before the baseline visit • Administration of an investigational drug in the last 8 weeks or within 5 half-lives (whichever is longer) • Treatment with B cell-depleting biologics in the last 6 months or other biologics within the last 16 weeks or 5 half-lives (whichever is longer)
Trial drugs	<u>Induction:</u> Lebrikizumab 250 mg Q2W + TCS Placebo Q2W + TCS <u>Maintenance:</u> Lebrikizumab 250 mg Q2W + TCS Lebrikizumab and placebo were administered as subcutaneous injections. TCS was administered as a topical cream
Number of participants (randomised to treatment)	Lebrikizumab + TCS (n = 220) Placebo + TCS (n = 111)
Permitted and disallowed concomitant medication	Participants were allowed to use non-medical topical moisturizers at the Investigator's discretion. Following a 1-week washout period, all participants were required to use concomitant TCS. Up to Week 16, participants were to use mid-potency TCS applied at least once daily to affected areas until lesions were under control (clear or almost clear) and then switch to low-potency TCS and treat previously affected areas once daily for 7 days

Trial	ADvantage
	and then stop. In place of mid-potency TCS, low-potency TCS could have been used on areas of thin skin (face, neck, folds, and genital areas) and areas with skin atrophy. From Week 16 to Week 52, TCS use was at the Investigator's discretion. If medically necessary (e.g. to control intolerable AD symptoms), high-potency TCS or systemic treatments (e.g. oral corticosteroids, phototherapy) could be used. Inhaled corticosteroids and bronchodilators were permitted to control asthma. The use of concomitant medications for other medical conditions (e.g., hypertension, diabetes, acute infections) was permitted. The following medications were not permitted: • Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, JAK inhibitors, azathioprine, methotrexate) • Chronic treatment with systemic antibiotics • Cannabinoid treatments for AD Use of tanning booths/parlours was not permitted
Primary outcomes (including scoring methods and timings of assessments)	Percentage of participants achieving EASI 75 (i.e. a 75% reduction from baseline in EASI) at Week 16
Other outcomes used in the economic model/specified in the scope	• Measures of symptom control • Adverse effects of treatment
Pre-planned subgroups	Prior dupilumab exposure

Key: AAD, American Academy of Dermatology; AD, atopic dermatitis; CsA, ciclosporin A; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroids; UK, United Kingdom

ADjoin

ADjoin (NCT04392154) is an ongoing study to assess the long-term safety and efficacy of lebrikizumab in adults and adolescents with moderate-to-severe AD. Participants who completed ADvocate 1, ADvocate 2, ADhere, ADore (a study in adolescents only) and ADopt-VA (a US study evaluating the effect of lebrikizumab on vaccine responses in adults with AD) were eligible to enrol. The study design is shown in Figure 6.

Figure 6: ADjoin study design

[a]The treatment regimen assignment remained blinded until unblinding, except for participants who received open-label study drug. Placebo injections were used to maintain the blind and ensure all patients received the same number and frequency of injections. Some patients received a loading dose of lebrikizumab 500 mg at baseline and Week 2; [b]Baseline (Visit 1) = parent study exit visit (excluding direct entry participants); [c]Last injection of study drug = Week 98; [d]In the US only, the study also allowed direct enrolment of approximately 100 participants who had not taken part in a parent study but otherwise met the inclusion criteria; the aim was to increase the long-term safety database for lebrikizumab and this group is not discussed further in this submission
Key: Q2W, every 2 weeks; Q4W, every 4 weeks

Participants who enrolled from ADvocate 1 & 2 continued to receive their maintenance period dosing regimen during ADjoin (i.e. lebrikizumab 250 mg Q4W or lebrikizumab 250 mg Q2W). Participants who had achieved EASI 75 by Week 16 in ADhere were randomised 2:1 to lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W at enrolment to ADjoin; those who had not achieved EASI by Week 16 received lebrikizumab 250 mg Q2W. Patients enrolling from ADhere could continue or stop TCS use, as needed. Placebo injections were used to maintain blinding and ensure that all participants received the same number of injections, regardless of their assigned regimen.

Table 8 summarises the methodology of ADjoin.

Table 8: Summary of trial methodology: ADjoin

Trial	ADjoin
Location	Australia, Bulgaria, Canada, Estonia, France, Germany, Latvia, Lithuania, Mexico, Poland, Singapore, South Korea, Spain, Taiwan, Ukraine, US
Trial design	Long-term study to assess the safety and efficacy of lebrikizumab in adults and adolescents with moderate-to-severe AD 100 weeks
Eligibility criteria for participants who rolled over from a parent study	Key inclusion criteria: • Received treatment in one of the following lebrikizumab studies: o ADvocate 1 o ADvocate 2 o ADhere o ADore o ADapt-VA • Adequately completed the study treatments and last participant visit of the parent study Key exclusion criteria: • A serious adverse event during the parent study that was considered related to lebrikizumab and led to treatment discontinuation, which could indicate that continued treatment with lebrikizumab could present an unreasonable risk for the participant • Conditions during the parent study consistent with protocol-defined criteria for permanent treatment discontinuation, if considered related to lebrikizumab or led to investigator- or sponsor-initiated withdrawal of the participant from the study (e.g. non-compliance, inability to complete study assessments, etc)
Trial drugs	Lebrikizumab 250 mg Q4W Lebrikizumab 250 mg Q2W
Number of participants	[redacted] participants, of whom [redacted] were enrolled from ADvocate 1 and 2, and [redacted] from ADhere
Permitted and disallowed concomitant medication	Patients enrolling from ADvocate 1 and 2 were allowed intermittent use of TCS. Those enrolling from ADhere could continue or stop TCS as appropriate. Use of short-term systemic treatments for symptoms of AD had to be discussed on a case-by-case basis. Participants requiring long-term use of systemic treatments for AD had to be withdrawn from the study The use of concomitant medications for other ongoing medical conditions was permitted

Trial	ADjoin
	The following treatments were not permitted: • Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, JAK inhibitors, azathioprine, methotrexate) • Phototherapy • Cannabinoid treatments for AD
Primary outcomes (including scoring methods and timings of assessments)	Percentage of participants discontinued from study treatment because of adverse events through the last treatment visit
Other outcomes used in the economic model/specified in the scope	• Measures of symptom control
Pre-planned subgroups	N/A

B.2.3.2. Outcome definitions

Definitions of the key outcomes used in the lebrikizumab studies are given in Table 9.

Table 9: Outcomes used in the lebrikizumab studies

Outcome	Definition
EASI	Assesses the extent of disease at four body regions (head/neck, upper extremities, trunk, lower extremities) and measures four clinical signs (erythema, induration/papulation, excoriation and lichenification). The total score ranges from 0 to 72, with moderate AD being defined as a score of 6 to 22 and severe AD as a score of 23 to 72
IGA	Measures the investigator's assessment of the patient's overall disease severity on a 5-point scale based on the degree of erythema, papulation/induration, oozing/crusting and lichenification: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe)
Itch NRS	Used to rate worst itch severity over the last 24 hours. Scale ranges from 0 (no itch) to 10 (the worst imaginable itch). The MCID is 3 points; a 4-point change is a more conservative assessment of clinical impact
Sleep loss scale	A patient-reported daily scale that measures the extent of sleep loss due to itch interference during the previous night. Scale ranges from 0 (not at all) to 4 (unable to sleep at all)
EQ-5D	Measures patients' health status across 5 domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Three response levels: 'no problem', 'some/moderate problems', 'extreme problems/unable to do', and a VAS (where 0 = worst health and 100 = best health. Patients use today as a reference point. Responses are used to generate an overall health index from -0.59 (worst health) to 1 (full health)

DLQI (patients aged >16 years)	Patients rate the impact of AD over the last week on the following: itch; embarrassment; shopping/home/garden; clothes; social/leisure; sprots; work/study; partner/close friends/relatives; sexual difficulties; treatment. Each item has 4 response categories, ranging from 'Not at all' (0) to 'Very much' (3); 'Not relevant' is also a valid response and is marked as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30; higher scores indicate greater HRQoL impairment. A 4-point change from baseline is considered the MCID
CDLQI (children aged 12 to16 years)	Patients rate the impact of AD over the last week on the following: itch; embarrassment; friendships; clothes/shoes; leisure/hobbies; swimming/sports; school/holidays; teasing/bullying; sleep; treatment. Scoring is the same as for the DLQI
POEM	Measures the following concepts: skin dryness; itching; flaking; cracking; sleep loss; bleeding; weeping. Each item has 5 response categories, ranging from 'No days' (0) to 'Every day' (4). Total possible scores range from 0 to 28; higher scores indicate worst HRQoL
PROMIS Anxiety and Depression short forms	Assess the following symptoms over the past week: • Anxiety: self-reported fear (fearfulness, panic); anxious misery (worry, dread); hyperarousal (tension, nervousness, restlessness); somatic symptoms related to arousal (racing heart, dizziness) • Depression: self-reported negative mood (sadness, guilt); views of self (self-criticism, worthlessness); social cognition (loneliness, interpersonal alienation); decreased positive affect and engagement (loss of interest, meaning and purpose) Response options range from 1 (almost never) to 5 (almost always). Total scores are converted to T-scores, with higher scores indicating greater anxiety/depression

Key: CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQoL 5-dimensions; HRQoL, health-related quality of life; IGA, Investigator's global assessment; MCID, minimal clinically important difference; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; PROMIS, Patient-Reported Outcomes Measurement Information System

B.2.3.3. Baseline characteristics

ADvocate 1, ADvocate 2, ADhere

Table 10 shows baseline demographics and disease characteristics in the three pivotal studies. Overall, these were generally well balanced between treatment groups within each study. Participants in the ADvocate studies had more severe disease at baseline than those in ADhere, as shown by mean EASI scores, the proportion of participants with IGA scores of 3 vs IGA scores of 4, the proportion of BSA affected and DLQI scores.

Between 46% and 60% of participants had previously received systemic treatments for their AD.

Table 10: Baseline demographics and disease characteristics in the ADvocate and ADhere studies

	ADvocate 1		ADvocate 2		ADhere	
	PBO N = 141	LEB 250 Q2W N = 283	PBO N = 146	LEB 250 Q2W N = 281	PBO N = 66	LEB 250 Q2W N = 145
Age (years), mean (SD)	34.2 (16.4)	36.1 (17.8)	35.3 (17.2)	36.6 (16.8)	36.7 (17.9)	37.5 (19.9)
Adults (≥18 years), n (%)	123 (87.2)	246 (86.9)	129 (88.4)	251 (89.3)	52 (78.8)	113 (77.9)
Adolescents (12-18 years), n (%)	18 (12.8)	37 (13.1)	17 (11.6)	30 (10.7)	14 (21.2)	32 (22.1)
Female, n (%)	73 (51.8)	141 (49.8)	75 (51.4)	136 (48.4)	33 (50.0)	70 (48.3)
Race, n (%)						
White	93 (66.0)	196 (69.3)	85 (58.2)	168 (59.8)	40 (60.6)	90 (62.1)
Black	16 (11.3)	33 (11.7)	10 (6.8)	25 (8.9)	9 (13.6)	19 (13.1)
Asian	31 (22.0)	39 (13.8)	44 (30.1)	78 (27.8)	13 (19.7)	18 (12.4)
Weight (kg), mean (SD)	79.0 (22.7)	77.0 (19.7)	76.0 (21.1)	76.7 (20.5)	79.8 (24.4)	74.6 (23.3)
BMI (kg/m^2), mean (SD)	27.8 (7.2)	26.6 (5.8)	26.3 (6.3)	26.7 (6.6)	27.9 (7.5)	26.5 (7.2)
Duration since AD onset (years), mean (SD)	23.8 (15.4)	22.0 (14.9)	20.1 (14.1)	20.8 (15.2)	21.2 (13.9)	21.0 (17.4)
Previous use of systemic treatment, n (%)	85 (6.)	144 (50.9)	81 (55.5)	156 (55.5)	34 (51.5)	66 (45.5)
IGA, n (%)						
3, moderate	83 (58.9)	170 (60.1)	95 (65.1)	175 (62.3)	48 (72.7)	98 (67.6)
4, severe	58 (41.1)	113 (39.9)	51 (34.9)	106 (37.7)	18 (27.3)	47 (32.4)
EASI, mean (SD)	31.0 (12.9)	28.8 (11.3)	29.6 (10.8)	29.7 (12.0)	26.4 (10.6)	27.7 (11.1)
Sleep-loss scale score, mean (SD)	2.3 (1.0)	2.3 (1.0)	2.2 (0.9)	2.2 (0.9)	1.9 (0.9)	2.1 (0.9)
% BSA affected, mean (SD)	47.8 (23.9)	45.3 (22.5)	46.0 (21.1)	46.1 (22.6)	38.2 (20.8)	40.4 (21.9)
Itch NRS, mean (SD)	7.3 (1.7)	7.2 (1.9)	7.2 (1.9)	7.1 (1.9)	6.8 (2.0)	7.3 (1.8)
DLQI, mean (SD)	15.7 (7.2)	15.3 (7.4)	15.9 (7.6)	15.4 (7.0)	13.5 (7.5)	14.9 (7.2)

Key: AD = atopic dermatitis, BMI = body mass index, BSA = body surface area, DLQI = Dermatology Life Quality Index, EASI = Eczema Area and Severity Index, IGA = Investigator's Global Assessment, IQR = interquartile range, LEB = lebrikizumab, NRS = numerical rating scale, PBO = placebo, Q2W = every 2 weeks, SD = standard deviation
Source: Silverberg et al (2023) (72), Simpson et al, (2023) (77)

ADvantage

Table 11 shows the baseline characteristics from ADvantage. Overall, the baseline demographic and disease characteristics were well balanced across treatment groups. The mean EASI score was 28.1. Approximately 61% of participants in each group had moderate disease (based on an IGA score of 3) and approximately 39% in each group had severe disease (based in an IGA score of 4). Mean itch NRS scores were around 7 in both groups. Mean DLQI scores were slightly higher in the placebo + TCS group than in the lebrikizumab + TCS group.

More than half of participants in each group had previously received CsA and approximately one-sixth in each group had previously received dupilumab for their AD.

Table 11: Baseline demographics and disease characteristics in the ADvantage study

	PBO + TCS N = 111	LEB 250 Q2W + TCS N = 220
Age (years), mean (SD)	34.1 (15.2)	33.7 (14.9)
Adults (≥18 years), n (%)	98 (88.3)	194 (88.2)
Adolescents (12-<18 years), n (%)	13 (11.7)	26 (11.8)
Female, n (%)	56 (50.5)	100 (45.5)
Race, n (%)		
White	104 (93.7)	206 (93.6)
Black	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	24.9 (5.6)	25.0 (5.1)
Duration since AD onset (years), mean (SD)	23.2 (14.0)	25.4 (14.6)
Previously received ciclospirin A	[redacted]	[redacted]
Previously received dupilumab, n (%)	19 (17.1)	36 (16.4)
IGA, n (%)		
3, moderate	68 (61.3)	135 (61.4)
4, severe	43 (38.7)	85 (38.6)

	PBO + TCS N = 111	LEB 250 Q2W + TCS N = 220
EASI, mean (SD)	27.1 (9.8)	28.7 (10.6)
Sleep-loss scale score, mean (SD)	[redacted]	[redacted]
% BSA affected, mean (SD)	44.5 (20.3)	45.8 (19.4)
Itch NRS, mean (SD)	6.9 (2.1)	6.9 (1.9)
Skin pain NRS, mean (SD)	[redacted]	[redacted]
DLQI, mean (SD)	16.4 (7.5)	15.2 (6.9)

Key: BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IGA, investigator global assessment; NRS, numeric rating scale; Q2W = every two weeks; SD = standard deviation; TCS, topical corticosteroid
Source: Warren et al (2023) (79); ADvantage clinical study report (80)

ADjoin

Table 12 summarises the baseline characteristics of the patients who entered ADjoin from the ADvocate studies or ADhere. Currently, data from ADjoin are only available for lebrikzumab responders (i.e. those participants who responded to lebrikizumab at Week 16 in the parent studies).

Table 12: Baseline characteristics: ADjoin LTE

	ADvocate 1 & 2 → ADjoin		ADhere → ADjoin	
	LEB 250 Q4W (N = 99)	LEB 250 Q2W (N = 82)	LEB 250 Q4W (N = 29)	LEB 250 Q2W (N = 57)
Age (years), mean (SD)	35.8 (17.2)	35.5 (16.2)	29.8 (15.9)	37.0 (19.9)
Adolescent (≥12 to <18 years)	14 (14.1)	11 (13.4)	10 (34.5)	15 (26.3)
Adult (≥18 years)	85 (85.9)	71 (86.6)	19 (65.5)	42 (73.7)
Female, n (%)	60 (60.6)	42 (51.2)	15 (51.7)	27 (47.4)
BMI (kg/m^2), mean (SD)	26.4 (6.3)	26.4 (6.2)	25.2 (6.9)	26.3 (6.6)
Duration since AD onset (years), mean (SD)	22.4 (14.2)	23.6 (14.7)	21.7 (14.1)	21.6 (18.2)
IGA, n (%)				
3 (moderate)	63 (63.6)	50 (61.0)	20 (69.0)	39 (68.4)
4 (severe)	36 (36.4)	32 (39.0)	9 (31.0)	18 (31.6)
EASI, mean (SD)	28.9 (12.2)	29.2 (11.2)	26.2 (7.8)	28.2 (11.1)
Itch NRS, n (%)				
<4, n (%)	9 (9.2)	3 (3.7)	2 (7.4)	3 (5.5)
≥4, n (%)	89 (90.8)	79 (96.3)	25 (92.6)	52 (94.5)

Key: BMI = body mass index; EASI = Eczema Area and Severity Index; IGA, investigator global assessment; LEB = lebrikizumab; LTE = long-term extension; NRS, numeric rating scale; Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation; TCS, topical corticosteroid
Source: Guttman-Yassky et al (2023) (82)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Primary hypothesis and sample size calculations

The primary hypothesis was that lebrikizumab (as monotherapy or in combination with TCS) would be more effective than placebo in controlling the signs and symptoms of moderate-to-severe AD in adults and adolescents.

In ADvocate 1 and 2, it was estimated that a sample size of 96 in the lebrikizumab group and 48 in the placebo group for each study would have 95% power to detect a statistically significant difference with a two-sided significance level of 0.05 assuming an IGA (0,1) response rate of 34.7% for lebrikizumab and 7.7% for placebo (72). This was based on data from a Phase 2b trial (84). However, to ensure sufficient safety data were collected and to ensure sufficient responders for the maintenance period, the sample size was increased to approximately 400 patients per study, with a randomisation ratio of 2:1 lebrikizumab:placebo (72).

In ADhere, it was estimated that a sample size of 150 in the lebrikizumab group and 75 in the placebo group would give >95% power to detect superiority of lebrikizumab over placebo (77). This was based on an assumed IGA 0, 1 response rate at Week 16 of 38% for lebrikizumab and 13% for placebo, and an assumed EASI 75 response rate at Week 16 of 58% for lebrikizumab and 20% for placebo.

In ADvantage, it was estimated that a sample size of 208 in the lebrikizumab group and 104 in the placebo group would give >95% power to detect a statistically significant difference of 25% (55% in the lebrikizumab group vs 30% in the placebo group) in the proportion of participants achieving EASI 75 at Week 16.

B.2.4.2. Analysis populations

Table 13 shows the analysis populations in the ADvocate, ADhere and ADvantage studies.

Table 13: Analysis populations

	ADvocate 1	ADvocate 2	ADhere	ADvantage
Efficacy data				
Induction (to Week 16)	Intention to treat (ITT): all randomised participants, regardless of whether they received study medication or completed the trial Lebrikizumab Q2W (n = 283) Placebo (n = 141)	Modified ITT[a] Lebrikizumab Q2W (n = 281) Placebo (n = 146)	Modified ITT[b] Lebrikizumab Q2W + TCS (n = 145) Placebo + TCS (n = 66)	Full analysis set (FAS): all randomised participants who received at least one dose of study medication Lebrikizumab Q2W + TCS (n = 220) Placebo + TCS (n = 111)
Maintenance (Weeks 16 to 52)	Maintenance primary population (MPP): all participants who responded to treatment with lebrikizumab during the induction period and were re-randomised to lebrikizumab Q2W, lebrikizumab Q4W or placebo in the maintenance period[c] Lebrikizumab Q2W (n = 62) Lebrikizumab Q4W (n = 63) Placebo (n = 32)	Modified MPP Lebrikizumab Q2W (n = 51) Lebrikizumab Q4W (n = 55) Placebo (n = 28)	N/A	Not yet available[d]

	ADvocate 1	ADvocate 2	ADhere	ADvantage
Safety data				
Induction (to Week 16)	Safety population: all randomised participants who received at least one dose of lebrikizumab or placebo Lebrikizumab Q2W (n = 282) Placebo (n = 141)	Modified safety population Lebrikizumab Q2W (n = 281) Placebo (n = 145)	Modified safety population Lebrikizumab Q2W + TCS (n = 145) Placebo + TCS (n = 66)	Safety analysis set (SAF): all randomised participants who received at least one dose of lebrikizumab or placebo Lebrikizumab Q2W + TCS (n = 220) Placebo + TCS (n = 111)
Maintenance (Weeks 16 to 52)	MPP Lebrikizumab Q2W (n = 62) Lebrikizumab Q4W (n = 63) Placebo (n = 32)	Modified MPP Lebrikizumab Q2W (n = 51) Lebrikizumab Q4W (n = 55) Placebo (n = 28)	N/A	Not yet available[d]
Combined induction and maintenance periods	All lebrikizumab safety population: all randomised patients who received at least one dose of lebrikizumab during the combined induction and maintenance periods (n = 399)	Modified all lebrikizumab safety population (n = 407)	N/A	Not yet available[d]

[a]Excluded 18 participants from one site because some or all did not have moderate-to-severe AD; [b]Excluded 17 participants from one site owing to a critical audit finding; [c]Participants who responded to placebo during the induction period were included in the maintenance secondary population; data for this population are not presented in this submission; [d]Data for the maintenance period of ADvantage are not yet available

Key: FAS, full analysis set; ITT, intention to treat; MPP, maintenance primary population;Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; TCS, topical corticosteroids

Source: Silverberg et al (2023) (72); Simpson et al (2023) (77); ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); ADhere clinical study report (78); ADvantage clinical study report (80)

B.2.4.3. Statistical methods

Pivotal studies

Categorical endpoints were analysed using the Cochran-Mantel-Haenzel test. For induction period data (i.e. to Week 16) the analyses were adjusted for region, age group and baseline disease severity (IGA = 3/IGA = 4). For maintenance period data (Weeks 16 to 52; ADvocate studies only), the analyses were adjusted for region.

Continuous endpoints were analysed using analysis of covariance (ANCOVA). For induction period data (i.e. to Week 16) the analyses were adjusted for region, age group and baseline disease severity (IGA = 3/IGA = 4), trial group and baseline value. For maintenance period data (Weeks 16 to 52; ADvocate studies only), the analyses were adjusted for region.

Pooled analyses of maintenance period data were also adjusted for study.

Induction period (to Week 16)

To assess whether lebrikizumab was associated with superior results compared with placebo, the primary and key secondary endpoints were tested sequentially according to a graphical approach to adjust for multiplicity. For the primary estimand (Table 14), participants who received rescue medication or discontinued treatment owing to lack of efficacy were considered as non-responders and Markov Chain Monte Carlo Multiple Imputation (MCMC-MI) was used to input missing data. This method takes into account each patient's own data and borrows information from other patients in the same treatment group to input missing data. For the supportive estimand for categorical endpoints, participants who received rescue medication or discontinued treatment owing to lack of efficacy, or had missing data were considered as non-responders. Full details of the supportive estimands can be found in the clinical study reports (75, 76, 78) .

Table 14: Primary estimand and handling of missing data: induction period (ADvocate 1 & 2, ADhere)

	Analysis strategy for intercurrent events			Missing data imputation method
	Rescue medication	Treatment discontinuation		
		Lack of efficacy	Any other reason	
Primary estimand (hybrid)	Set to baseline	Set to baseline	Set to missing	MCMC-MI

In ADvocate 1 & 2, use of topical treatments (high, moderate or low potency TCS, TCI or crisabole) or systemic treatments (oral glucocorticoids, CsA, dupilumab, tralokinumab or phototherapy) were considered rescue therapy. In ADhere, use of high-potency TCS or systemic therapy was considered rescue therapy.
Key: MCMC-MI, Markov Chain Monte Carlo

Maintenance period (Weeks 16 to 52; ADvocate studies only)

In the maintenance period, for the primary estimand (Table 15), participants who received systemic rescue medication, discontinued treatment owing to lack of efficacy or transferred to the escape arm were considered as non-responders. Data were considered missing after use of topical rescue medication or treatment discontinuation for any reason other than lack of efficacy. Missing data were imputed using MCMC-MI. For the supportive estimand, participants who received any rescue medication, discontinued treatment for any reason, or transferred to the escape arm were considered as non-responders. Intermittent missing data were also considered as non-response. Full details of the supportive estimands can be found in the clinical study reports (75, 76, 78).

Table 15: Primary estimand and handling of missing data: maintenance period (ADvocate 1 & 2)

	Analysis strategy for intercurrent events					Missing data imputation method
	Rescue medication		Treatment discontinuation		Transfer to escape arm	
	Topical	Systemic	Lack of efficacy	Any other reason		
Primary estimand (hybrid)	Set to missing	Set to baseline	Set to baseline	Set to missing	Set to baseline	MCMC-MI

Key: MCMC-MI = Markov Chain Monte Carlo

ADvantage

The primary endpoint was analysed using the Cochran-Mantel-Haenzel test adjusted for country, age (adult/adolescent), prior use of dupilumab (yes, no) and baseline disease severity (IGA = 3/IGA = 4).

In the induction period, for the primary estimand (Table 16), the intercurrent events (of use of rescue or prohibited medication for AD and discontinuation due to lack of efficacy) used a composite strategy with values set to baseline, while for discontinuation due to other reasons a hypothetical strategy was used with values set to missing. MCMC-MI was used for all other missing data. For the supportive estimand of the primary and key secondary efficacy endpoints, NRI was used to handle missing data. For the supportive estimand of continuous other secondary efficacy endpoints, MMRM was used. Secondary efficacy endpoints were not adjusted for multiplicity. Full details of the supportive estimands can be found in the clinical study report (80).

Table 16: Primary estimand and handling of missing data (ADvantage study)

	Analysis strategy for intercurrent events			Missing data imputation method
	Rescue medication	Treatment discontinuation		
		Lack of efficacy	Any other reason	
Primary estimand (hybrid)	Set to baseline	Set to baseline	Set to missing	MCMC-MI

Key: MCMC-MI = Markov Chain Monte Carlo; MMRM, mixed model for repeated measures, NRI = non-responder imputation

ADjoin

Data presented in this submission are from lebrikizumab Week 16 responders who rolled over from ADvocate 1 & 2 or ADhere into ADjoin (81-83). As observed analyses were carried out; these used all collected data regardless of rescue medication use. Response rates were reported as descriptive. For participants who enrolled from ADvocate 1 & 2, efficacy outcomes were assessed during the maintenance periods of these studies (Week 16 to 52) and then for 52 weeks in ADjoin (Weeks 52 to 104). For participants who enrolled from ADhere, efficacy

outcomes were assessed up to 88 weeks in ADjoin (Weeks 16-104). Safety data were assessed from ADjoin enrolment up to a data cut-off date of 14th April 2023.

B.2.4.4. Participant flow

Pivotal studies

The flow of participants through ADvocate 1, ADvocate 2 and ADhere is shown in Appendix D1.2. This was similar between the studies. Overall, 93% of the 656 participants who received lebrikizumab and 87% of the 308 who received placebo completed the first 16 weeks of treatment. In ADvocate 1 and 2, 79% of the 113 lebrikizumab responders who were re-randomised to lebrikizumab Q2W and 89% of the 118 re-randomised to lebrikizumab Q4W completed the maintenance period, compared with 74% of the 60 who were re-randomised to placebo. Of the 435 participants who entered the escape arms in ADvocate 1 and 2, [redacted] ([redacted]%) completed treatment at Week 52.

CsA failures study (ADvantage)

The flow of participants through ADvantage is shown in Appendix D1.2. Overall, [redacted]% of the [redacted] participants who received lebrikizumab and [redacted]% of the [redacted] who received placebo completed the induction period.

Long-term extension study (ADjoin)

The flow of participants through ADjoin is shown in Appendix D1.2. Overall, [redacted] participants entered the study. Of these, [redacted] discontinued before randomisation and a further [redacted] from a single site were excluded after randomisation. Of the remaining [redacted] participants, [redacted] received lebrikizumab Q4W and [redacted] received lebrikizumab Q2W. At a data cut-off date of 6th July 2022, [redacted] patients were still receiving treatment (83).

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 17 shows a summary of the quality assessment results for ADvocate 1 & 2, ADhere and ADvantage. A complete quality assessment for each study is provided in Appendix D.

Table 17: Quality assessment results for lebrikizumab studies

Trial number (acronym)	ADvocate 1 ADvocate 2	ADhere	ADvantage	ADjoin
Was randomisation carried out appropriately?	Y	Y	Y	Y
Was the concealment of treatment allocation adequate?	Y	Y	Y	Y
Were the groups similar at the outset of the study in terms of prognostic factors?	Y	Y	Y	Y
Were the care providers, participants and outcome assessors blind to treatment allocation?	Y	Y	Y	Y
Were there any unexpected imbalances in drop-outs between groups?	N	N	N	N
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N	N	N	N/A
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y	Y	Y	Y

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.6 Clinical effectiveness results of the relevant studies

Summary of clinical effectiveness results

- A significantly greater proportion of patients treated with lebrikizumab (as monotherapy or in combination with TCS) achieved clinically meaningful improvements in skin clearance, itch severity and quality of life compared with placebo at Week 16
- The onset of clinical benefit with lebrikizumab was seen within 1 to 6 weeks
- Lebrikizumab Q2W also led to rapid and clinically meaningful improvements at Week 16 in the signs and symptoms of moderate-to-severe AD in patients who were not adequately controlled with CsA, or for whom CsA was not medically advisable
- The clinical response with lebrikizumab was maintained through Week 52
- Continuing therapy beyond 16 weeks in per-protocol non-responders can lead to high levels of response at Week 24 that are maintained through Week 52
- Response was maintained over 2 years of continuous lebrikizumab treatment

B.2.6.1. Efficacy of lebrikizumab as monotherapy and in combination with TCS: ADvocate 1, ADvocate 2, ADhere

Note: In this section, Week 52 data for ADvocate 1 and ADvocate 2 are presented for those participants who responded to treatment with lebrikizumab during the induction period (the maintenance primary population). Data for those who responded to placebo (the maintenance secondary population) are not shown. Data are shown for both doses of lebrikizumab (i.e. 250 mg Q4W and 250 mg Q2W); the recommended maintenance dose is 250 mg Q4W.

Data for participants who did not respond to treatment by Week 16, or who received rescue therapy between baseline and Week 16 and were assigned to the escape arm are shown in Section B.2.6.2.

EASI 75

Table 18 shows the EASI 75 response at Week 16 (co-primary endpoint). Across all three studies, the EASI 75 response rate was significantly higher with lebrikizumab than with placebo. More than half of those treated with lebrikizumab as monotherapy achieved EASI 75; the response rate was higher when lebrikizumab was used in combination with TCS.

Table 18: EASI 75 response at Week 16 (ADvocate 1 & 2, ADhere)

	ADvocate 1		ADvocate 2		ADhere	
EASI 75 Week 16	**PBO (n = 141)**	**LEB 250 Q2W (n = 283)**	**PBO (n = 146)**	**LEB 250 Q2W (n = 281)**	**PBO + TCS (n = 66)**	**LEB + TCS (n = 145)**
MCMC-MI						
% of participants	16.2	58.8	18.1	52.1	42.2	69.5
Difference (95% CI)	42.0 (33.3 to 50.6)		33.3 (24.4 to 42.2)		26.4 (12.1 to 40.8)	
P value	<0.001		<0.001		<0.001	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI
Key: CI, confidence interval; EASI, Eczema Activity and Severity Index, LEB, lebrikizumab; ITT, intention to treat, MCMC-MI, Markov chain Monte Carlo multiple imputation; mITT, modified intention to treat; PBO, placebo; Q2W, every 2 weeks
Source: Silverberg et al (2023) (72), Silverberg et al (2023) (supplementary material) (85), ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), Simpson et al (2013) (77), ADhere clinical study report (78)

There was a greater proportion of responders in the placebo+TCS group in ADhere than in the placebo groups in ADvocate 1 and 2. However, this is to be expected given the approach to TCS use in ADhere: participants were provided with TCS and its use was at their discretion; they were allowed to taper or stop TCS if they felt they were not needed to manage their symptoms. The lower baseline disease severity in ADhere relative to the ADvocate studies, the use of triamcinolone as a mid-potency TCS (it is considered high-potency in some countries) and potential systemic absorption of triamcinolone (depending on the treated area) may also have contributed to a high placebo + TCS response rate in ADhere.

At Week 16, participants treated with lebrikizumab + TCS had a numerically greater mean percentage of TCS/TCI-free days vs placebo, but the difference was not statistically significant: LS mean (SE): 23.9 (4.8) vs 31.2 (3.5); LS mean difference (SE) [95% CI]: 7.3 (5.1) [-2.78 to 17.4] (77). However, statistical significance was reached at Weeks 6, 8 and 10. By the end of the study, 50% of participants in the lebrikizumab + TCS group were TCS/TCI-free, whereas the placebo + TCS group did not reach this threshold (77).

Figure 7 shows EASI 75 responses over time to Week 16. The onset of efficacy was rapid with lebrikizumab: a meaningful treatment response was seen within the first 2 weeks in ADvocate 1 and the first 4 weeks in ADvocate 2 and ADhere. The results were similar, regardless of the method used for imputing missing data (i.e. MCMC-MI or NRI).

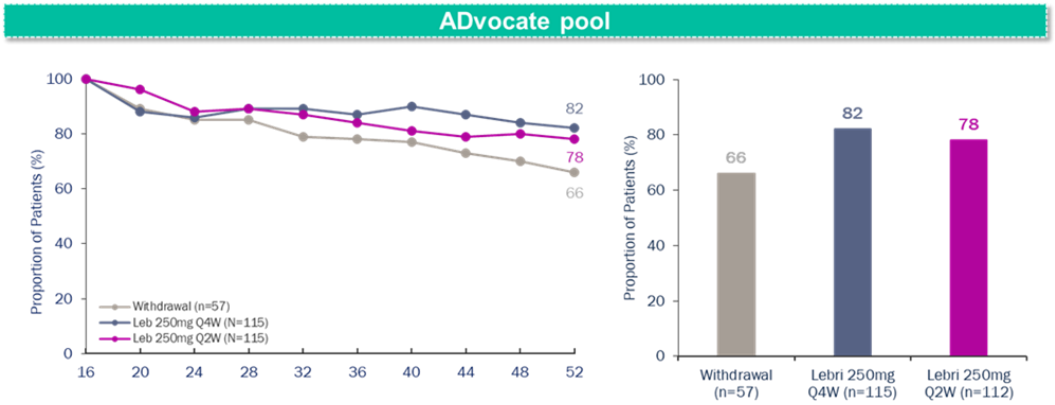
Figure 7: EASI 75 response rates to Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere
P-values vs placebo: ***P≤0.001; **P≤0.01; *P≤0.05.
Key: EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, MCMC-MI = Markov Chain Monte Carlo Multiple Imputation, mITT = modified intention to treat, NRI, non-responder imputation; ns = not significant; Q2W = every 2 weeks
Source: Silverberg et al (2023) (72), Silverberg et al (2023) (supplementary information) (85); ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), Simpson et al (2023) (77); Simpson et al (2023) (supplementary information), (86) ADhere clinical study report (78)

Lebrikizumab-treated participants who achieved EASI 75 at Week 16 maintained a durable response through Week 52 in the ADvocate studies (Figure 8). The proportion of patients who maintained EASI 75 was higher in the groups re-randomised to lebrikizumab compared with the group re-randomised to placebo (the

lebrikizumab withdrawal group). The EASI 75 response was similar in the lebrikizumab Q4W and Q2W groups.

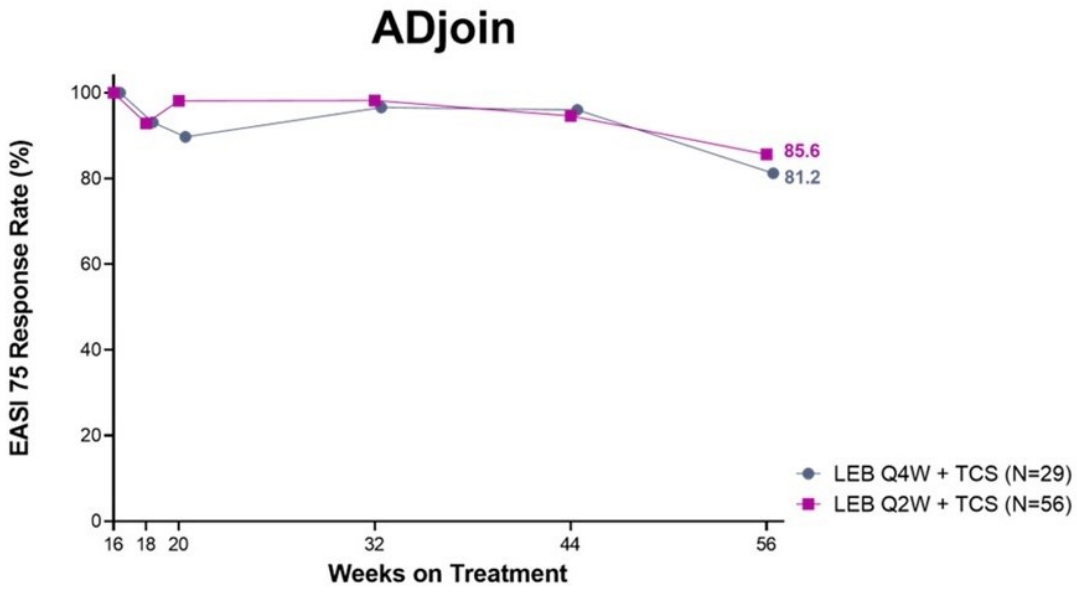
Figure 8: Maintenance of EASI 75 through Week 52 (pooled ADvocate study populations)



Data are shown for the MPP in ADvocate 1 and the mMPP in ADvocate 2. Missing data were imputed using MCMC-MI.
Key: EASI 75 = 75% improvement in Eczema Area and Severity Index from baseline; Leb = lebrikizumab; Q2W, every 2 weeks; Q4W = every 4 weeks
Source: Adapted from Blauvelt et al (2023) (73)

An interim analysis of data from ADjoin showed that in lebrikizumab Week 16 responders who rolled over from ADhere, EASI 75 response rates were maintained up to Week 56, regardless of TCS use during ADhere (Figure 9). Longer-term (2-year) data from ADjoin is presented in Section B.2.6.4.

Figure 9: Maintenance of EASI 75 in lebrikizumab responders who rolled over from ADhere to ADjoin



In ADjoin, participants continued or stopped TCS use as needed; 73.3% of patients used TCS (LEB Q4W: 79.3%; LEB Q2W: 70.2%).
Key: EASI = Eczema Area and Severity Index; LEB=lebrikizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; TCS=topical corticosteroids
Source: ADjoin interim clinical study report (83); Guttman-Yassky et al (2023) (81)

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

An IGA score of 0 or 1 corresponds to clear to almost clear skin in AD. Across all three studies, a significantly greater proportion of patients achieved IGA (0,1) with a ≥2-point improvement from baseline at Week 16 (co-primary endpoint) in the lebrikizumab group than in the placebo group (Table 19).

Table 19: IGA (0,1) with ≥2-point reduction at Week 16

	ADvocate 1		ADvocate 2		ADhere	
IGA (0,1) with ≥2-point reduction Week 16	**PBO (n = 141)**	**LEB 250 Q2W (n = 283)**	**PBO (n = 146)**	**LEB 250 Q2W (n = 281)**	**PBO + TCS (n = 66)**	**LEB + TCS (n = 145)**
MCMC-MI						
% of participants	12.7	43.1	10.8	33.2	22.1	41.2
Difference (95% CI)	29.7 (21.6 to 37.8)		21.9 (14.2 to 29.6)		18.3 (5.1 to 31.5)	
P value	<0.001		<0.001		[redacted]	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI
Key: CI, confidence interval; EASI, Eczema Activity and Severity Index, LEB, lebrikizumab; ITT, intention to treat, MCMC-MI, Markov Chain Monte Carlo multiple imputation; mITT, modified intention to treat, PBO, placebo; Q2W, every 2 weeks
Source: Silverberg et al (2023) (72), Silverberg et al (2023) (supplementary information) (85), ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), Simpson et al (2013) (77), Simpson et al (2023) (supplementary information) (86), ADhere clinical study report (78)

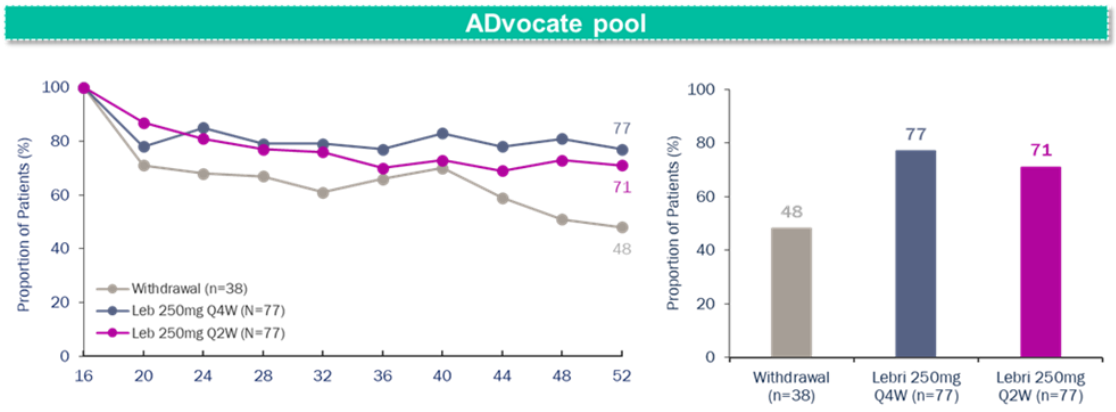
Figure 10 shows IGA (0,1) with a 2-point improvement from baseline over time to Week 16. As with EASI 75, a meaningful response was seen within the first 4 weeks of starting treatment with lebrikizumab. Again, the results were similar regardless of the method used to impute missing data.

Figure 10: IGA (0,1) with 2-point reduction from baseline at Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere
P-values vs placebo: ***P≤0.001; **P≤0.01; *P≤0.05.
Key: EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, MCMC-MI = Markov Chain Monte Carlo Multiple Imputation, mITT = modified intention to treat, NRI, non-responder imputation; ns = not significant; Q2W = every 2 weeks
Source: Silverberg et al (2023) (72), Silverberg et al (2023) (supplementary information) (85), ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), Simpson et al (2013) (77), Simpson et al (2023) (supplementary information) (86), ADhere clinical study report (78)

Lebrikizumab-treated participants who achieved IGA (0,1) with ≥2-point reduction from baseline at Week 16 maintained a durable response through Week 52 in the ADvocate studies (Figure 11). The proportion of patients who maintained IGA (0,1) was higher in the groups re-randomised to lebrikizumab Q4W or Q2W compared with the group re-randomised to placebo (the lebrikizumab withdrawal group).

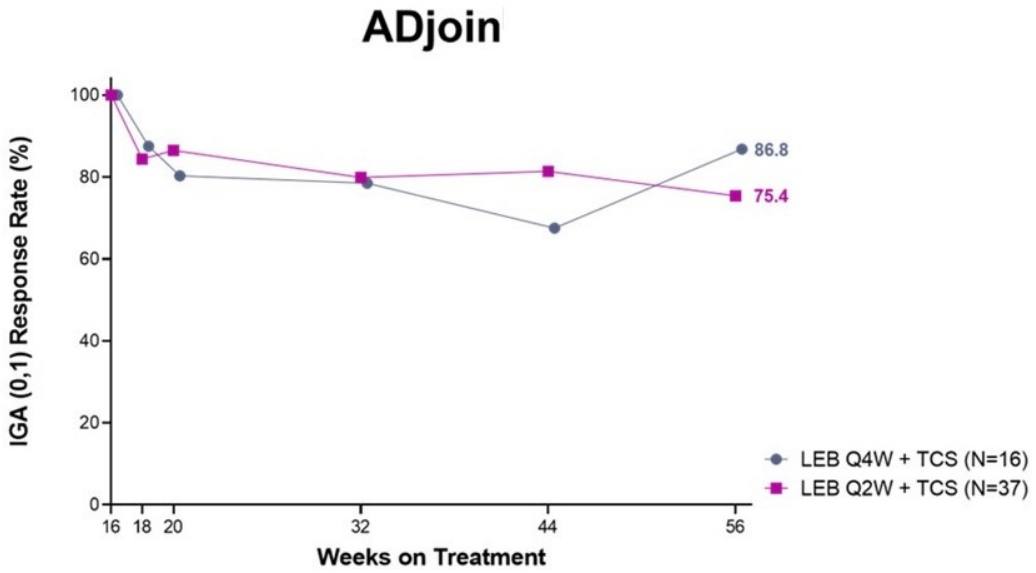
Figure 11: Maintenance of IGA 0/1 response through Week 52 (pooled ADvocate study populations)



Data are shown for the MPP in ADvocate 1 and the mMPP in ADvocate 2. Missing data were imputed using MCMC-MI.
Key: IGA, Investigator Global Assessment; Leb, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation; MPP, maintenance primary population; mMPP, modified maintenance primary population; PBO, placebo;Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Adapted from Blauvelt et al (2023) (73)

An interim analysis of data from ADjoin showed that in lebrikizumab Week 16 responders who rolled over from ADhere, IGA (0,1) response rates were maintained up to Week 56, regardless of TCS use during ADhere (Figure 12). Longer-term (2-year) data from ADjoin is presented in Section B.2.6.4.

Figure 12: Maintenance of IGA (0,1) response rates in lebrikizumab responders who rolled over from ADhere to ADjoin



In ADjoin, patients rolling over from ADhere continued or stopped TCS use, as needed; a total of 73.3% of patients used TCS (LEB Q4W: 79.3%; LEB Q2W: 70.2%)
Key: IGA=Investigator's Global Assessment; LEB=lebrikizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; TCS=topical corticosteroids
Source: ADjoin interim clinical study report (83); Guttman-Yassky et al (2023) (81)

Other EASI endpoints

EASI 90 at Week 16

Table 20 shows the EASI 90 response at Week 16. In all three studies, significantly more patients in the lebrikizumab groups achieved EASI-90 at Week 16 than in the placebo groups. The EASI-90 response rate was higher with lebrikizumab in combination with TCS than with lebrikizumab in monotherapy.

Table 20: EASI 90 at Week 16 (ADvocate 1 & 2, ADhere)

	ADvocate 1		ADvocate 2		ADhere	
	PBO (n = 141)	LEB 250 Q2W (n = 283)	PBO (n = 146)	LEB 250 Q2W (n = 281)	PBO + TCS (n = 66)	LEB + TCS (n = 145)
EASI 90 Week 16						
% of participants	9.0	38.3	9.5	30.7	21.7	41.2
Difference (95% CI)	28.8 (21.3 to 36.3)		20.7 (13.3 to 28.1)		18.9 (6.1 to 31.7)	
P value	<0.001		<0.001		<0.01	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI

Key: CI, confidence interval; EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, mITT = modified intention to treat, PBO, placebo; Q2W = every 2 weeks

Source: Silverberg et al (2023) (72), Simpson et al (2013) (77)

Figure 13 shows EASI 90 response over time to Week 16. The results show that a meaningful treatment response with lebrikizumab was seen within the first 2 to 8 weeks.

Figure 13: EASI 90 response through Week 16 (ADvocate 1 & 2, ADhere)

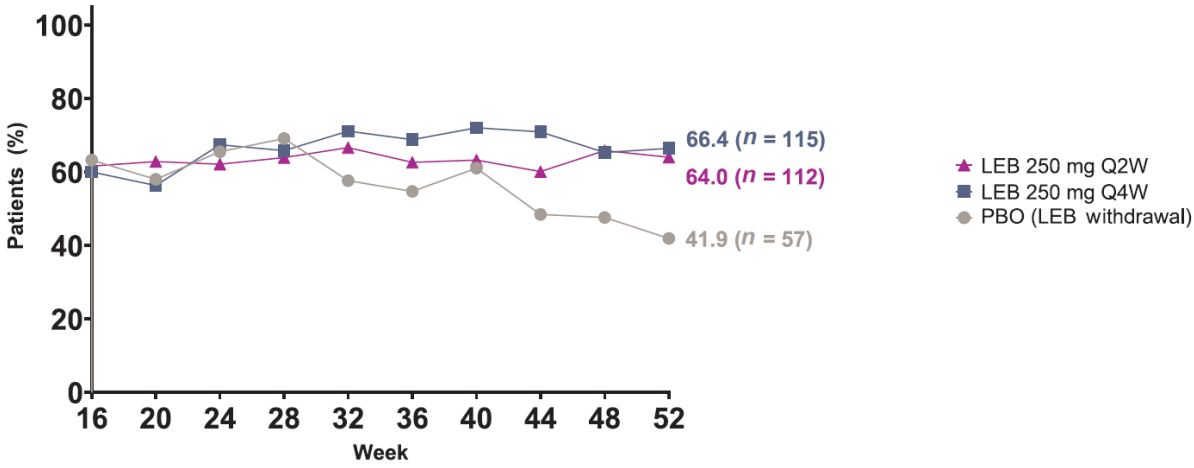
Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI

Key: CI, confidence interval; EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, mITT = modified intention to treat, PBO, placebo; Q2W = every 2 weeks

Source: Silverberg et al (2023) (72), Simpson et al (2013) (77), ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76); ADhere clinical study report (78)

Lebrikizumab-treated participants who achieved EASI 90 at Week 16 maintained a durable response through Week 52 in the ADvocate studies (Figure 14). Results were similar in the lebrikizumab Q4W and the lebrikizumab Q2W groups.

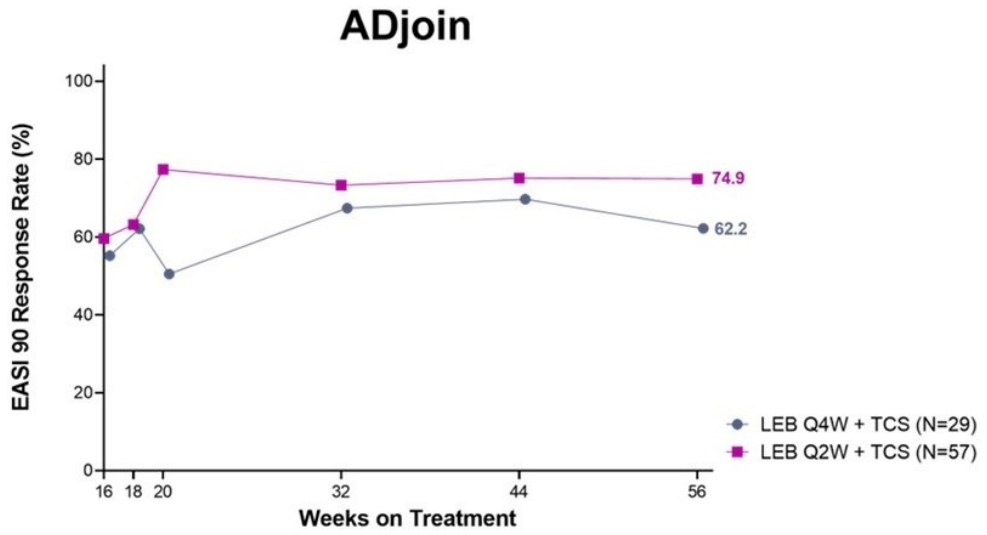
Figure 14: Maintenance of EASI 90 response through Week 52 (pooled ADvocate 1 & 2 population)



Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI
Key: CI, confidence interval; EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, mITT = modified intention to treat, PBO, placebo; Q2W = every 2 weeks
Source: Blauvelt et al (2023) (73)

An interim analysis of data from ADjoin showed that in lebrikizumab Week 16 responders who rolled over from ADhere, EASI 90 was maintained or increased up to Week 56, regardless of TCS use during ADhere (Figure 15). Longer-term (2-year) data from ADjoin is presented in Section B.2.6.4.

Figure 15: Maintenance of EASI 90 in lebrikizumab responders who rolled over from ADhere to ADjoin



In ADjoin, participants who rolled over from ADhere continued or stopped TCS use, as needed; a total of 73.3% of patients used TCS (LEB Q4W: 79.3%; LEB Q2W: 70.2%)
Key: EASI 75/90=75%/90% improvement from baseline in Eczema Area and Severity Index; IGA=Investigator's Global Assessment; LEB=lebrikizumab; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; TCS=topical corticosteroids
Source: ADjoin interim clinical study report (83); Guttman-Yassky et al (2023) (81)

EASI percent change from baseline at Week 16

Table 21 shows the percent change from baseline in EASI at Week 16.

Table 21: EASI percent change from baseline at Week 16 (ADvocate 1 & 2, ADhere)

	ADvocate 1		ADvocate 2		ADhere	
	PBO (n = 141)	LEB 250 Q2W (n = 283)	PBO (n = 146)	LEB 250 Q2W (n = 281)	PBO + TCS (n = 66)	LEB + TCS (n = 145)
EASI % CFB Week 16						
LS mean (SE)s	-26.0 (4.0)	-64.3 (3.2)	-28.0 (3.9)	-61.5 (3.3)	-53.1 (5.1)	-76.8 (4.1)
Difference (SE)	-38.3 (4.2)		-33.6 (3.9)		-23.6 (5.1)	
P value	<0.001		<0.001		<0.001	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data were imputed using MCMC-MI
Key: CFB, change from baseline; CI, confidence interval; EASI = Eczema Activity and Severity Index, LEB = lebrikizumab; ITT = intention to treat, mITT = modified intention to treat, PBO, placebo; Q2W = every 2 weeks; SE, standard error
Source: Silverberg et al (2023) (supplementary information) (85), Simpson et al (2013) (supplementary information) (86)

Figure 16 shows the EASI % change from baseline through Week 16. With lebrikizumab monotherapy, a significant change was seen by Week 2. In

combination with TCS, lebrikizumab produced a significant change in EASI from baseline by Week 4. In all three studies, the EASI percent change from baseline continued to improve through Week 16.

Figure 16: EASI % change from baseline through Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere P-values vs placebo: ***P≤0.001; **P≤0.01; *P≤0.05.
Key: EASI = Eczema Activity and Severity Index, IGA = Investigator's Global Assessment, ITT = intention to treat, LEB = lebrikizumab, MCMC-MI = Markov Chain Monte Carlo Multiple Imputation, mITT = modified intention to treat, ns = not significant, Q2W = every 2 weeks, TCS = topical corticosteroids
Source: Silverberg et al (2023); Simpson et al (2023) ; ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76); ADhere clinical study report (78)

Itch NRS

Itch NRS ≥4-point improvement from baseline

Table 22 shows the proportion of patients who had ≥4-point improvement from baseline in their itch NRS score at Week 16. Note that this analysis was carried out in those participants who had a score of at least 4 at baseline.

In all three studies, a significantly greater proportion of participants treated with lebrikizumab reported an improvement of at least 4 points in itch NRS scores at Week 16 compared with placebo.

Table 22: Itch NRS 4-point improvement at Week 16

	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 130)	LEB 250 Q2W (N = 263)	PBO (N = 134)	LEB 250 Q2W (N = 253)	PBO + TCS (N = 57)	LEB + TCS (N = 130)

Week 16						
% of participants	13.0	45.9	11.5	31.8	31.9	50.6
Difference (95% CI)	32.9 (24.6 to 41.3)		20.4 (12.3 to 28.6)		19.2 (4.3 to 34.1)	
P value	<0.001		<0.001		[redacted]	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI.
Key: CI, confidence interval; ITT, intention to treat; LEB, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation mITT, modified intention to treat; PBO, placebo; TCS, topical corticosteroids
Source: Silverberg et al (2023) (72), Simpson et al (2023) (77); ADhere clinical study report (78)

Figure 17 shows NRS ≥4-point improvement from baseline over time to Week 16. Onset of itch relief was rapid, with significant differences between lebrikizumab and placebo seen as early as Week 2 in ADvocate 1 and Week 4 in ADvocate 2 and ADhere.

Figure 17: Itch NRS 4-point improvement to Week 16

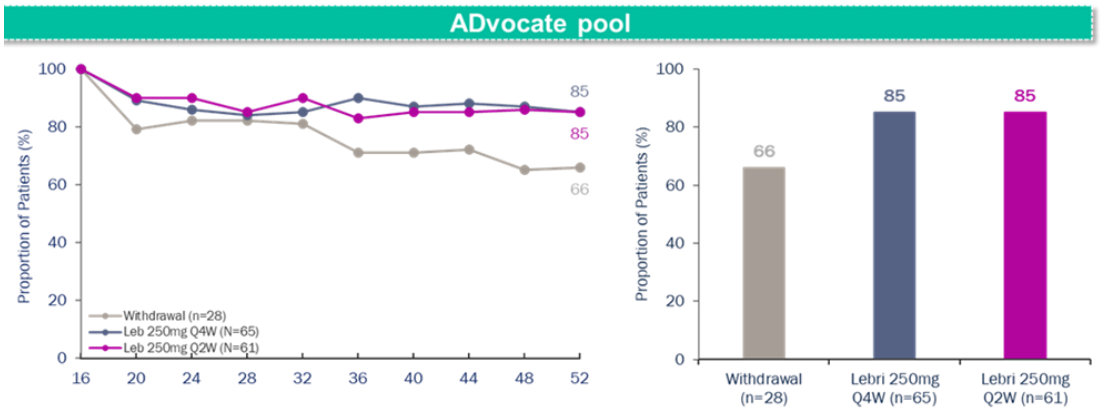
[redacted]

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere
P-values vs placebo: ***P≤0.001; **P≤0.01; *P≤0.05.
Key: EASI = Eczema Activity and Severity Index, IGA = Investigator's Global Assessment, ITT = intention to treat, LEB = lebrikizumab, MCMC-MI = Markov Chain Monte Carlo Multiple Imputation, mITT = modified intention to treat, ns = not significant, Q2W = every 2 weeks, TCS = topical corticosteroids
Source: Silverberg et al (2023); Simpson et al (2023) ; ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76); ADhere clinical study report (78)

In the ADvocate studies, the itch response was maintained through Week 52 among lebrikizumab Week 16 responders who also had a 4-point itch NRS improvement at Week 16 (and a NRS of at least 4 at baseline) (

Figure 18). Across both studies, the proportion of participants who maintained a reduction in itch at Week 52 was higher in the lebrikizumab groups than in the lebrikizumab withdrawal group, although the differences were not statistically significant.

Figure 18: Maintenance of Itch NRS 4-point improvement through Week 52 (ADvocate pooled populations)



Data are shown for the MPP in ADvocate 1 and the mMPP in ADvocate 2. Missing data were imputed using MCMC-MI.
Key: NRS, numerical rating scale; Leb/Lebri: lebrikizumab; Q2W, every 2 weeks; Q4W, every 4 weeks
Source: Adapted from Blauvelt et al (2023) (73)

Itch NRS percent change from baseline

Table 23 shows the percent change from baseline in itch NRS at Week 16.

Table 23: Percent change from baseline in itch NRS at Week 16

	ADvocate 1		ADvocate 2		ADhere	
Itch NRS % CFB Week 16	**PBO (n = 141)**	**LEB 250 Q2W (n = 283)**	**PBO (n = 146)**	**LEB 250 Q2W (n = 281)**	**PBO + TCS (n = 66)**	**LEB + TCS (n = 145)**
LSM (SE)	-15.1 (3.8)	-45.5 (3.1)	-9.0 (3.9)	-36.6 (3.3)	-35.5 (6.4)	-50.7 (4.5)
LSM difference (SE)	-30.4 (3.9)		-27.5 (3.8)		-15.2 (6.4)	
P value	<0.001		<0.001		0.02	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI.
Key: CFB, change from baseline; ITT, intention to treat; LEB, lebrikizumab; LSM, least squares mean; MCMC-MI, Markov Chain Monte Carlo multiple imputation; mITT, modified intention to treat; NRS, numerical rating scale; PBO, placebo; SE, standard error; TCS, topical corticosteroids
Source: Silverberg et al (2023) (supplementary information) (85) ; Simpson et al (2023) (77); Simpson et al (2023) (supplementary information) (86)

Figure 19 shows the percent change from baseline in itch NRS over time. As monotherapy, lebrikizumab produced a significant change in itch NRS from baseline by Week 1. In combination with TCS, lebrikizumab produced a significant change in itch NRS from baseline by Week 6. In all three studies, the itch NRS percent change from baseline continued to improve through Week 16.

Figure 19: Percent change from baseline in itch NRS to Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI.
P-values vs placebo: ***P≤0.001; **P≤0.01; *P≤0.05.
Key: ITT, intention to treat; Lebri, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation; mITT, modified intention to treat; ns, not significant; Q2W, every 2 weeks
Source: Silverberg et al (2023) (supplementary information) (85); ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); ADhere clinical study report (78)

Sleep-loss scale

Sleep-loss scale ≥2-point improvement from baseline

The sleep loss scale assessed the extent of sleep loss due to itch during the previous night. In all three studies, a significantly greater proportion of patients treated with lebrikizumab reported an improvement of at least 2 points in sleep-loss scale scores at Week 16 compared with placebo (Table 24). Note that this analysis only included patients who reported a sleep-loss scale score ≥2 at baseline.

Table 24: Sleep-loss scale ≥2-point improvement from baseline at Week 16

	ADvocate 1		ADvocate 2		ADhere	
Sleep loss score ≥2 point improvement Week 16	**PBO (n = 91)**	**LEB 250 Q2W (n = 195)**	**PBO (n = 97)**	**LEB 250 Q2W (n = 161)**	**PBO + TCS (n = 34)**	**LEB + TCS (n = 88)**
% of participants	4.7	39.0	8.2	28.0	[redacted]	
Difference (95% CI)	34.6 (26.2 to 43.0)		18.9 (9.6 to 28.1)		[redacted]	
P value	<0.001		<0.001		[redacted]	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI.
Key: CI, confidence interval; ITT, intention to treat; LEB, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation mITT, modified intention to treat; PBO, placebo; TCS, topical corticosteroids
Source: Silverberg et al (2023); ADhere clinical study report (78)

The proportion of participants with a ≥2-point improvement from baseline in sleep-loss scale over time is shown in Figure 20.

Figure 20: Proportion of participants with ≥2-point improvement from baseline in sleep-loss score through Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI (primary analysis) or NRI (supportive analysis).
Key: CI = confidence interval, ITT, intention to treat; Lebri, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation mITT, modified intention to treat;, Q2W, every 2 weeks,
Source: ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), ADhere clinical study report (78)

Sleep-loss scale change from baseline

The change from baseline in sleep-loss score at Week 16 was significantly greater with lebrikizumab than with placebo in all three studies.

DLQI

≥4-point improvement from baseline at Week 16

This analysis included patients who reported a DLQI total score ≥4 at baseline. In all three studies, a significantly greater proportion of patients treated with lebrikizumab reported an improvement of at least 4 points in DLQI scores at Week 16 compared with placebo (Table 25).

Table 25: ≥4-point improvement from baseline in DLQI at Week 16

	ADvocate 1		ADvocate 2		ADhere	
DLQI ≥4-point improvement Week 16	**PBO (n = 116)**	**LEB 250 Q2W (n = 226)**	**PBO (n = 115)**	**LEB 250 Q2W (n = 215)**	**PBO + TCS (n = 48)**	**LEB + TCS (n = 105)**
MCMC-MI						
% of participants	33.8	75.6	33.6	66.3	58.7	77.4

Difference (95% CI)	41.8 (31.2 to 52.3)	33.0 (22.2 to 43.8)	17.2 (0.1 to 34.3)
P value	<0.001	<0.001	[redacted]

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI
Key: CI, confidence interval, DLQI, Dermatology Life Quality Index; ITT, intention to treat; LEB, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation; mITT, modified intention to treat; PBO, placebo, Q2W, every 2 weeks, SE, standard error; TCS, topical corticosteroid
Source: Silverberg et al (2023) (supplementary information) (72); Simpson et al (2023) (77); Simpson et al (2023) (supplementary information) (86); ADhere clinical study report (78)

DLQI scores started to improve rapidly after initiation of lebrikizumab, with statistically significant differences between treatment groups seen at the first timepoint (Week 4) (Figure 21).

Figure 21: Proportion of participants with ≥4-point improvement from baseline in DLQI through Week 16

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI (primary analysis) and NRI (supportive analysis).
Key: CI = confidence interval; ITT, intention to treat; Lebri, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation; mITT, modified intention to treat; NRI, non-responder imputation; Q2W, every 2 weeks
Source: Silverberg et al (2023) (supplementary information) (85); ADvocate 1 clinical study report (75), ADvocate 2 clinical study report (76), Simpson et al (2023) (77), Simpson et al (2023) (supplementary information) (86), ADhere clinical study report (78)

Mean DLQI scores at Week 52

Table 26 shows DLQI scores at Week 52 in ADvocate 1 and 2.

Table 26: Mean (SD) DLQI scores at Week 52

	ADvocate 1			ADvocate 2		
	PBO (LEB withdrawal) N = 32	**LEB 250 Q4W N = 63**	**LEB 250 Q2W N = 62**	**PBO (LEB withdrawal)** N = 28	**LEB 250 Q4W N = 55**	**LEB 250 Q2W N = 51**
DLQI, mean (SD)	4.4 (4.3)	3.7 (4.9)	3.5 (4.6)	5.3 (5.7)	3.2 (4.2)	4.4 (4.7)

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using MCMC-MI.
Key: CI = confidence interval; ITT, intention to treat; Lebri, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple

imputation; mITT, modified intention to treat; NRI, non-responder imputation; Q2W, every 2 weeks
Source: Blauvelt et al (2023) (supplementary information)

Other patient-reported outcomes and quality of life measures

POEM and PROMIS

In all three studies, lebrikizumab-treated participants had a statistically significantly greater reduction (improvement) in POEM scores at Week 16 than placebo-treated patients (Table 27).

Table 27: Change from baseline in POEM score at Week 16

	ADvocate 1		ADvocate 2		ADhere	
POEM score CFB Week 16	**PBO (N = [redacted])**	**LEB 250 Q2W (N = [redacted])**	**PBO (N = [redacted])**	**LEB 250 Q2W (N = [redacted])**	**PBO + TCS (N = 40)**	**LEB + TCS (N = 101)**
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	-6.2 (1.0)	-10.2 (0.7)
LS mean difference (SE)	[redacted]		[redacted]		-4.0 (1.1)	
P value	[redacted]		[redacted]		<0.001	

N represents number of patients with non-missing data at Week 16. Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere.
Key: CFB, change from baseline; LEB, lebrikizumab; LS, least squares; PBO, placebo; POEM, Patient Oriented Eczema Measure; Q2W, every 2 weeks; SE, standard error; TCS, topical corticosteroids
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); Simpson et al (2023) (77)

There were also improvements in anxiety and depression among adult participants at Week 16, as measured using PROMIS (Table 28).

Table 28: Change from baseline in PROMIS anxiety and depression scores at Week 16 (adults)

	ADvocate 1		ADvocate 2		ADhere	
PROMIS CFB Week 16	**PBO**	**LEB 250 Q2W**	**PBO**	**LEB 250 Q2W**	**PBO + TCS**	**LEB + TCS**
Anxiety						
N	[redacted]	[redacted]	[redacted]	[redacted]	43	101
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	-1.1 (1.4)	-1.9 (1.0)
LS mean difference (SE)	[redacted]		[redacted]		-0.8 (1.4)	
P value	[redacted]		[redacted]		[redacted]	
Depression						

N	[redacted]	[redacted]	[redacted]	[redacted]	43	101
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	-1.2 (1.1)	-1.4 (0.8)
LS mean difference (SE)	[redacted]		[redacted]		-0.2 (1.1)	
P value	[redacted]		[redacted]		[redacted]	

N represents the number of patients with non-missing data at Week 16. Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere.
Key: CFB, change from baseline; LEB, lebrikizumab; LS, least squares; PBO, placebo; PROMIS, Patient Reported Outcomes Measurement Information System; Q2W, every 2 weeks; SE, standard error; TCS, topical corticosteroids
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); Simpson et al (2023) (77); ADhere clinical study report (78)

At Week 52, improvements in POEM were greater in the lebrikizumab groups than in the placebo group; the differences were statistically significant in ADvocate 1, but not in ADvocate 2 (Table 29). Improvements in PROMIS anxiety were also greater in the lebrikizumab groups than in the placebo group at Week 52; the differences were not statistically significant in either study (75, 76).

Table 29: Change from baseline in POEM at Week 52

	ADvocate 1			ADvocate 2		
	PBO (LEB withdrawal)	**LEB 250 Q4W**	**LEB 250 Q2W**	**PBO (LEB withdrawal)**	**LEB 250 Q4W**	**LEB 250 Q2W**
POEM						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (SE)	-	[redacted]	[redacted]	-	[redacted]	[redacted]
P value	-	[redacted]	[redacted]	-	[redacted]	[redacted]

N represents the number of patients with non-missing data at Week 52. Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2.
Key: LEB, lebrikizumab; LS, least squares; PBO, placebo; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; SE, standard error
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76)

EQ-5D-5L

In all three studies, the improvement in EQ-5D-5L VAS scores at Week 16 was greater in the lebrikizumab group than in the placebo group. In the ADvocate studies, the treatment difference was statistically significant (Table 30).

Table 30: Change from baseline in EQ-5D-5L VAS scores at Week 16

	ADvocate 1		ADvocate 2		ADhere	
	PBO (n = 141)	LEB 250 Q2W (n = 282)	PBO (n = 145)	LEB 250 Q2W (n = 277)	PBO + TCS (n = 65)	LEB + TCS (n = 143)
LS mean (SE) % change	[redacted]	[redacted]	[redacted]	[redacted]	6.5 (2.4)	10.1 (1.8)
LS mean difference (SE)	[redacted]		[redacted]		3.6 (2.4)	
P value	[redacted]		[redacted]		[redacted]	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using LOCF.
Key: ITT, intention to treat; LEB, lebrikizumab; LOCF, last observation carried forward; LS, least squares; mITT, modified intention to treat; PBO, placebo; Q2W, every 2 weeks; SE, standard error
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); ADhere clinical study report (78); Simpson et al (2023) (77)

In all three studies, treatment with lebrikizumab resulted in statistically significant improvements in the EQ-5D-5L Health State Index Score (UK algorithm) at Week 16 compared with placebo (Table 31).

Table 31: Change from baseline in EQ-5D-5L Health State Index (UK) Score at Week 16

	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = [redacted])	LEB 250 Q2W (N = [redacted])	PBO (N = [redacted])	LEB 250 Q2W (N = [redacted])	PBO + TCS (N = 65)	LEB + TCS (N = 143)
LS mean (SE) % change	[redacted]	[redacted]	[redacted]	[redacted]	0.05 (0.03)	0.15 (0.02)
LS mean difference (SE)	[redacted]		[redacted]		0.1 (0.03)	
P value	[redacted]		[redacted]		<0.001	

Data shown for the ITT population in ADvocate 1 and the mITT population for ADvocate 2 and ADhere. Missing data imputed using LOCF.
Key: ITT, intention to treat; LEB, lebrikizumab; LOCF, last observation carried forward; LS, least squares; mITT, modified intention to treat; PBO, placebo; Q2W, every 2 weeks; SE, standard error
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); Simpson et al (2023) (77)

In the ADvocate studies, the improvement in EQ-5D-5L VAS scores [redacted] with lebrikizumab than with placebo at Week 52 (75, 76). Treatment with lebrikizumab [redacted] in EQ-5D-5L Health State Index scores at Week 52 compared with placebo (75, 76).

Table 32: Change from baseline in EQ-5D-5L VAS and Health State Index (UK) Scores at Week 52: ADvocate 1 & 2 (pooled data)

	ADvocate 1 & 2 pooled data (pmMPP)		
	PBO (LEB withdrawal) (N = 60)	LEB 250 Q4W (N = 118)	LEB 250 Q2W (N = 113)
ED-5D-5L VAS			
n	[redacted]	[redacted]	[redacted]
LS mean (SE) % change	[redacted]	[redacted]	[redacted]
LS mean difference (SE) vs placebo (LEB withdrawal)	-	[redacted]	[redacted]
P value	-	[redacted]	[redacted]
ED-5D-5L Health State Index			
n	[redacted]	[redacted]	[redacted]
LS mean (SE) % change	[redacted]	[redacted]	[redacted]
LS mean difference (SE) vs placebo (LEB withdrawal)	-	[redacted]	[redacted]
P value	-	[redacted]	[redacted]

Missing data imputed using LOCF.
Key: LEB, lebrikizumab; LOCF, last observation carried forward; LS, least squares; PBO, placebo; pmMPP, pooled modified maintenance primary population; Q2W, every 2 weeks; SE, standard error
Source: ADvocate pooled EQ-5D-5L data (87)

Rescue medication use

Rescue medication use was lower with lebrikizumab than with placebo through Week 16 (Table 33).

Table 33: Rescue medication use through Week 16

	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 141)	LEB 250 Q2W (N = 283)	PBO (N = 146)	LEB 250 Q2W (N = 281)	PBO + TCS (N = 66)	LEB + TCS (N = 145)
Use of any rescue medication, n (%)	47 (33.3)	31 (11.0)	58 (39.7)	52 (18.5)	7 (10.6)	6 (4.1)
Topical[a]	44 (31.2)	27 (9.5)	54 (37.0)	48 (17.1)	3 (4.5)	2 (1.4)
Systemic[b]	11 (7.8)	7 (2.5)	9 (6.2)	8 (2.8)	5 (7.6)	5 (3.4)

[a]TCS, TCI and crisaborole in ADvocate 1 & 2; high-potency TCS only in ADhere. [b]Systemic corticosteroids, immunosuppressants, biologics and phototherapy/photochemotherapy. Data are shown for the ITT population in ADvocate 1 and the mITT population in ADvocate 2 and ADhere.

Key: ITT, intention to treat; LEB, lebrikizumab; mITT, modified intention to treat; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroids

Source: Silverberg et al (2023), supplementary information (85); Simpson et al (2013), supplementary information (86)

During the maintenance period, rescue medication use remained low across the treatment arms (14.0% of all participants in ADvocate 1 and 16.4% in ADvocate 2 used rescue medication) (73). In the pooled analysis, the proportion of participants using rescue medication was comparable among treatment groups: 12.4% with LEB Q2W, 16.1% with LEB Q4W and 18.3% in the lebrikizumab withdrawal group (Table 34). Most rescue medication use was topical; rates of systemic rescue use were low in all three treatment groups (LEB Q2W: 1.8%; LEB Q4W: 2.5%; lebrikizumab withdrawal group: 0%) (73).

Table 34 Rescue medication use during the maintenance period (ADvocate 1 & 2)

	ADvocate 1 and 2 pooled results (pmMPP)		
	PBO (LEB withdrawal) (N = 60)	LEB Q4W (N = 118)	LEB Q2W (N = 113)
Use of any rescue medication, n (%)	11 (18.3)	19 (16.1)	14 (12.4)
Topical	11 (18.3)	16 (13.6)	13 (11.5)
TCS	8 (13.3)	14 (11.9)	11 (9.7)
Low-to-moderate potency	3 (5.0)	9 (7.6)	6 (5.3)
High potency	6 (10.0)	6 (5.1)	5 (4.4)
TCI	3 (5.0)	2 (1.7)	4 (3.5)
Systemic	0	3 (2.5)	2 (1.8)

Key: LEB, lebrikizumab; pmMPP, pooled modified maintenance primary population; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids
Source: Blauvelt et al (2023) supplementary information (88)

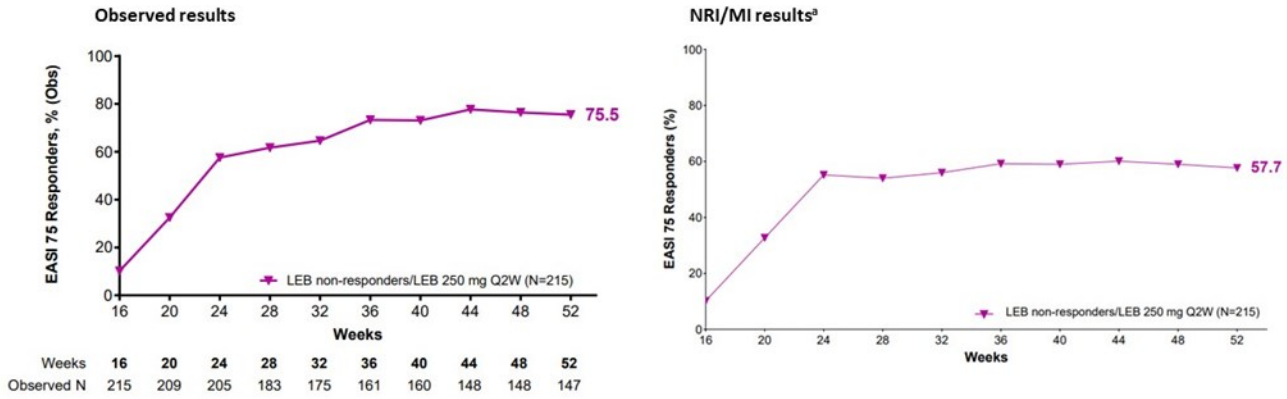
B.2.6.2. Per-protocol non-responders

At Week 16, participants in ADvocate 1 and ADvocate 2 who received placebo or lebrikizumab 250 mg Q2W and did not achieve IGA 0,1 or EASI 75, or used rescue medication were enrolled in the escape arm and received open-label lebrikizumab 250 mg Q2W (89) for an additional 36 weeks. Any participants who did not achieve or maintain EASI 50 after eight weeks in the escape arm were discontinued from the study.

Of the participants who received lebrikizumab in ADvocate 1 and ADvocate 2, 231 (41%) were assigned to the escape arm. Sixteen of these were found to be incorrectly assigned and were excluded from the analysis, resulting in a corrected population of 215 (38.1%). Despite not achieving the protocol-defined response at Week 16, most of these participants (58.1%) had achieved EASI 50 (90).

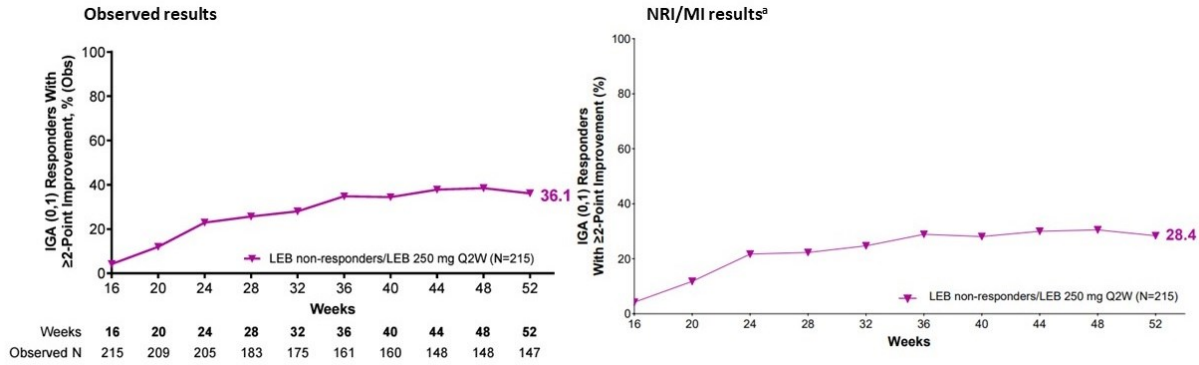
A substantial proportion of lebrikizumab-treated participants who entered the escape arm achieved EASI 75 by Week 24; response was maintained through Week 52 (Figure 22). There were also improvements in IGA (0,1) response by Week 24 that were maintained through Week 52 (Figure 23).

Figure 22: EASI 75 response rates among Week 16 per-protocol non-responders (ADvocate 1 & 2 pooled data)



Data are shown for the maintenance escape population. Response rate at Week 16 does not start from 0 as 22 patients achieved EASI 75 with use of rescue medication prior to Week 16. [a]Data after treatment discontinuation due to lack of efficacy were imputed with NRI; data after discontinuation due to other reasons and other missing data were imputed with MI.
Key: EASI, Eczema Area and Severity Index; LEB, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo Multiple Imputation; NonResp, non-responders; Obs, observed; PBO, placebo, Q2W, every 2 weeks
Source: Guttman-Yassky et al (2023) (89); Guttman-Yassky et al (2023) supplementary information (91)

Figure 23: IGA (0,1) response rates among Week 16 per-protocol non-responders (ADvocate 1 & 2 pooled data)



Data are shown for the maintenance escape population. Response rate at Week 16 does not start from 0 as 22 patients achieved EASI 75 with use of rescue medication prior to Week 16. [a]Data after treatment discontinuation due to lack of efficacy were imputed with NRI; data after discontinuation due to other reasons and other missing data were imputed with MI.
Key: IGA, Investigator's Global Assessment; LEB, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo Multiple Imputation; NonResp, non-responders; Obs, observed; PBO, placebo, Q2W, every 2 weeks
Source: Guttman-Yassky et al (2023) (89); Guttman-Yassky et al (2023) supplementary information (91)

B.2.6.3. Efficacy of lebrikizumab in patients who have previously failed, or are not suitable for, treatment with CsA: ADvantage

The data presented here are from an interim analysis of the ADvantage study (data cut-off 18 April 2023) conducted when all patients had either completed the 16-week induction period or discontinued from the study prior to Week 16.

EASI 75

The percentage of participants achieving EASI 75 at Week 16 (the primary endpoint) was statistically significantly higher in the lebrikizumab group than in the placebo group (Table 35).

Table 35: EASI response at Week 16 (ADvantage study)

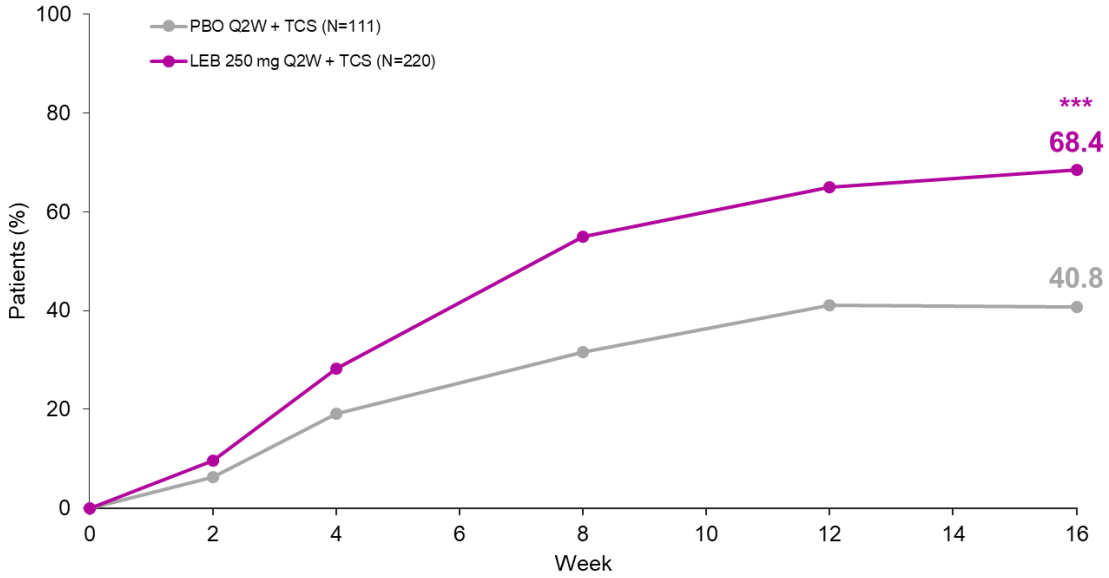
EASI 75 Week 16	PBO + TCS (N = 111)	LEB 250 Q2W + TCS (N = 220)
% of participants	40.8	68.4
Difference (95% CI)	[redacted]	
P value	<0.001	

Data shown for the FAS. Missing data were imputed using MCMC-MI
Key: CI, confidence interval; EASI, Eczema Activity and Severity Index, FAS, full analysis set; LEB, lebrikizumab; MCMC-MI,

Markov chain Monte Carlo multiple imputation; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroids
Source: Warren et al (2023) (79); ADvantage clinical study report (80)

Figure 24 shows the EASI 75 response over time. A statistically significant difference between the groups was evident by Week 8. The median time to EASI response was [redacted] days for lebrikizumab + TCS-treated patients vs. [redacted] days in the placebo + TCS group (P<0.001).

Figure 24: EASI 75 response to Week 16: ADvantage study



Data are shown for the FAS. ***P<0.001 versus placebo.
Key: EASI, Eczema Area Severity Index; FAS, full analysis set; Lebri, lebrikizumab; MCMC-MI, Markov Chain Monte Carlo multiple imputation; Q2W, every 2 weeks; TCS, topical corticosteroid
Source: Warren et al (2023) (79)

IGA (0,1)

At Week 16, more participants in the lebrikizumab + TCS group than in the placebo + TCS group had achieved IGA (0,1) with a ≥2-point improvement (key secondary endpoint) (Table 36).

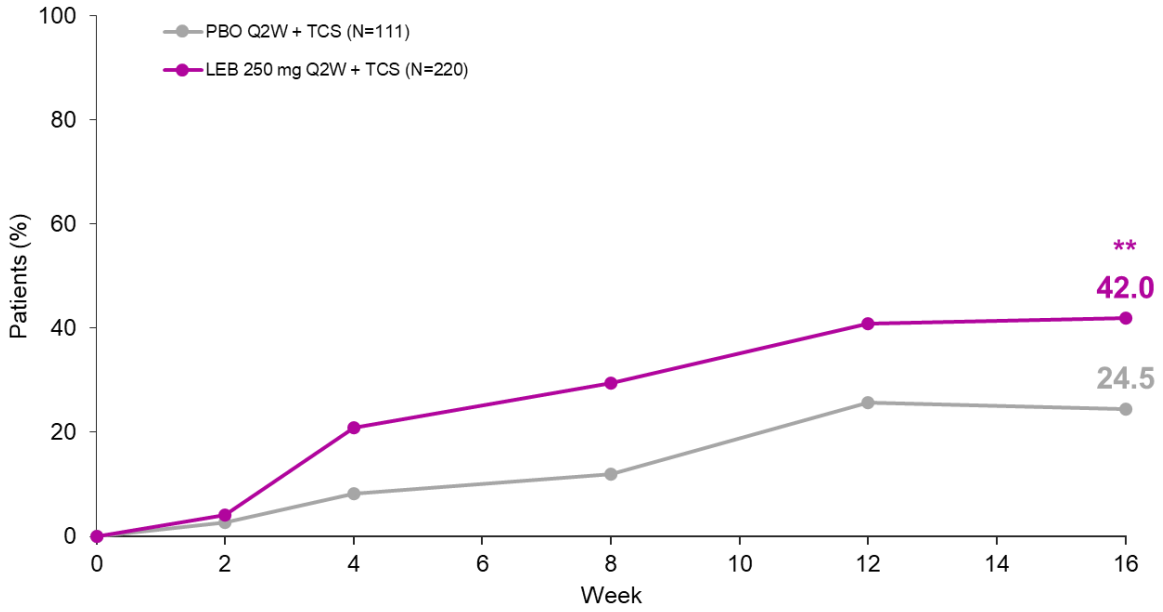
Table 36: IGA 0/1 response at Week 16 (ADvantage study)

IGA 0/1 Week 16	PBO + TCS (N = 111)	LEB 250 Q2W + TCS (N = 220)
% of participants	24.5	42.0
Difference (95% CI)	[redacted]	
P value	<0.01	

Data shown for the FAS. Missing data were imputed using MCMC-MI
Key: CI, confidence interval; FAS, full analysis set; LEB, lebrikizumab; IGA, Investigators Global Assessment; MCMC-MI, Markov chain Monte Carlo multiple imputation; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroids
Source: Warren et al (2023) (79); ADvantage clinical study report (80)

Figure 25 shows IGA 0/1 response over time to Week 16. A statistically significant treatment difference was evident at Week 4.

Figure 25: IGA (0,1) response at Week 16: ADvantage study



Data are shown for the FAS. ** p<0.01; lebrikizumab+TCS versus placebo+TCS
Key: IGA = Investigator Global Assessment; Lebri = lebrikizumab; MCMC-MI = Markov chain Monte Carlo with multiple imputation; Q2W = every two weeks; TCS = topical corticosteroids
Source: Warren et al (2023) (79)

Other EASI endpoints

The proportion of patients achieving EASI 90 and EASI 50 was higher in the lebrikizumab group than in the placebo group at Week 16 (Table 37). Statistically significant differences were seen between treatment groups at Week 4 for EASI 90 and Week 8 for EASI 50.

Table 37: EASI 90 and EASI 50 response at Week 16 response rates by visit: ADvantage study

Week 16	PBO + TCS (N = 111)		LEB 250 Q2W + TCS (N = 220)
EASI 90			
% of participants	20.8		42.9
P value		<0.001	
EASI 50			
% of participants	[redacted]		[redacted]
P value		[redacted]	

Data are shown for the FAS.
Key: EASI, Eczema Area and Severity Index; FAS, full analysis set; LEB, lebrikizumab; PBO, placebo; Q2W, every two weeks; TCS, topical corticosteroid
Source: Warren et al (2023) (79); ADvantage clinical study report (80)

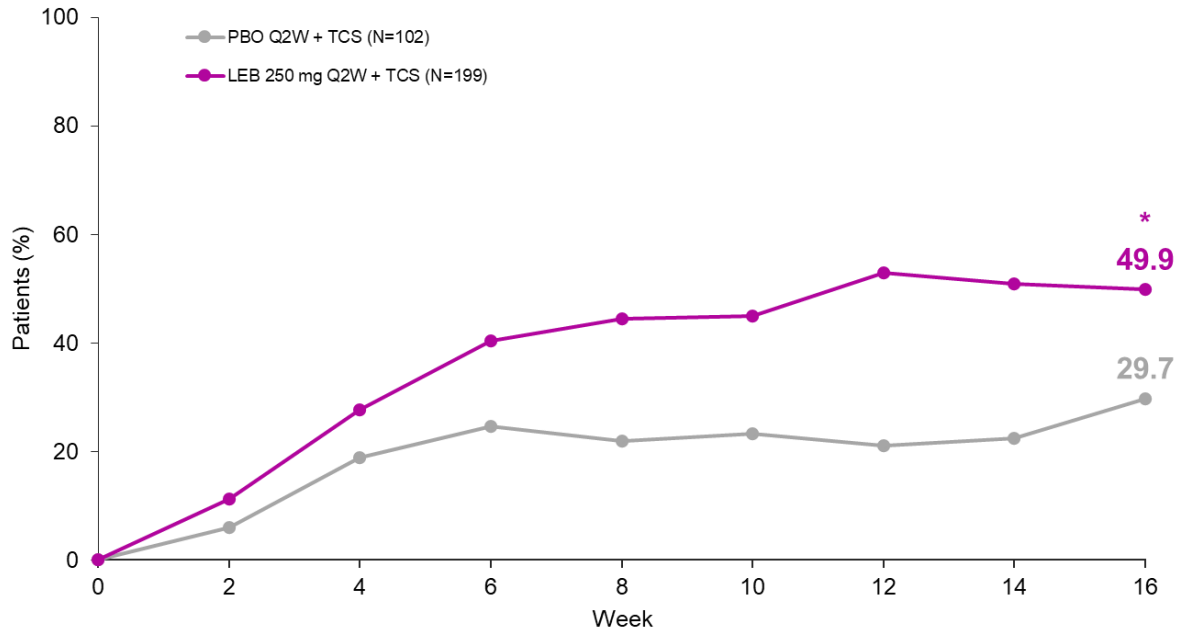
The median time to EASI response was:

- EASI 90: [redacted] days for lebrikizumab-treated patients [redacted] for the placebo group ([redacted])
- EASI 50: [redacted] days for lebrikizumab-treated patients vs. [redacted] days in the placebo group ([redacted])

Itch NRS

At Week 16, more participants in the lebrikizumab group than in the placebo group who had itch NRS ≥4 at baseline had achieved a ≥4-point improvement (key secondary endpoint): 49.9% versus 29.7% (common risk difference [redacted] [95% CI: [redacted] to [redacted]; P<0.05). A statistically significant treatment difference was seen at Week 8 (Figure 26).

Figure 26: Itch NRS ≥4 point improvement at Week 16: ADvantage study



Data are shown for the FAS. *P<0.05 versus placebo
Key: Lebri, lebrikizumab; MCMC-MI, Markov chain Monte Carlo – multiple imputation; Q2W, every 2 weeks; TCS, topical corticosteroids
Source: Warren et al (2023) (79)

Reductions from baseline in itch NRS were seen in both groups, with greater reductions in the lebrikizumab group at Week 2 (mean change: -1.5 vs. -1.1, respectively; LS mean difference between groups [redacted] [95% CI: [redacted]; [redacted]]), and continuing up to Week 16 (mean change: [redacted] vs. [redacted]; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted], [redacted]]).

Skin pain NRS

ADvantage was the first lebrikizumab study to collect data on skin pain, which had increasingly been reported with by patients with AD. 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 as early as Week 10 ([redacted]% vs. [redacted]%, respectively; common risk difference [redacted]% [95% CI: [redacted] to [redacted]; [redacted]]), and continuing up to Week 16 ([redacted]% vs. [redacted]%, respectively; common risk difference [redacted]% [95% CI: [redacted] to [redacted]; [redacted]]).

Reductions in skin pain NRS scores were observed for both treatment groups at each visit, with larger reductions from baseline observed among the lebrikizumab +

TCS-treated participants compared to the placebo group as early as Week 2 (mean change: [redacted] vs. [redacted], respectively; LS mean difference [redacted] [95% CI[redacted], [redacted]], [redacted]), and continuing up to Week 16 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted]], [redacted]]).

Patient-reported outcomes

DLQI

Among participants who had a baseline DLQI ≥4, no difference was observed between treatment groups in the percentage of lebrikizumab + TCS-treated participants who achieved a ≥4-point improvement at Week 16 ([redacted] in the lebrikizumab + TCS group vs. [redacted] in the placebo + TCS group; common risk difference [redacted] [95% CI: [redacted], [redacted]; [redacted]]).

Reductions in DLQI scores were observed for both groups at each visit, with larger reductions from baseline observed among the lebrikizumab + TCS-treated participants compared to the placebo + TCS group as early as Week 4 (mean change: [redacted] vs. [redacted], respectively; LS mean difference [redacted] [95% CI: ([redacted], [redacted]], [redacted]), and continuing through Week 16 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted]], [redacted]]).

After 16 weeks of treatment, the overall impact of AD on QoL was decreased almost to none (DLQI ≤5; Hongbo et al 2005 (92)) in lebrikizumab + TCS-treated participants (mean [redacted]), compared to a moderate effect (DLQI 6 to 10, Hongbo et al 2005 (92)) in the placebo + TCS group (mean [redacted]).

CDLQI

Reductions from baseline CDLQI scores were observed for both groups at each visit. No difference between groups was observed in CDLQI at Week 16 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted]], [redacted]]), but the number of adolescents included in the analysis was small (N=39).

POEM

At baseline, the mean POEM scores for participants in the lebrikizumab + TCS and placebo + TCS groups were [redacted] and [redacted], respectively, consistent with severe disease (POEM ≥17) (93). Reductions in AD severity were observed for both groups at each visit, with larger reductions from baseline observed among the lebrikizumab + TCS-treated participants compared to the placebo + TCS group as early as Week 4 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted]; [redacted]]), and continuing up to Week 16 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted], [redacted]]).

SCORAD

At baseline, the mean SCORAD scores for participants in the lebrikizumab + TCS and placebo + TCS groups were [redacted] and [redacted], respectively, indicating severe AD (SCORAD >50). Reductions in disease severity were observed for both groups at Week 8, with larger reductions from baseline among the lebrikizumab + TCS-treated participants compared to the placebo + TCS group (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted]; [redacted]]), and also at Week 16 (mean change: [redacted] vs. [redacted], respectively; LS mean difference between groups [redacted] [95% CI: [redacted], [redacted], [redacted]]).

B.2.6.4. Long-term efficacy of lebrikizumab

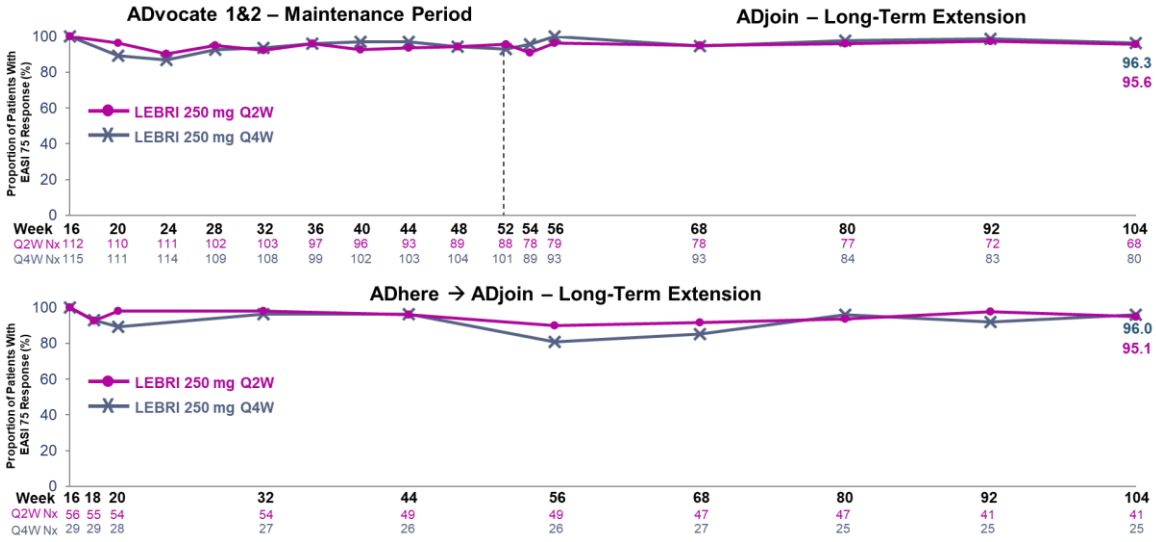
The long-term efficacy of lebrikizumab is being assessed in the ongoing ADjoin LTE study (see Section B.2.11). An interim analysis was carried out that included participants who were Week 16 responders in ADvocate 1, ADvocate 2 or ADhere (82). Efficacy outcomes were assessed up to 104 weeks (2 years) of lebrikizumab treatment:

- ADvocate 1 & 2 → ADjoin: efficacy outcomes were assessed during the maintenance period of ADvocate 1 & 2 (Weeks 16 to 52) and then for 52 weeks in ADjoin (Weeks 52 to 104)

- ADhere → ADjoin: efficacy outcomes were assessed up to 88 weeks in ADjoin (Weeks 16 to 104)

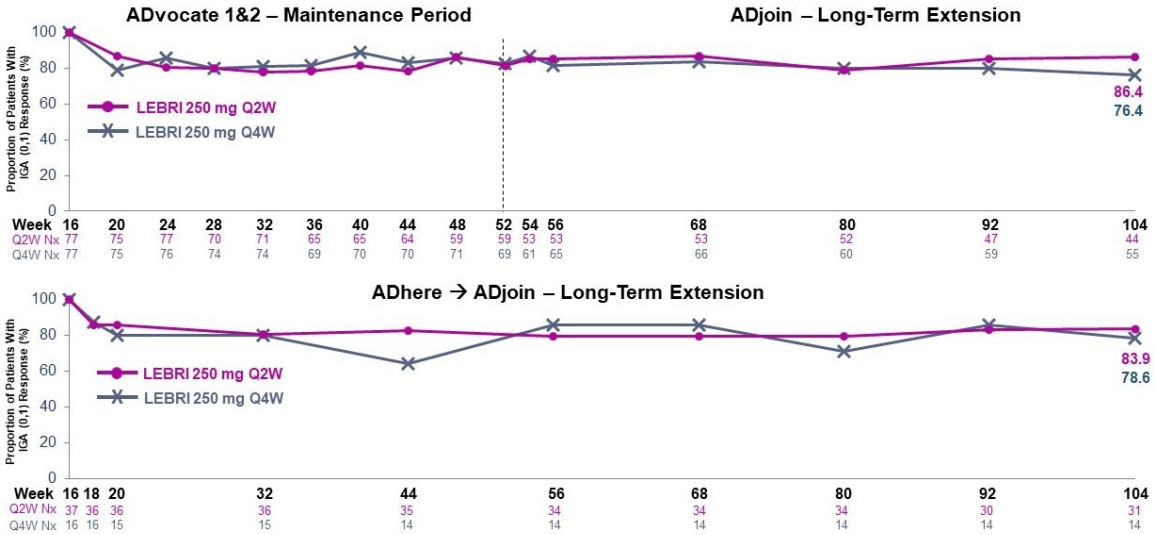
EASI 75 and IGA (0,1) response rates were maintained up to Week 104 in participants receiving lebrikizumab Q4W or Q2W (Figure 27 and Figure 28).

Figure 27: Maintenance of EASI 75 through Week 104 (ADjoin study)



Data are presented for participants achieving EASI 75 at Week 16 of the parent study
Key: EASI=Eczema Area and Severity Index; LEBRI=lebrikizumab; Nx=number of patients with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks
Source: Guttman-Yassky et al (2023) (82)

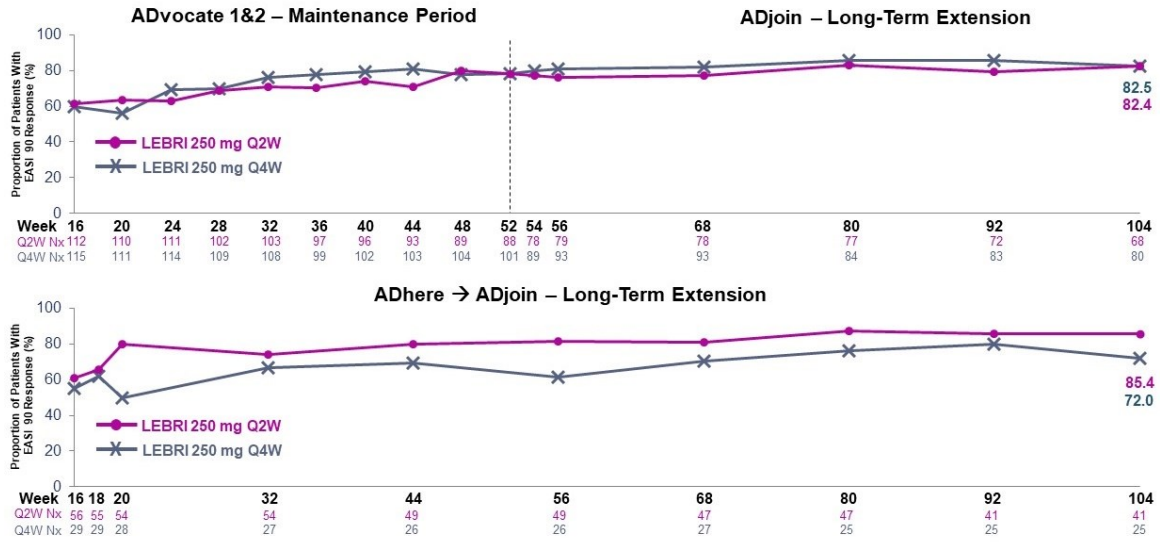
Figure 28: Maintenance of IGA (0,1) through Week 104 (ADjoin study)



Data are presented for participants achieving IGA (0,1) at Week 16 of the parent study
Key: IGA=Investigator's Global Assessment; LEBRI=lebrikizumab; Nx=number of patients with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks
Source: Guttman-Yassky et al (2023) (82)

EASI 90 response rates were maintained or improved up to Week 104 in participants receiving lebrikizumab Q4W or Q2W (Figure 29).

Figure 29: Maintenance of EASI 90 through Week 104 (ADjoin study)



Data are presented for participants achieving EASI 75 at Week 16 of the parent study
Key: IGA=Investigator's Global Assessment; LEBRI=lebrikizumab; Nx=number of patients with non-missing values; Q2W=every 2 weeks; Q4W=every 4 weeks
Source: Guttman-Yassky et al 2023 (82)

B.2.7 Subgroup analysis

Note: this section includes a summary of the pre-planned and *post-hoc* subgroup analyses carried out for the lebrikizumab studies. Full details of the results can be found in Appendix E.

B.2.7.1. Pre-planned subgroup analyses

Pivotal studies

Table 38 shows the pre-planned subgroup analyses carried out on Week 16 ITT/mITT data for IGA (0,1), EASI 75, EASI 90 and itch NRS from ADvocate 1, ADvocate 2 and ADhere.

Table 38: Pre-planned subgroup analyses (ADvocate 1, ADvocate 2, ADhere)

• Age (12 to <18, ≥18, ≥18 to <65, ≥65 to <75, ≥75 years)
• Age (adolescents 12 to <18 years, adults ≥18 years)
• Sex

- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Other, Not reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, missing)
- Geographic region (US, Europe, Rest of World)
- Baseline weight (<60, ≥60 to <100, ≥100 kg)
- Baseline BMI (underweight <18.5, normal ≥18.5 to <25, overweight ≥25 to <30, obese ≥30 to <40, extreme obese ≥40 kg/m^2)
- Duration since AD onset (0 to <2, 2 to <5, 5 to <10, 10 to <20, ≥20 years)
- Baseline IGA score (3, 4)
- Baseline itch score (<4, ≥4)
- Prior use of systemic treatment (Yes/No)

Key: AD, atopic dermatitis; BMI, body mass index; IGA, Investigator's Global Assessment; US, United States
Source: ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); ADhere clinical study report (78)

An MCMC-MI approach was used, as per the primary analysis. A logistic regression analysis was used, with treatment, subgroup and treatment-by-subgroup interaction as factors. The treatment-by-subgroup interaction was tested using the Firth correction (94) at the 10% significance level. Treatment group differences were evaluated within each subgroup using the chi-square test. Where any group within a subgroup (e.g. yes, no) was <10% of the population, inferential testing was not performed.

In ADvocate 1 and ADvocate 2, the results were consistent with the overall population, with a similar treatment effect across all subgroups (75, 76). In ADhere, analysis by sex showed a significant effect in EASI 75 and EASI 90 at Week 16 with a greater risk difference in males; there were no significant effects in other subgroups (77).

ADvantage

Exploratory analyses were carried out for the primary and secondary endpoints by previous dupilumab exposure (80). As only [redacted] patients ([redacted]) in the study were previously exposed to dupilumab, caution is needed in interpretation of the results. For the primary and key secondary endpoints, response patterns were [redacted]

[redacted] between dupilumab-exposed and dupilumab-naïve patients. Response rates were higher among dupilumab-exposed and dupilumab-naïve patients who received lebrikizumab + TCS than among those who received placebo + TCS.

B.2.7.2. *Post-hoc* subgroup analyses

Previous treatments

In ADvocate 1 & 2, [redacted] participants who received lebrikizumab Q2W and [redacted] who received placebo had previously been exposed to CsA. *Post-hoc* analyses of EASI 75, IGA 0,1, NRS itch 4-point improvement and EASI 90 at Week 16 were carried out in this subgroup. The proportion of participants who achieved each of these endpoints at Week 16 was [redacted] in the CsA prior use subgroup than in the overall population (95).

A similar analysis was carried out on the [redacted] patients in ADhere who had previously been exposed to CsA. The proportions of participants who achieved IGA 0,1, NRS 4-point improvement and EASI 90 were [redacted] in the CsA prior use subgroup than the overall population (95). The proportion of patients achieving EASI 75 was [redacted] in the prior CsA subgroup than in the overall population for lebrikizumab, and [redacted] in the CsA subgroup than the overall subgroup for placebo. The results should be interpreted with caution owing to the small number of participants in the CsA subgroup.

ADhere also allowed inclusion of participants who had previously received dupilumab. [redacted] patients who previously received dupilumab were enrolled: [redacted] were randomised to lebrikizumab + TCS and [redacted] to placebo + TCS. In this subgroup, the proportion of participants who achieved EASI 75 at Week 16 was higher in the lebrikizumab + TCS group than in the placebo + TCS group (95).

When considering subgroup analyses of prior exposure to certain treatments, it is important to consider the following:

- It is difficult to make unbiased comparisons as the patients in the ‘no prior treatment’ group may have been receiving other treatments that may have affected the results

- Treatments have evolved over time, making it difficult to compare like-for-like. Patients going into more recent trials may be more refractory than those in the older trials and have experienced various treatments before entering the lebrikizumab trials.

Composite endpoint: EASI 50 + DLQI ≥4-point improvement

Analysis were carried out on the composite EASI 50 + DLQI ≥4-point improvement at Weeks 16 and 52 for the adult and adolescent subgroups in ADvocate 1, ADvocate 2 and ADhere (95). The analyses included those participants who had baseline DLQI ≥4; at Week 16 all eligible participants were included, regardless of whether they had responded to treatment or not.

The results were similar between the two subgroups, with approximately [redacted] of participants treated with lebrikizumab achieving the composite endpoint at Week 16 in ADvocate 1 & 2 (pooled data) and ADhere.

At Week 52, almost [redacted] of adults who received lebrikizumab (Q2W or Q4W) achieved the composite endpoint (ADvocate 1 & 2 only; pooled data).

B.2.8 Meta-analysis

The nature of the clinical effectiveness evidence means that it is not possible to conduct a pairwise meta-analysis. Head-to-head data comparing lebrikizumab with the comparators defined in the scope are not available; therefore, indirect treatment comparisons (ITCs) were carried out to estimate the relative efficacy of relevant therapies.

B.2.9 Indirect and mixed treatment comparisons

Summary of indirect treatment comparison results

- A network meta-analysis provided evidence that, in the monotherapy setting, lebrikizumab was [redacted] and comparable to [redacted] at week 16 across [redacted]

- In the combination setting, lebrikizumab + TCS was also shown to be [redacted]:
  - Lebrikizumab + TCS demonstrated superiority to [redacted] at Week 16
  - Lebrikizumab + TCS demonstrated comparability to [redacted]
- A matching-adjusted indirect treatment comparison showed that lebrikizumab Q4W may provide equal or superior long-term maintenance of efficacy (measured with EASI 75 and IGA 0,1) compared to dupilumab QW/Q2W, with the advantage of requiring less frequent doses.

B.2.9.1. Network meta-analysis

A network meta-analysis was carried out to estimate the relative efficacy of lebrikizumab, tralokinumab, dupilumab and JAK inhibitors at Week 16 (96). The NMA was based on evidence identified in a systematic literature review (SLR). Full details of the SLR can be found in Appendix D. A total of 72 studies in adults and adolescents with moderate-to-severe AD identified in the SLR, and assessed for their eligibility for the NMA. A further three studies that were not identified as part of the SLR were also assessed for their eligibility for the NMA. Of these 75 studies, 38 were deemed eligible: 22 monotherapy studies and 16 combination therapy studies. (Table 39). The included studies are described in detail in Appendix D.

Table 39: Studies included in the NMA

Intervention	Eligible studies
Monotherapy	
Lebrikizumab 250 mg Q2W	ADvocate1 ADvocate 2 J2T-DM-KGAF

Intervention	Eligible studies
Dupilumab 300 mg Q2W	LIBERTY AD ADOL LIBERTY AD SOLO 1 LIBERTY AD SOLO 2 EFC15116 R668-AD-1021
Tralokinumab 300 mg Q2W	ECZTRA 1 ECZTRA 2 ECZTRA 5 ECZTRA 6
Baricitinib 2 mg QD	BREEZE-AD1 BREEZE-AD2 BREEZE-AD5
Baricitinib 4 mg QD	BREEZE-AD1 BREEZE-AD2
Abrocitinib 100 mg QD	B7451006 JADE MONO-1 JADE MONO-2 JADE-MOA
Abrocitinib 200 mg QD	B7451006 JADE MONO-1 JADE MONO-2
Upadacitinib 15 mg QD Upadacitinib 30 mg QD	MEASURE UP 1 MEASURE UP 2 M16-048
Combination therapy	
Lebrikizumab 250 mg Q2W	ADHERE-J ADHERE ADOPT-VA ADVANTAGE
Dupilumab 300 mg Q2W	LIBERTY AD CAFE LIBERTY AD CHRONOS JADE COMPARE
Tralokinumab 300 mg Q2W	ECZTRA 3 ECZTRA 7

Intervention	Eligible studies
	ECZTRA 8
Baricitinib 2 mg QD	BREEZE-AD4 BREEZE-AD7 I4V-MC-JAHG
Baricitinib 4 mg QD	BREEZE-AD4 BREEZE-AD8 I4V-MC-JAHG
Abrocitinib 100 mg QD	JADE COMPARE
Abrocitinib 200 mg QD	JADE TEEN
Upadacitinib 15 mg QD	AD UP
Upadacitinib 30 mg QD	RISING UP

Key: QD, once-daily; Q2W, every two weeks

The following outcomes were included in the NMA:

- EASI response at Week 16
- IGA (0,1) response at Week 16
- ≥4-point improvement in pruritus/itch NRS at Week 16
- ≥4-point improvement in pruritus/itch NRS at Week 4

Full details of the NMA methods, including network diagrams, are provided in Appendix D.

Results of the NMA

Table 40 summarises the results of the NMA. Full details of the results, including odds ratios and Forest plots are provided in the full technical report (96).

Table 40: Summary of NMA results, random effects model

Reference Treatment	Monotherapy: Lebrikizumab 250 mg Q2W vs Reference Treatment				Combination Therapy: Lebrikizumab 250 mg Q2W + TCS vs Reference Treatment + TCS			
	EASI Response (Week 16)	IGA 0/1 Response (Week 16)	≥4 point improvement in Pruritus/ Itch NRS (Week 16)	≥4 point improvement in Pruritus/ Itch NRS (Week 4)	EASI Response (Week 16)	IGA 0/1 Response (Week 16)	≥4 point reduction in Pruritus/ Itch NRS (Week 16)	≥4 point reduction in Pruritus/ Itch NRS (Week 4)
Dupilumab 300 mg Q2W								
Tralokinumab 300 mg Q2W								
Baricitinib 2 mg QD								
Baricitinib 4 mg QD								
Abrocitinib 100 mg QD								
Abrocitinib 200 mg QD								
Upadacitinib 15 mg QD								
Upadacitinib 30 mg QD								
Placebo								

NOTE: Table contains confidential content

Dark green indicates where lebrikizumab 250 mg Q2W was statistically superior compared to the reference treatment; **light green** indicates where there was numerical evidence in favour of lebrikizumab 250 mg Q2W compared to the reference treatment; **dark red** indicates where lebrikizumab 250 mg Q2W was statistically inferior compared to the reference treatment; **light red** indicates where there was numerical evidence in favour of the reference treatment compared to lebrikizumab 250 mg Q2W

Key: EASI, eczema area and severity index; IGA, investigator global assessment; NRS, numerical rating scale; QD, daily; Q2W, every two weeks; TCS, topical corticosteroids

Monotherapy networks

In the monotherapy setting at Week 16, lebrikizumab 250 mg Q2W had [redacted] estimates for IGA 0/1 and EASI (50/75/90), and a [redacted] compared to [redacted], and [redacted]). The IGA 0/1 estimates for lebrikizumab 250 mg Q2W were statistically comparable to [redacted].

Credible intervals for [redacted] overlapped with lebrikizumab 250 mg Q2W, indicating that their IGA 0/1 response rates were not statistically different.

For pruritus/itch NRS response at Week 16, lebrikizumab 250 mg Q2W had [redacted] response rates than the other biologics. Lebrikizumab 250 mg Q2W also had more favorable [redacted] than [redacted]

Combination therapy networks

In the combination therapy setting at Week 16, lebrikizumab 250 mg Q2W + TCS had [redacted] estimates for EASI (50/75/90) and IGA (0,1), and a [redacted] compared to [redacted]

The IGA 0/1 estimates for lebrikizumab 250 mg Q2W + TCS were statistically comparable to [redacted]

Credible intervals for [redacted] overlapped with lebrikizumab 250 mg Q2W + TCS, indicating that their IGA 0/1 response rates were not statistically different.

For pruritus/itch NRS response at Week 16, lebrikizumab 250 mg Q2W + TCS had [redacted] response rates than [redacted]

B.2.9.2. Matching-adjusted treatment comparison (MAIC)

A MAIC was carried out to compare the efficacy and safety of lebrikizumab monotherapy with dupilumab monotherapy at Week 52 (97, 98). The analysis was carried out on the following outcomes:

- EASI 75
- IGA 0,1
- Overall AEs
- Discontinuations due to AE.

For lebrikizumab, the analyses used individual patient data (IPD) from ADvocate 1 & 2. For dupilumab, aggregate data from the SOLO-CONTINUE trial (NCT02395133) were used (99). The IPD data from ADvocate 1 & 2 were reweighted to align with SOLO-CONTINUE's prognostic factors and effect modifiers. To allow meaningful comparisons, a subset of patients in the ADvocate trials that matched the inclusion criteria of the QW/Q2W participants in SOLO-CONTINUE were identified; this subset is referred to as the SOLO-like sample from the ADvocate studies.

A full description of the MAIC methods is provided in Appendix D.

Results

The results suggest that patients treated with lebrikizumab are more likely to maintain IGA 0,1 over the long-term than those treated with dupilumab (Table 41). Both treatments showed comparable efficacy in terms of EASI 75 rates and similar AE rates. Results for discontinuations due to AEs are not shown: there were no reported discontinuations due to AEs in the QW/Q2W SOLO-CONTINUE study arm, whereas there were two in the SOLO-like sample from the ADvocate studies, so the results would inevitably favour dupilumab, regardless of participant weighting.

Table 41: Results of the MAIC (98)

	LEB Q4W Eff. n (cases)	DUP Sample (cases)	Risk ratios (95% CI)				Odds ratios (95% CI)			
			RR	95% CI	SE	P value	OR	95% CI	SE	P value
EASI 75										
Naïve	101.0 (69.0)	169 (116)	0.995	[0.842, 1.177]	0.085	0.956	0.985	[0.577, 1.682]	0.273	0.956
MAIC	88.6 (57.0)	169 (116)	0.937	[0.778, 1.128]	0.095	0.490	0.823	[0.448, 1.512]	0.311	0.530
IGA 0,1										
Naïve	101.0 (56.0)	169 (68)	1.378	[1.069, 1.776]	0.129	0.014	1.848	[1.118, 3.056]	0.256	0.017
MAIC	88.6 (47.6)	169 (68)	1.334	[1.022, 1.742]	0.136	0.035	1.721	[0.988, 3.015]	0.286	0.058
Overall AEs										
Naïve	101.0 (74.0)	167 (118)	1.037	[0.890, 1.208]	0.078	0.643	1.138	[0.652, 1.987]	0.284	0.649
MAIC	88.6 (65.9)	167 (118)	1.052	[0.900, 1.230]	0.080	0.526	1.203	[0.654, 2.213]	0.311	0.553

Naïve = not baseline adjusted. In the MAIC, EASI and BSA were used as covariates

Key: AE, adverse event; CI, confidence interval; DUP, dupilumab; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LEB, lebrikizumab; MAIC, matching adjusted indirect treatment comparison; OR, odds ratio; RR, risk ratio; SE, standard error

Heterogeneity in the indirect treatment comparisons

NMA

Heterogeneity in patient baseline characteristics was assessed for studies eligible for the NMA.

Monotherapy studies

For monotherapy studies, there was some evidence of heterogeneity in the mean age with two studies (ECZTRA 6 and LIBERTY AD ADOL) reporting solely on adolescent patients. The proportion of white patients was mostly homogeneous across studies, however, one study (EFC15116) included solely Asian patients. Age and race were not considered to be TEMs and so this was not considered to be a concern for the NMA.

There were too few studies reporting on baseline weight (8/22) to appropriately adjust for differences in this characteristic in the NMA, however, it was assumed that studies were relatively well balanced in terms of weight, based on the available data. Baseline EASI scores and the proportion of patients with a baseline IGA score of 4 were well reported, with some variation identified in baseline EASI scores and patients with an IGA score of 4.

Combination therapy studies

For combination therapy studies, there was some evidence of heterogeneity in the mean baseline age, where one study (JADE TEEN) reported solely on adolescent patients, in the remaining studies, mean age was relatively homogenous. There was some heterogeneity in race between studies, where three studies (ECZTRA 8, Rising UP, and Adhere-J) included only Asian patients and three studies (ECZTRA 7, LIBERTY AD CAFÉ and ADvantage) included almost exclusively white patients.

Similar to the monotherapy studies, there were too few studies reporting on baseline weight (9/16) to appropriately adjust for differences in this characteristic, however, it was assumed that studies were relatively well balanced in terms of weight, based on the available data.

Baseline EASI scores and the proportion of patients with a baseline IGA score of 4 were well reported, with some variation identified in baseline EASI scores and patients with an IGA score of 4.

Comparability of placebo arms

Placebo response and the heterogeneity of the placebo arms of each included study was assessed to ensure that placebo arms were comparable and therefore suitable as a connecting node between lebrikizumab and the comparators of interest. Across both settings, there was variation in placebo EASI-50 response; this was between approximately 10–50% in the monotherapy setting with the combination therapy setting having an even wider variation in placebo + TCS response (approximately between 25–80%).

In the monotherapy setting, variation was expected to arise primarily from differences in patient and study characteristics. In the combination therapy setting, the connecting node was placebo in combination with TCS, and as such variation may also be explained by differences in the definition of this treatment across studies. Most studies required that patients apply low- to moderate-potency TCS as needed, however the frequency of application and type of TCS varied across studies, or was not explicitly reported. The number of TCS options available was in general not reported clearly across studies. Differences in TCS treatment may therefore lead to differences in the placebo + TCS response across studies, and limit the reliability of comparisons drawn between active interventions in this setting.

The use of baseline risk models to adjust for differences in placebo response was therefore considered to be valuable across both the monotherapy and combination therapy networks.

B.2.9.3. Uncertainties in the indirect and mixed treatment comparisons

NMA

Although the feasibility assessment was thorough and identified suitable evidence, baseline weight was identified as a potential treatment effect modifier and was not sufficiently reported across studies to investigate potential imbalances across studies. However, reported baseline weight values were well balanced across studies which did report this. In general, there were some differences across studies in other patient characteristics such as race and time since AD diagnosis, though these were not identified as treatment effect modifiers and the use of random effect models to allow for such differences is particularly pertinent. Additionally, differences across studies in terms of baseline EASI and IGA scores (which were considered to be treatment effect modifiers) were identified. However, adjustment for baseline EASI and IGA did not bring about improvements in model fit and conclusions were considered to be comparable to the primary analysis.

Since Week 12 was the key timepoint for the induction period of abrocitinib trials and data were generally not reported at Week 16, Week 12 data were used for abrocitinib trials in included in the Week 16 networks in the monotherapy setting, which may have introduced heterogeneity given the difference in timepoints being compared. In addition, there were some differences across trials in terms of population reported on (intention-to-treat versus modified intention-to-treat), but efforts were made to ensure that trials with an unsuitable denominator (e.g. due to many patients withdrawing consent) were excluded.

In the combination therapy setting, studies differed in terms of the type, potency and frequency of TCS treatment, and who decided if TCS needed to be used (i.e. investigator or participant). Differences in TCS treatment may therefore bias reported response rates and limit the reliability of comparing responses on the active interventions. Baseline risk adjusted analyses were thus suitable from this perspective in the combination therapy setting.

An assumption was also required for each network in derivation of absolute response rates for each treatment. In particular, the assumption for each outcome was formulated based on the RCTs informing the networks, rather than based on external data. However, this approach is typically employed in NMAs and ensures that the derived absolute response rates relate to the population of interest (i.e. adults and adolescents with moderate-to-severe AD).

Of note, the NMA findings are in line with a very recently published NMA(100) i which generally found to have similar efficacy response rates with dupilumab, abrocitinib 100 mg, and baricitinib 4 mg, with baricitinib 2 mg and tralokinumab were generally ranked lower across all efficacy outcomes.

MAIC

The analyses could not be adjusted for disease severity, as reported data for SOLO-CONTINUE do not include baseline prior to induction. The analyses therefore rely on the assumption that AD patients achieving EASI 75 or IGA 0,1 at Week 16 are essentially similar at that point, irrespective of the treatment they receive. Any potential contribution of variables related to weight are also unaccounted for as these were not reported in SOLO-CONTINUE.

In SOLO-CONTINUE, data for dupilumab QW and Q2W are pooled, however, the approved maintenance regimen for dupilumab is Q2W.

B.2.10 Adverse reactions

Summary of safety results

- Lebrikizumab shows an acceptable safety profile to Week 16, with few SAEs reported, including in patients who had previously failed CsA, or for whom CsA is not medically advised
- Most AEs were mild to moderate in intensity and few led to treatment discontinuation
- TEAEs did not increase with longer exposure to lebrikizumab (up to 2 years)

B.2.10.1. Pivotal studies: TEAEs from baseline through Week 16 (induction period)

Overview of AEs

Table 42 shows an overview of TEAEs in ADvocate 1, ADvocate 2 and ADhere through Week 16. Most TEAEs were mild to moderate in intensity and did not lead to treatment discontinuation.

Table 42: Overview of TEAEs through Week 16: ADvocate 1, ADvocate 2, ADhere studies

	n (%) of participants					
	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 141)	LEB 250 Q2W (N = 282)	PBO (N = 145)	LEB 250 Q2W (N = 281)	PBO (N = 66)	LEB 250 Q2W (N = 145)
Any TEAE	73 (51.8)	129 (45.7)	96 (66.2)	150 (53.0)	23 (34.8)	63 (43.4)
Mild	34 (24.1)	78 (27.7)	40 (27.6)	73 (26.0)	12 (18.2)	32 (22.1)
Moderate	32 (22.7)	45 (16.0)	49 (33.8)	70 (24.9)	10 (15.2)	28 (19.3)
Severe	7 (5.0)	6 (2.1)	7 (4.8)	7 (2.5)	1 (1.5)	3 (2.1)
SAEs	1 (0.7)	6 (2.1)	4 (2.8)	2 (0.7)	1 (1.5)	2 (1.4)
Deaths	0	0	1 (0.7)	0	0	0
AEs leading to treatment discontinuation	1 (0.7)	3 (1.1)	4 (2.8)	9 (3.2)	0	3 (2.1)

Data shown for the safety population in ADvocate 1 and the modified safety populations in ADvocate 2 and ADhere.
Key: AE, adverse event ; LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; SAE, serious adverse event ; TEAE, treatment-emergent adverse event
Source: Silverberg et al (2023) (72), Simpson et al (2023) (77)

Common TEAEs

Table 43 shows the TEAEs reported by ≥5% of patients in any lebrikizumab group. In all three studies, conjunctivitis events were consistently more common with lebrikizumab than with placebo. Exacerbations of AD were consistently less common with lebrikizumab than with placebo.

Table 43: Most common TEAEs (reported by ≥5% of patients in any lebrikizumab group) through Week 16: ADvocate 1, ADvocate 2, ADhere studies

	n (%) of participants					
	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 141)	LEB 250 Q2W (N = 282)	PBO (N = 145)	LEB 250 Q2W (N = 281)	PBO + TCS (N = 66)	LEB 250 Q2W + TCS (N = 145)
Conjunctivitis	4 (2.8)	21 (7.4)	3 (2.1)	21 (7.5)	0	7 (4.8)
Exacerbation of AD	30 (21.3)	17 (6.0)	39 (26.9)	29 (10.3)	3 (4.5)	3 (2.1)
Nasopharyngitis	4 (2.8)	11 (3.9)	3 (2.1)	21 (7.5)	4 (6.1)	3 (2.1)
Headache	2 (1.4)	9 (3.2)	6 (4.1)	14 (5.0)	1 (1.5)	7 (4.8)

Data shown for the safety population in ADvocate 1 and the modified safety populations in ADvocate 2 and ADhere.
Key: AD = atopic dermatitis; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks
Source: Silverberg et al (2023) (72), Simpson et al (2023) (77)

SAEs

In ADvocate 1, six lebrikizumab-treated participants (2.1%) reported a total of six SAEs through Week 16: arthralgia (n = 1), synovitis (n = 1), myocardial infarction (n = 1), peripheral oedema (n = 1), accidental overdose (n = 1), carpal tunnel syndrome (n = 1). The SAE of [redacted] was considered to be [redacted] lebrikizumab, and the SAE of [redacted] led to study discontinuation. One patient (0.7%) in the placebo group reported two SAEs: cellulitis and sepsis; neither of these led to discontinuation.

In ADvocate 2, two lebrikizumab-treated participants (0.7%) reported a total of five SAEs through Week 16: cardiac failure (n = 1); large intestine infection (n = 1), multiple injuries (n = 1), cerebellar syndrome (n = 1), atopic dermatitis (n = 1). All of these events, [redacted], were considered unrelated to lebrikizumab; the SAE of [redacted]

[redacted] led to study discontinuation. In the placebo group, four participants (2.8%) reported 5 SAEs: uterine leiomyoma (n = 1), myocardial infarction (n = 1), fibula fracture (n = 1), tibia fracture (n = 1), atopic dermatitis (n = 1). The SAE of myocardial infarction led to the participant's death.

In ADhere, two lebrikizumab-treated participants (1.4%) reported a total of two SAEs through Week 16: sinus node dysfunction (n = 1), fall (n = 1). In the placebo group, one patient (1.5%) reported two SAEs (dehydration and kidney failure). No SAEs were considered related to treatment and none led to study discontinuation.

TEAEs leading to treatment discontinuation

In ADvocate 1, three participants (1.1%) in the lebrikizumab group had AEs during the induction period that led to permanent treatment discontinuation: folliculitis (n = 1), peripheral oedema (n = 1) and atopic dermatitis (n = 1). One participant (0.7%) in the placebo group had conjunctivitis that led to treatment discontinuation. All these events were moderate in severity.

In ADvocate 2, nine participants (3.2%) in the lebrikizumab group reported AEs that led to permanent treatment discontinuation: atopic dermatitis ([redacted]), conjunctivitis ([redacted]), bacterial conjunctivitis ([redacted]), atopic keratoconjunctivitis ([redacted]), keratitis ([redacted]), cerebellar syndrome ([redacted]) and panic attack ([redacted]). Four participants (2.8%) in the placebo group discontinued because of AEs: atopic dermatitis ([redacted]), skin infection ([redacted]) and myocardial infarction ([redacted]). All events, except for cerebellar syndrome and myocardial infarction, were mild or moderate in severity.

In ADhere, three participants (2.1%) reported AEs that led to permanent treatment discontinuation: injection site rash (n = 1), drug hypersensitivity (n = 1) and conjunctivitis (n = 1). There were no AEs leading to permanent treatment discontinuation in the placebo group.

Conjunctivitis

Conjunctivitis is considered an AE of special interest based on the heightened likelihood for conjunctivitis in AD and AEs observed for other drugs in AD (i.e. dupilumab, tralokinumab).

Across all three studies, conjunctivitis was more common with lebrikizumab than with placebo through Week 16. All conjunctivitis events were mild to moderate in severity. Four lebrikizumab-treated participants in ADvocate 2 and one lebrikizumab + TCS-treated participant in ADhere discontinued treatment because of conjunctivitis. Two lebrikizumab-treated participants in ADvocate 2 discontinued because of keratitis. Table 44 shows the incidence of all conjunctivitis events across the three studies.

Table 44: Incidence of conjunctivitis events through Week 16: ADvocate 1, ADvocate 2, ADhere studies

	n (%) of participants					
	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 141)	LEB 250 Q2W (N = 282)	PBO (N = 145)	LEB 250 Q2W (N = 281)	PBO + TCS (N = 66)	LEB 250 Q2W + TCS (N = 145)
Conjunctivitis cluster	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	4 (2.8)	21 (7.4)	3 (2.1)	21 (7.5)	0 (0.0)	7 (4.8)
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Conjunctivitis bacterial	-	-	[redacted]	[redacted]	-	-
Dry eye	-	-	-	-	[redacted]	[redacted]
Blepharitis	-	-	-	-	[redacted]	[redacted]
Eye irritation	-	-	-	-	[redacted]	[redacted]
Keratitis cluster						
Vernal keratoconjunctivitis	[redacted]	[redacted]	-	-	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Atopic keratoconjunctivitis	-	-	[redacted]	[redacted]	-	-

Data shown for the safety population in ADvocate 1 and the modified safety populations in ADvocate 2 and ADhere.
Key: LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks.
Source: Silverberg et al (2023) (72); Simpson et al (2023) (77); ADvocate 1 clinical study report (75); ADvocate 2 clinical study report (76); ADhere clinical study report (78)

Other TEAEs of special interest

Table 45 shows other TEAEs of clinical interest through Week 16. Injection site reactions were more frequently reported in lebrikizumab-treated participants than in those who

received placebo, although the incidence was low. All injection site reactions were mild to moderate in severity. One participant who received lebrikizumab + TCS in ADhere discontinued treatment because of an injection site reaction. The incidence of infection was similar between lebrikizumab and placebo. One participant in ADhere who received lebrikizumab + TCS reported an eosinophil-related disorder.

Table 45: TEAEs of special interest through Week 16 : ADvocate 1, ADvocate 2, ADhere studies

	n (%) of participants					
	ADvocate 1		ADvocate 2		ADhere	
	PBO (N = 141)	LEB 250 Q2W (N = 282)	PBO (N = 145)	LEB 250 Q2W (N = 281)	PBO + TCS (N = 66)	LEB 250 Q2W + TCS (N = 145)
Infection[a]	28 (19.9)	61 (21.6)	30 (20.7)	65 (23.1)	9 (13.6)	24 (16.6)
Skin infection	8 (5.7)	8 (2.8)	9 (6.2)	4 (1.4)	1 (1.5)	2 (1.4)
Potential opportunistic infection[b]	1 (0.7)	1 (0.4)	1 (0.7)	3 (1.1)	0 (0.0)	3 (2.1)
Herpes infection[c]	6 (4.3)	9 (3.2)	7 (4.8)	8 (2.8)	1 (1.5)	5 (3.4)
Eosinophilia	3 (2.1)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)	1 (0.7)
Eosinophil-related disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Injection site reaction[d]	3 (2.1)	3 (1.1)	1 (0.7)	6 (2.1)	1 (1.5)	4 (2.8)
Cancer	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.4)	[redacted]	[redacted]

Data shown for the safety population in ADvocate 1 and the modified safety populations in ADvocate 2 and ADhere. [a]Defined using MedDRA preferred terms from the Infections and Infestations System Organ Class. [b]All assessed as not opportunistic in a blinded medical review carried out before database lock. [c]Defined using the MedDRA high level term herpes viral infection. [d]Defined as MedDRA high level term injection site reactions.
Key: LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks.
Source: Silverberg et al (2023) (72); Simpson et al (2023) (77); ADhere clinical study report (78)

B.2.10.2. Pivotal studies: TEAEs Weeks 16 to 52 (maintenance period)

Table 46 shows an overview of the TEAEs reported during the maintenance period in ADvocate 1 and ADvocate 2. Owing to the small number of patients in each treatment group at Week 52 in both studies, which limits interpretation of the findings, pooled data are presented (data for the individual studies are presented in Appendix F). Overall, TEAEs did not increase with longer exposure to lebrikizumab and there were no

meaningful differences between participants who received lebrikizumab Q2W and those who received it Q4W.

Table 46: Overview of TEAEs from Week 16 to Week 52: ADvocate 1 & 2

	n (%) of participants		
	PBO (LEB withdrawal) (N = 60)	LEB 250 Q4W (N = 118)	LEB 250 Q2W (N = 113)
Any TEAE	30 (50.0)	61 (51.7)	56 (49.6)
Mild	15 (25.0)	24 (20.3)	35 (31.0)
Moderate	15 (25.0)	31 (26.3)	17 (15.0)
Severe	0 (0.0)	6 (5.1)	4 (3.5)
SAEs	1 (1.7)	2 (1.7)	2 (1.8)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to treatment discontinuation	0 (0.0)	2 (1.7)	1 (0.9)
TEAEs reported in ≥5% of lebrikizumab groups[a]			
COVID-19	2 (3.3)	11 (9.3)	3 (2.7)
Nasopharyngitis	3 (5.0)	9 (7.6)	4 (3.5)
Atopic dermatitis	7 (11.7)	7 (5.9)	5 (4.4)
Allergic conjunctivitis	2 (3.3)	7 (5.9)	2 (1.8)
Headache	1 (1.7)	5 (5.2)	1 (0.9)
Conjunctivitis	3 (5.0)	6 (5.1)	0 (0.0)
Other TEAEs of clinical interest			
Herpes infections[b]	2 (3.3)	7 (5.9)	3 (2.7)
Skin infections[c]	1 (1.7)	4 (3.4)	4 (3.5)
Potential opportunistic infections[d]	1 (1.7)	1 (0.8)	1 (0.9)
Injection site reactions[e]	0 (0.0)	1 (0.8)	0 (0.0)
Eosinophilia[f]	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophil-related disorders[g]	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies[h]	0 (0.0)	0 (0.0)	0 (0.0)
Parasitic infections[i]	0 (0.0)	0 (0.0)	0 (0.0)

Data shown for the safety population in ADvocate 1 and the modified safety populations in ADvocate 2 and ADhere. [a]TEAEs are represented as single preferred terms. [b]Defined using the MedDRA high level term herpes viral infection. [c]Defined using the MedDRA high level term of skin structures and soft tissue infections, and additional single preferred terms of cellulitis, eczema impetiginous,

folliculitis, staphylococcal skin infection, cellulitis staphylococcal, furuncle, erysipelas, and fungal skin infection. [d]All assessed as not opportunistic in a blinded medical review carried out before database lock. [e]Defined using the MedDRA high level term of injection site reactions excluding joint-related preferred terms. [f]Defined using the MedDRA preferred terms of eosinophilia and allergic eosinophilia, as well as eosinophil count abnormal, eosinophil count increased and eosinophil percentage increased, which fall under the high level term of white blood cell analysis. [g]Defined as all MedDRA preferred terms under the high level term of eosinophilic disorders, except eosinophilia and allergic eosinophilia. [h]Defined using MedDRA malignant tumours standardised MeDRA query. [i]Defined using MedDRA high level terms, including cestode infections, helminthic infections, nematode infections and trematode infections.
Key: AE, adverse event; LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TEAEs, treatment-emergent adverse events
Source: Blauvelt et al (2023) (supplementary information) (88)

B.2.10.3. Integrated safety analysis

Stein Gold et al (2023) carried out an integrated analysis of safety data from the following eight lebrikizumab trials (74):

- A phase 2 open-label study (ARBAN; NCT02465606) (101)
- A phase 2 double-blind randomised, placebo-controlled dose-ranging study (NCT03443024) (102)
- A phase 2, double-blind, randomised placebo-controlled study (TREBLE; NCT02340234) (84)
- ADvocate 1 and 2 (NCT04146363, NCT04178967) (72)
- ADhere (NCT04250337) (77)
- ADore (phase 3 open-label single-arm study in adolescents; NCT04250350) (103)
- ADjoin (ongoing LTE study; NCT04392154; see Sections B.2.10.5 and B.2.11) (83).

Two pooled datasets were analysed:

- AD placebo-controlled week 0-16 dataset (All-PC Week 0-16): assessed the safety profile of placebo vs lebrikizumab 250 mg Q2W during the 16-week placebo-controlled period in the dose ranging study, ADvocate 1 and 2, and ADhere. This dataset included 404 patients who received placebo and 783 who received lebrikizumab Q2W.

- AD all-LEB dataset (All-LEB): evaluated the long-term safety profile of lebrikizumab and included all patients who received at least one dose of lebrikizumab in any of the eight studies listed above. This dataset included 1720 patients.

In the All-PC Week 0-16 dataset, the proportion of patients with ≥1 TEAE was similar in the placebo and lebrikizumab groups (53.1% vs 49.2%) and most events were mild or moderate in severity (91.6% vs 95.3%). Conjunctivitis and AD were the most common TEAEs, with AD reported more frequently in the placebo group and conjunctivitis reported more frequently in the lebrikizumab group (Table 47). Nasopharyngitis, headache, allergic conjunctivitis, dry eye and allergic rhinitis were also more common with lebrikizumab than with placebo.

In the All-LEB dataset, the most common TEAEs were nasopharyngitis, COVID-19, AD and conjunctivitis.

Table 47: Common TEAEs (i.e. reported by ≥1% of patients) in the All-PC Week 0-16 and All-LEB datasets

	N (adjusted %[a]) of patients [adjusted IR[a]]		
	All-PC Week 0-16		**All-LEB[a]**
	Placebo (N = 404) [PY = 113.8]	**LEB 250 mg Q2W (N = 783) [PY = 233.3]**	**(n = 1720) [PY = 1637.0]**
Nasopharyngitis	13 (3.2) [11.8]	34 (4.4) [15.2]	157 (9.1) [10.2]
COVID-19	5 (1.3) [4.4]	9 (1.1) [3.8]	133 (7.7) [8.4]
Atopic dermatitis	74 (18.4) [76.9]	7 (6.0) [21.2]	128 (7.4) [8.3]
Conjunctivitis	7 (1.8) [6.2]	51 (6.5) [22.8]	112 (6.5) [7.2]
Headache	12 (2.9) [10.5]	34 (4.4) [15.0]	81 (4.7) [5.1]
Allergic conjunctivitis	3 (0.7) [2.6]	14 (1.8) [6.1]	70 (4.1) [4.4]
URTI	7 (1.7) [6.3]	3 (0.4) [1.3]	66 (3.8) [4.1]
Oral herpes	9 (2.3) [8.1]	15 (1.9) [6.5]	50 (2.9) [3.1]
Pruritus	7 (1.8) [6.4]	9 (1.2) [3.9]	33 (1.9) [2.0]
Urinary tract infection	2 (0.5) [1.7]	5 (0.6) [2.1]	32 (1.9) [2.0]
Hypertension	4 (1.0) [3.6]	9 (1.1) [3.8]	31 (1.8) [1.9]
Diarrhoea	1 (0.2) [0.9]	4 (0.5) [1.7]	29 (1.7) [1.8]
Arthralgia	3 (0.7) [2.5]	6 (0.8) [2.6]	27 (1.6) [1.7]
Cough	1 (0.3) [0.9]	5 (0.7) [2.2]	27 (1.6) [1.7]
Acne	3 (0.7) [2.6]	2 (0.3) [0.8]	26 (1.5) [1.6]
Vaccination complication	0	3 (0.4) [1.3]	25 (1.5) [1.5]

	N (adjusted %[a]) of patients [adjusted IR[a]]		
	All-PC Week 0-16 Placebo (N = 404) [PY = 113.8]	**LEB 250 mg Q2W (N = 783) [PY = 233.3]**	**All-LEB[a] (n = 1720) [PY = 1637.0]**
Dry eye	4 (0.9) [3.4]	11 (1.4) [4.8]	25 (1.5) [1.5]
Fatigue	3 (0.7) [2.6]	5 (0.6) [2.2]	25 (1.5) [1.5]
Anxiety	3 (0.7) [2.6]	6 (0.8) [2.6]	23 (1.3) [1.4]
Nausea	2 (0.5) [1.8]	6 (0.8) [2.6]	21 (1.2) [1.3]
Folliculitis	5 (1.2) [4.3]	5 (0.6) [2.2]	21 (1.2) [1.3]
ALT increased	0	3 (0.4) [1.3]	21 (1.2) [1.3]
Injection site reaction	1 (0.30) [0.9]	5 (0.6) [2.1]	21 (1.2) [1.3]
Asthma	1 (0.3) [0.9]	5 (0.6) [2.1]	20 (1.2) [1.2]
Allergic rhinitis	1 (0.2) [0.9]	8 (1.0) [3.5]	18 (1.0) [1.1]
Herpes dermatitis	2 (0.5) [1.7]	1 (0.1) [0.4]	18 (1.0) [1.1]
Abdominal pain	0	2 (0.3) [0.9]	17 (1.0) [1.0]
Impetigo	6 (1.5) [5.4]	6 (0.8) [2.6]	17 (1.0) [1.0]
Back pain	2 (0.5) [1.8]	2 (0.3) [0.9]	17 (1.0) [1.0]

[a]Adjusted percentage and IRs shown only for the placebo-controlled data set; percentages in this analysis are study-size adjusted to avoid Simpson's paradox, where crude incidence from pooled data comprised of studies with different randomisation ratios could give misleading results; IRs in this analysis are exposure-adjusted IRs calculated as the number of patients reporting an event per 100 PY at risk or patient-years exposed. [b]Includes patients who received lebrikizumab 250 mg Q2W, 250 mg Q4W, 125 mg single dose, 125 mg Q4W and 250 mg single dose
Key: ALT = alanine aminotransferase; IR = incidence rate; LEB = lebrikizumab; PY = patient years; Q2W = every 2 weeks; Q4W = every 4 weeks; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection
Source: Stein Gold et al (2023) (74)

This analysis was consistent with the safety profile of lebrikizumab described in the individual studies and confirmed that the incidence of most TEAEs does not increase with longer duration of exposure to lebrikizumab.

B.2.10.4. CsA failures study (ADvantage)

Overview of TEAEs

Table 48 shows a summary of TEAEs during the induction period of ADvantage. The incidence of TEAEs was higher in the lebrikizumab + TCS group than in the placebo + TCS group. Most AEs were mild or moderate in intensity and did not lead to treatment discontinuation.

Table 48 Overview of TEAEs during the induction period: ADvantage

	n (%) of patients	
	PBO + TCS (n = 111)	**LEB 250 Q2W + TCS (n = 220)**
Any TEAE	59 (53.2)	136 (61.8)
Severe TEAEs	1 (0.9)	5 (2.3)
TEAEs related to treatment	[redacted]	[redacted]
SAEs	1 (0.9)	3 (1.4)
TEAEs leading to discontinuation	2 (1.8)	2 (0.9)
Deaths	0	0

Data are shown for the safety analysis set
Key: LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; SAE, serious adverse event; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event
Source: Warren et al (2023) (79); ADvantage clinical study report (80)

Common TEAEs

The most common TEAEs with lebrikizumab + TCS were nasopharyngitis, conjunctivitis and allergic conjunctivitis (Table 49).

Table 49 TEAEs reported by ≥5% of participants in either treatment group during the induction period: ADvantage study

	n (%) of patients	
	PBO + TCS (n = 111)	**LEB 250 Q2W + TCS (n = 220)**
Nasopharyngitis	14 (12.6)	28 (12.7)
Conjunctivitis	2 (1.8)	25 (11.4)
Allergic conjunctivitis	3 (2.7)	18 (8.2)
Oral herpes	3 (2.7)	11 (5.0)
COVID-19	7 (6.3)	8 (3.6)
Upper respiratory tract infection	7 (6.3)	8 (3.6)
Headache	6 (5.4)	6 (2.7)

Data are shown for the safety analysis set
Key: LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event
Source: Warren et al (2023) (79)

SAEs

SAEs were reported by 3 (1.4%) lebrikizumab + TCS-treated participants ([redacted]) and 1 (0.9%) participant ([redacted]) in the placebo + TCS group. None of the SAEs were considered related to study drug.

AEs leading to discontinuation

TEAEs leading to study drug discontinuation were reported for 2 (0.9%) lebrikizumab + TCS-treated participants ([redacted]) and 2 participants (1.8%) in the placebo + TCS group [redacted]). The event of [redacted] in the lebrikizumab + TCS group was considered at least possibly related to study drug.

Conjunctivitis

Table 50 summarises the incidence of conjunctivitis and other eye conditions during the induction period. In the conjunctivitis cluster, events were reported for a higher proportion of participants in the lebrikizumab + TCS group ([redacted]) compared with the placebo group + TCS ([redacted]). All the events were nonserious and mild or moderate in intensity; one event led to study drug discontinuation. Conjunctivitis was the most frequently reported treatment-related AE.

In the keratitis cluster, events were reported for [redacted] lebrikizumab + TCS-treated participants and [redacted] participants in the placebo + TCS group. These events were nonserious, mild (keratitis) or moderate (atopic keratoconjunctivitis) in intensity, and possibly related to study drug; neither participant discontinued study drug due to these events.

In the lebrikizumab + TCS group, approximately [redacted] of patients ([redacted]%) had a prior history of conjunctivitis, compared with one quarter ([redacted]%) in the placebo + TCS group.

Table 50 Conjunctivitis events during the induction period: ADvantage

	n (%) of patients	
	PBO + TCS (n = 111)	**LEB 250 Q2W + TCS (n = 220)**
At least one conjunctivitis event	[redacted]	[redacted]
Conjunctivitis cluster[a]	[redacted]	[redacted]
Conjunctivitis	2 (1.8)	25 (11.4)
Allergic conjunctivitis	3 (2.7)	18 (8.2)
Bacterial conjunctivitis	[redacted]	[redacted]
Keratitis cluster[b]	[redacted]	[redacted]
Atopic keratoconjunctivitis	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]

Data are shown for the safety analysis set. [a]Conjunctivitis cluster included the following preferred terms: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and giant papillary conjunctivitis. [b]Keratitis cluster includes the following preferred terms: keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, and vernal keratoconjunctivitis

Key: LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event

Source: Warren et al (2023) (79); ADvantage clinical study report (80)

Other TEAEs of special interest

Table 51 summarises other TEAEs of special interest.

The TEAE of [redacted] reported in the lebrikizumab + TCS group was mild in intensity and considered possibly related to study drug. Study drug was continued. This event had not resolved at the time of database lock.

All skin infections were mild or moderate in intensity and none were considered related to study drug.

There were no anaphylactic reactions in either treatment group. [redacted] in each group had immediate hypersensitivity: [redacted] in the lebrikizumab + TCS group and [redacted] in the placebo + TCS group. Both events were mild in intensity and the event of [redacted] was considered possibly related to study drug.

One or more injection site reaction was reported in [redacted] lebrikizumab + TCS-treated participants and [redacted] participants in the placebo + TCS group. All injection site reactions were mild or moderate in intensity and at least possibly related to study drug; none led to study drug discontinuation.

All atopic dermatitis exacerbation events were mild or moderate, and all were not related to study drug except one event in the placebo group. An AE of dermatitis atopic reported for one participant in the placebo + TCS group led to study drug discontinuation.

There were no reports of malignancy or parasitic infection. [redacted] participants [redacted] in the lebrikizumab + TCS group had herpes simplex infection; however, these were deemed not to be opportunistic infections.

Table 51 AEs of special interest during the induction period: ADvantage study

	n (%) of patients	
	PBO + TCS ([redacted])	LEB 250 Q2W + TCS ([redacted])
Eosinophilia	[redacted]	[redacted]
Eosinophil-related disorders	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Immediate hypersensitivity	[redacted]	[redacted]
Injection site reactions	[redacted]	[redacted]
Atopic dermatitis exacerbation	[redacted]	[redacted]

Data are shown for the safety analysis set
Key: LEB, lebrikizumab; PBO, placebo; Q2W, every 2 weeks; TCS, topical corticosteroid; TEAE, treatment-emergent adverse event
Source: ADvantage clinical study report (80)

B.2.10.5. Long-term safety of lebrikizumab

The long-term safety of lebrikizumab is being assessed in the ongoing ADjoin LTE study (see Section B.2.11). An interim analysis (with a data cut-off date of 14 April 2023) was carried out that included 267 patients who had responded to lebrikizumab treatment at Week 16 in ADvocate 1, ADvocate 2 or ADhere (82). Table 52 shows a summary of TEAEs in these participants from enrolment in ADjoin through data cut-off.

Table 52: Summary of TEAEs for participants entering ADjoin from ADvocate 1 & 2 or ADhere

	ADvocate 1 & 2 → ADjoin		ADhere → ADjoin	
	LEB 250 Q4W (N = 99)	LEB 250 Q2W (N = 82)	LEB 250 Q4W (N = 29)	LEB 250 Q2W (N = 57)
Patients with ≥1 TEAE, n (%)	58 (58.6)	56 (68.3)	17 (58.6)	35 (61.4)
Mild	26 (26.3)	31 (37.8)	12 (41.4)	15 (26.3)
Moderate	27 (27.3)	22 (26.8)	4 (13.8)	19 (33.3)
Severe	5 (5.1)	3 (3.7)	1 (3.4)	1 (1.8)
Serious AE	3 (3.0)	2 (2.4)	2 (6.9)	3 (5.3)
Death	0	0	0	1 (1.8)[a]
Discontinuation from study treatment due to AE	2 (2.0)	2 (2.4)	0	2 (3.5)
Conjunctivitis cluster[b]	4 (4.0)	2 (2.4)	3 (10.3)	7 (12.3)
Keratitis cluster[c]	0	0	0	0
Infections	38 (38.4)	34 (41.5)	11 (37.9)	24 (42.1)
Potential opportunistic infections[d]	1 (1.0)	2 (2.4)	1 (3.4)	0
Herpes infections	3 (3.0)	5 (6.1)	1 (3.4)	2 (3.5)
Parasitic infections	0	0	1 (3.4)	0
Injection site reactions	0	1 (1.2)	1 (3.4)	1 (1.8)
Malignancies[e]	0	0	0	0
Anaphylactic reactions	0	0	0	0
Eosinophilia[f]	0	1 (1.2)	0	0

[a] As reported by the investigator, a male patient died of natural causes on Study Day 462 and the event was assessed to be unrelated to study treatment; the patient had a medical history of hypertension, cardiac ablation, AD, insomnia, and gastroesophageal reflux; [b] The preferred terms of conjunctivitis, conjunctivitis allergic and conjunctivitis viral, were reported under the conjunctivitis cluster; [c] Includes preferred terms of keratitis, atopic keratoconjunctivitis, allergic keratitis, ulcerative keratitis, and vernal keratoconjunctivitis; [d] All potential opportunistic infections were assessed as not opportunistic based on the Winthrop criteria; [e] Includes both NMSC and malignancies excluding NMSC; [f] Eosinophilia reported as a TEAE

Key: LEB=lebrikizumab; NMSC=non-melanoma skin cancer; Q2W=every 2 weeks; Q4W=every 4 weeks; TEAE=treatment-emergent AE

Source: Guttman-Yassky et al (2023) (82)

Overall, the safety profile of lebrikizumab in the ADjoin study was consistent with that reported in the ADvocate studies and ADhere.

B.2.10.6. Safety conclusions

Overall, the safety analyses presented above show that the safety profile of lebrikizumab is comparable with placebo with low rates of TEAEs, SAEs and AEs of special interest. There were few discontinuations owing to TEAEs and the rate of injection site reactions was low. There were no important differences in safety profiles between participants who

received lebrikizumab monotherapy and those who received lebrikizumab in combination with TCS.

A longer duration of exposure to lebrikizumab over 52 weeks did not result in a higher incidence of conjunctivitis or any clinically meaningful differences in AEs when compared with 16 weeks of therapy. Interim Week 104 results from the long-term ADjoin study support the long-term safety of lebrikizumab.

No clinically meaningful differences in TEAEs were seen between patients who were given lebrikizumab every 4 weeks and those who received it more frequently (every 2 weeks).

B.2.11 Ongoing studies

Table 53 shows details of ongoing studies that are expected to provide additional evidence in the next 12 months for lebrikizumab in the treatment of adolescents and adults with moderate-to-severe AD.

Table 53: Ongoing studies

Study	Design	N	Treatments	Primary endpoint	Expected completion date
ADjoin NCT04392154	Long-term extension study Patients who completed ADvocate 1, ADvocate 2, ADhere, ADore or ADopt-VA, or who otherwise meet the inclusion criteria 100 weeks Global	~1000	LEB 250 mg Q2W LEB 250 mg Q4W Open-label or blinded, depending on the participant's parent study	% of participants who discontinue study treatment because of AEs	Sept 2024 (interim results available[a]; final results expected Q3 2024)
ADapt NCT05369403	Study in adults and adolescents who were previously treated with dupilumab 24 weeks US only	~120	LEB 250 mg Open-label	% of participants achieving EASI 75 at Week 16	March 2024 (results expected Oct 2024)

ADmirable NCT05372419	Study in adults and adolescents with moderate-to-severe AD and skin of colour 24 weeks US only	~80	LEB 250 mg Open-label	% of participants achieving EASI 75 at Week 16	August 2024 (results expected Nov 2024)

[a]An interim analysis of ADjoin has been carried out with a data cut-off date of 14 April 2023 (82). Efficacy data from this analysis are shown in Section B.2.6.4; safety data from this analysis are shown in Section B.2.10.5.

Key: EASI, Eczema Area and Severity Index, LEB, lebrikizumab; Q2W, every 2 weeks; Q4W, every 4 weeks

B.2.12 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence base

The clinical evidence base shows that lebrikizumab (as monotherapy and in combination with TCS) significantly improved skin clearance (as measured by IGA and EASI), itch (as measured by itch NRS), interference of itch with sleep (as measured by the Sleep-Loss Scale) and patient-reported outcomes (as measured by DLQI/cDLQI and POEM), in both adolescents and adults with moderate to severe AD at Week 16. Meaningful improvements in skin clearance and itch were seen in the first 1 to 4 weeks.

Participants' response to treatment with lebrikizumab was maintained through Week 52. Response was similar regardless of whether patients received lebrikizumab every 4 weeks (as per the recommended maintenance regimen) or every 2 weeks. Results from the escape arm show that some patients with initial partial response may improve further with continued treatment Q2W up to Week 24.

Lebrikizumab reduced the need for rescue therapy compared with placebo.

Treatment with lebrikizumab also led to rapid and clinically meaningful improvements in the signs and symptoms of moderate-to-severe AD in patients who were not adequately controlled with CsA or for whom CsA is not medically advisable. The anticipated positioning of lebrikizumab is as a second line systemic treatment for moderate-to-severe AD (i.e. after the condition has not responded to at least 1 systemic immunosuppressant, or these are not suitable).

Lebrikizumab was well tolerated, with low rates of TEAEs, SAEs and AEs of special interest. Few TEAEs led to treatment discontinuation. There were no new safety signals with longer-term (up to two years) of treatment with lebrikizumab. There were no important differences between the safety profiles of participants treated with lebrikizumab monotherapy and those who received lebrikizumab in combination with TCS.

Strengths and limitations of the clinical evidence base

Strengths

The three pivotal trials (ADvocate 1 & 2 and ADhere) were large, placebo-controlled RCTs and therefore provide robust evidence for the efficacy and safety of lebrikizumab in adults and adolescents with moderate-to-severe AD. Two of the trials, ADvocate 1 & 2, investigated lebrikizumab as monotherapy; this allowed determination of the effect size of lebrikizumab separately from TCS. In ADhere, lebrikizumab was combined with TCS to mimic clinical practice. All three trials included participants who were inadequately controlled after optimisation on topical therapies. In addition, ADvantage evaluated lebrikizumab in participants who were inadequate responders, or intolerant or contraindicated to CsA.

Limitations

The evidence base contains no direct comparison of lebrikizumab vs other treatments for moderate-to-severe AD. However, it was possible to conduct an NMA that allowed derivation of relative efficacy estimates for lebrikizumab versus dupilumab, the most relevant clinical comparator.

There were no UK patients in ADvocate 1 & 2 or ADhere. In ADvantage, 10 out of 331 participants were from the UK (seven in the lebrikizumab group and three in the placebo group).

Validity of the clinical evidence

The clinical evidence for lebrikizumab reflects UK clinical practice, with the study populations including patients who are typically candidates for systemic therapy in the UK.

The outcomes used in the clinical trials are consistent with the consensus-based Harmonising Outcome Measures for Eczema (HOME) initiative, which recommends using EASI to assess clinical signs of eczema, POEM to assess patient-reported symptoms, and DLQI to assess quality of life (104). In previous NICE appraisals of treatments for moderate-to-severe AD, a composite endpoint of EASI 50 combined with an improvement in DLQI of at least 4 points was considered the most relevant for decision making (1-3).

Regarding patient demographics, UK clinical experts have indicated that they would expect the UK patient population to be more ethnically diverse than the population in the clinical trials, with a greater proportion of Afro-Caribbean and south Asian patients. The experts were concerned that this may affect generalisability of the results to the UK population. A Phase 3 single-arm study is currently underway to evaluate lebrikizumab in adults and adolescents with skin of colour (ADmirable; NCT05372419); results are expected in Q4 2024. NICE guidance on other systemic treatments for moderate-to-severe AD states that healthcare professionals should take into account skin colour and how this may affect EASI scores when assessing response to treatment (1-3).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An economic systematic literature review (SLR) was conducted to identify published economic models and available economic evidence including economic evaluations, costs, and resource use. A detailed description of the SLR is provided in Appendix G.

In summary, a total of 22 were included for the economic models review: five were SMC appraisals (105-109), four were CADTH reports (110-113), three were NICE technology appraisals (1-3), four were full text publications (114-117), two were conference abstracts reporting budget impact analyses (118, 119), two were conference abstracts reporting Italian cost-utility analyses (120, 121) and two were ICER reports (122, 123). All 22 models considered the use of dupilumab (seven studies included dupilumab as combination therapy with TCS (3, 105, 106, 108, 110, 111, 117) while the other studies did not specify). The dupilumab dosing and regimen reported in NICE TA534 (1) was often used as the reference. Dupilumab was the experimental intervention being evaluated in nine studies and was included as a comparator intervention in the remaining thirteen.

Overall, the most relevant economic analysis that has informed the development of the lebrikizumab cost-effectiveness model is the recent NICE TA814 multiple technology appraisal.(3, 24) Clinical and health economic experts consulted in the development of this submission agreed that this was the most appropriate approach.(124)

The relevant studies identified from the SLR are summarised in Table 54 below.

Table 54: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Cost-utility models reporting ICERs per QALY						
Kuznik et al.(114)	2017	Cost-utility models reporting ICERs per QALY Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon and 3% annual discounting.	Adults with moderate-to-severe AD. Patients modelled had characteristics similar to those in the SOLO trials, with 58% being male, and having a mean age of 38 years, median disease duration of 26 years, and a median EASI score of 29.9.	QALYs: Dupilumab = 15.95 SOC = 14.83 Years with response: Dupilumab = 7.21 SC = 3.05	US dollars Total annual costs, excluding dupilumab drug costs: Dupilumab arm: $299,449 SOC arm: 331,538	Cost of dupilumab to meet $100,000 per QALY gained threshold was $28,769, and for $150,000 per QALY gained threshold was $39,941
Zimmermann et al. (116)	2018	Markov model with a lifetime time-horizon and 3% annual discounting.16-week cycle, plus a half-cycle correction	Adults with moderate-to-severe AD, inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. The modelled population had a mean age of 38 years and 53% were male. The base case assumed 53% had moderate disease and 47% had severe disease.	QALYs for the base case population: Dupilumab: 16.28 SOC: 14.37 Dupilumab provided an additional 1.91 quality-adjusted life years (QALYs) over the remaining lifetime of a patient	US dollars Total costs and drug costs for the base case population: Dupilumab list price: $509,593; $267,797 Dupilumab net price: $466,168; $224,372 SOC: $271,461; $NA The expected lifetime cost for patients treated with dupilumab was $509,600, including $267,800 in dupilumab drug costs and $241,800 in other healthcare costs. Average lifetime cost for usual care was $271,500.	Dupilumab lead to an incremental cost-effectiveness ratio (ICER) of $124,500. In the subgroup analysis the ICER was lower for patients with severe AD ($95,800) than those with moderate AD ($160,000).
Costanzo et al. (115)	2020	1-year decision tree, followed by a lifetime horizon Markov model with a lifetime time-horizon and 3% annual discounting. 16-week cycle Health states categorised by treatment response. Treatment response was defined as	Adults with severe AD, for whom CsA treatment is contraindicated, ineffective or not tolerated. The modelled population were 60% male and had a mean age of 38.1 years.	QALYs: 16.96 in the dupilumab group 14.57 in the SOC group	Italian National Health care Service; Euros (Currency year not reported) Total costs: €137,267 for dupilumab €56,744 for SOC	Dupilumab plus SOC lead to an ICER per QALY gained of $33,263.

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		achieving either EASI-50, -75, -90.				
Pedone et al. (121)	2022	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon and Not reported discounting. 1-year cycle Health states in the model included treatment response (defined as a composite outcome of achieving EASI-50 plus ≥4 points reduction in DLQI), non-response, and death.	Children aged 6-11 and adolescents 12-17 years eligible for systemic therapy, for whom treatment with topical medications is contraindicated, ineffective, or not tolerated. The "overall" population was modelled, regardless of use rescue medication.	Adolescent population: QALYs gained = 1.60	Italian National Health care Service; Euros (Currency year not reported) Total cost of treatment: dupilumab = €118,000 SC = €75,042	Adolescent population: ICER = €26,886 / QALY
Fanelli et al. (120)	2020	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon and not reported discounting. Cycle length not reported. Treatment response was measured at 16 and 52 weeks.	Adolescents (aged 12-17) with uncontrolled moderate-to-severe AD. Full analysis set was used (all patients regardless of use of rescue medication). Patient subgroup analysis included those with prior use of topical corticosteroids or calcineurin inhibitors.	QALYs gained = 1.53	Italian National Health care Service; Euros (Currency year not reported) Total costs were not reported.	Dupilumab vs SOC resulted in an ICER of €33,918.29 per QALY gained
NICE [TA534; Dupilumab] (1)	2018	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon and 3.5% annual discounting.	Adult patients with moderate-to-severe AD who were contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. Dupilumab monotherapy arm are based on SOLO-CAFÉ-like patients, and combination arm are based on CAFÉ and CHRONOS-CAFÉ-like patients. SOC arm is based on pooled data from trials placebo groups.	Total and incremental QALYs, life-years gained and costs were not reported.	English National Health Service; 2016-17 UK sterling Total and incremental QALYs, life-years gained and costs were not reported.	Dupilumab compared to SOC/placebo: CAFÉ FAS + CHRONOS CAFÉ-like pool including dupilumab every 2 weeks patients: ICER = £28,874/QALY SOLO CAFÉ-like pool including dupilumab every 2 weeks patients: ICER = £24,703/QALY

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE [TA681; Baricitinib] (2)	2021	Markov state transition model with a lifetime time-horizon and 3.5% annual discounting. 1-year cycle with a half-cycle correction (not applied to non-responders) Treatment response was defined as a composite outcome of EASI-50 plus a DLQI reduction ≥4. Treatment discontinuation was applied annually for dupilumab patients in long-term model.	Adult patients with moderate-to-severe AD who have failed at least one current systemic immunosuppressant	Total and incremental QALYs, life-years gained and costs were not reported.	English National Health Service and Personal Social Services; 2018-2019 UK sterling Total and incremental QALYs, life-years gained and costs were not reported.	Pairwise comparison of baricitinib vs SOC: ICER = £17,941/QALY Pairwise comparison of baricitinib vs dupilumab: baricitinib cost-effective in the SW quadrant ICER = 203,525/QALY foregone Dupilumab vs. SOC in the base case population: estimate ICER range £28,874/QALY to £24,703/QALY (with and without TCS respectively)
NICE [TA814; Abrocitinib, tralokinumab or upadacitinib] (3, 24)	2022	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime (up to a maximum age of 100 years) and 3.5% annual discounting. 4-week cycle, but no half-cycle correction Health states include treatment response, non-response, and death. Treatment response was defined as achieving a composite outcome of EASI-50 with DLQI reduction ≥4. Treatment discontinuation was applied annually for dupilumab and SOC patients in long-term model.	Adults and adolescents with moderate-to-severe AD, who are eligible for systemic treatment who achieve inadequate response to, cannot tolerate, or are contraindicated to CsA.	Total and incremental QALYs redacted	English National Health Service; 2019-2020 UK sterling Total and incremental costs redacted	Adult first-line systemic treatment population, combination therapy – EASI 75: Upadacitinib 15 mg + TCS vs CsA + TCS: Deterministic ICER = £82,059 Probabilistic ICER = £79,834 Upadacitinib 30 mg + TCS vs CsA + TCS: Deterministic ICER = £148,375 Probabilistic ICER = £145,774 Adult second-line systemic treatment population, monotherapy – EASI 50 + DLQI ≥4: Abrocitinib 100 mg vs dupilumab: Deterministic ICER = £81,897 Probabilistic ICER = £92,860 Abrocitinib 200 mg vs dupilumab: Deterministic ICER = £60,343 Probabilistic ICER = £63,186 Upadacitinib 15 mg vs dupilumab:

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Deterministic ICER = Dominant Probabilistic ICER = Dominant Upadacitinib 30 mg vs dupilumab: Deterministic ICER = £66,196 Probabilistic ICER = £65,541 Tralokinumab vs dupilumab: Deterministic ICER = £271,903* Probabilistic ICER = £258,869* Adult second-line systemic treatment population, combination therapy – EASI 50 + DLQI ≥4: Abrocitinib 100 mg + TCS vs dupilumab + TCS: Deterministic ICER = £67,274* Probabilistic ICER = £58,920* Abrocitinib 200 mg + TCS vs dupilumab + TCS : Deterministic ICER = £107,901 Probabilistic ICER = £116,885 Upadacitinib 15 mg+ TCS vs dupilumab + TCS : Deterministic ICER = £181,963* Probabilistic ICER = £204,598* Upadacitinib 30 mg+ TCS vs dupilumab + TCS : Deterministic ICER = £128,561 Probabilistic ICER = £117,944 Tralokinumab + TCS vs dupilumab + TCS : Deterministic ICER = £223,279* Probabilistic ICER = £285,653* Adolescents, monotherapy – EASI 75: Abrocitinib 100 mg vs dupilumab: Deterministic ICER = Dominant Probabilistic ICER = Dominant Abrocitinib 200 mg vs

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						dupilumab: Deterministic ICER = Dominant Probabilistic ICER = Dominant Upadacitinib 15 mg vs dupilumab: Deterministic ICER = Dominant Probabilistic ICER = Dominant
Heinz KC et al. (117)	2022	Markov cohort model with lifetime time horizon, from age 18 years plus, long-term Markov model with a lifetime time horizon, 3.5% annual discounting. 1-year cycle, plus a half-cycle correction Health states included treatment response, non-response, and death.	Patients aged ≥18 years, with moderate-to-severe AD who have exhausted all previous lines of therapies due to loss of response.	In the base case, upadacitinib 30mg had higher total QALYs (+0.023) than dupilumab.	In the base case, upadacitinib 30mg had higher total costs (+£5,103.78) than dupilumab.	ICER of £219,733.88 (costs per QALY gained) for upadacitinib 30mg compared to dupilumab, assuming a price of £57.54 per day for upadacitinib 30mg
SMC2011 [Dupilumab (Dupixent)] (106)	2018	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon. Health states were induction phase response, then responders (defined as EASI-50, -75, or -90), non-responders, and death. Health states were treatment response, composite outcome measure of EASI- 50 plus DLQI>4 assessed at 16 weeks, non-response, and death. 16-week cycles.	Patients aged ≥18 years, with moderate-to-severe AD not adequately controlled by topical therapies and who are contraindicated to, intolerant of, have had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.	Base case incremental QALYs: CAFÉ FAS+ CHRONOS CAFÉ-like pool = 1.81 SOLO CAFÉ-like pool = 1.41	Scottish National Health Service; UK sterling (Currency year not reported) SOC Base case incremental cost (with PAS): CAFÉ FAS+ CHRONOS CAFÉ-like pool = £63,911 SOLO CAFÉ-like pool = £41,532 Total cost per year for dupilumab: Year 1 = £17,708 Year 2 onwards = £16,444	Base case ICER per QALY gained: CAFÉ FAS+ CHRONOS CAFÉ-like pool = £35,351 SOLO CAFÉ-like pool = £29,504
SMC2337 [Baricitinib	2021	Markov state transition model with a lifetime time-horizon. 1-year	Adult patients who are candidates for systemic therapy who have failed at least one	Not reported	Scottish National Health Service;	ICER (£/QALY): vs SOC (list price) = £65,466 vs dupilumab (list price) =

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
(Olumiant)] (107)		cycle Health states were treatment response, composite outcome measure of EASI- 50 plus DLQI>4 assessed at 16 weeks, non-response, and death. The economic model used 'all observed' data rather than the 'primary analysis' data set where patients were considered non-responders after rescue medication. Treatment discontinuation was applied annually for dupilumab patients in long-term model. A discontinuation rate of 3.7% per year was applied to the dupilumab arm of the model.	current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control		UK sterling (Currency year not reported) Cost of treatment per year for Baricitinib: 4 mg once daily = £10,472 2 mg once daily = £10,472	£113,459 (SW Quadrant)
SMC2403 [Tralokinumab (Adtralza)] (108)	2022	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon. 4-week cycle Health states in the model were treatment response, defined as EASI-75 at 16 weeks, no response, or death. After year 1, all cause discontinuation rate at week 52 was used to calculate a constant rate of discontinuation.	Adult patients with moderate-to-severe AD and an inadequate response or unsuitability to an existing systemic immunosuppressant.	Not reported	Scottish National Health Service; UK sterling (Currency year not reported) Tralokinumab list price (£): Year 1 = 10,165 to 14,980 Subsequent years = 9,630 and 14,445 Other costs not reported	Base-case for monotherapy in ECZTRA 7–like population: vs SOC (with PAS): ICER = £25,090; vs dupilumab (list price): ICER = £98,127 (SW Quadrant) Base-case for combination therapy in ECZTRA 7–like population: vs SOC + TCS (with PAS): ICER = £27,448; vs dupilumab + TCS (list price): ICER = £107,354 (SW Quadrant)

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
SMC2417 [Upadacitinib (Rinvoq)] (105)	2022	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime time-horizon. 1-year cycle Health states were treatment response, non-response, or death. Treatment response was defined as achieving the composite endpoint of EASI-50 plus DLQI reduction ≥4.	Adults and adolescents 12 years and older with moderate-to-severe AD who are candidates for systemic therapy. An "all-observed" population was used, uncensored for the use of rescue medication. Subgroup analysis included adults and adolescents 12 years and older with moderate-to-severe AD in whom the disease has not responded to at least one other conventional systemic immunosuppressant therapy (ciclosporin, methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic therapy is not suitable	Not reported	Scottish National Health Service; UK sterling (Currency year not reported) Upadacitinib 15mg or 30mg orally once daily: Total cost per year = £10,472 to £20,945 Other costs not reported	Base case (adult systemic-exposed): ICER (£/QALY): upadacitinib (list price) vs dupilumab: upadacitinib 15 mg + TCS = £87,736 (SW Quadrant) upadacitinib 30 mg + TCS = £116,943 upadacitinib (PAS) vs SOC: upadacitinib 15 mg + TCS = £10,028 upadacitinib 30 mg + TCS = £18,366
CADTH [Dupilumab (Dupixent)] (110)	2020	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime (assumed to be 86 years) time-horizon and 1.5% annual discounting. 1-year cycle, but no half-cycle correction was used (instead weekly decision nodes were used) Treatment response, defined as a composite outcome of EASI-50 and DLQI response ≥4 was based on the "all-observed" population (all patients included regardless of rescue medication). Other health states were non-response or death. Patients achieving a response at either assessment were	Patients with moderate-to-severe AD, aged ≥12 years old, who were non-responsive to topical treatment or where topical treatment was contraindicated. Plus, a subgroup analysis of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies.	Dupilumab + SOC was associated with 2.55 QALYs compared with SOC alone over the 86-year time horizon Total QALYs for dupilumab + SOC was 26.22, and SOC was 23.67. Incremental QALYs = 2.55 (CADTH reanalysis calculated incremental QALYs as 1.26)	Perspective of the Canadian publicly funded health care payer; 2019 Canadian dollars Dupilumab + SOC was associated with an additional $127,607 compared with SOC alone over the 86-year time horizon At the submitted price of $959.94 for each of the 200 mg and 300 mg injections, the first-year cost of DUP is $25,918 per patient and the annual maintenance cost is $24,958 per patient.	Dupilumab + SOC ICER of $50,133 per QALY gained for Dupilumab + SOC compared to SOC alone. Subgroup analysis of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies found the ICER for Dupilumab + SOC compared to SOC alone was $52,168 per QALY gained.

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		assumed to remain on the assigned active treatment, with an annual discontinuation rate applied in year 2 onwards.				
CADTH [Abrocitinib (Cibinqo)] (111)	2022	Short-term decision tree (1-year) followed by a long-term Markov model with a lifetime (up to patient age 110 years) time-horizon. 1-year cycle, plus a half-cycle correction Health states in the decision tree were response or no response, health states in the Markov model were response, no response, or death. Response was defined as EASI-50. The dupilumab arm continued dupilumab in response and switched to SOC in no response. The SOC arm continued SOC in both health states. Dupilumab discontinuation rate per model cycle was 6.3%.	Adults and adolescents (≥ 12 years) with moderate-to-severe AD who have had an inadequate response to topical therapies, or for whom these treatments are not advisable (patients are assumed to have had no prior use of immunosuppressants)	QALYs and life-years gained were not reported.	Perspective of the Canadian publicly funded health care payer; Canadian dollars (Currency year not reported) Annual treatment cost: Abrocitinib 100 mg = $17,765 Abrocitinib 200 mg = $19,882	Results of the company submission are not reported. Data is from the CADTH reanalysis (The estimated ICERs from the CADTH reanalysis were higher than those submitted by the sponsor). ICER per QALY gained for patients refractory or ineligible for systemic IMMs: Abrocitinib 200 + SOC vs. abrocitinib 100 + SOC = $231,013 Abrocitinib 100 + SOC vs. SOC alone = $156,735
CADTH [Upadacitinib (Rinvoq)] (112)	2022	Decision tree and Markov model hybrid with a 10 year time-horizon. Treatment response (starting at 16 weeks). Other details not reported.	Adolescents and adults (patients aged 12 years or over) with AD who are eligible for conventional systemic therapies	QALYs not reported.	Perspective of the Canadian publicly funded health care payer; Canadian dollars (Currency year not reported) Total annual treatment cost: Upadacitinib, 15 mg = $17,768 Upadacitinib, 30 mg = $27,010	Results of the company submission are not reported. Data is from the CADTH reanalysis. The cost-effectiveness of upadacitinib is unknown due to a lack of clinical data and limitations with the sponsor's model. ICERs for the adult population:

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Upadacitinib 15 mg + TCS vs SOC = $48,616 Upadacitinib 30 mg + TCS vs 15 mg = $372,226 Dupilumab dominated by upadacitinib 15 mg + TCS
ICER [Dupilumab] (122)	2017	Markov model with a lifetime time-horizon and 3% annual discounting. Clinical response at 16 weeks (no details reported but assumed to be response, no response or death)	Adults with moderate-to-severe AD who had failed topical therapy. The modelled population had a mean age of 38 years and was 53% male. The baseline patient population consisted of 53% with moderate disease (IGA3) and the remaining 47% with severe disease (IGA4). Subgroup analyses were performed for severe and moderate patients separately.	Dupilumab provided an additional 1.91 QALYs over the remaining lifetime of patients Total QALYs: Dupilumab: 16.28 Usual Care: 14.37	United States payer perspective; 2017 US Dollars Average total lifetime cost for patients treated with dupilumab was $509,600 using the list price for the drug and $466,200 using the net price for the drug. This included dupilumab drug costs of $267,800 or $224,400, respectively (accounting for discontinuation). Patients with AD treated with usual care had an average total lifetime cost of $271,500.	The incremental cost-effectiveness ratio for dupilumab was $124,541 per additional QALY gained using the list price for the drug, and $101,830 per additional QALY gained using the net price for the drug. Subgroup analyses: Patients with moderate disease had slightly lower healthcare costs but higher drug costs compared to the total population. Patients with moderate disease also gained fewer QALYs with dupilumab treatment compared with severe patients. Patients with severe disease had slightly higher healthcare costs but lower drug costs compared to the total population. The resulting ICERs were $160,000 for patients with moderate AD and $95,800 for patients with severe disease with the list price for the drug, and $130,800 for patients with moderate AD and $78,300 for patients with severe disease with the net price for the drug.
ICER [JAK inhibitors and monoclonal antibodie	2021	Markov model (Adapted from the ICER's 2017 report on dupilumab) with a 5-years time-horizon and 3% annual discounting. 16-week cycle	Adult patients with moderate-to-severe AD. The modelled population had a mean age of 35.8 years and 66% of the cohort were male. The patient population is assumed to	Total QALYs and Life-years gained for each intervention were as follows: Abrocitinib: 3.59; 4.85 Baricitinib: 3.23; 4.85 Tralokinumab: 3.29;	United States payer perspective; 2021 US Dollars Drug cost and total costs for each intervention were as follows:	With SOC as the comparator, the ICER per QALY was as follows: Abrocitinib: $148,300 Baricitinib: $71,600 Tralokinumab: $129,400 Upadacitinib: $248,400

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
s] (123)		Health states included treatment response (defined as EASI-50, -75, -90), no response, and death. Treatment discontinuation was applied annually for dupilumab and SOC patients in long-term model.	exclude patients over 50 with increased cardiovascular risk, as JAK inhibitors will likely not be approved in that population.	4.85 Upadacitinib: 3.51; 4.85 Dupilumab: 3.47; 4.85 SOC: 2.98; 4.85	Abrocitinib: $113,200; $178,400 Baricitinib: $26,900; $105,300 Tralokinumab: $51,700; $127,700 Upadacitinib: $151,300; $219,700 Dupilumab: $72,400; $141,900 SOC: $n/a; $87,800 There were no prices available for abrocitinib and tralokinumab, so the cost estimates and incremental cost-effectiveness ratios were based on placeholder prices.	Dupilumab: $110,300 With dupilumab as the comparator, the ICER per QALY was as follows: Abrocitinib: $303,400 Baricitinib: less costly, less effective Tralokinumab: less costly, less effective Upadacitinib: $1,912,200
Cost-minimisation analyses						
SMC2431 [Abrocitinib] (109)	2022	Cost minimisation analysis with a 20 year time-horizon. 16-week cycle, plus a half-cycle correction Health states in the Markov model were responders (defined as EASI-50, -75, or -90), non-responders, and death. Once in a response state, patients were not allowed to transition between responder categories. Patients could transition back to the non-responder state as they discontinued treatment, for any reason. Patients could also transition from any health state to death. Treatment specific per-cycle discontinuation rates were modelled for the first year and then for	Adults and adolescents, 12 years and older, with moderate-to-severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated.	N/A (cost minimisation)	Scottish National Health Service UK sterling (Currency year not reported) The base case results using list prices for all medicines for the adult and adolescent combination therapy populations indicated that the total cost of treatment with abrocitinib was less than that expected with dupilumab. Abrocitinib cost per year = £11,619	N/A (cost minimisation)

Study	Year	Summary of model	Patient population (average age in years)	QALYS (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		all subsequent years where data was available.				
CADTH [Tralokinumab (Adtralza)] (113)	2022	Cost minimisation analysis with a 2 year time-horizon.	Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and have had an adequate trial or are ineligible for each of the following therapies: phototherapy (where available), methotrexate, and cyclosporine.	N/A (cost minimisation)	Perspective of the Canadian publicly funded health care payer; Canadian dollars (Year not reported) Total year 1 costs: dupilumab = $26,425 tralokinumab = $19.762 Total year 2 costs: dupilumab = $25,070 tralokinumab = $17,306 Total costs over 2-year time horizon: dupilumab = $51,495 tralokinumab = $37,068 Incremental costs vs dupilumab: dupilumab = reference tralokinumab = –$14,427	N/A (cost minimisation)
Budget impact analyses						
Chalmers et al.(119)	2022	Budget impact model. No further details reported.	Adults with moderate-to-severe AD with eligibility for systemics.	N/A – BIM	Tralokinumab was found to decrease the average budget over the time horizon by 9% - a saving of £9,821,579.	N/A – BIM
Kim et al. (118)	2022	Budget impact analysis with a 3-year time horizon. No further details reported.	Hypothetical population of one million commercially-insured adults in the US who already have access to dupilumab, upadacitinib and abrocitinib for the treatment of moderate-to-severe AD.	N/A – BIM	US dollars Tralokinumab scenario: total cost decrease of $179,197 after year one. Over three years cumulative saving totalled $2.5million compared to No tralokinumab scenario. Average cost per member per month decreased by $0.01 in year 1 and $0.13 in year 3.	N/A – BIM

Key: AD = Atopic dermatitis; ABRO = Abrocitinib; BAR = Baricitinib; CsA = Ciclosporin; DUP = Dupilumab; ICER = Incremental cost-effectiveness ratio; NMA=Network-meta-analysis; PAS = Patient access scheme; QALY = Quality adjusted life-year; SOC = Standard of care; TCI = Topical calcineurin inhibitor; TCS = Topical corticosteroid; TRALO = Tralokinumab; UPA = Upadacitinib

B.3.2 Economic analysis

No economic evaluations were identified that evaluated the cost-effectiveness of lebrikizumab thus a *de novo* cost-effectiveness model was developed.

B.3.2.1. Patient population

The patient population included in the cost-effectiveness analysis is 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. This population is narrower than the lebrikizumab marketing authorisation but is aligned with that of other targeted therapies for moderate-severe AD recommended by NICE(1-3).

B.3.2.2. Model structure

The model structure and underlying assumptions are aligned with that of the recent NICE multiple technology appraisal, TA814, abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (3, 59). A hybrid economic model was developed comprising a short-term (1-year) decision tree component, to capture the treatment induction phase and treatment response assessments, followed by a long-term (lifetime), Markov model.

All patients enter the first-line systemic treatment, short-term decision tree model (Figure 30), starting treatment on either lebrikizumab or a comparator and remain on treatment for 16 weeks (treatment induction phase). At week 16, response to treatment is assessed, defined as achieving EASI 50 + DLQI≥4. Responders at week 16 remain on treatment until week 52, whereas non-responders at week 16 discontinue treatment and receive BSC. The model includes the functionality to assume a bundle of active treatments that non-responders may receive once they discontinue their initial treatment, however this is not detailed in this submission as this was not included as a scenario in the NICE MTA (TA814).

Between week 16 and 52, responders may lose response to treatment or discontinue treatment for other reasons and will enter the long-term Markov model (Figure 31) in the 'subsequent treatment' phase and receive BSC. Week 16 responders who sustain their response between week 16 and 52 and are still on treatment enter the long-term Markov model in the 'initial treatment' phase in the responder health state. Sustained response for the intervention at week 52 is based on conditional discontinuation data, defined as the proportion of patients discontinuing treatment at week 52 from those who achieve response at week 16.

In the short-term model, the BSC health state is comprised of responders and non-responders and these proportions are informed by week 16 response data. This approach was applied in the NICE MTA (TA814) and was also accepted in TA681 as an appropriate way to capture the waxing and waning nature of response to BSC treatment.

At the end of the short-term decision tree (start of year 2), patients enter a long-term Markov model. Health states in the model are response, partial response, non-response and death. Due to a lack of data to inform the proportion of partial responders for all comparators, the partial response health state is not included in the model base-case. That is, patients are only categorised as responders or non-responders and no patients occupy the partial response health state.

Patients who have maintained a response at week 52 and still on treatment enter the Markov model in the maintenance health state and remain there until loss of response (via treatment waning) or if they discontinue treatment for any reason (all-cause discontinuation). If patients lose response or discontinue treatment, they transition to the non-responder state and then initiate treatment with BSC in the subsequent treatment phase in the next model cycle.

Patients that have discontinued treatment to BSC in the short-term decision tree enter the Markov model in the subsequent treatment phase and remain there until death. As with the BSC health state in the short-term decision tree model, the Markov model subsequent treatment phase is composed of responders and non-responders and these

proportions are informed by week 16 response data, in line with approach accepted in TA681.

At any time in the model, patients can transition to the death state. As treatment for AD is not expected to affect mortality, transitions to the death state are informed by general population mortality rates.

In the long-term model, an annual cycle length has been implemented and half cycle correction applied. The time horizon of the model is lifetime (up to a maximum age of 100 years). The perspective of the analysis is the NHS in England. Costs and outcomes are discounted at a rate of 3.5%, in line with the NICE reference case.

Figure 30: Short-term decision tree model structure

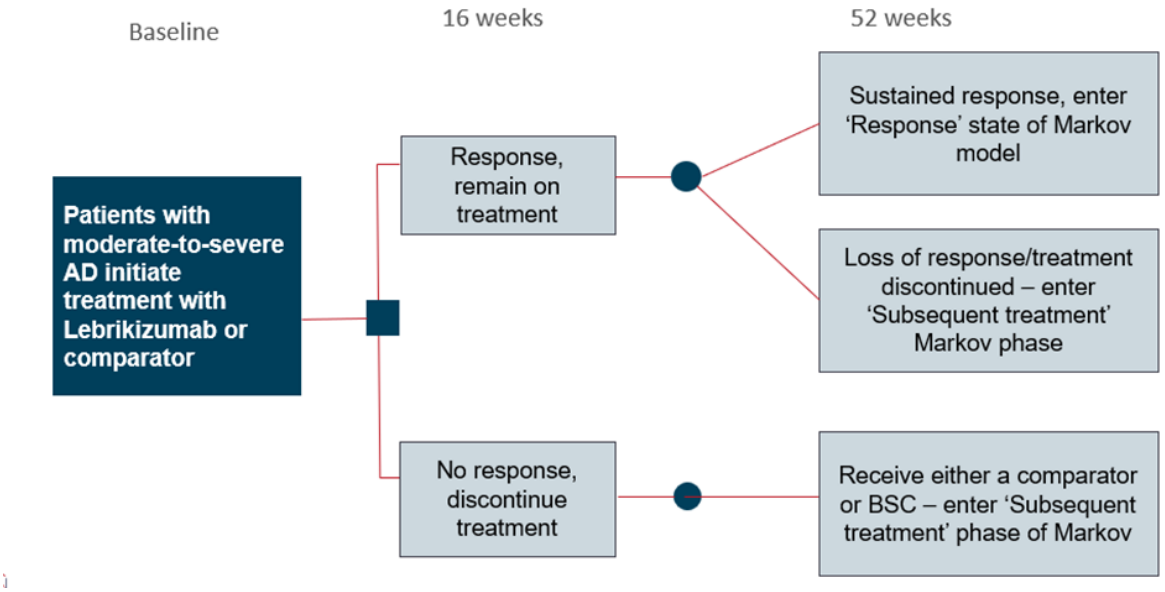


Figure 31: Long-term Markov model structure

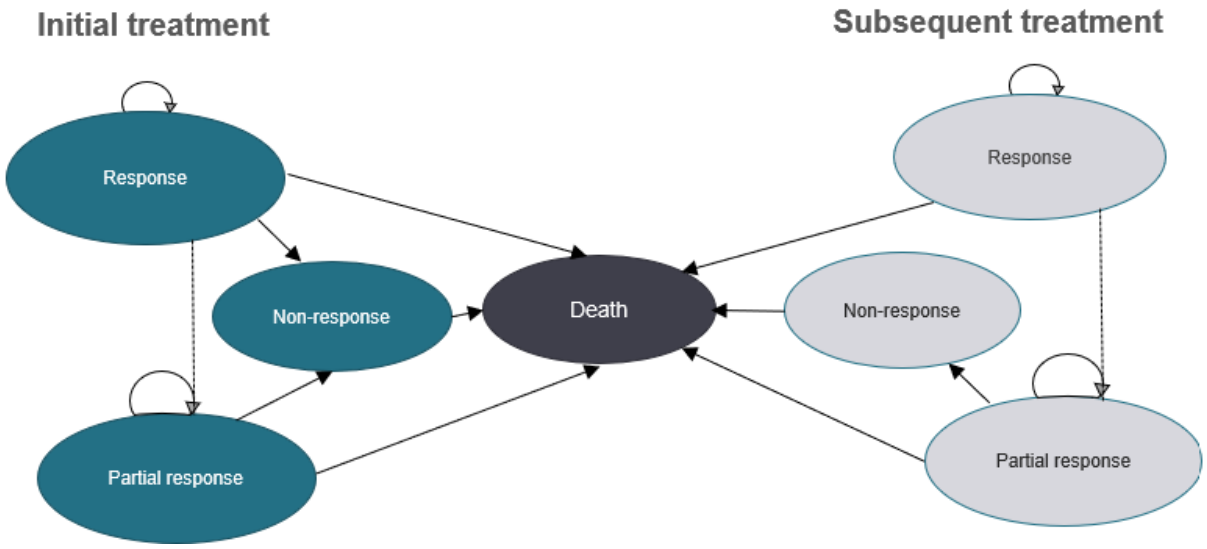


Table 55: Features of the economic analysis

	Previous evaluations			Current evaluation	
Factor	**TA534 dupilumab**	**TA681 baricitinib**	**TA814 abrocitinib, tralokinumab or upadacitinib**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	AD is a chronic disease
Treatment waning effect?	Yes	Yes	Yes	Yes	BSC placebo effect in clinical study
Source of utilities	Manufacturer clinical studies	Manufacturer clinical studies	Manufacturer clinical studies	Manufacturer clinical studies	Utility hierarchy favours EQ-5D from clinical studies
Source of costs	Secondary care case notes review and NHS reference costs	From TA534	From TA534	From TA814	Consistent with other AD appraisals.

B.3.2.3. Intervention technology and comparators

The modelled intervention is lebrikizumab, novel, high-affinity, monoclonal antibody or biological agent that selectively inhibits interleukin 13 (IL-13) for the treatment of atopic dermatitis (eczema). The setting of care for lebrikizumab is secondary care, as is the case for existing biologics such as dupilumab and tralokinumab that are used in the treatment of moderate to severe AD, as well as JAK inhibitors. The anticipated position of lebrikizumab in the treatment pathway is as a second or later line systemic treatment for moderate-to-severe AD, that is, after the condition has not responded to at least 1 first line systemic treatment, or unsuitability for first line systemic treatment (Figure 2).

The comparators considered in the model are alternative treatments that are recommended by NICE after the condition has not responded to at least 1 first line systemic treatment, or unsuitability for first line systemic treatment of moderate-to-severe AD. The comparators are dupilumab, tralokinumab, abrocitinib, upadacitinib and baricitinib. All treatments in the model are evaluated as both monotherapies and in combination with topical corticosteroid (TCS). In the base-case, it is assumed that all patients receive combination treatment with TCS, based on UK clinical expert feedback (124) that this is standard practice.

Also in line with the NICE MTA:

- 50% of upadacitinib patients are assumed to receive 15mg and 50% 30mg dosing
- 50% of abrocitinib patients are assumed to receive 100mg and 50% 200mg dosing
- 90% of tralokinumab patients are assumed to receive Q2W and 10% Q4W dosing

B.3.3 Clinical parameters and variables

B.3.3.1. Baseline characteristics

Baseline characteristics for the modelled population were informed by the phase 3 lebrikizumab ADvantage study, as this was the study closest to the population of interest (patients with moderate-to-severe AD that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable), summarised below.

Table 56: Model population baseline characteristics

Parameter	Value	Source
Age (years), mean (SD)	34 (15.24)	ADvantage study (80)
Adults (≥18 years), n (%)	292/331 (88%)	
Adolescents (12-18 years)	12%	
Female, n (%)	156/331 (47%)	

Effectiveness in adolescents is not considered separately to that of adults. This is because, firstly, there is no evidence that efficacy of lebrikizumab differs between adults and adolescents. Secondly, in the NICE AD MTA, the committee concluded that the results of the 'combination therapy' analysis for adults who had tried systemic immunotherapy would likely be generalisable to adolescents. Unit costs of NHS care for paediatric patients are however applied to this subpopulation in the model where applicable.

B.3.3.2. Treatment effectiveness

The primary treatment outcome assessed in the model is response to treatment at Week 16, defined using a composite outcome of EASI 50 & DLQI ≥ 4. This was the response definition selected by the EAG to inform the base-case model in the NICE MTA as it was the committee-preferred outcome in TA534 and TA681 as it was deemed to be sensitive to changes in treatment outcomes and more clinically relevant than EASI 75. The

suitability of this composite endpoint as the primary outcome in the model was confirmed with clinical experts as part of a conceptual model validation exercise as well as those attending a HTA advisory board.(124)

The model includes the functionality for several additional response criteria which are:

- EASI 50
- EASI 75
- EASI 90
- IGA 0/1

There are no head-to-head trial data to compare the effectiveness of lebrikizumab vs. the comparators for the treatment of moderate-to-severe AD, thus relative treatment effects are informed by a network meta-analysis (NMA), as described in section B.2.9. Odds ratios from the NMA were applied to a baseline response rate considered representative of BSC to derive Week 16 treatment response probabilities for the comparators applied in the economic model. Separate NMAs were conducted for both the monotherapy and combination therapy settings and for each of the outcomes listed above, excluding the EASI 50 & DLQI ≥ 4. Unfortunately, it was not possible to conduct an NMA on the EASI 50 & DLQI ≥ 4 as the response rates for this outcome are not published for comparator studies, these values being redacted for multiple comparators in past NICE appraisals. The EASI 75 NMA was therefore considered to be the next best option, based on delivering the closest relative response rates in the lebrikizumab studies. As all patients are expected to receive combination treatment with TCS, the random effects, baseline adjusted combination therapy NMA for the EASI 75 therefore informs the model base-case.

Implementation of NMA outputs

To calculate the probability of response at Week 16 for each of the treatments, a baseline level of treatment response for patients on BSC was needed for the economic model, informed by placebo responses from the clinical studies. The population of interest is that

for whom systemic therapies have been inadequately effective, not tolerated or contraindicated. It should be noted that the characteristics of this population are likely to have changed substantially since the dupilumab appraisal, where patients unsuitable for immunomodulators such as CsA, mycophenolate mofetil (MMF), methotrexate and azathioprine had no other licensed systemic therapy options. In the lebrikizumab studies, eligible patients had alternative treatment options to immunomodulators, including other biologics (in the ADvantage study) and/or JAKs. Similarly, patients in the lebrikizumab studies previously treated with CsA may have also previously received targeted treatments such as biologics and/or JAKs. This is evident from *post-hoc* analyses of the pooled ADvocate studies, in which only [redacted] of patients had previously been treated with CsA, but [redacted] had received prior CsA, MMF, methotrexate, azathioprine, JAK inhibitors, or biologics.

We therefore considered the most relevant subgroup to provide baseline responses to be patients who had received prior systemic therapy, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors, or biologics in with combination TCS.

Placebo response is available for the pooled subgroups of patients from ADvocate 1 and ADvocate 2 (monotherapy) and ADhere and ADvantage (combination therapy) who had received prior systemic therapy (CsA, MMF, methotrexate, azathioprine, JAK inhibitors, biologics). However, we also include in the model the baseline response rates considered to be most generalisable to clinical practice by the EAG in the AD MTA based on consultation with its clinical experts. For the monotherapy analyses, the EAG's clinical experts considered that the upadacitinib Measure UP 1 & 2 trials were most appropriate. For the adult first- and second-line combination analyses, the upadacitinib AD-UP trial was considered most appropriate.

Clinical experts attending a HTA advisory board were presented with the alternative placebo response rates and recommended that the upadacitinib trial rates should be applied in the model base-case. Placebo response rates from the lebrikizumab studies are applied in two scenario analyses, including:

- Response rates in the pooled subgroup of patients who failed prior systemic therapy in ADhere and ADvantage, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors and biologics.

- Response rates in the subgroup of patients who failed prior systemic therapy in ADhere, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors and biologics, pooled with the ADvantage FAS.

The BSC response rates applied in the model are reported in Table 57.

Table 57: Baseline BSC treatment response at Week 16 applied in the economic model

Population	Baseline response (95% CI)	Base case/Scenario	Source
Monotherapy – second-line systemic treatment	[redacted]	Base case	Pooled placebo response data from Measure UP 1 ([redacted]) and Measure UP 2 ([redacted]).
	[redacted]	Scenario	Pooled placebo response data from ADvocate 1 and ADvocate 2 prior systemic therapy subgroup
Combination therapy - second-line systemic treatment	[redacted]	Base case	AD UP – [redacted] patients responded to placebo at Week 16
	[redacted]	Scenario	Pooled placebo response data from ADhere and ADvantage prior systemic therapy subgroup

	[redacted]	Scenario	Pooled placebo response data from ADhere prior systemic therapy subgroup and ADvantage full analysis set (FAS)

The baseline EASI 50 & DLQI ≥ 4, week 16 treatment response was converted into odds to be applied to the odds ratios from the EASI 75 NMA (representing treatment versus placebo) to estimate baseline-adjusted odds for each treatment. The baseline-adjusted odds for each treatment were then transformed to calculate the probability of patients responding to treatment at Week 16. Table 58 presents the Week 16 treatment response probabilities for each subgroup.

Table 58: Week 16 treatment response probabilities, EASI 50 +DLQI ≥4

Treatment	Monotherapy	Combination therapy
Adult Second-line systemic treatment		
Lebrikizumab	[redacted]	[redacted]
Dupilumab	64%	78%
Baricitinib	42%	59%
Upadacitinib	80%	85%
Abrocitinib	69%	78%
Tralokinumab	45%	70%
BSC	20%	42%

B.3.3.3. Week 52 treatment response outcomes

By the end of the time horizon in the short-term decision tree model (Week 52), a proportion of responders to treatment at week 16 may not continue on to long-term maintenance treatment. In line with the NICE MTA and committee preference NICE TA681, week 52 treatment response outcomes are modelled using conditional discontinuation data. Conditional discontinuation refers to the all-cause stopping rate for people whose condition responded to treatment at week 16 but withdrew from treatment at week 52. This takes into account that loss of response is not the only reason for treatment discontinuation in week 16 responders as patients may not be able to tolerate longer-term treatment due to adverse events or any other reasons. In line with the NICE MTA and TA681, conditional discontinuation data was used to estimate the probability of Week 16 responders transitioning to long-term maintenance treatment at Week 52.

For lebrikizumab combination therapy, conditional discontinuation was calculated as the discontinuation rate observed between week 16 and week 52 in ADhere (95). For lebrikizumab monotherapy, conditional discontinuation was calculated as the discontinuation rate observed between week 16 and week 52 in the pooled ADvocate 1 and 2 population (95), conditional on achieving EASI 50 & DLQI ≥4 from a post-hoc analysis. Conditional discontinuation data for the comparators was sourced from the NICE MTA.

Table 59: Conditional discontinuation data applied in the model

Treatment	Conditional discontinuation at Week 52	Source/assumptions
Monotherapy – Adults, EASI 50 + DLQI ≥4		
Lebrikizumab	5.17%	Discontinuation rate between week 16 and week 52 in pooled ADvocate studies, conditional on achieving EASI 50 & DLQI ≥4
Abrocitinib	[redacted]	Assumed to be the same as upadacitinib
Baricitinib	[redacted]	Assumed to be the same as upadacitinib
Dupilumab	3.70%	Assumed to be the same as dupilumab combination therapy

Tralokinumab Q2W	7.55%	Pooled data from ECZTRA 1 and ECZTRA 2: % dosed in maintenance phase who discontinued, Figure S3 from Wollenberg et al., 2021
Tralokinumab Q4W	10.71%	Pooled data from ECZTRA 1 and ECZTRA 2: % dosed in maintenance phase who discontinued, Figure S3 from Wollenberg et al., 2022
Upadacitinib	[redacted]	Pooled data from Measure UP 1 (n/N = 1/28) and Measure UP 2 (n/N = 1/52) in 15mg upadacitinib arm. Pooled data from Measure UP 1 (n/N = 1/25) and Measure UP 2 (n/N = 2/43) in 30mg upadacitinib arm. Weighted by the proportion of patients receiving upadacitinib 15 mg vs. 30 mg
Combination therapy – Adults, EASI 50 + DLQI ≥4		
Lebrikizumab	[redacted]	Discontinuation rate between week 16 and week 52 in ADhere, conditional on achieving EASI 50 & DLQI ≥4
Abrocitinib	[redacted]	Assumed to be the same as upadacitinib
Baricitinib	[redacted]	Assumed to be the same as upadacitinib
Dupilumab	3.70%	Estimate accepted by the committee in TA534. Data based on annual discontinuation in CHRONOS, defined as non-completers in the 52-week treatment period among responders at week 16.
Tralokinumab Q2W	1.45%	ECZTRA 3, figure S2, Silverberg et al., 2021
Tralokinumab Q4W	4.35%	ECZTRA 3, figure S2, Silverberg et al., 2022
Upadacitinib	[redacted]	AD UP. Data are based on second-line systemic treatment

		subgroup only (n/N = [redacted]) in 15mg arm & (n/N = [redacted]) in 30mg arm. Weighted by the proportion of patients receiving upadacitinib 15 mg vs. 30 mg
Mean (applied to all treatments in base case)	[redacted]	Average of all active combination TCS treatments, assuming 90% Q2W tralokinumab and 10% Q4W tralokinumab

B.3.3.4. Long-term discontinuation

No long-term (year 2 onwards) treatment discontinuation data are available for any of the treatments considered in the model. In NICE TA534 and TA681, due to a lack of long-term data, it was assumed that the long-term treatment discontinuation rate is equal to the conditional discontinuation rate for each individual treatment. However, as discussed in detail during the appraisal committee meetings for the NICE MTA (TA814), there are several problems with this approach. Clinical experts did not deem it plausible to assume that the 36-week conditional discontinuation rate would be representative of the long-term treatment discontinuation rates applied over a lifetime horizon. Furthermore, if long-term discontinuation rates are assumed equal to conditional discontinuation rates, this will result in counterintuitive results. As detailed in the committee papers for TA814, this results in a situation where the model overstates the QALY gains for treatments with lower response rates and higher rates of discontinuation. Thus, for the present model, consistent with the week 52 conditional response rates, we assume that long-term discontinuation is equal across treatments, as deemed suitable by a panel of experts who attended a HTA advisory board for this submission. It is our understanding that this is also the approach that was adopted by the committee in the NICE MTA. The long-term discontinuation rate is calculated as the average of the conditional discontinuation rates for all active treatments.

B.3.3.5. Treatment waning

Over time, patients may lose response to treatment, whether on active treatment with biologics or BSC. Treatment waning assumptions are in line with those accepted in NICE TA534 and applied by the ERG in the NICE MTA (TA814). Specifically, we assume that in years 2, 3, 4 and 5 onwards, 2%, 5%, 7% and 8% of patients will lose response to active treatment and discontinue to BSC. Thus, as soon as patients no longer achieve EASI 50 + DLQI ≥4, they are considered non-responders. As acknowledged by the EAG in TA814, there may be overlap between the proportion of patients losing response to treatment and long-term all-cause treatment discontinuation, as lack of efficacy is included as a reason to stop treatment. However, due to lack of data, the size of the overlap between treatment waning and all-cause discontinuation is unknown.

B.3.3.6. Mortality

Treatments for moderate-to-severe AD are not expected to affect mortality, thus only all-cause mortality is considered in the model. Age- and gender-adjusted all-cause mortality is estimated using the Office of National Statistics (ONS) National Life Tables for England and Wales

B.3.3.7. Adverse events

Adverse events for lebrikizumab monotherapy were sourced from pooled ADvocate study data and from ADhere for lebrikizumab combination therapy. Adverse event rates for all comparators were sourced from the NICE MTA; their original sources are provided in the table below. The adverse event rates for all treatments were based on those observed during the induction period, i.e. they represent 16-week rates. The rates in Table 60 were thus converted to 36-week rates for the maintenance period of the decision tree and annual rates for the long-term Markov model.

Table 60: 16-week adverse event rates

Treatment	Injection site reaction	Allergic conjunctivitis	Infectious conjunctivitis	Oral herpes	Upper respiratory tract infection	Acne	Source (as cited in NICE TA814 (24)
Monotherapy - Adults							
Lebrikizumab	1.60%	2.50%	7.50%	2.30%	0.20%	0.20%	ADvocate 1 & 2, Q4W arm
Abrocitinib 100 mg	0.00%	0.96%	1.27%	1.59%	7.96%	0.96%	JADE MONO 1, MONO 2 and Silverberg 2020
Abrocitinib 200 mg	0.00%	0.32%	1.29%	0.97%	5.18%	4.21%	JADE MONO 1, MONO 2 and Silverberg 2020
Baricitinib	0.00%	0.00%	0.00%	3.60%	2.70%	3.60%	Assumed same as combination therapy
Dupilumab	10.97%	3.01%	4.30%	3.66%	2.80%	0.00%	Pooled data from SOLO1 and SOLO2
Tralokinumab	10.97%	3.01%	4.30%	3.66%	2.80%	0.00%	Redacted In the NICE MTA, thus assumed equal to dupilumab
Upadacitinib 15 mg	0.00%	2.10%	0.62%	2.49%	6.85%	5.44%	Pooled data from Measure UP 1 and Measure UP 2
Upadacitinib 30 mg	0.00%	0.41%	1.02%	4.49%	9.18%	16.46%	Pooled data from Measure UP 1 and Measure UP 2
Combination therapy - Adults							
Lebrikizumab	2.80%	0.00%	4.80%	1.40%	0.70%	1.40%	ADhere
Abrocitinib 100 mg	0.00%	0.00%	0.84%	1.68%	5.04%	2.94%	JADE COMPARE
Abrocitinib 200 mg	0.00%	0.00%	1.33%	0.88%	3.98%	6.64%	JADE COMPARE

Baricitinib	0.00%	0.00%	0.00%	3.60%	2.70%	3.60%	BREEZE AD 7 (Reich 2020)
BSC	0.00%	0.33%	1.65%	1.65%	6.93%	1.98%	Placebo data from AD UP
Dupilumab	5.53%	10.60%	5.53%	2.76%	3.96%	0.00%	Pooled data from CHRONOS and CAFÉ
Tralokinumab	5.53%	10.60%	5.53%	2.76%	3.96%	0.00%	Redacted In the NICE MTA, thus assumed equal to dupilumab
Upadacitinib 15 mg	0.00%	0.00%	1.15%	3.83%	7.66%	9.58%	AD UP
Upadacitinib 30 mg	0.00%	0.77%	0.77%	8.85%	7.31%	13.85%	AD UP

B.3.3.8. Flares

During treatment for moderate-to-severe AD, patients may experience acute exacerbations of symptoms, called flares. The rate of flare can vary depending on the treatment received by a patient but treatments for flare are similar. In TA534 and TA681, the receipt of rescue medication was accepted as a proxy for flare, an approach also used in the NICE MTA. Flare rates for lebrikizumab were sourced from the rescue therapy rates in the pooled ADvocate 1 & 2 Q4W maintenance period data (monotherapy) and ADhere (combination therapy). For the comparators and BSC, flare rates were sourced from the NICE MTA, other than tralokinumab, for which values were redacted. Data for tralokinumab was sourced from the rescue therapy rates in the relevant ECZTRA trials (125), (126). The study-reported flare rates are reported in Table 61. The duration (weeks) over which flares were observed varied between studies and thus the available treatment-specific flare data was converted to the appropriate time (16-week, 36-week and annual rates) where necessary. In the model base-case, the combination therapy-specific rates were applied for all treatments.

Table 61: Study-reported flare rates

Treatment	Proportion of patients experiencing flare	Duration of follow-up (weeks)	Source (as cited in NICE TA814 (24)
Monotherapy			
Lebrikizumab	16%	36	Pooled ADvocate 1 & 2 data, observed during week 16-52
Dupilumab	18%	16	16-week data from SOLO1 (n/N = 47/224) & SOLO2 (n/N = 35/233), reported in TA534.
Baricitinib	50%	16	Pooled 16-week data from BREEZE-AD1 and BREEZE-AD2, Table S5
Upadacitinib - 15 mg	[redacted]	16	Pooled 16-week data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted]).

Upadacitinib - 30 mg	[redacted]	16	Pooled 16-week data from Measure UP 1 (n/N = [redacted]) & Measure UP 2 (n/N = [redacted])
Upadacitinib	[redacted]	16	Weighted average
Abrocitinib - 100 mg	43%	40	40-week data from REGIMEN, reported in company submission.
Abrocitinib - 200 mg	19%	40	40-week data from REGIMEN, reported in company submission.
Abrocitinib	31%	40	Weighted average
Tralokinumab	29%	16	Pooled 16-week rescue therapy rates from ECZTRA 1 and 2 reported in Wollenberg et al, 2021
Combination therapy			
Lebrikizumab	4%	16	ADhere week 0-16 data
Dupilumab	16%	52	52-week data from CHRONOS, reported in TA534 (n/N = 17/106).
Baricitinib	5%	16	16-week data from BREEZE-AD7 (n/N = 6/111)
Upadacitinib - 15 mg	[redacted]	16	16-week data from AD-UP (n/N = [redacted])
Upadacitinib - 30 mg	[redacted]	16	16-week data from AD-UP (n/N = [redacted])
Upadacitinib	[redacted]	16	Weighted average
Abrocitinib - 100 mg	43%	40	40-week data from REGIMEN, reported in company submission.
Abrocitinib - 200 mg	19%	40	40-week data from REGIMEN, reported in company submission.
Abrocitinib	31%	40	Weighted average
Tralokinumab	3%	16	16-week rescue therapy rates from ECZTRA 3 reported in Silverberg et al, 2021
BSC – Second-line	[redacted]	16	16-week placebo data from AD-UP (n/N = [redacted])

B.3.4 Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

The clinical benefit of lebrikizumab is evaluated based on health-related quality of life (HRQoL) and is measured in quality-adjusted life years (QALYs) as per the NICE reference case.

Each health state (based on response status) in the model is associated with a utility weight specific to that state. As explained in section B.2.6.1, the EQ-5D-5L was captured prospectively as part of the lebrikizumab pivotal trials (ADvocate 1, ADvocate 2 and ADhere). The EQ-5D-5L data collected in the pivotal trials were mapped to EQ-5D-3L utilities using the Hernandez-Alava algorithm (127) to provide lebrikizumab and BSC response-associated utility values for use in the cost-effectiveness model.

EQ-5D-5L responses were captured in the lebrikizumab pivotal studies as follows:

- ADvocate 1 and ADvocate 2 at baseline, week 16 and week 52
- ADhere at week 16 only.

Full details of the methodology, including data considerations, coding and missing data analysis, can be found in the EQ-5D utility mapping report and accompanying Excel data file.(128, 129)

In our methodology, we considered the following measures in defining responder criteria for the model health states: EASI 50; EASI 75; EASI 90; and EASI 50 & DLQI≤4 composite endpoint. A different regression model was generated for each responder criterion with regression analyses conducted on the following 3 lebrikizumab datasets:

- Pooled ADvocate 1 & 2 and ADhere (to increase statistical power): mixed model for repeated measures (MMRM)
- ADvocate 1 & 2 alone (monotherapy): MMRM

- ADhere alone (combination therapy): ordinary least squares (OLS) model, data only available up to 16 weeks.

The characteristics of the patients considered for selection as independent variables in the regression model (i.e. covariates) were based on the clinical study protocol, including relevant characteristics that could impact quality of life. Thus, age, sex, Body Mass Index (BIM), patient group (adolescent or adults) (trial stratification factor), geographic region (trial stratification factor), race, ethnicity, duration since disease onset, prior systemic treatment, baseline Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Dermatology Life Quality Index (DLQI) and EQ-5D-5L scores (IGA was trial stratification factor) were identified as relevant characteristics that could impact quality of life. Baseline EQ-5D were systematically included.

Covariates were excluded based on forward and backward selection process excepting the following that were considered important for the model:

- Prior systemic therapy (CsA, azathioprine, methotrexate, MMF, JAKs, biologics)
- Treatment (on off lebrikizumab)*response interaction
- Due to crossover nature of study, being on/off lebrikizumab was a time-varying covariate defined by whether a patient had been on lebrikizumab for at least 16 weeks
- Time was also investigated as interaction term, in case QoL diminishes over time regardless of response status (e.g. placebo effect on wellbeing).

The results from the mapping exercise showed that responder vs. non-responder findings were statistically significant in all analyses.(128, 129)

- Treatment * response interaction were statistically significant in some analyses and for some endpoints (e.g. EASI 75 & EASI 90)
- Prior systemic therapy results were not statistically significant in any analysis

- Time * response interaction statistically significant in some analyses and for some endpoints (EASI 75 & EASI 90)
- TCS use was not found to be a statistically significant predictor.

The models selected for the cost-effectiveness model were as follows:

- Advocate 1&2 MMRM for monotherapy, including the treatment arm*response interaction and the prior systemic therapy=yes covariate
- ADhere OLS for combination therapy (base case) including the treatment arm*response interaction and prior systemic therapy=yes covariate.

We found no statistically significant differences between the utility reported at baseline for patients randomised to placebo vs. those with lebrikizumab. Baseline utility for patients who had received prior systemic therapy was significantly different in ADvocate 2 only (see Table 62) and borderline significant across the pooled trials.

Table 62: Baseline utilities for patients with prior systemic therapy or naive, by study

	Advocate 1	**ADvocate 2**	**ADhere**	**All pooled**
Prior systemic	[redacted]	[redacted]	[redacted]	[redacted]
No prior systemic	[redacted]	[redacted]	[redacted]	[redacted]
Combined	[redacted]	[redacted]	[redacted]	[redacted]
P value for difference (prior systemic vs no prior systemic)	[redacted]	[redacted]	[redacted]	[redacted]
	Pooled ADvocate 1&2 results			
Prior systemic	[redacted]			
No prior systemic	[redacted]			
Combined	[redacted]			

	Advocate 1	ADvocate 2	ADhere	All pooled
	[redacted]			

A summary of the results, including type of regression model (MMRM or OLS), dataset in use for running each model (Pooled, Advocate studies, or just ADhere), and the predictive utilities for responders and non-responders (on lebrikizumab or placebo), is provided in Table 63 and in the full mapping report.(128, 129) Utility was calculated from the preferred regressions using the following formula:

$$EQ\text{-}5D_{Health\ state} = Intercept + \alpha.EQ\text{-}5D_{baseline} + \beta.Prior\ treatment + \gamma.Response + \delta.Treatment + \varepsilon.Treatment \times Response$$

The utility values for lebrikizumab responders are higher than the placebo responder utility values. Additionally, as the stringency of the response measure increases (from EASI 50 on the left to the composite endpoint to the right), the utility value of the responder increases which is in line with what to expect with patterns of utilities.

Table 63: Summary of HRQoL results

		Preferred for monotherapy				Preferred for combination therapy			
Model		MMRM 2.1				OLS 2.2			
Dataset		ADvocate 1&2				ADhere			
Response definition		EASI 50	EASI 75	EASI 90	EASI50 DLQI	EASI 50	EASI 75	EASI 90	EASI50 DLQI
Baseline (prior systemic)		[redacted]							
Predictive utilities									
LEB	Responder	[redacted]							
	Non-responder	[redacted]							
PBO	Responder	[redacted]							
	Non-responder	[redacted]							
Estimates were statistically significant?									
Intercept		✓	✓	✓	✓	✓	✓	✓	✓
EQ5D3L at baseline		✓	✓	✓	✓	✓	✓	✓	✓

Prior treatment	×	×	×	×	×	×	×	×
On treatment	✓	✓	✓	✓	×	✓	✓	×
Response	✓	✓	✓	✓	✓	✓	×	✓
treatment#response	×	✓	✓	×	×	×	×	×
Model fit								
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F probability					[redacted]	[redacted]	[redacted]	[redacted]
R^2					[redacted]	[redacted]	[redacted]	[redacted]
Adjusted R^2					[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criteria; BIC, Bayesian information criteria;

The methodology and results of this mapping exercise were validated with a panel of experts (including two independent health economists) in the form of an advisory board. It was noted that the mapped EQ-5D values for lebrikizumab were in line with those for past appraisals and the recent NICE MTA TA814.

B.3.4.2. Mapping

As the EQ-5D-5L was collected during the lebrikizumab clinical studies, no additional mapping was required other than mapping from 5L responses to 3L utilities.(128, 129)

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify HRQoL data and is detailed in Appendix H.

B.3.4.4. Adverse reactions

Previous NICE appraisals for AD treatments have not accounted for the utility decrements associated with adverse events. The reasoning behind this has been that it was expected that any utility decrements associated with treatment-related adverse events would be accounted for within the prospective EQ-5D data collected in the relevant clinical trials. In the phase 3 ADhere study, which informs the health state utilities in the model base-case, EQ-5D was only collected at week 16 and it is likely that the impact of treatment-related adverse events, which often occur at the start of treatment, would not have been detected by the EQ-5D at this late stage. Utility

decrements associated with treatment-related adverse events and flares are thus accounted for in the model base-case.

Disutilities associated with treatment-related adverse events were sourced from the literature and are reported in Table 64. The disutility values were also adjusted for duration. In instances where the original source for the disutility value did not report the duration over which the disutility was assumed to occur, it was assumed that it was an annual value. It was assumed that the duration of all disutilities, excluding injections site reaction was a week. For injection site reaction, a duration of 3 days was assumed. A scenario was explored where the disutilities associated with adverse events were not included in the model.

Table 64: Disutilities associated with treatment adverse events

Adverse event	Mean utility decrement	Source
Injection site reaction	0.004	Zimmerman et al., 2018 (116)
Allergic conjunctivitis	0.030	per 4-month cycle disutility in Zimmerman et al., 2018 (116)
Infectious conjunctivitis	0.030	per 4-month cycle disutility in Zimmerman et al., 2018 (116)
Oral herpes	0.050	Disutility for herpes, Fisman, 2005 (130)
Upper respiratory tract infection	0.037	Sullivan et al., 2011 (131)
Acne	0.050	Disutility for 'other skin disorders' from Sullivan et al., 2011
Flare	0.030	Difference in health state utility for 'not flaring' and 'currently flaring' reported for UK subgroup in Kleyn, 2022 (20)

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the health state utility values applied in the model is provided in Table 65. As described in section B.3.4.1, utility values were available from the lebrikizumab clinical trials. As the base case population is 100% combination therapy with TCS, the OLS 2.2 regression model of ADhere was used to generate utilities in the base case, with a responder defined as having achieved the EASI 50 & DLQI ≥ 4. For all utility values, baseline utility was sourced from the subgroup of patients with prior systemic therapy, defined as CsA, MMF, methotrexate, azathioprine, JAK inhibitors, or biologics and the coefficient for prior systemic therapy was included in the calculation of utility value from the regression.

Utility, conditional on response, was not assumed to differ by treatment, all comparators being allocated the utility of responder or non-responder from patients who had received lebrikizumab in the 16 weeks before their EQ-5D reading in the clinical study. The exception to this was the utilities allocated to patients on BSC, which was allocated the utility of responder or non-responder from patients who had received BSC in the 16 weeks before their EQ-5D reading in the clinical study.

In the initial decision tree, BSC isn't split into responder vs. non-responder health states and we have modelled BSC utility in line with the NICE MTA, assuming a weighted average of responder vs. non-responder utility. The utility of BSC (both responder and non-responder health states) is waned to a floor value over time, the floor being the utility at baseline in the lebrikizumab clinical studies. In line with TA534 sensitivity analysis 1 (see Table 124 in the MTA EAG report) utilities are waned by 82% in year 2, 90% in year 3, 94% in year 4 and 96% thereafter. This is due to the placebo effect which we expect would not last. A scenario analysis is also available for TA534 sensitivity analysis 2 (Table 66). No waning of utility is modelled for active treatment as this is already captured by the waning described in section B.3.3.5.

Table 65: Summary of utility values for cost-effectiveness analysis (combination therapy)

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
Baseline	[redacted]	[redacted]	B.3.4.1	NICE prefers EQ-5D from the clinical study
Response	[redacted]	[redacted]	B.3.4.1	As above
Non-response	[redacted]	[redacted]	B.3.4.1	As above
BSC	[redacted]	[redacted]	B.3.4.1	As above
BSC responder	[redacted]	[redacted]	B.3.4.1	As above
BSC non-responder	[redacted]	[redacted]	B.3.4.1	As above

Key: BSC: best supportive care

Table 66: Summary of utility waning assumptions on BSC

Year	BSC – TA534 sensitivity analysis 1	BSC – TA534 sensitivity analysis 2
2	82%	57%
3	90%	82%
4	94%	92%
5+	96%	97%

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An Economic SLR was conducted to identify published economic models as well as costs and healthcare resource use relevant to moderate to severe atopic dermatitis. Appendix I provides details of the SLR and identified studies. Whilst published costs and healthcare resource use studies were identified, the NICE MTA (TA814) was considered the most relevant source for this appraisal due to its recent publication and relevance (i.e. same population, treatment options, outcomes, model structure, etc). Clinical and health

economic experts consulted in the development of this submission advised that this was the most appropriate approach.

B.3.5.1. Intervention and comparators' costs and resource use

The list price for lebrikizumab is £2,271.26 per pack of two 250mg prefilled pens or prefilled syringes (henceforth referred to as 'syringes' in this section). Almirall are proposing a simple patient access scheme discount (PAS) of [redacted]% on the list price, resulting in a pack price of [redacted] and [redacted] per syringe. A loading dose of 500 mg is administered at weeks 0 and 2, after which 250 mg is administered every 2 weeks (Q2W dosing) until week 16 (11 syringes). If patients respond to treatment, then they receive maintenance dose of 250 mg every 4 weeks (Q4W) from week 16 onwards (8 syringes in year 1, 1 annually thereafter). The drug cost calculations for lebrikizumab are reported in Table 67.

Table 67: Costs of lebrikizumab induction and maintenance treatment (with PAS applied)

Dosing regimen	Number of administrations		
	Weeks 0 - 16	Weeks 17 - 52	Year 2 onwards
250 mg Q4W: 500 mg administered at week 0 and week 2 (loading dose) and 250 mg given Q2W until week 16. 250 mg given Q4W from week 16 onwards	11	8	13
Total cost	[redacted]	[redacted]	[redacted]

Drug acquisition costs for the comparators were sourced from the BNF (132). As discussed earlier there are two available doses for both upadacitinib and abrocitinib and due to a lack of data to inform the split of patients amongst doses, a 50/50 split of patients amongst both doses was assumed. The costs of these treatments are thus applied as a weighted average.

As tralokinumab comes in packs of 4, a non-responder would require 5 packs of 4 syringes to provide 18 induction units, of which two would be wasted. The cost of 2 tralokinumab syringes is therefore added to the “non-responder” branch of the 16-week decision tree.

Similarly, as lebrikizumab comes in packs of 2, a non-responder would require 6 packs of 2 syringes to provide 11 induction units, of which one would be wasted. The cost of 1 lebrikizumab syringe is therefore added to the “non-responder” branch of the 16-week decision tree.

Table 68: Comparator drug costs

Treatment	Strength (mg)	Pack size	Pack cost (list prices)	Cost per unit	Dose	Units required - induction	Units required - maintenance	Units required - annually (post-year 1)
Upadacitinib - 15 mg	15	28	£805.56	£28.77	15 mg once daily	112	252	365.25
Upadacitinib - 30 mg	30	28	£1,281.54	£45.77	30 mg once daily	112	252	365.25
Abrocitinib - 100 mg	100	28	£893.76	£31.92	100 mg once daily	112	252	365.25
Abrocitinib - 200 mg	200	28	£893.76	£31.92	200 mg once daily	112	252	365.25
Baricitinib	4	28	£805.56	£28.77	4 mg once daily	112	252	365.25
Dupilumab	300mg/2ml	2	£1,264.89	£632.45	600 mg followed by 300 mg Q2W	9	18	26
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	18	36	52
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	18	18	26

Table 69: Comparator drug costs applied in the model

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

*Annual cost in subsequent years (that is, excluding the loading dose)

Based on the resource use assumptions from previous technology appraisals (TA814, TA534 and TA681) it is assumed that patients treated with subcutaneous (SC) formulations receive training on how to self-administer treatment. It is assumed that each patient only receives one self-injection training session, requiring 30 minutes of patient contact with a hospital-based Band 6 nurse at a cost of £63.75 (PSSRU 2021,150 note: each hour spent with a client requires 2.5 paid hours). This cost is incurred when the SC treatment is prescribed (that is, the first model cycle). Almirall will provide training on the self-administration of lebrikizumab to the NHS free of charge, thus no administration costs are applied to the intervention arm. In the NICE MTA, the submitting company for tralokinumab stated that they would do the same and no administration costs were incurred by tralokinumab-treated patients in the EAG's base case analysis. We have applied the same assumptions in the present appraisal. Orally administered drugs (baricitinib, upadacitinib and abrocitinib) are assumed to incur no administration costs in the model.

B.3.5.2. Concomitant medication costs

In line with the NICE MTA, TA681 and as confirmed with clinical experts, it is assumed that patients receive concomitant medications, consisting of:

- emollient products
- mid-potency background TCS (mometasone 0.1% ointment)
- Topical calcineurin inhibitors (TCI) (protopic 0.1% ointment)

In line with the NICE MTA, it is assumed that:

- The weekly cost of emollients is derived by averaging the weekly cost of the most commonly prescribed emollients;
- Responders to systemic treatment have a 50% reduction of resource use for concomitant emollients and TCS compared to non-responders; and,
- Responders do not require TCI.
- There is no reduction in use of emollients and TCS for patients who discontinue systemic maintenance treatment and go on to BSC.

The concomitant medication costs included in the model are summarised in Table 70. Costs for the BSC health stated are weighted by the proportion of responders and non-responders to BSC at the week 16 assessment point.

Table 70: Concomitant medication costs included in the model

Medication	Cost	Source	Responders to systemic treatment		Non-responders		Responders to BSC	
			Amount per week*	Cost per week	Amount per week*	Cost per week	Amount per week*	Cost per week
TCI								
Protopic 0.1% ointment (cost per 60g, g per week)	£28.76	BNF (133)	0.00	£0.00	1.75	£1.33	0.00	£0.00
TCS								
Mometasone 0.1% ointment (cost per 100g, g per week)	£2.34	eMIT (134)	56.70	£1.46	112.04	£2.89	112.04	£2.89
Emollient (cost per pack, packs per week)								
Aveeno cream	£6.47	BNF (132)	0.50	£3.24	1.00	£6.47	1.00	£6.47
Cetraben ointment	£5.67		0.50	£2.70	1.00	£5.39	1.00	£5.39
Dermol cream	£6.63		0.50	£3.32	1.00	£6.63	1.00	£6.63
Epaderm ointment	£12.89		0.25	£3.11	0.50	£6.21	0.50	£6.21
Hydromol ointment	£5.50		0.25	£2.08	0.50	£4.16	0.50	£4.16
White soft paraffin 50% / Liquid paraffin 50% ointment	£4.57		0.50	£2.16	1.00	£4.32	1.00	£4.32
Oilatum cream	£5.28		0.25	£1.32	0.50	£2.64	0.50	£2.64
Total cost per week			**£18.91**		**£38.64**		**£37.80**	
Total cost per year			**£983.54**		**£2,009.05**		**£1,965.43**	

Abbreviations: BSC, best supportive care; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids
*Sourced from TA534

B.3.5.3. Health-state unit costs and resource use

In the model, health care resource use (HRU) depends on:

- the stage of treatment (induction vs maintenance)
- the treatment response (responder vs non-responder)
- the treatment received (BSC is associated with more visits and tests than biologics)

As per clinical feedback from KOLs during primary research interviews, HRU is assumed to be the same for adults and adolescents. The unit costs attached to the HRU however, differ for some resource use items where there are paediatric codes (Table 71 and Table 72). These costs were then weighted by the proportion of adolescent vs. adult patients in the model.

HRU in the economic model was informed by the NICE MTA, which originally took the ERG estimates for TA534 and the company estimates for TA681, which were accepted by their relevant appraisal committees and were verified by the EAG's clinical experts. The types of visits and tests considered in the economic model include:

- outpatient visits to a dermatologist;
- outpatient visits to a dermatology nurse;
- visits to a general practitioner (GP);
- visits to accident and emergency (A&E);
- hospital admissions;
- hospital day case visits;
- full blood counts (FBCs) (an additional test for patients on BSC);
- phototherapy (an additional service for patients who are non-responders to BSC); and,
- psychological support (an additional service for patients who are non-responders to BSC).

When any systemic treatment is initiated, patients are assumed to visit their dermatologist twice during the induction period. These visits are in addition to the ongoing monitoring a dermatologist will provide. The ongoing health care resource use data applied in the economic model, according to response status, is given in Table 73. The health state costs weighted by the proportion of adolescent vs. adult patients in the model are reported in also reported in Table 73.

HRU is stratified by induction (weekly frequency in year 1) and maintenance (annual frequency in year 2+) to ensure that the correct frequency of visits or tests is captured in the appropriate period in the short- and long-term models. It is assumed that resource use in the induction phase of the short-term model is based on non-responders until the initial treatment assessment point.

Table 71: Unit costs associated with HRU, adults

Visit/test	Unit cost	Source
Dermatologist outpatient consultation	£172	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A, WF02D (135)
Dermatologist nurse visit	£32	PSSRU Unit Costs of Health and Social Care 2021. 15 minutes of a band 6 hospital-based nurse (£51 per working hour). Note: each hour spent with a client requires 2.5 paid hours (136)
GP consultation	£39	PSSRU Unit Costs of Health and Social Care 2021. Per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications (136)
A&E visit	£268	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Weighted average VB06Z-VB09Z (135)
Hospitalisation	£2,192	National Schedule of NHS Costs - Year 2021- NHS trusts and NHS foundation trusts. Skin Disorders:Non-elective short stay, weighted average JD07A-JD07K (134,484 at £587) Non-elective long stay, weighted average JD07A-JD07K (99,096 at £3,001) (135)
Day case	£711	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Day case, Skin Disorders, weighted average JD07A-JD07K (135)
FBC	£4	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. DAPS05 Haematology (135)
Phototherapy	£201	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. JC47Z Total HRGs & Currencies Phototherapy or Photochemotherapy (135)
Psychological support	£321	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Service code 656, clinical psychology, consultant led, weighted average WF01A-WF01D, WF02A, WF02B (135)

Table 72: Unit costs associated with HRU, adolescents

Visit/test	Unit cost	Source
Dermatologist outpatient consultation	£201	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Service code 257, paediatric dermatology, consultant led, weighted average WF01A-WF01D, WF02A, WF02B (135)
Dermatologist nurse visit	£32	PSSRU Unit Costs of Health and Social Care 2021. 15 minutes of a band 6 hospital-based nurse (£51 per working hour). Note: each hour spent with a client requires 2.5 paid hours (136)
GP consultation	£39	PSSRU Unit Costs of Health and Social Care 2021. Per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications (136)
A&E visit	£268	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Weighted average VB06Z-VB09Z (135)
Hospitalisation	£2,192	National Schedule of NHS Costs - Year 2021- NHS trusts and NHS foundation trusts. Skin Disorders: Non-elective short stay, weighted average PJ35B:J35D Non-elective long stay, weighted average PJ35A:PJ35D (135)
Day case	£839	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Day case, Paediatric skin Disorders, weighted average PJ35A:PJ35D (135)
FBC	£4	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. DAPS05 Haematology (135)
Phototherapy	£201	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. JC47Z Total HRGs & Currencies Phototherapy or Photochemotherapy (135)
Psychological support	£321	National Schedule of NHS Costs - Year 2021 - NHS trusts and NHS foundation trusts. Service code 656, clinical psychology, consultant led, weighted average WF01A-WF01D, WF02A, WF02B (135)

Table 73: Costs of ongoing health care resource use

Visit/test	Number per annum			Number per week		
	Responder (systemic treatment)	Responder (BSC)	Non- responder (BSC)	Responder (systemic treatment)	Responder (BSC)	Non-responder (BSC)
Dermatologist outpatient consultation	4.320	4.320	6.000	0.083	0.083	0.115
Dermatologist nurse visit	0.350	0.350	0.460	0.007	0.007	0.009
GP consultation	6.150	6.150	12.810	0.118	0.118	0.246
A&E visit	0.021	0.021	0.082	0.000	0.000	0.002
Hospitalisation	0.017	0.017	0.130	0.000	0.000	0.002
Day case	0	0.000	0.200	0	0.000	0.004
FBC	0	4.000	4.000	0	0.077	0.077
Phototherapy	0	0.000	0.060	0	0.000	0.001
Psychological support	0	0.000	0.070	0	0.000	0.001
Total cost	**£20.15**	**£20.15**	**£20.15**	**£1,051.81**	**£1,066.33**	**£2,060.89**

It is assumed that non-responders to systemic treatment incur the health care resource use costs associated with BSC when they transition to the subsequent treatment (BSC). As mentioned previously, 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 monitoring costs applied to BSC in the base case analysis are given in Table 74.

Table 74: Health care resource cost applied to BSC in the base case

Population	BSC responders	BSC non-responders	Weighted annual cost	Weighted weekly cost
First-line systemic treatment – Adults, monotherapy	33%	67%	£1,355.42	£25.98
Second-line systemic treatment – Adults, monotherapy	20%	80%	£1,457.24	£27.93
Second-line systemic treatment – Adults, combination therapy	42%	58%	£1,288.96	£24.70
Adolescents, monotherapy	14%	86%	£1,500.47	£28.76

Abbreviations: BSC, best supportive care.

B.3.5.4. Adverse reaction unit costs and resource use

Costs of managing adverse events

The sources of unit costs for managing adverse events were identified from the NICE MTA and aligned with the most recent unit cost publication, for instance, the most recent NHS reference costs release. During the decision-tree phase (year 1) it is assumed that non-responders to systemic treatment incur the AE costs associated with BSC.

The unit costs associated with each AE (Table 75) are multiplied by the weekly (short-term model) and annual (long-term model) proportion of patients experiencing each AE calculated based on 16-week data reported in Table 60 to estimate weekly and annual treatment-specific AE costs.

Table 75: Adverse event unit costs

Adverse event	Unit cost	Source
Injection site reaction	£124.83	National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D (135)
Allergic conjunctivitis	£39.23	PSSRU Unit Costs of Health and Social Care 2021 GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications: (136)
Infectious conjunctivitis	£65.93	Unit Costs of Health and Social Care 2021. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications. £39.00 (80% weight from TA681) National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts. Service code 130, ophthalmology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D. £110.66 (20% weight from TA681) (135)
Oral herpes	£39.23	PSSRU Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes.

		Including direct care staff costs and qualifications (£39.23) (136)
Upper respiratory tract infection	£39.23	Unit Costs of Health and Social Care 2020. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications
Acne	£235.60	Unit Costs of Health and Social Care 2021. GP per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications (£39.23) National Schedule of NHS Costs - Year 2020-21 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D (£124.83) 3 months Epiduo (£19.53 per month, BNF) and oral lymecycline (£8.67 per month, BNF) (135)

Costs of managing flares

The treatments used and associated costs to manage a flare are sourced from the NICE MTA and are reported in Table 76.

The costs associated with flare treatments are multiplied by the distributions of flare treatments (Table 77) to estimate a treatment-specific flare cost. The treatment-specific flare costs are then multiplied by the treatment specific rate of flare (Table 61) to estimate weekly and annual treatment-specific flare costs for the short- and long-term parts of the economic model. In the short-term part of the model, it is assumed that non-responders to systemic treatment incur the flare costs associated with BSC.

Table 76: Flare medication acquisition costs

Medication	Cost per pack	Packs per flare	Cost per flare	Unit cost source
TCS potent				
Betamethasone valerate cream	£2.71	1	£16.83	BNF, 2023 (137) (138)
Cutivate 0.005% ointment	£4.24	3.33		
TCS very potent				
Eumovate 0.05% ointment	£5.44	1	£13.34	BNF, 2023 (139)
Dermovate 0.05% cream	£7.90	1		
Systemic steroid				
Prednisolone 5mg	£0.40	1	£0.40	BNF, 2023 (140)
TCI				
Protopic 0.1% ointment	£45.56	0.4	£18.22	BNF, 2023 (133)

Table 77: Distribution of flare medications

Treatment	TCS potent	TCS very potent	Systemic steroid*	TCI	Cost of flare treatment	Source (as cited in NICE TA814 (24)
Monotherapy						
Lebrikizumab	0.00%	0.00%	15.90%	0.00%	£0.06	Assumed same as dupilumab
Dupilumab	0.00%	0.00%	15.90%	0.00%	£0.06	TA534
Baricitinib						
Upadacitinib 15mg – second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.
Upadacitinib 30mg – second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from Measure UP 1 & 2.
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Weighted average
Abrocitinib 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
Abrocitinib 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 30 mg
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Weighted average
Tralokinumab Q2W	0.00%	0.00%	15.90%	0.00%	£0.06	Redacted in MTA, thus assumed equal to dupilumab
Combination therapy						
Lebrikizumab	42.00%	23.00%	29.00%	0.00%	£10.25	Assumed same as dupilumab
Dupilumab	42.00%	23.00%	29.00%	0.00%	£10.25	TA534. For TCIs, rate was reported as 0% in TA534, however the EAG's experts considered TCI use would be the same as BSC.
Baricitinib	0.00%	66.70%	0.00%	0.00%	£8.90	BREEZE-AD7 (Reich 2020)
Upadacitinib - 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP

Upadacitinib - 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	AD UP
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Weighted average
Abrocitinib - 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 15 mg
Abrocitinib - 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed to be the same as upadacitinib 30 mg
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Weighted average
Tralokinumab	42.00%	23.00%	29.00%	0.00%	£10.25	Redacted in MTA, thus assumed equal to dupilumab
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Placebo data from AD UP

B.3.6 Severity

Lebrikizumab does not meet the criteria for a severity weighting. The QALY shortfall for Lebrikizumab was calculated using the online calculator tool published by Schneider et al., 2021. Due to minimal differences in QALYs between lebrikizumab and the comparators, which is as expected in treatments for atopic dermatitis, the proportional QALY shortfall is less than 85%, thus achieving a QALY weighting of 1. Previous NICE evaluations in atopic dermatitis were published before the introduction of the severity modifier and thus no QALY shortfall calculations were provided in these appraisals.

Table 78: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	53% male (Table 56)	Baseline characteristics
Starting age	34 (Table 56)	Baseline characteristics

Table 79: Summary of 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
[redacted]	Dupilumab	[redacted]	[redacted]
[redacted]	Baricitinib	[redacted]	[redacted]
[redacted]	Upadacitinib	[redacted]	[redacted]
[redacted]	Abrocitinib	[redacted]	[redacted]
[redacted]	Tralokinumab	[redacted]	[redacted]

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1. Summary of base-case analysis inputs

A summary of the base-case analysis inputs is provided in Appendix M: Summary of parameter inputs.

B.3.7.2. Assumptions

Table 80: Summary of assumptions applied in the model

Assumption	Justification
Patients who discontinue their initial treatment go on to receive BSC	This assumption is applied in the base-case, aligned with the NICE MTA. There is a lack of data to inform the proportions of discontinuing patients who go on to receive alternative 'active' treatments as a subsequent therapy. Consulted KOLs provided heterogenous responses when asked about this and it is not clear whether, for example, if a patient received a biologic as their initial treatment, they would go on to receive a second biologic, or would instead be treated with a JAK-inhibitor.
Long-term discontinuation is assumed equal after year 1	Due to a lack of long-term data to inform treatment discontinuation after year 1, it was deemed appropriate to assume that the long-term treatment discontinuation is equal across treatments. This is in line with the approach taken following the final committee meeting for the NICE MTA of AD products and was confirmed with KOLs at a UK advisory board.
Resource use in the induction phase of the short-term model is based on non-responders until the initial treatment assessment point.	This assumption is based on the NICE MTA. In TA681, responder resource use estimates were applied in the treatment induction phase (weeks 0-16). However, the EAG considered that a conservative assumption for all treatment arms is to assume non-responder resource use until treatment response is assessed at week 16.
Responders on maintenance treatment who discontinue to BSC have no reduction in resource use of emollients and TCS.	This assumption is based on the NICE MTA. According to clinical experts that were consulted by the EAG, emollients and TCS are key components of BSC and no reduction in use should be assumed if a patient loses response to systemic treatment

Monitoring resource use is the same for adults and adolescents	This was deemed appropriate by consulted KOLs, who confirmed that adolescents typically follow the same treatment pathway as adults

B.3.8 Base-case results

B.3.8.1. Base-case incremental cost-effectiveness analysis results

The base-case incremental results are presented in Table 81. Lebrikizumab is the least costly treatment and is thus ranked first in the incremental results. Lebrikizumab dominates baricitinib and tralokinumab as it is less costly but also more effective. These results indicate that lebrikizumab is a highly cost-effective treatment.

For the remaining comparators (dupilumab, abrocitinib and upadacitinib), lebrikizumab is less costly but is also associated with a very small loss in QALYs, with incremental QALYs ranging from [redacted] to [redacted]. This is predominantly due to the conditional discontinuation rate for lebrikizumab combination therapy being slightly higher than that for these comparators. In this situation where the intervention is less costly but there is a very minimal loss in QALYs, the ICERs can be misleading as they are very high (£366,791 to £1,407,517), but this is purely due to the minute difference in QALYs between the two treatments. Net monetary benefit (NMB) can be a more helpful indicator in this situation and is also presented for lebrikizumab vs. each comparator in Table 81. The NMB for lebrikizumab vs. all comparators is positive, ranging from £8,195 to £35,731, indicating that lebrikizumab is cost-effective against all comparators.

Table 81: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER vs. Lebrikizumab(£/QALY)	Incremental ICER (£/QALY)	NMB
Lebrikizumab	[redacted]	22.99	[redacted]	-	-	-	-	-	-
Baricitinib	[redacted]	22.99	[redacted]	[redacted]	0.00	[redacted]	Lebrikizumab dominates	Dominated	£8,195
Abrocitinib	[redacted]	22.99	[redacted]	[redacted]	0.00	[redacted]	£569,303	Extendedly dominated	£17,575
Tralokinumab	[redacted]	22.99	[redacted]	[redacted]	0.00	[redacted]	Lebrikizumab dominates	Dominated	£27,505
Upadacitinib	[redacted]	22.99	[redacted]	[redacted]	0.00	[redacted]	£366,791	£366,791	£27,505
Dupilumab	[redacted]	22.99	[redacted]	[redacted]	0.00	[redacted]	£1,407,517	Dominated	£35,731

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NMB, net monetary benefit

Table 82: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

B.3.9 Exploring uncertainty

A range of sensitivity analyses were conducted to explore the underlying uncertainty in the base-case cost-effectiveness results. These include deterministic and probabilistic sensitivity analyses and are detailed below.

B.3.9.1. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values and a distribution was assigned to these parameters (**Error! Reference source not found.**). A PSA was conducted for lebrikizumab vs. each individual comparator. 1,000 simulations were run for the probabilistic sensitivity analysis (PSA), by which time the ICERs had converged to a stable mean, represented by the probabilistic ICERs. The probabilistic results (Table 83) lie very close to the base-case results, indicating that the cost-effectiveness results are robust.

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane in Figure 32. The PSA results are in line with the base-case model results, indicating that the model is robust. For instance, in the PSAs for lebrikizumab vs. baricitinib and lebrikizumab vs. tralokinumab, all scatter points (which represent the simulated incremental costs and QALYs), are in the south-east quadrant. This indicates that lebrikizumab is associated with less costs and higher QALYs compared to these comparators, that is, lebrikizumab dominates these comparators, as it did in the model base-case. For the remaining comparators, the majority of the scatter points lie in the southwest quadrant, indicating that lebrikizumab is less costly but also slightly less effective, as shown in the base-case. Overall, the variation in incremental costs and QALYs is limited, indicating little impact of parameter uncertainty on the results and that the analysis is robust.

The PSA results were also plotted in the form of a cost-effectiveness acceptability curve (CEAC), as shown in Figure 33. The CEAC shows the probability of cost effectiveness for lebrikizumab vs. comparators given varying willingness to pay (WTP) thresholds for a QALY. It can be seen that lebrikizumab is the treatment with

the greatest probability of being the most cost-effective treatment at all WTP thresholds.

Table 83: Probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	NMB
Lebrikizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£1,369,080	£36,471
Baricitinib	[redacted]	[redacted]	[redacted]	[redacted]	Lebrikizumab dominates	£8,420
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	£366,407	£28,092
Abrocitinib	[redacted]	[redacted]	[redacted]	[redacted]	£512,571	£18,093
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	Lebrikizumab dominates	£21,634

Figure 32: PSA output on the cost-effectiveness plane, lebrikizumab vs. dupilumab

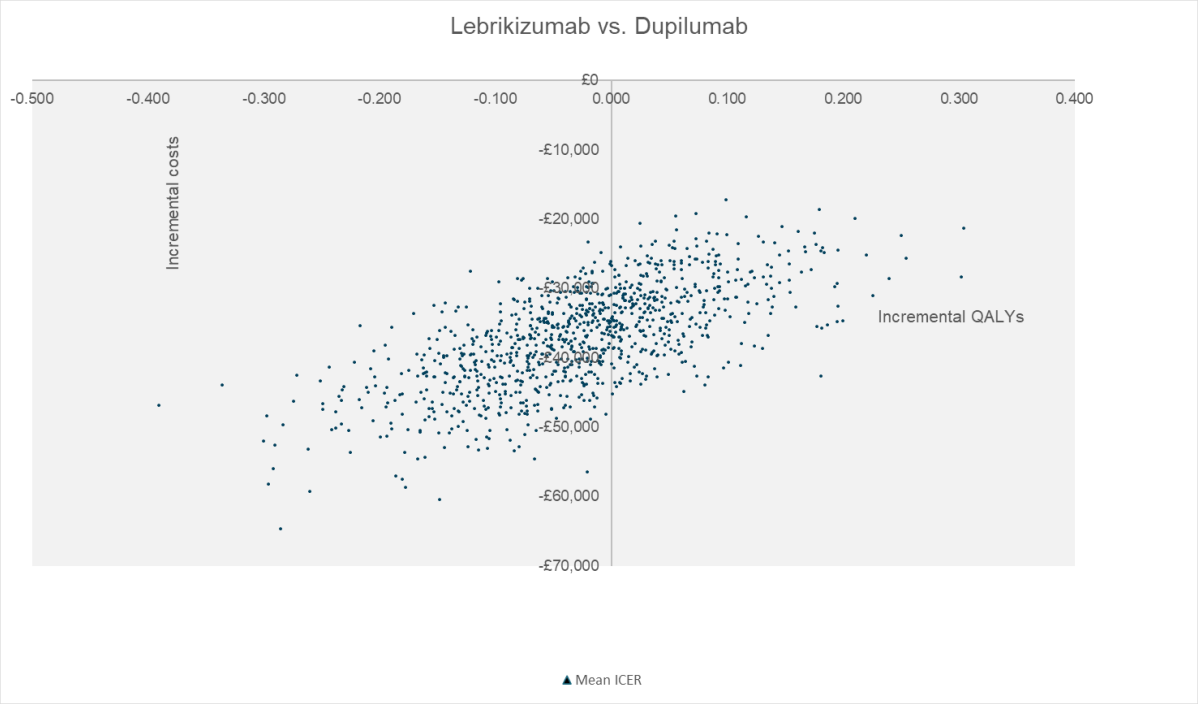


Figure 33: PSA output on the cost-effectiveness plane, lebrikizumab vs. baricitinib

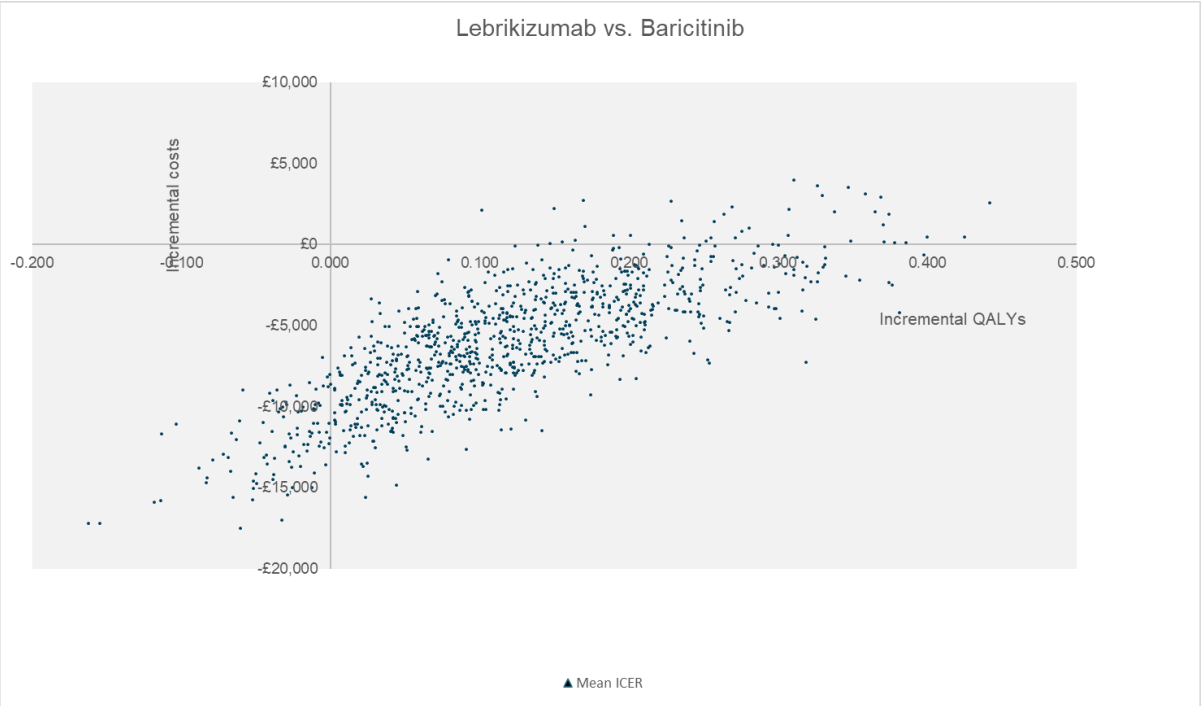


Figure 34: PSA output on the cost-effectiveness plane, lebrikizumab vs. upadacitinib

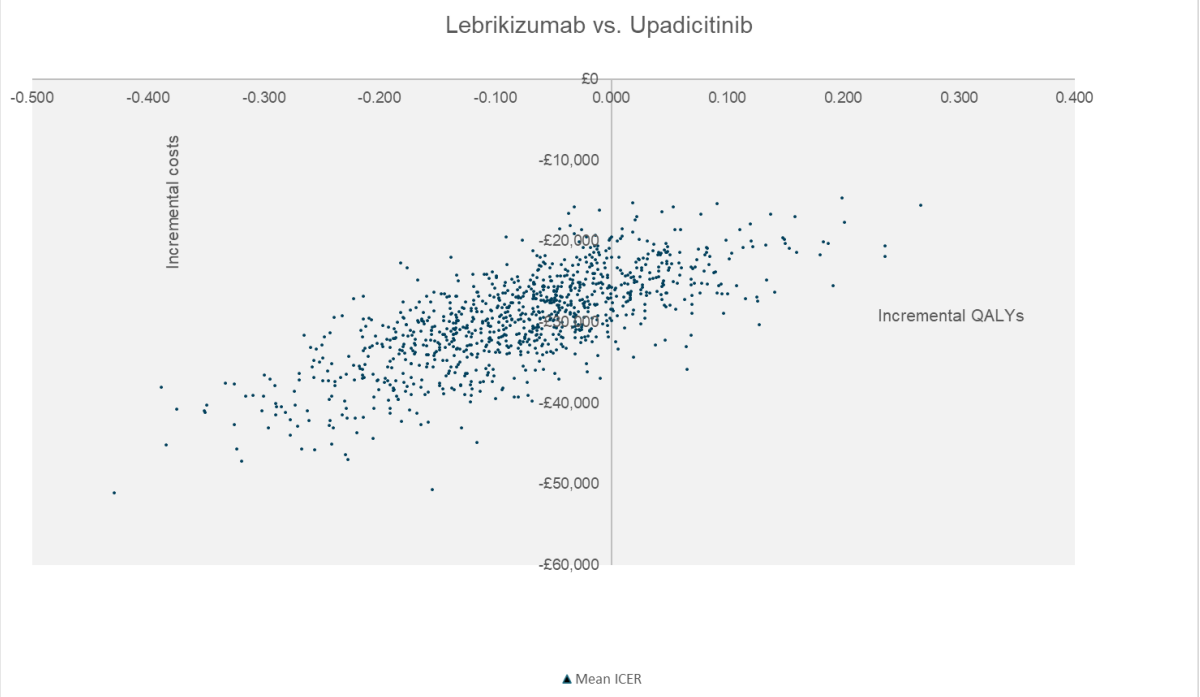


Figure 35: PSA output on the cost-effectiveness plane, lebrikizumab vs. abrocitinib

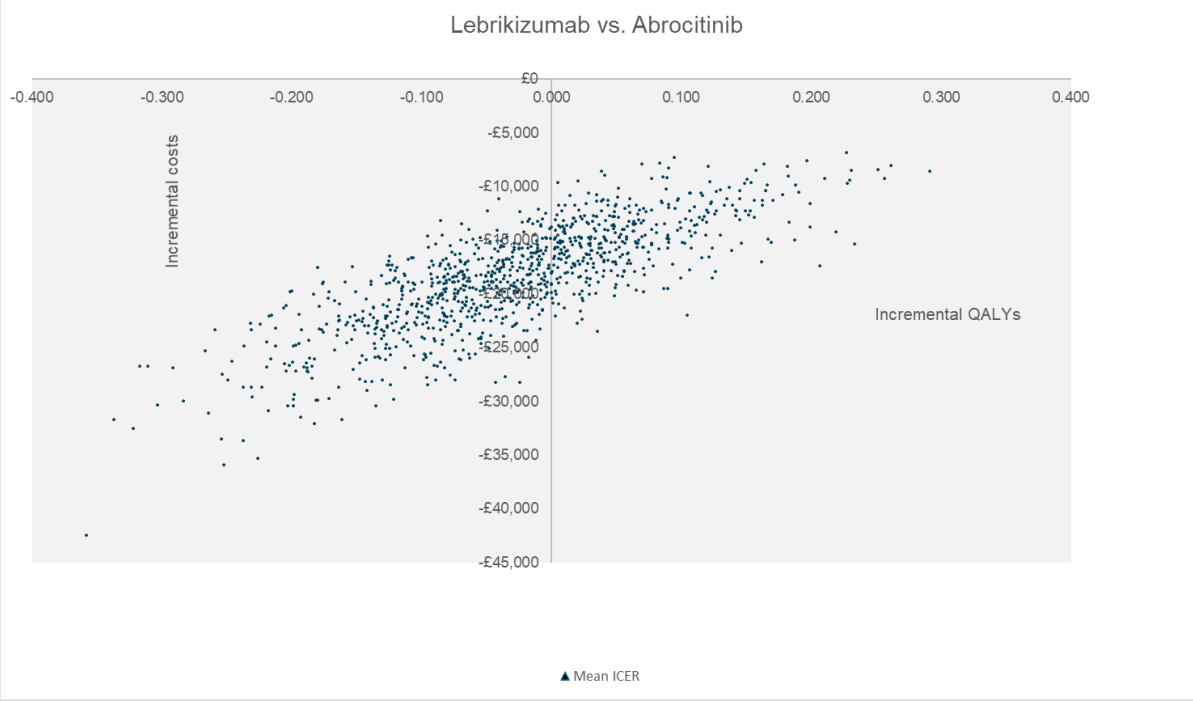


Figure 36: PSA output on the cost-effectiveness plane, lebrikizumab vs. tralokinumab

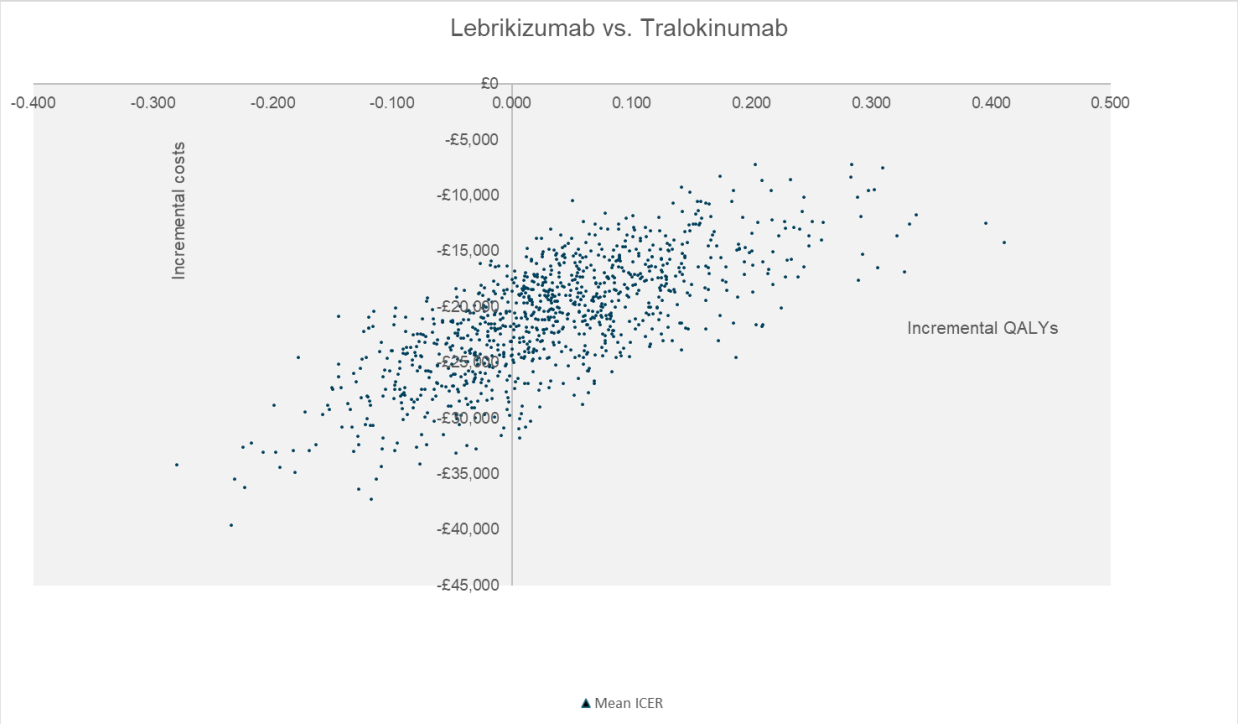
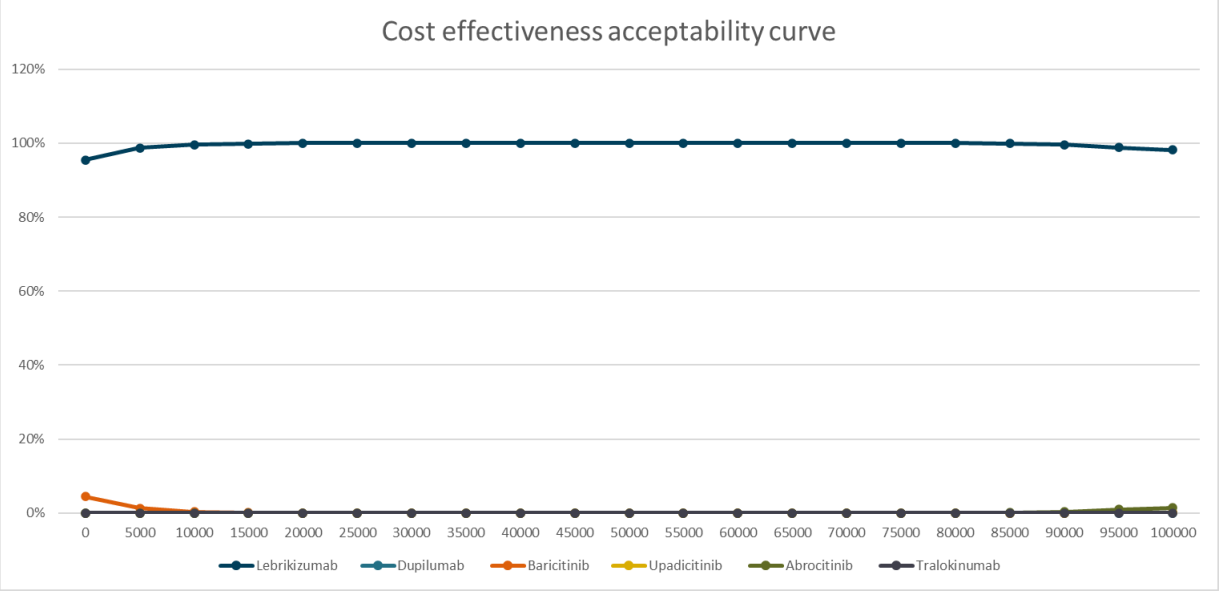


Figure 37: Cost-effectiveness acceptability curve, lebrikizumab vs. all treatments



B.3.9.2. Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. The results from the OWSA are presented in the form of a tornado diagram where the ten parameters with the largest influence on the cost-effectiveness results are presented in Figure 38 to Figure 42. Due to lebrikizumab dominating against some of the comparators and the misleading high ICERs against some of the other comparators, NMB rather than the ICER is chosen as the outcome of interest in the OWSAs.

Influence on the NMB was defined as the absolute difference between the upper bound and the lower bound. Parameters that could not be varied without compromising the integrity of the Markov model were excluded from the OWSA.

The tornado diagram below shows that across all OWSAs, discontinuation at week 52 is the parameter that has the largest impact on the NMB for lebrikizumab vs. comparators. Other parameters that have a large impact are the long-term (annual) treatment discontinuation rate and placebo response rates at week 16.

Figure 38: Tornado diagram – lebrikizumab vs. dupilumab

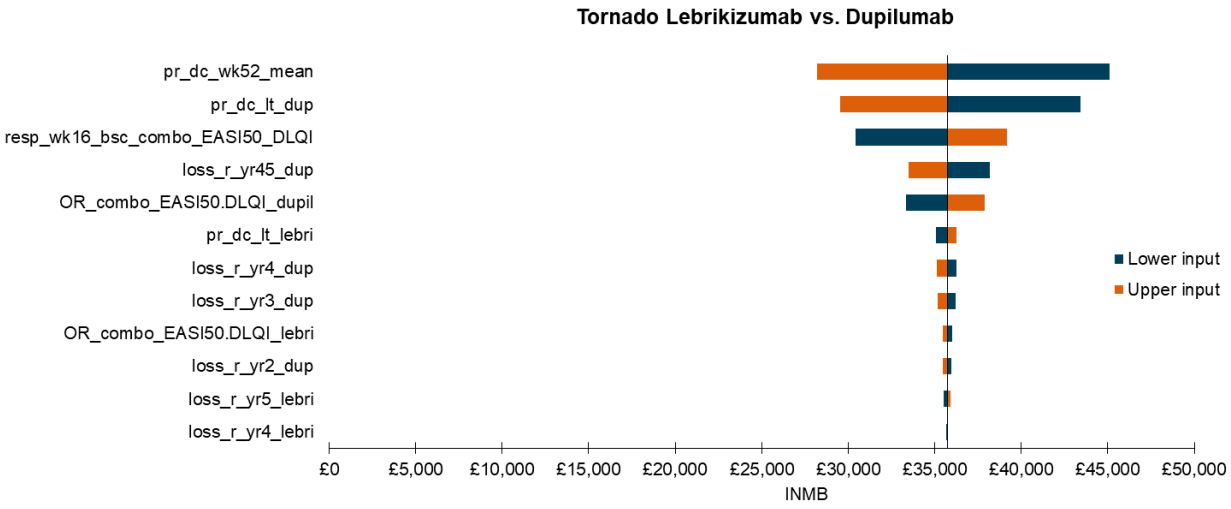


Table 84: OWSA results, lebrikizumab vs. dupilumab

Parameter	INMB		
	Lower bound	Upper bound	Difference
pr_dc_wk52_mean	£45,115	£28,207	£16,907
pr_dc_lt_dup	£43,428	£29,512	£13,917
resp_wk16_bsc_combo_EASI50_DLQI	£30,418	£39,189	£8,771
loss_r_yr45_dup	£38,171	£33,503	£4,668
OR_combo_EASI50.DLQI_dupil	£33,342	£37,876	£4,535
pr_dc_lt_lebri	£35,086	£36,247	£1,162
loss_r_yr4_dup	£36,259	£35,100	£1,159
loss_r_yr3_dup	£36,201	£35,166	£1,035
OR_combo_EASI50.DLQI_lebri	£36,004	£35,478	£526
loss_r_yr2_dup	£35,964	£35,449	£515
loss_r_yr5_lebri	£35,525	£35,917	£392
loss_r_yr4_lebri	£35,690	£35,781	£92

Figure 39: Tornado diagram – lebrikizumab vs. baricitinib

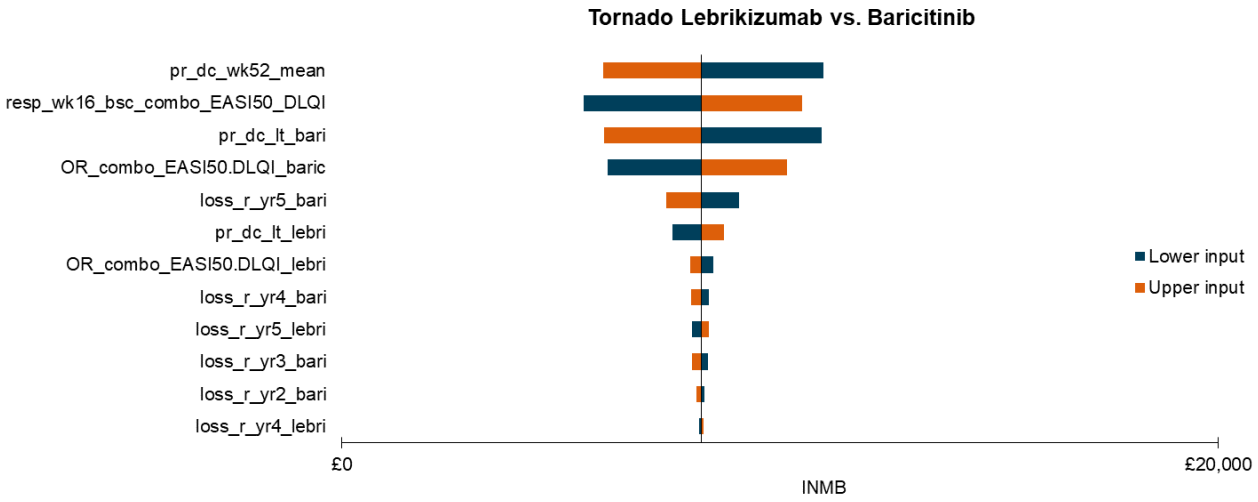


Table 85: OWSA results, lebrikizumab vs. baricitinib

Parameter	INMB		
	Lower bound	Upper bound	Difference
pr_dc_wk52_mean	£10,979	£5,964	£5,015
resp_wk16_bsc_combo_EASI50_DLQI	£5,511	£10,504	£4,993
pr_dc_lt_bari	£10,939	£5,980	£4,959
OR_combo_EASI50.DLQI_baric	£6,062	£10,160	£4,099
loss_r_yr5_bari	£9,065	£7,401	£1,664
pr_dc_lt_lebri	£7,549	£8,711	£1,162
OR_combo_EASI50.DLQI_lebri	£8,467	£7,941	£526
loss_r_yr4_bari	£8,382	£7,971	£410
loss_r_yr5_lebri	£7,989	£8,380	£392
loss_r_yr3_bari	£8,361	£7,995	£366
loss_r_yr2_bari	£8,279	£8,094	£185
loss_r_yr4_lebri	£8,153	£8,245	£92

Figure 40: Tornado diagram – lebrikizumab vs. upadacitinib

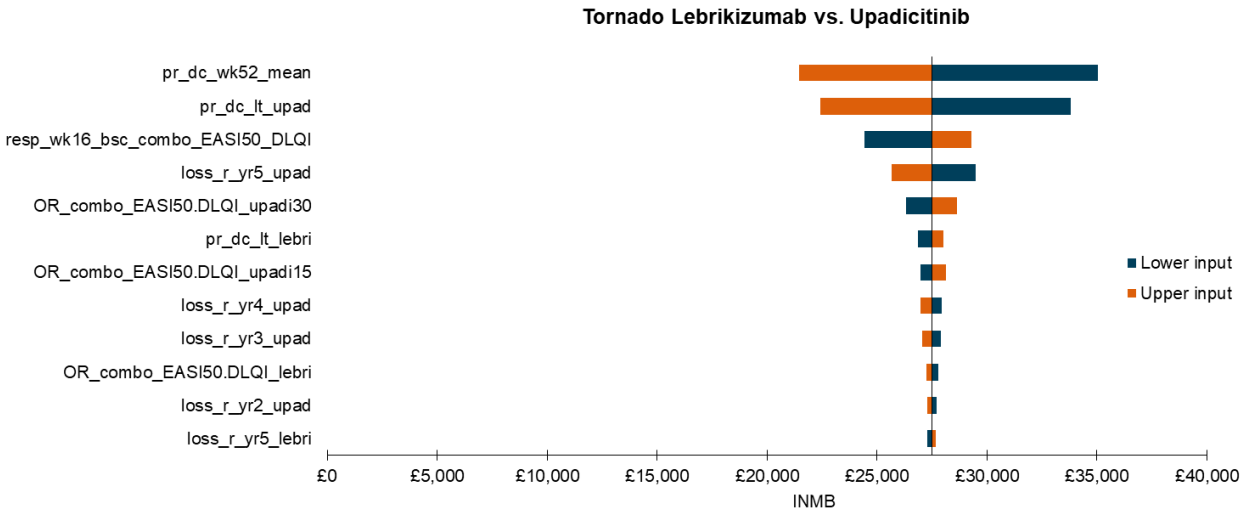


Table 86: OWSA results, lebrikizumab vs. upadacitinib

Parameter	INMB		
	Lower bound	Upper bound	Difference
pr_dc_wk52_mean	£35,038	£21,463	£13,575
pr_dc_lt_upad	£33,808	£22,413	£11,395
resp_wk16_bsc_combo_EASI50_DLQI	£24,418	£29,299	£4,881
loss_r_yr5_upad	£29,503	£25,681	£3,823
OR_combo_EASI50.DLQI_upadi30	£26,341	£28,651	£2,310
pr_dc_lt_lebri	£26,859	£28,021	£1,162
OR_combo_EASI50.DLQI_upadi15	£26,984	£28,132	£1,148
loss_r_yr4_upad	£27,936	£26,989	£947
loss_r_yr3_upad	£27,889	£27,043	£846
OR_combo_EASI50.DLQI_lebri	£27,777	£27,251	£526
loss_r_yr2_upad	£27,696	£27,273	£423
loss_r_yr5_lebri	£27,299	£27,690	£392

Figure 41: Tornado diagram – lebrikizumab vs. abrocitinib

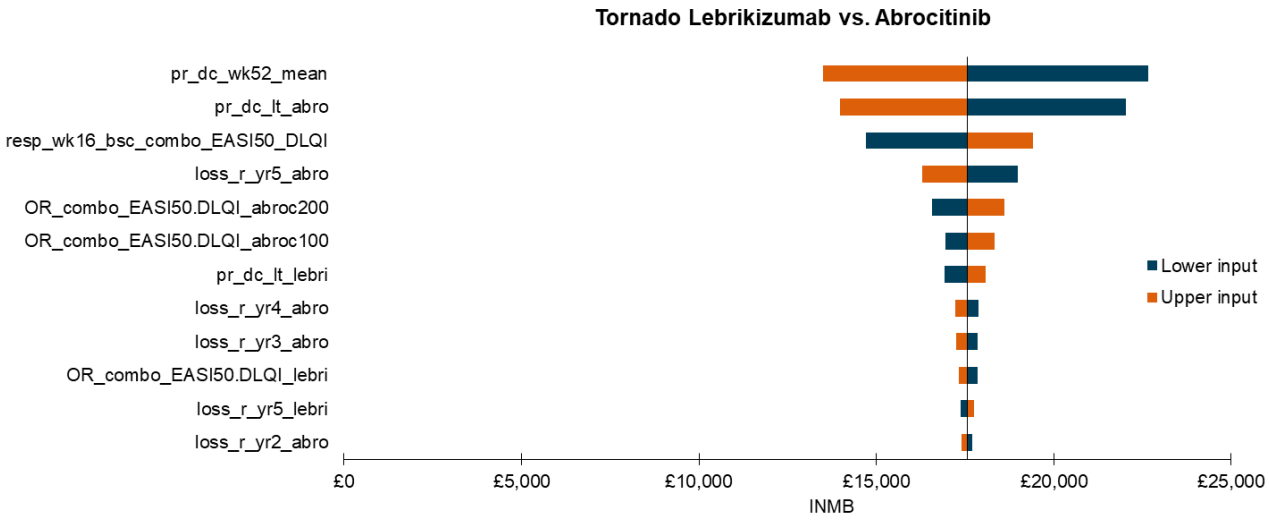


Table 87: OWSA results, lebrikizumab vs. abrocitinib

Parameter	INMB		
	Lower bound	Upper bound	Difference
pr_dc_wk52_mean	£22,651	£13,505	£9,147
pr_dc_lt_abro	£22,035	£13,975	£8,060
resp_wk16_bsc_combo_EASI50_DLQI	£14,712	£19,411	£4,699
loss_r_yr5_abro	£18,990	£16,285	£2,704
OR_combo_EASI50.DLQI_abroc200	£16,574	£18,607	£2,033
OR_combo_EASI50.DLQI_abroc100	£16,940	£18,324	£1,384
pr_dc_lt_lebri	£16,930	£18,091	£1,162
loss_r_yr4_abro	£17,880	£17,211	£668
loss_r_yr3_abro	£17,846	£17,250	£597
OR_combo_EASI50.DLQI_lebri	£17,848	£17,322	£526
loss_r_yr5_lebri	£17,369	£17,761	£392
loss_r_yr2_abro	£17,711	£17,411	£300

Figure 42: Tornado diagram – lebrikizumab vs. tralokinumab

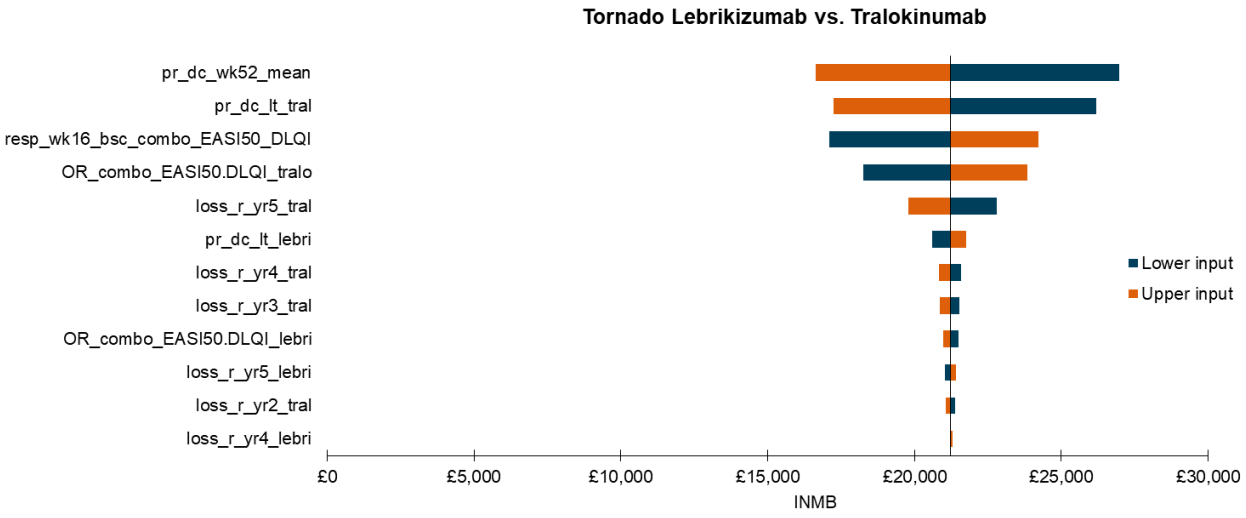


Table 88: OWSA results, lebrikizumab vs. tralokinumab

Parameter	INMB		
	Lower bound	Upper bound	Difference
pr_dc_wk52_mean	£26,970	£16,641	£10,328
pr_dc_lt_tral	£26,193	£17,234	£8,959
resp_wk16_bsc_combo_EASI50_DLQI	£17,093	£24,234	£7,141
OR_combo_EASI50.DLQI_tralo	£18,242	£23,838	£5,596
loss_r_yr5_tral	£22,808	£19,803	£3,005
pr_dc_lt_lebri	£20,591	£21,753	£1,162
loss_r_yr4_tral	£21,576	£20,832	£744
loss_r_yr3_tral	£21,539	£20,874	£664
OR_combo_EASI50.DLQI_lebri	£21,509	£20,983	£526
loss_r_yr5_lebri	£21,031	£21,422	£392
loss_r_yr2_tral	£21,388	£21,055	£332
loss_r_yr4_lebri	£21,195	£21,287	£92

B.3.9.3. Scenario analysis

The scenario analysis results are reported in Table 89. None of the scenarios explored had a significant impact on the model results, as they follow a similar pattern to the base-case.

Table 89: Scenario analysis results

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. lebrikizumab
Base-case			Dupilumab	[redacted]	[redacted]	£1,407,517
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£366,791
			Abrocitinib	[redacted]	[redacted]	£569,303
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
Choice of endpoint used to define response	EASI 50 & DLQI ≥ 4	EASI 75	Dupilumab	[redacted]	[redacted]	£1,404,360
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£368,272
			Abrocitinib	[redacted]	[redacted]	£571,312
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
% of patients having combination treatment with TCS	100%	0%	Dupilumab	[redacted]	[redacted]	£1,393,952
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£171,123
			Abrocitinib	[redacted]	[redacted]	£254,955
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates

		50%	Dupilumab	[redacted]	[redacted]	£1,361,610
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£239,354
			Abrocitinib	[redacted]	[redacted]	£366,234
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
Source of baseline (placebo) response	Upadacitinib studies	ADhere & ADvantage 1	Dupilumab	[redacted]	[redacted]	£1,857,069
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£466,687
			Abrocitinib	[redacted]	[redacted]	£730,265
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
Health state utility source	Lebrikizumab studies	NICE TA681	Dupilumab	[redacted]	[redacted]	£1,345,042
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£351,919
			Abrocitinib	[redacted]	[redacted]	£546,287
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
		NICE TA534	Dupilumab	[redacted]	[redacted]	£1,230,072
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates

			Upadacitinib	[redacted]	[redacted]	£324,238
			Abrocitinib	[redacted]	[redacted]	£503,429
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates
Utility decrements for adverse events	Included	Excluded	Dupilumab	[redacted]	[redacted]	£1,301,546
			Baricitinib	[redacted]	[redacted]	Lebrikizumab dominates
			Upadacitinib	[redacted]	[redacted]	£365,158
			Abrocitinib	[redacted]	[redacted]	£575,829
			Tralokinumab	[redacted]	[redacted]	Lebrikizumab dominates

B.3.10 Subgroup analysis

No subgroup analyses have been performed.

B.3.11 Benefits not captured in the QALY calculation

Lebrikizumab maintenance therapy (treatment after 16 weeks) is based on Q4W dosing, which is a less intensive dosing regimen compared to nearly all comparators. Upadacitinib, abrocitinib and baricitinib are taken as once daily oral treatments, whereas dupilumab is administered as a Q2W injection. Tralokinumab is available as a Q4W injection option in some patients, however based on discussions with KOLs, our understanding is that this is not common and only around 10% of patients treated with tralokinumab will have Q4W maintenance treatment. There is therefore a reduced patient burden with lebrikizumab maintenance therapy compared to that of the comparators. This is not something that would be picked up in the EQ-5D data that was collected as part of the trial, however Almirall believes it is an important patient benefit that should be considered.

B.3.12 Validation

B.3.12.1. Validation of cost-effectiveness analysis

The model was developed internally by a team of health economists and is based on a published model that was utilised in a NICE MTA of relevant comparators. The key assumptions underpinning the model are in-line with the final accepted guidance based on committee preference in the MTA. The structure and clinical assumptions of the model were discussed and ratified as part of an advisory board which included UK clinical experts.(124) In addition to the advisory board, KOL engagement was enhanced with primary research interviews with dermatologists who treat patients in the relevant population, where the model assumptions were discussed in more detail before finalisation. All feedback and external ratification went into the final model and this written submission. The model has undergone thorough internal validation and a quality control (QC) check by an external health economist.

B.3.12.2. Interpretation and conclusions of economic evidence

Over a lifetime horizon, patients treated with lebrikizumab accrued [redacted] QALYs, which is greater than the QALYs associated with baricitinib and tralokinumab ([redacted] and [redacted] respectively), but slightly lower than those achieved with dupilumab, upadacitinib and abrocitinib and ([redacted], [redacted] and [redacted] respectively). However, lebrikizumab is less costly compared to all comparator technologies included in the economic analysis. The reduction in costs associated with lebrikizumab ranges from [redacted] to [redacted] (Table 81), whilst any reductions in QALYs are extremely small ([redacted] to [redacted]). Due to the nature of the results (very small difference in incremental QALYs and reduction in costs), the ICERs may be misleading, however the NMB for lebrikizumab is positive against all comparators (Table 81), indicating that lebrikizumab is likely to be a cost-effective treatment.

References

1. National Institute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe atopic dermatitis (TA534 final guidance). 2018.

2. National Institute for Health and Care Excellence (NICE). Baricitinib for treating moderate to severe atopic dermatitis (TA681 final guidance). 2021.

3. National Institute for Health and Care Excellence (NICE). Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.

4. European Medicines Agency. Ebglyss lebrikizumab. Summary of opinion (initial authorisation) 2023 [Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-ebglyss_en.pdf.

5. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol. 2017;139(4s):S58-s64.

6. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. ISRN Allergy. 2014;2014:354250.

7. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am. 2015;35(1):161-83.

8. Tsoi LC, Rodriguez E, Degenhardt F, Baurecht H, Wehkamp U, Volks N, et al. Atopic Dermatitis Is an IL-13-Dominant Disease with Greater Molecular Heterogeneity Compared to Psoriasis. J Invest Dermatol. 2019;139(7):1480-9.

9. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. Allergy. 2020;75(1):54-62.

10. Miron Y, Miller PE, Hughes C, Indersmitten T, Lerner EA, Cevikbas F. Mechanistic insights into the antipruritic effects of lebrikizumab, an anti-IL-13 mAb. J Allergy Clin Immunol. 2022;150(3):690-700.

11. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130(6):1344-54.

12. La Grutta S, Richiusa P, Pizzolanti G, Mattina A, Pajno GB, Citarrella R, et al. CD4(+)IL-13(+) cells in peripheral blood well correlates with the severity of atopic dermatitis in children. Allergy. 2005;60(3):391-5.

13. Suárez-Fariñas M, Tintle SJ, Shemer A, Chiricozzi A, Nograles K, Cardinale I, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. J Allergy Clin Immunol. 2011;127(4):954-64.e1-4.

14. Falissard B, Simpson EL, Guttman-Yassky E, Papp KA, Barbarot S, Gadkari A, et al. Qualitative Assessment of Adult Patients' Perception of Atopic Dermatitis Using Natural

Language Processing Analysis in a Cross-Sectional Study. Dermatol Ther (Heidelb). 2020;10(2):297-305.

15. Von Kobyletzki L, Thomas K, Schmitt J, Chalmers J, Deckert S, Aoki V. What factors are important to patients when assessing treatment response: an international cross-sectional survey. Acta Derm Venereol 2017;96(7):86-90.

16. Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Ständer S, et al. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. J Eur Acad Dermatol Venereol. 2020;34(1):142-52.

17. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. J Eur Acad Dermatol Venereol. 2014;28(6):719-26.

18. Luger T, Romero WA, Gruben D, Smith TW, Cha A, Neary MP. Clinical and humanistic burden of atopic dermatitis in Europe: analyses of the National Health and Wellness Survey. Dermatol Ther (Heidelb). 2022;12(4):949-69.

19. Ezzedine K, Shourick J, Merhand S, Sampogna F, Taieb C. Impact of atopic dermatitis in adolescents and their parents: a French study. Acta Derm Venereol. 2020;100(17):adv00294.

20. Kleyn CE, Barbarot S, Reed C, Losi S, von Arx LB, Robert C, et al. Burden of Moderate to Severe Atopic Dermatitis in Adults from France, Italy, and the UK: Patient-Reported Outcomes and Treatment Patterns. Dermatol Ther (Heidelb). 2022;12(8):1947-65.

21. Misery L, Seneschal J, Reguiai Z, Merhand S, Heas S, Huet F, et al. Patient burden is associated with alterations in quality of life in adult patients with atopic dermatitis: results from the ECLA study. Acta Derm Venereol. 2018;98(7):713-4.

22. Ring J, Zink A, Arents BWM, Seitz IA, Mensing U, Schielein MC, et al. Atopic eczema: burden of disease and individual suffering - results from a large EU study in adults. J Eur Acad Dermatol Venereol. 2019;33(7):1331-40.

23. Hendricks AJ, Lio PA, Shi VY. Management Recommendations for Dupilumab Partial and Non-durable Responders in Atopic Dermatitis. Am J Clin Dermatol. 2019;20(4):565-9.

24. National Institute for Health and Care Excellence (NICE). Upadacitinib, abrocitinib and tralokinumab for dermatitis (MTA assessment report for TA814). 2021.

25. European Medicines Agency. Janus kinase inhibitors (JAKi) 2023 [Available from: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki.

26. Medicines and Healthcare products Regulatory Agency (MHRA). Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality 2023 [Available from: https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality.

27. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73(6):1284-93.

28. Augustin M, Costanzo A, Pink A, Seneschal J, Schuster C, Mert C, et al. Real-World Treatment Patterns and Treatment Benefits among Adult Patients with Atopic Dermatitis: Results from the Atopic Dermatitis Patient Satisfaction and Unmet Need Survey. Acta Derm Venereol. 2022;102:adv00830.

29. National Eczema Association. Atopic dermatitis 2018 [Available from: https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/.

30. Arkwright PD, Motala C, Subramanian H, Spergel J, Schneider LC, Wollenberg A. Management of difficult-to-treat atopic dermatitis. J Allergy Clin Immunol Pract. 2013;1(2):142-51.

31. Avena-Woods C. Overview of atopic dermatitis. The American journal of managed care. 2017;23(8 Suppl):S115-23.

32. Kleyn CE, McKenzie R, Meeks A, Gittens B, von Arx LB. Prevalence and treatment patterns of adult atopic dermatitis in the UK Clinical Practice Research Datalink. Skin Health Dis. 2023;3(4):e232.

33. National Institute for Health and Care Excellence (NICE). Resource impact report: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.

34. Chan LN, Magyari A, Ye M, Al-Alusi NA, Langan SM, Margolis D, et al. The epidemiology of atopic dermatitis in older adults: A population-based study in the United Kingdom. PLoS One. 2021;16(10):e0258219.

35. Abuabara K, Magyari A, McCulloch CE, Linos E, Margolis DJ, Langan SM. Prevalence of Atopic Eczema Among Patients Seen in Primary Care: Data From The Health Improvement Network. Ann Intern Med. 2019;170(5):354-6.

36. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. The epidemiology of eczema in children and adults in England: A population-based study using primary care data. Clin Exp Allergy. 2021;51(3):471-82.

37. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. Supplementary information to: The epidemiology of eczema in children and adults in England: A population-based study using primary care data. Clin Exp Allergy. 2021;51(3):471-82.

38. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131(1):67-73.

39. Rodríguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009;123(6):1361-70.e7.

40. Peng W, Novak N. Pathogenesis of atopic dermatitis. Clin Exp Allergy. 2015;45(3):566-74.

41. Hsu CK, Akiyama M, Nemoto-Hasebe I, Nomura T, Sandilands A, Chao SC, et al. Analysis of Taiwanese ichthyosis vulgaris families further demonstrates differences in FLG mutations between European and Asian populations. Br J Dermatol. 2009;161(2):448-51.

42. Polcari I, Becker L, Stein SL, Smith MS, Paller AS. Filaggrin gene mutations in African Americans with both ichthyosis vulgaris and atopic dermatitis. Pediatr Dermatol. 2014;31(4):489-92.

43. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365(14):1315-27.

44. Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. Trends Microbiol. 2018;26(6):484-97.

45. Silverberg JI, Kantor R. The Role of Interleukins 4 and/or 13 in the Pathophysiology and Treatment of Atopic Dermatitis. Dermatol Clin. 2017;35(3):327-34.

46. Silverberg NB, Silverberg JI. Inside out or outside in: does atopic dermatitis disrupt barrier function or does disruption of barrier function trigger atopic dermatitis? Cutis. 2015;96(6):359-61.

47. Sanchez-Perez J, Dauden-Tello E, Mora AM, Lara Surinyac N. Impact of atopic dermatitis on health-related quality of life in Spanish children and adults: the PSEDA study. Actas dermo-sifiliograficas. 2013;104(1):44-52.

48. Bruin-Weller M, Pink AE, Patrizi A, Gimenez-Arnau AM, Agner T, Roquet-Gravy PP, et al. Disease burden and treatment history among adults with atopic dermatitis receiving systemic therapy: baseline characteristics of participants on the EUROSTAD prospective observational study. J Dermatolog Treat. 2021;32(2):164-73.

49. Ferrucci SM, Tavecchio S, Angileri L, Surace T, Berti E, Buoli M. Factors associated with affective symptoms and quality of life in patients with atopic dermatitis. Acta Derm Venereol. 2021;101(11):adv00590.

50. Beikert FC, Langenbruch AK, Radtke MA, Kornek T, Purwins S, Augustin M. Willingness to pay and quality of life in patients with atopic dermatitis. Arch Dermatol Res. 2014;306(3):279-86.

51. Capucci S, Hahn-Pedersen J, Vilsbøll A, Kragh N. Impact of Atopic Dermatitis and Chronic Hand Eczema on Quality of Life Compared With Other Chronic Diseases. Dermatitis. 2020;31(3):178-84.

52. Barbarot S, Silverberg JI, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. The Family Impact of Atopic Dermatitis in the Pediatric Population: Results from an International Cross-sectional Study. J Pediatr. 2022;246:220-6.e5.

53. Augustin M, Misery L, von Kobyletzki L, Armario-Hita JC, Mealing S, Redding M. Unveiling the true costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. J Eur Acad Dermatol Venereol. 2022;36 Suppl 7:3-16.

54. Zink AGS, Arents B, Fink-Wagner A, Seitz IA, Mensing U, Wettemann N, et al. Out-of-pocket Costs for Individuals with Atopic Eczema: A Cross-sectional Study in Nine European Countries. Acta Derm Venereol. 2019;99(3):263-7.

55. Andersen L, Nyeland ME, Nyberg F. Higher self-reported severity of atopic dermatitis in adults is associated with poorer self-reported health-related quality of life in France, Germany, the U.K. and the U.S.A. Br J Dermatol. 2020;182(5):1176-83.

56. Demos. The costs of atopic dermatitis. Demos is an independent, educational charity, registered in England and Wales (Charity Registration no. 1042046); 2023.

57. Girolomoni G, Luger T, Nosbaum A, Gruben D, Romero W, Llamado LJ, et al. The Economic and Psychosocial Comorbidity Burden Among Adults with Moderate-to-Severe Atopic Dermatitis in Europe: Analysis of a Cross-Sectional Survey. Dermatol Ther (Heidelb). 2021;11(1):117-30.

58. National Institute for Health and Care Excellence (NICE). Frequency of application of topical corticosterids for atopic eczema (TA81 final guidane). 2004.

59. National Institute for Health and Care Excellence (NICE). Tacrolimus and pimecrolimus for atopic eczema (TA82 final guidance). 2004.

60. National Institute for Health and Care Excellence (NICE). Dupliumab for children with severe atopic dermatitis (TS ID 10434). 2023.

61. Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies. J Allergy Clin Immunol Pract. 2017;5(6):1519-31.

62. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32(6):850-78.

63. Jo CE, Finstad A, Georgakopoulos JR, Piguet V, Yeung J, Drucker AM. Facial and neck erythema associated with dupilumab treatment: A systematic review. J Am Acad Dermatol. 2021;84(5):1339-47.

64. Kreeshan FC, Al-Janabi A, Warren RB, Hunter HJA. Real-World Experience and Laboratory Monitoring of Dupilumab in Patients with Moderate to Severe Atopic Dermatitis in a Tertiary Centre. Dermatol Ther (Heidelb). 2021;11(1):149-60.

65. Medicines.org.uk. Olumiant (baricitinib) 2 mg film-coated tablets (summary of product characteristics). 2022.

66. Medicines.org.uk. Rinvoq (upadacitinib) 15 mg prolonged-release tablets (Great Britain). Summary of Product Characteristics. 2023.

67. Medicines.org.uk. Cibinqo (abrocitinib) 100 mg film-coated tablets. Summary of Product Characteristics.; 2023.

68. Elsgaard S, Danielsen AK, Thyssen JP, Deleuran M, Vestergaard C. Drug survival of systemic immunosuppressive treatments for atopic dermatitis in a long-term pediatric cohort. Int J Womens Dermatol. 2021;7(5Part B):708-15.

69. Johansson EK, Brenneche A, Trangbaek D, Stelmaszuk MN, Freilich J, Anderson CD. Treatment Patterns among Patients with Atopic Dermatitis in Secondary Care: A National, Observational, Non-interventional, Retrospective Study in Sweden. Acta Derm Venereol. 2022;102:adv00774.

70. Pino Lopez J, Kromer C, Herr R, Schmieder A, Bayerl C, Schaarschmidt ML. Drug survival rates and reasons for drug discontinuation in patients with atopic dermatitis: a retrospective study of adult outpatients. Eur J Dermatol. 2021;31(2):233-8.

71. Sangha AM. Dermatological Conditions in Skin of Color: Managing Atopic Dermatitis. J Clin Aesthet Dermatol. 2021;14(3 Suppl 1):S20-s2.

72. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. New England Journal of Medicine. 2023.

73. Blauvelt A, Thyssen JP, Guttman-Yassky E, Bieber T, Serra-Baldrich E, Simpson E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol. 2023.

74. Stein Gold L, Thaçi D, Thyssen JP, Gooderham M, Laquer V, Moore A, et al. Safety of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: An Integrated Analysis of Eight Clinical Trials. Am J Clin Dermatol. 2023:1-13.

75. Eli Lilly and Company. [Data on File: ADvocate 1 (KGAB) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 1). Clinical study report.; 2022.

76. Eli Lilly and Company. [Data on File: ADvocate 2 (KGAC) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 2). Clinical study report.; 2022.

77. Simpson EL, Gooderham M, Wollenberg A, Weidinger S, Armstrong A, Soung J, et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA dermatology. 2023.

78. Eli Lilly and Company. [Data on File: ADhere (KGAD) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroid treatment in patients with moderate-to-severe atopic dermatitis (ADhere). Clinical study report.; 2022.

79. Warren R, de Bruin-Weller M, Tsianakas A, Khemis A, Szepietowski J, Hong H, et al. Lebrikizumab improves signs and symptoms of moderate-to-severe atopic dermatitis in patients inadequately controlled or ineligible for cyclosporine: a placebo-controlled, randomized phase 3 clinical study (ADvantage). (Oral presentation). EADV 2023 (European Academy of Dermatology and Venereology); Berlin2023.

80. Almirall. [Data on File: ADvantage CSR] A randomised, double-blind, placebo-controlled phase 3 clinical trial to assess the efficacy and safety of lebrikizumab in combination with topical corticosteroids in adult and adolescent patients with moderate-to-severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable (ADvantage). Clinical study report. 2023.

81. Guttman-Yassky E, Weidinger S, Silverberg J, Gooderham M, Thyssen JP, Irvine A, et al., editors. Maintenance of efficay and safety with lebrikizumab up to one year of treatment in patients with moderste-to-severe atopic dermatitis with or without topical corticosteroids. Oral presentation given at the World Congress of Dermatology; 2023; Singapore.

82. Guttman-Yassky E, Weidinger S, Simpson E, Gooderham M, Irvine A, Spelman L, et al., editors. Efficacy and safety of lebrikizumab is maintained to two years in patients with moderate-to-severe atopic dermatitis. Oral presentation given at the Fall Clinical Dermatology Conference; 2023; Las Vegas, NV, USA.

83. Eli Lilly and Company. [Data on File: ADjoin (KGAA) CSR] A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADjoin). Abbreviated clinical study report.; 2022.

84. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol. 2020;156(4):411-20.

85. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A, et al. Supplementary information to: Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. N Engl J Med. 2023;388(12):1080-91.

86. Simpson EL, Gooderham M, Wollenberg A, Weidinger S, Armstrong A, Soung J, et al. Supplementary information to: Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA Dermatol. 2023;159(2):182-91.

87. Almirall. Data on file: ADvocate 1 & 2 pooled EQ-5D-5L data. 2023.

88. Blauvelt A, Thyssen JP, Guttman-Yassky E, Bieber T, Serra-Baldrich E, Simpson E, et al. Supplementary information to: Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol. 2023.

89. Guttman-Yassky E, Rosmarin D, Thyssen JP, Weidinger S, Bieber T, Elmaraghy H, et al. Efficacy of lebrikizumab in patients who did not achieve protocol-defined criteria for reposnse after initial 16 weeks of therapy (poster). American Academy of Dermatology (AAD); Virtual/New Orleans, USA. 2023. 17-21 March2023.

90. Almirall. Data on file: Partial responders. 2023.

91. Guttman-Yassky E, Rosmarin D, Thyssen JP, Weidinger S, Bieber T, Elmaraghy H, et al., editors. Supplementary information to: Efficacy of lebrikizumab in patients who did not achieve pritocol-defined criteria for response after initial 16 weeks of therapy (poster).

American Academy of Dermatology (AAD); 2023; Virtual/New Orleans, USA. 17-21 March 2023.

92. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005;125(4):659-64.

93. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. 2013;169(6):1326-32.

94. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993;80(1):27-38.

95. Almirall. Data on file: ADvocate 1, ADvocate 2 and ADhere post-hoc analyses. 2023.

96. Almirall. Data on file: Full technical report, Network meta-analysis of outcomes at Week 16. 2023.

97. Almirall. Data on file: Technical report, MAIC and STC for w16-w52. 2023.

98. Rand K, Ramos-Goñi JM, Akmaz B, Solé-Feu L, Armario-Hita JC. Matching-Adjusted Indirect Comparison of the Long-Term Efficacy Maintenance and Adverse Event Rates of Lebrikizumab versus Dupilumab in Moderate-to-Severe Atopic Dermatitis. Dermatol Ther (Heidelb). 2023.

99. Worm M, Simpson EL, Thaçi D, Bissonnette R, Lacour JP, Beissert S, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(2):131-43.

100. Silverberg JI, Hong HC, Calimlim BM, Lee WJ, Teixeira HD, Collins EB, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis without Topical Corticosteroids: An Updated Network Meta-analysis. Dermatol Ther (Heidelb). 2023;13(10):2247-64.

101. ClinicalTrials.gov. A study to evaluate the safety of lebrikizumab compared to topical corticosterois in adult patients with atopic dermatitis 2015 [updated 27 January 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02465606?term=NCT02465606&draw=2&rank=1.

102. ClinicalTrials.gov. A study of lebrikizumab (LY3650150) in participants with moderate-to-severe atopic dermatitis 2018 [updated 4 May 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT03443024?term=NCT03443024&draw=2&rank=1.

103. ClinicalTrials.gov. Study to assess the safety and efficacy of lebrikizumab (LY3650150) in adolescent participants with moderste-to-severe atopic dermatitis 2020 [updated 24 February 2023. Available from: https://clinicaltrials.gov/ct2/show/NCT04250350?term=NCT04250350&draw=2&rank=1.

104. Williams HC, Schmitt J, Thomas KS, Spuls PI, Simpson EL, Apfelbacher CJ, et al. The HOME Core outcome set for clinical trials of atopic dermatitis. J Allergy Clin Immunol. 2022;149(6):1899-911.

105. Scottish Medicines Consortium. SMC2417 Upadacitinib 15mg and 30mg prolonged-release tablets (Rinvoq®). Healthcare Improvement Scotland: Scottish Medicines Consortium; 2022.

106. Scottish Medicines Consortium. SMC2011 Dupilumab 300mg solution for injection in pre-filled syringe (Dupixent®). Health Improvement Scotland (HIS): Scottish Medicines Consortium (SMC); 2018.

107. Scottish Medicines Consortium. SMC2337 Baricitinib 2mg and 4mg film-coated tablets (Olumiant®). Health Improvement Scotland (HIS). Scottish Medicines Consortium (SMC); 2021.

108. Scottish Medicines Consortium. SMC2403 Tralokinumab 150mg solution for injection in pre- filled syringe (Adtralza®). Health Improvement Scotland (HIS). Scottish Medicines Consortium (SMC); 2021.

109. Scottish Medicines Consortium. SMC2431 Abrocitinib 50mg, 100mg, and 200mg film-coated tablets (Cibinqo®). Health Improvement Scotland (HIS). Scottish Medicines Consortium (SMC); 2022.

110. CADTH Canadian Agency for Drugs and Technologies in Health. Drug Reimbursement Review Dupilumab (Dupixent). Canadian Agency for Drugs and Technologies in Health (CADTH). 2020.

111. CADTH Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Recommendation: Abrocitinib (Cibinqo). Canadian Agency for Drugs and Technologies in Health (CADTH). 2022.

112. CADTH Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Recommendation: Upadacitinib (Rinvoq). Canadian Agency for Drugs and Technologies in Health (CADTH). 2022.

113. CADTH Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review Tralokinumab (Adtralza). Canadian Agency for Drugs and Technologies in Health (CADTH). 2022.

114. Kuznik A, Bégo-Le-Bagousse G, Eckert L, Gadkari A, Simpson E, Graham CN, et al. Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. Dermatol Ther (Heidelb). 2017;7(4):493-505.

115. Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy. Glob Reg Health Technol Assess. 2020;7:57-65.

116. Zimmermann M, Rind D, Chapman R, Kumar V, Kahn S, Carlson J. Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis. J Drugs Dermatol. 2018;17(7):750-6.

117. Heinz KC, Willems D, Hiligsmann M. Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. J Med Econ. 2022;25(1):491-502.

118. Kim YG, K. Vazquez, M. Claxton, A. et al. L2 Budget Impact of Tralokinumab for Treatment of Moderate-to-Severe Atopic Dermatitis from a US Payer Perspective. J Manag Care Spec Pharm. 2022;28.

119. Chalmers KS, L. Petersen, AS. et al. EE354 Budget Impact Analysis of Tralokinumab in Patients With Moderate-to-Severe Atopic Dermatitis in the UK. Value in Health. 2022;25.

120. Fanelli FP, MP. Serra, A. Bitonti, R. Furneri, G. PBI11 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Atopic Dermatitis in Adolescent Patients in Italy. Value in Health. 2020;23.

121. Pedone MS, A. Bitonti, R. Furneri, G. POSA50 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Severe Atopic Dermatitis in Adolescent and Children Patients in Italy. Value in Health. 2022;25.

122. ICER Institute for Clinical and Economic Review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. ICER Institute for Clinical and Economic Review.; 2017.

123. ICER Institute for Clinical and Economic Review. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value. ICER Institute for Clinical and Economic Review.; 2021.

124. Almirall. Data on file: Lebrikizumab UK HTA Advisory Board meeting minutes (September 2023). 2023.

125. Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021;184(3):450-63.

126. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2021;184(3):437-49.

127. Wailoo A, Hernandez Alava, M., Pudney, S. NICE DSU Technical Support Document 22 Mapping to estimate health state utilities. 2023. NICE; 2023 2023.

128. Almirall. Data on file: Lebrikizumab EQ-5D Utility mapping report (September 2023). 2023.

129. Almirall. Data on file: Lebrikizumab EQ-5D Utility mapping (Excel data analyses) (September 2023). 2023.

130. Fisman DN. Health related quality of life in genital herpes: a pilot comparison of measures. Sex Transm Infect. 2005;81(3):267-70.

131. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;31(6):800-4.

132. National Institute for Health and Care Excellence (NICE). British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/.

133. National Institute for Health and Care Excellence (NICE). Tacrolimus, British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/drugs/tacrolimus/.

134. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT) 2023 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

135. NHS England. 2021/22 National Cost Collection Data Publication 2023 [Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/.

136. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care 2022 Manual. Personal Social Services Research Unit (PSSRU); 2022.

137. National Institute for Health and Care Excellence (NICE). Betamethasone, British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/drugs/betamethasone/.

138. National Institute for Health and Care Excellence (NICE). Topical corticosteroids: British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/treatment-summaries/topical-corticosteroids/.

139. National Institute for Health and Care Excellence (NICE). Clobetasone butyrate, British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/drugs/clobetasone-butyrate/.

140. National Institute for Health and Care Excellence (NICE). Prednisolone, British National Formulary (BNF) 2023 [Available from: https://bnf.nice.org.uk/drugs/prednisolone/.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Summary of Information for Patients (SIP)

November 2023

File name	Version	Contains confidential information	Date
ID4025_Lebrikizumab_Almirall_SIP_FINAL_3.11.23 [ACIC]	FINAL	Yes/no	3.11.23

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Response:
Lebrikizumab. The brand name is Ebglyss®.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
The population comprises adults and adolescents 12 years and over weighing at least 40kg with moderate to severe atopic dermatitis that are suitable for systemic treatment if the disease has not responded to at least 1 systemic immunosuppressant, or these are not suitable. This is in line with the population for previous NICE appraisals for currently available second-line systemic treatments.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
Lebrikizumab is currently being evaluated by the Medicines and Healthcare products Regulatory Agency (the organisation that gives companies the legal right to sell medicines in the UK). More

information on the anticipated date of approval is given in Section B.1.2 of the main submission (Document B).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

National Eczema Society (NES)

- Grant provision of £20k provided in December 2022 for annual support to the society – this has been provided as an unrestricted grant
- Support for patient education podcasts, produced by the NES: £3,850
- Working with NES to establish a patient forum/advisory board to be held in November 2023.

Eczema Outreach (EO)

- Working with EO to establish a patient forum/advisory board to be held in November 2023.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

Atopic dermatitis (AD; also known as atopic eczema) is a chronic (long-lasting) disease that causes dry, itchy and inflamed skin. It usually starts in childhood, but can occur at any age. The inflamed areas of dry skin flare up from time to time and then settle down. Sometimes, the inflamed areas can become infected.

Estimates of the number of people in England living with AD vary widely. A recent study, based on data collected between 2009 and 2018, estimated that approximately 1 in 10 children and 1 in 20 adults are affected (1). Calculations done by NICE suggest that by 2026/27, there will be 157,500 adolescents (i.e. people aged 12-18 years) and adults in England who have AD that is classed as moderate or severe (2).

Itch is the main symptom of AD and has a significant burden on patients. Patients associate itch with pain and with feeling uncomfortable and tired (3). Relief of itch is an important treatment goal for patients (4, 5).

People with AD also have disrupted sleep, often due to itch. In one study, approximately a quarter of patients said their sleep was disturbed often or every night because of severe itching (6).

Mental health issues such as anxiety and depression are significantly more common in adults with AD than in those without AD (7).

Adults with AD have reported worse quality of life then those with other skin conditions, including vitiligo (pale white patches on the skin), psoriasis (scaly patches on the skin) and rosacea (red patches on the face) (8). Patients with moderate or severe disease report worse quality of life then those with mild disease (9, 10).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

To diagnose AD, healthcare professionals will talk to the patient about their symptoms, examine their skin and check their medical history. They may also do tests to identify allergies and rule out any other skin conditions, but there is no specific test for AD. No additional diagnostic tests will be required for patients treated with lebrikizumab.

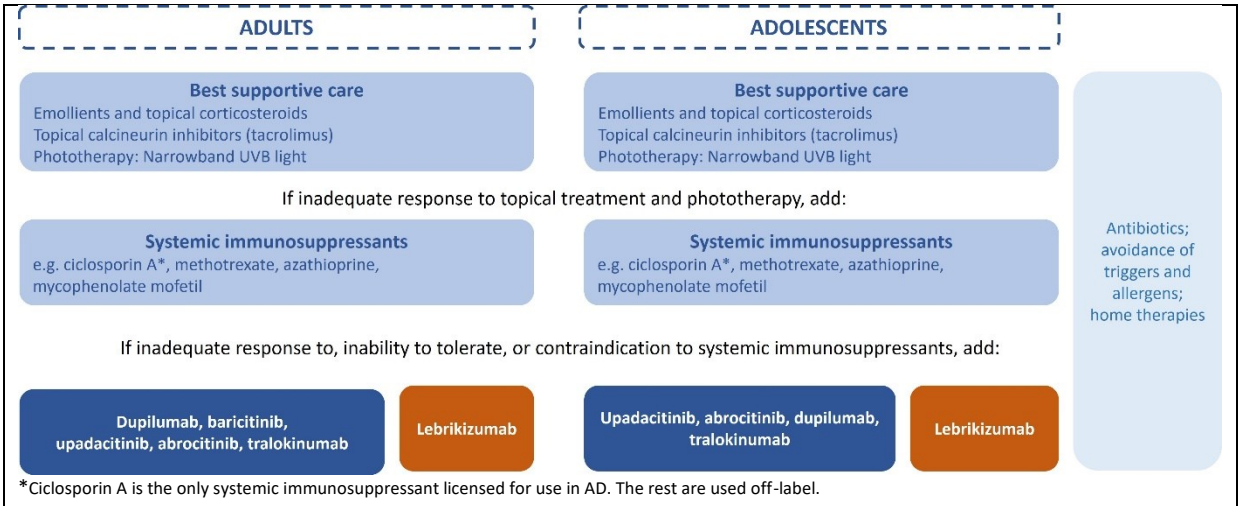
2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

The aims of treatment are to reduce skin inflammation and itch, restore the skin's barrier function and improve quality of life. The current typical treatment pathway for adults and adolescents with moderate-to-severe AD and the anticipated position of lebrikizumab within it is shown in the diagram below.



*Ciclosporin A is the only systemic immunosuppressant licensed for use in AD. The rest are used off-label.

Emollients are the foundation of treatment and are used to hydrate and repair the skin. If symptoms persist after correct use of emollients, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) are introduced (topical means applied to the skin). However, continuous long-term use of TCS is not recommended because of the risk of side effects, including thinning of the skin, skin discolouration and high blood pressure. If TCS and TCI are not adequate, phototherapy (exposure to ultraviolet light) can be used, although this is a time-consuming procedure and is not available in all parts of the UK.

If AD is not sufficiently controlled with appropriate topical treatments and phototherapy, systemic therapy is introduced. Conventional systemic therapies (commonly used first line) include the immunosuppressants ciclosporin A, methotrexate, azathioprine and mycophenolate mofetil. Advanced therapies (commonly used after conventional systemics) include the biologics dupilumab and tralokinumab, and the Janus-kinase (JAK) inhibitors abrocitinib, baricitinib and upadacitinib.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

Relief of itch is an important treatment goal for patients. In an international survey of 688 adults with AD and 423 parents of children with AD, 95% rated itch as being ‘quite important’ or ‘very important’ when deciding whether a treatment is working (von Koby 2017).

The UK think-tank, Demos, interviewed adult patients as part of its research into the costs of atopic dermatitis (11). Quotes supplied by these patients illustrate patient needs and experience. For example:

"I started a job that didn't have any sick pay for the first 6 months, and I had a few days that I needed to take off because of the pain I was in, and I didn't get paid for those days, which… I understand why they do it, but for someone with a chronic illness, it feels very unfair, because no one can help getting sick"

"Even things like getting up in the morning and getting ready for work, or if you're running late - you can't just throw on your clothes and scrag your hair back and go. I have to put cream on every morning, and every evening before bed religiously, otherwise I feel uncomfortable and obviously, my skin would suffer"

"You're just trying to get through each day, and you're in pain, everywhere is hurting all over your body, so that's a huge mental cost"

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Lebrikizumab is a biologic (a type of medicine that is produced in living cells). Biologics are designed to target specific parts of the immune system.

Lebrikizumab works by stopping a protein called interleukin-13 (IL-13) from binding to the surface of cells. IL-13 drives a number of the signs and symptoms of AD, including inflammation, allergic responses, itch, disruption to the outer layer of the skin and skin thickening. By blocking IL-13 lebrikizumab can improve AD and reduce the associated itching and skin pain.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of

life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
Response: Lebrikizumab can be administered on its own or in combination with medicines that are applied to the skin (corticosteroids or calcineurin inhibitors).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Response: Lebrikizumab is injected into the thigh or the abdomen (the area of the body between the chest and the pelvis), except for 5 cm around the belly button. Patients can self-inject, or the patients' caregiver can give the injection (if their doctor says this is appropriate). If the caregiver administers the injection, it can be given in the upper arm. Patients should change the injection site for each injection. The initial dose is 500 mg (given as two 250 mg injections) at Week 0 and Week 2. After this, the recommended dose is 250 mg every two weeks until Week 16. Most patients will then move onto the maintenance dose of 250 mg every four weeks. However, for some patients, doctors may recommend an extra eight weeks of fortnightly dosing. Doctors may consider stopping treatment in patients who have not responded by 16 weeks. Once response is achieved, lebrikizumab only needs to be taken once every 4 weeks. In contrast, it is recommended that the other available biologics (dupilumab and tralokinumab) are taken every two weeks (although tralokinumab may be given every 4 weeks in some patients if the prescriber thinks this is appropriate). The JAK inhibitors, which are taken orally, need to be taken every day.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Response: **Completed trials** There are four completed trials of lebrikizumab in adults and adolescents with moderate-to-severe AD: ADvocate 1, ADvocate 2, ADhere and ADvantage. **ADvocate 1 (NCT04146363) and ADvocate 2 (NCT04178967)** had identical designs and were carried out in Europe, Asia, North America and Central America. The studies enrolled patients who were aged ≥12 years, weighed ≥40 kg and had been diagnosed with AD more than a year before the study started. To take part, patients had to have moderate-to-severe AD, with a score of 16 or more on the Eczema Area and Severity Index, a score of 3 or more on the Investigators Global

Assessment, and at least 10% of their body surface affected. They were not allowed to take part if they had previously been treated with the biologics dupilumab or tralokinumab.

In each study, patients were randomly allocated to either lebrikizumab 250 mg every 2 weeks (Q2W) or placebo (a dummy medicine that was designed to look like lebrikizumab and be given in the same way but does not contain an active medicine). The allocation of treatment was double-blinded, which means neither the patients nor the people running the study knew which treatment each patient was taking. Patients received treatment for 16 weeks. At this point, these who were considered to have responded to treatment went through another random allocation to either lebrikizumab 250 mg Q2W, lebrikizumab 250 mg every four weeks (Q4W) or placebo. Patients who had not responded to treatment remined on lebrikizumab 250 mg Q2W. Treatment continued for another 36 weeks. In these studies, lebrikizumab was given as monotherapy (which means it was not given in combination with any other medications for AD).

In total, 424 patients were enrolled in ADvocate 1: 283 were allocated to lebrikizumab and 141 to placebo. ADvocate 2 included 427 patients: 281 who were allocated to lebrikizumab and 146 were allocated to placebo.

Both trials completed in 2022 and have been published in the New England Journal of Medicine (12) and the British Journal of Dermatology (13).

ADhere (**NCT04250337)** was designed to assess lebrikizumab in combination with TCS. It was carried out in Canada, Germany, Poland and the United States. Patients could enter the study if they were aged ≥12 years, weighed ≥40 kg and had been diagnosed with atopic dermatitis more than a year before the study started. They also had to have moderate-to-severe AD, with a score of 16 or more on the Eczema Area and Severity Index, a score of 3 or more on the Investigators Global Assessment, and at least 10% of their body surface affected. They were not allowed to take part if they had ever had a side-effect to TCS, including an allergic reaction or significant thinning of the skin.

Patients were randomly allocated to either lebrikizumab 250 mg Q2W + TCS or placebo + TCS. The allocation of treatment was double-blinded. Treatment lasted for 16 weeks.

In total, 211 patients were enrolled: 145 received lebrikizumab + TCS and 66 received placebo + TCS.

The trial completed in 2021 and the results have been published in JAMA Dermatology (14).

ADvantage (NCT05149313) was designed to assess lebrikizumab in patients who had previously failed treatment with ciclosporin A or who cannot take ciclosporin A. It was carried out in Europe (Austria, Belgium, France, Germany, Netherlands, Poland, Spain and the UK). Patients could enter the study if they were aged ≥12 years, weighed ≥40 kg and had been diagnosed with atopic dermatitis more than a year before the study started. They also had to have moderate-to-severe AD, with a score of 16 or more on the Eczema Area and Severity Index, a score of 3 or more on the Investigators Global Assessment, and at least 10% of their body surface affected. They were not allowed to take part if they had previously taken part in another study of lebrikizumab or had used TCS in the week before the start of the study.

Patients were randomly allocated to either lebrikizumab 250 mg Q2W + TCS or placebo Q2W + TCS. The allocation of treatment was double-blinded. Patients received treatment for 16 weeks. After this, all patients were treated with lebrikizumab 250 mg Q2W + TCS for another 36 weeks.

The study completed in 2022, and the data from the first 16 weeks of treatment have been presented at a scientific conference. However, the results are not yet fully published. Details of the study methods are available on ClinicalTrials.gov (15).

Other/ongoing studies

The four studies described above are directly relevant to NICE's evaluation of lebrikizumab. A number of other studies have been carried out or are ongoing, but these are not relevant to the evaluation:

- ADjoin (NCT04250350): assessed lebrikizumab in adolescents with moderate-to-severe AD (Paller)
- ADlong (NCT05916365): a 2-year extension of ADjoin in Germany and Poland only. Ongoing - expected to complete in April 2026
- ADorable (NCT05559359): to assess lebrikizumab in children aged 6 months to <18 years. Ongoing – expected to complete in July 2025
- ADapt (NCT05369403): to assess lebrikizumab in patients previously treated with dupilumab. Ongoing – expected to complete in March 2024
- Admirable (NCT05372419): to assess lebrikizumab in adults and adolescents with moderate-to-severe AD and skin of colour. Ongoing – expected to complete in April 2024.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

There are no trials that directly compare lebrikizumab with current treatments. ADvocate 1 & 2, ADhere and ADvantage all compared lebrikizumab with placebo.

Results from ADvantage were shared at a recent conference and showed that patients with moderate-to-severe AD who had previously were ineligible for treatment with cyclosporine, or who had inadequately controlled AD as a result of cyclosporine use, demonstrated clinical improvements when treated with a combination of lebrikizumab and a topical corticosteroid over a 16-week duration.(16) The ADvantage results are yet to be published so only ADvocate 1 & 2 and ADhere are summarised below. Further details on ADvantage are available in Section B.2.6.2 of the main submission (Document B).

ADvocate 1 & 2 and ADhere

In these trials, the effectiveness of lebrikizumab on patients' skin was assessed by measuring the percentage of patients who:

- had a 75% improvement in the Eczema Area and Severity Index (EASI 75). The EASI is used to assess the extent of skin redness, thickness, scratching and lichenification (where the skin becomes thick and leathery)
- achieved an Investigators Global Assessment score of 0 or 1 with at least a 2-point improvement (IGA (0,1)). An IGA score of 0 or 1 corresponds to clear to almost clear skin.

A significantly greater percentage of patients treated with lebrikizumab (either as monotherapy or in combination with TCS) achieved meaningful improvements in the appearance of their skin compared with placebo at Week 16:

- In ADvocate 1, 58.8% of patients treated with lebrikizumab achieved EASI 75 at Week 16, compared with 16.2% of patients who received placebo. 43.1% of patients treated with lebrikizumab achieved IGA (0,1) at Week 16, compared with 12.7% who received placebo (12)
- In ADvocate 2, 52.1% of patients treated with lebrikizumab achieved EASI 75 at Week 16, compared with 18.1% of patients who received placebo. 33.2% of patients treated with lebrikizumab achieved IGA (0,1) at Week 16, compared with 10.8% who received placebo (12)
- In ADhere, 69.5% of patients treated with lebrikizumab + TCS achieved EASI 75 at Week 16, compared with 42.2% of patients who received placebo + TCS. 41.2% of patients treated with lebrikizumab + TCS achieved IGA (0,1) at Week 16, compared with 22.1% who received placebo + TCS. (14)

As described in Section 2d above, relief of itch is an important treatment goal for patients. In the lebrikizumab trials, itch was assessed using an 11-point scale, where 0 = no itch and 10 = worst possible itch. Patients who reported a score of 4 or above at the start of the study were included in the analysis. A significantly greater percentage of patients treated with lebrikizumab (either as monotherapy or in combination with TCS) achieved meaningful reductions in itch compared with placebo at Week 16:

- In ADvocate 1, 45.9% of patients treated with lebrikizumab had a reduction of at least 4 points in their NRS score at Week 16, compared with 13.0% of patients who received placebo (12)
- In ADvocate 2, 39.8% of patients treated with lebrikizumab had a reduction of at least 4 points in their NRS score at Week 16, compared with 11.5% of patients who received placebo (12)
- In ADhere, 50.6% of patients treated with lebrikizumab had a reduction of at least 4 points in their NRS score at Week 16, compared with 31.9% of patients who received placebo. (14)

The onset of clinical benefit with lebrikizumab was rapid and was sustained for up to 2 years (17).

Although there are no trials that directly compare lebrikizumab with other available treatments, it is possible to compare them indirectly. One such indirect comparison has shown that lebrikizumab is comparable with other biologics and JAK inhibitors (18). The manufacturer of lebrikizumab is currently undertaking similar indirect comparisons; however the results of these are not yet publicly available.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

EQ-5D-5L was measured in ADvocate 1, ADvocate 2 and ADhere to capture the quality of life of patients. However, only results from ADhere are publicly available. Treatment with lebrikizumab + TCS resulted in greater improvements in patients' quality of life than treatment with placebo + TCS (14). It is important to note that the EQ-5D was not designed specifically for use in atopic dermatitis.

The Dermatology Life Quality Index (DLQI) is a questionnaire that is specifically designed for use in patients with skin conditions. It includes questions on symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. A higher score on the DLQI corresponds to worse quality of life. The Patient-Oriented Eczema Measure (POEM) is a questionnaire that is specifically designed for use in patients with atopic dermatitis. It asks patients about the frequency of the symptoms over the last week. A higher score on the POEM corresponds to worse quality of life. Both the DLQI and POEM questionnaires were used to assess patients' quality of life in the lebrikizumab studies.

Results from the DLQI show that patients' quality of life started to improve rapidly after starting treatment with lebrikizumab (either as monotherapy or in combination with TCS), with notable differences vs. placebo seen after just 4 weeks of treatment (which was the first timepoint in the study when patients completed the questionnaire) (12, 14).

Results for POEM are only publicly available from the ADhere study. At Week 16, patients treated with lebrikizumab + TCS has a significantly greater improvement in POEM scores than those who received placebo (14).

The studies also used the Patient Reported Outcomes Measurement Information System (PROMIS) to assess the impact of lebrikizumab on anxiety and depression. Results are only publicly available for ADhere; these showed that in adult patients, there were improvements in anxiety and depression after 16 weeks of treatment (14).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

In the lebrikizumab trials, the most common side effects of lebrikizumab were conjunctivitis (infection or inflammation of the outer layer of the eye), worsening of atopic dermatitis, nasopharyngitis (inflammation of the nasal passages and throat) and headache (12, 14). There were no important differences in side effects between patients who received lebrikizumab as monotherapy and those who received it in combination with TCS. There were also no meaningful differences between patients who received lebrikizumab every 4 weeks and those who received it more frequently (every 2 weeks).

Altogether, 18 patients in the trials stopped treatment with lebrikizumab because of side effects. The most common side effect that caused patients to stop treatment was conjunctivitis.

There were few serious side effects reported in the trials.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

Lebrikizumab selectively targets a protein called IL-13, which is thought to play a key role in development of atopic dermatitis. It stays attached to IL-13 for a long time, meaning that the effects of lebrikizumab are long-lasting. Clinical studies showed that lebrikizumab provides clinically relevant improvements in skin inflammation and itch over both the short-term (to Week 16) and the long-term (up to 2 years).

Once response is achieved, lebrikizumab only needs to be taken once every 4 weeks. In contrast, it is recommended that the other available biologics (dupilumab and tralokinumab) are taken every two weeks (although tralokinumab may be given every 4 weeks in some patients if the prescriber thinks this is appropriate, i.e. if the patient has clear or almost clear skin after 16 weeks of treatment. However, the probability of maintaining clear or almost clear skin may be lower with tralokinumab given every 4 weeks). The JAK inhibitors need to be taken every day, and some patients may occasionally forget to take a dose. Lebrikizumab therefore offers a more convenient dosing schedule than currently available treatments.

JAK inhibitors are associated with an increased risk of infection, cancer, major adverse cardiovascular events (MACE) and thrombosis (19-21) and their usage is more limited as a result, particularly in people aged 65 and over, smokers and ex-smoker, and people with risk factors for these conditions. Lebrikizumab provides a further non-JAK inhibitor option among the advanced therapies.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Lebrikizumab is given by injection under the skin. Some patients may feel anxious about having injections, either because they find them painful or because they have a phobia of needles.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

The manufacturer of lebrikizumab built an economic model in Microsoft Excel to explore the cost-effectiveness of lebrikizumab when compared with other biologics (dupilumab and tralokinumab) and JAK inhibitors (abrocitinib, upadacitinib, baricitinib) in adults and adolescents with moderate-to-severe atopic dermatitis that is not controlled with topical prescription medication.

The economic model shows the different ways in which a patient's health can change after treatment. It compares the total costs (drugs and healthcare resource use) generated by lebrikizumab and the other treatments as well as the survival and quality of life over their lifetime; a review of the quality of life change due to treatment on lebrikizumab and patients' survival produces a result called the quality-adjusted life year (QALY). One QALY is equal to one year of life in perfect health. The economic model can calculate the QALY change due to treatment with lebrikizumab compared to its comparators.

The model uses data from the ADvocate 1, ADvocate 2 and ADhere trials; a key trial input is patient response to treatment, defined as a 50% reduction in EASI and a ≥4-point improvement in DLQI at Week 16. The model also includes factors such as withdrawal from treatment, loss of treatment effect over time, flare-ups and side effects.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

Not applicable.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: The use of lebrikizumab is not expected to raise any equality issues. However, it is important to note that assessment of AD in patients with skin of colour can be challenging. For example, redness of the skin can be harder to detect in people with darker skin, as it often appears grey or dark brown in colour (22). NICE recommends that healthcare professionals should take skin colour into account when assessing response to treatment and make appropriate adjustments (23-25). NICE also recommends that healthcare professionals should take any physical, psychological, sensory or learning disabilities, or communication difficulties into account when asking patients to complete a self-assessment questionnaire.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: ADvocate 1 and 2 clinical trials: published papers in the New England Journal of Medicine and the British Journal of Dermatology: https://www.nejm.org/doi/10.1056/NEJMoa2206714 https://academic.oup.com/bjd/article/188/6/740/7095270 ADhere clinical trial: published paper in JAMA Dermatology https://jamanetwork.com/journals/jamadermatology/fullarticle/2800236 National Eczema Society: https://eczema.org Allergy UK: https://www.allergyuk.org/types-of-allergies/eczema/ Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS)

organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Abdomen – the area of the body between the chest and the pelvis

Allergic conjunctivitis – inflammation of the eye caused by an allergic reaction

Biologic – a type of medicine that is produced in living cells. Biologics are designed to target specific parts of the immune system

Chronic – long-lasting. A chronic illness is generally defined as one that lasts at least 3 months

Conjunctivitis – redness and discomfort in the eye caused by infection or inflammation of the eye's outer surface

Interleukin-13 – a small protein that lays a key role in the development of atopic dermatitis

Lichenification – where the skin becomes thick and leathery, usually due to repeated scratching

Nasopharyngitis – inflammation of the nasal passages, throat, or the area behind the nose and mouth

Phototherapy – a type of treatment that uses ultraviolet light to treat skin conditions

Placebo – a 'dummy' medication that looks identical to a real medication and is taken in the same way

Psoriasis – a condition resulting in scaly patches on the skin

Q2W – every 2 weeks

Q4W – every 4 weeks

QALY – quality adjusted life year. A measure of how well a treatment improves or lengthens a patient's life. One QALY is equal to one year of life in perfect health

Rosacea – a condition resulting in red patches on the face

Systemic – given by mouth or injection

Topical – applied to the skin

Vitiligo – a condition resulting in pale white patches on the skin

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. The epidemiology of eczema in children and adults in England: A population-based study using primary care data. Clin Exp Allergy. 2021;51(3):471-82.

2. National Institute for Health and Care Excellence (NICE). Resource impact report: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.

3. Falissard B, Simpson EL, Guttman-Yassky E, Papp KA, Barbarot S, Gadkari A, et al. Qualitative Assessment of Adult Patients' Perception of Atopic Dermatitis Using Natural Language Processing Analysis in a Cross-Sectional Study. Dermatol Ther (Heidelb). 2020;10(2):297-305.

4. Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Ständer S, et al. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. J Eur Acad Dermatol Venereol. 2020;34(1):142-52.

5. Von Kobyletzki L, Thomas K, Schmitt J, Chalmers J, Deckert S, Aoki V. What factors are important to patients when assessing treatment response: an international cross-sectional survey. Acta Derm Venereol 2017;96(7):86-90.

6. Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. J Eur Acad Dermatol Venereol. 2014;28(6):719-26.

7. Luger T, Romero WA, Gruben D, Smith TW, Cha A, Neary MP. Clinical and humanistic burden of atopic dermatitis in Europe: analyses of the National Health and Wellness Survey. Dermatol Ther (Heidelb). 2022;12(4):949-69.

8. Beikert FC, Langenbruch AK, Radtke MA, Kornek T, Purwins S, Augustin M. Willingness to pay and quality of life in patients with atopic dermatitis. Arch Dermatol Res. 2014;306(3):279-86.

9. Ezzedine K, Shourick J, Merhand S, Sampogna F, Taieb C. Impact of atopic dermatitis in adolescents and their parents: a French study. Acta Derm Venereol. 2020;100(17):adv00294.

10. Kleyn CE, Barbarot S, Reed C, Losi S, von Arx LB, Robert C, et al. Burden of Moderate to Severe Atopic Dermatitis in Adults from France, Italy, and the UK: Patient-Reported Outcomes and Treatment Patterns. Dermatol Ther (Heidelb). 2022;12(8):1947-65.

11. Demos. The costs of atopic dermatitis. Demos is an independent, educational charity, registered in England and Wales (Charity Registration no. 1042046); 2023.

12. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. New England Journal of Medicine. 2023.

13. Blauvelt A, Thyssen JP, Guttman-Yassky E, Bieber T, Serra-Baldrich E, Simpson E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol. 2023.

14. Simpson EL, Gooderham M, Wollenberg A, Weidinger S, Armstrong A, Soung J, et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA dermatology. 2023.

15. ClinicalTrials.gov. A study of lebrikizumab in combination with topical corticosteroids in participants having atopic dermatitis (AD) that are not adequately controlled or non-eligible for cyclosporine 2023 [Available from: https://www.clinicaltrials.gov/study/NCT05149313.

16. Dermatology Times. ADvantage, ADvocate Studies Support Clinical Improvements of AD With Lebrikizumab Dermatology Times website2023 [Article reporting data presented at EADV 2023]. Available from: https://www.dermatologytimes.com/view/advantage-advocate-studies-support-clinical-improvements-of-ad-with-lebrikizumab.

17. Guttman-Yassky E, Weidinger S, Simpson E, Gooderham M, Irvine A, Spelman L, et al., editors. Efficacy and safety of lebrikizumab is maintained to two years in patients with moderate-to-severe atopic dermatitis. Oral presentation given at the Fall Clinical Dermatology Conference; 2023; Las Vegas, NV, USA.

18. Silverberg JI, Hong HC, Calimlim BM, Lee WJ, Teixeira HD, Collins EB, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis without Topical Corticosteroids: An Updated Network Meta-analysis. Dermatol Ther (Heidelb). 2023;13(10):2247-64.

19. Medicines.org.uk. Olumiant (baricitinib) 2 mg film-coated tablets (summary of product characteristics). 2022.

20. Medicines.org.uk. Rinvoq (upadacitinib) 15 mg prolonged-release tablets (Great Britain). Summary of Product Characteristics. 2023.

21. Medicines.org.uk. Cibinqo (abrocitinib) 100 mg film-coated tablets. Summary of Product Characteristics.; 2023.

22. Sangha AM. Dermatological Conditions in Skin of Color: Managing Atopic Dermatitis. J Clin Aesthet Dermatol. 2021;14(3 Suppl 1):S20-s2.

23. National Institute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe atopic dermatitis (TA534 final guidance). 2018.

24. National Institute for Health and Care Excellence (NICE). Baricitinib for treating moderate to severe atopic dermatitis (TA681 final guidance). 2021.

25. National Institute for Health and Care Excellence (NICE). Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Company Response to EAG Clarification Questions

Updated May 2024

File name	Version	Contains confidential information	Date
ID4025 Lebri Clarification response (Dec2023)_REVISED_15.3.24 [CON]	**Final**	**Yes**	**16.5.24**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Company's decision problem and the place of lebrikizumab in the clinical pathway

A1. Priority question: We understand from CS, section B.1.3.5, that the company is positioning lebrikizumab in the clinical pathway as a treatment option for patients who have had an inadequate response to, inability to tolerate, or contraindication to systemic immunosuppressants. We also note that the NICE scope specifies the systemic immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) for treating "People for whom systemic therapy is suitable and have not previously received a systemic therapy" as among the comparators of interest for this appraisal of lebrikizumab. The company's decision problem, as set out in CS, Table 1, states that the company's selected comparators are the "Same as scope", yet the immunosuppressive therapies for people in whom systemic therapy is suitable and who have not previously received systemic therapy (i.e. azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) are not considered in the network meta-analysis (NMA) or economic model. We assume that this is because the company is positioning lebrikizumab in people whose condition has not responded to at least one other systemic therapy or

in whom these are not suitable. However, please elaborate why azathioprine, ciclosporin, methotrexate and mycophenolate mofetil are not considered relevant comparators for lebrikizumab and why the company has not positioned lebrikizumab as an alternative to these.

Company response: Apologies for any confusion relating to the positioning of lebrikizumab. We can confirm that Almirall is indeed positioning lebrikizumab in the treatment pathway as a second line systemic treatment for moderate-to-severe atopic dermatitis (AD) (i.e. after the condition has not responded to at least one first line systemic treatment, or if unsuitability for first line systemic treatment). This anticipated positioning is in line with the appraisals for other currently available second line systemics, including the recent MTA (NICE TA814). For this reason, treatments such as azathioprine, ciclosporin A (CsA), methotrexate and mycophenolate mofetil are not considered direct comparators for lebrikizumab. Of note, of these, only CsA is licensed in the UK (for treatment of severe AD only); while methotrexate, azathioprine and mycophenolate mofetil are used off-label. The direct comparators for lebrikizumab are the second line systemic treatments (i.e. dupilumab, tralokinumab, abrocitinib, baricitinib and upadacitinib).

A2. Priority question: Please clarify why consideration is given in the CS and the company's decision problem (CS, Table 1) to a sub-population of patients who have either had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised, but not to sub-populations of patients who have either had an inadequate response to azathioprine, methotrexate and mycophenolate mofetil or in whom use of these immunosuppressive therapies is not medically advised. Why does consideration of this sub-population reflect "the anticipated positioning of lebrikizumab in the UK treatment pathway" (CS, Table 1)?

Company response: You are correct that first-line systemic therapy includes the immunosuppressants CsA, methotrexate, azathioprine and mycophenolate mofetil. However, of these, only CsA is licensed in the UK (for treatment of severe AD only); the others are used off-label. Furthermore, the lebrikizumab ADvantage study, which contributes to the evidence base of the submission, was a 52-week European study in adults and adolescents with moderate-to-severe AD who had failed treatment with CsA or in whom CsA was not medically advisable. Of note, other trials have also

been conducted to study the clinical effectiveness of second-line systemics in patients who have not had adequate control with, or are intolerant or contraindicated to CsA. These include ECZTRA 7 a tralokinumab in combination with TCS study, BREEZE-AD4 a baricitinib in combination with TCS study, and CAFÉ a dupilumab in combination with TCS study.

A3. Please clarify the proportions of patients with moderate-to-severe atopic dermatitis treated in clinical practice in England who have had an inadequate response to topical treatment and phototherapy and who then receive ciclosporin A and each of the other immunosuppressive therapies listed in the NICE scope (azathioprine, methotrexate and mycophenolate mofetil). Please provide appropriate references or sources to support your answer.

Company response: We have not been able to provide additional data beyond information available in past appraisals that provide some insight into the proportion of patients along the clinical pathway.

Information from the recent MTA TA814's resource impact template estimate that moderate-to-severe AD makes up 7% of the AD population and 60% of these patients would be eligible for systemic therapy.(1)

Whilst not current data, the dupilumab TA534 company submission did provide real-world data on immunosuppressant prescriptions recorded at enrollment onto the dupilumab EAMS programme (provided in the dupilumab company submission dated March 2018).(2)

Table 1: Immunosuppressant prescriptions according to dupilumab company submission (March 2018)

	Young Adults (*n*=72)	Middle-Aged Adults (*n*=68)	Older Adults (*n*=25)	Total (*n*=165)
Immunosuppressant type*				
Azathioprine	5 (6.9%)	2 (2.9%)	0	**7 (4.2%)**
Ciclosporin	11 (15.3%)	8 (11.8%)	4 (16.0%)	**23 (13.9%)**
Mycophenolate mofetil	6 (8.3%)	5 (7.4%)	3 (12.0%)	**14 (8.5%)**
Methotrexate	8 (11.1%)	16 (23.5%)	1 (4.0%)	**25 (15.2%)**
Other†	0	1 (1.5%)	0	**1 (0.6%)**
Total number of immunosuppressants prescribed				
None reported	43 (59.7%)	37 (54.4%)	18 (72.0%)	**98 (59.4%)**
One	28 (38.9%)	30 (44.1%)	6 (24.0%)	**64 (38.8%)**
Two	1 (1.4%)	1 (1.5%)	1 (4.0%)	**3 (1.8%)**

*Categories are not mutually exclusive. †"Other" = Leflunomide

Source: Dupilumab company submission, Table 2.57 (March 2018); available at https://www.nice.org.uk/guidance/ta534/documents/committee-papers (2)

Other former NICE appraisals for moderate-to-severe AD also provide further insights into prior immunosuppressant usage. During baricitinib appraisal (NICE TA681, November 2020) technical engagement, the following estimations of treatment (including immunosuppressant) usage were provided by a stakeholder.(3)

Table 2: Treatment usage captured during TA681 technical engagement

Issue 2: Comparators

Approximately what proportion of people would be offered the following treatments in routine NHS practice, following failure on the first-line systemic immunosuppressants in the tables below (due to intolerance, contraindication or inadequate disease control)? Please provide a percentage for each treatment.

Following first-line **ciclosporin**	
Dupilumab (%)	10
Azathioprine (%)	20
Methotrexate (%)	60
Mycophenolate mofetil (%)	
BSC (%)	10
Other (%)	

Following first-line **methotrexate**	
Dupilumab (%)	10
Azathioprine (%)	20
Ciclosporin (%)	60
Mycophenolate mofetil (%)	
BSC (%)	10
Other (%)	

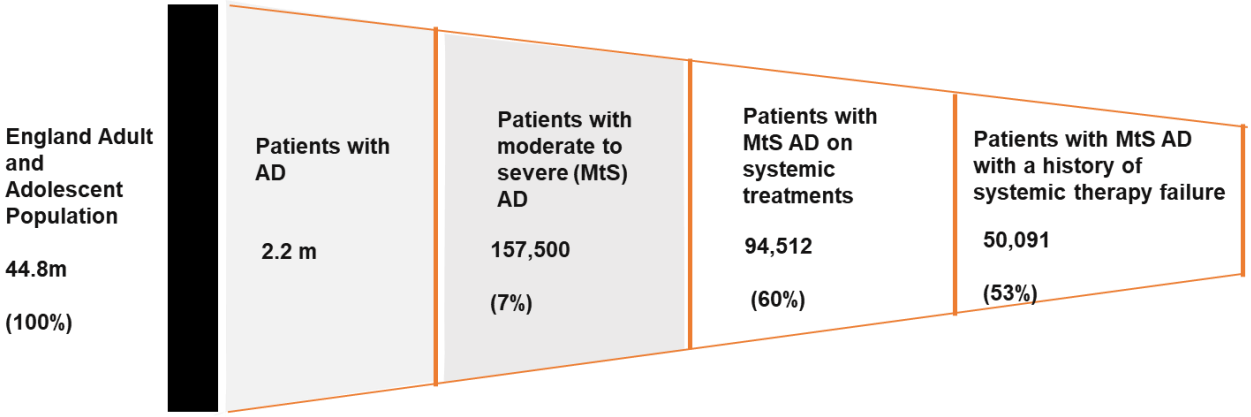
Following first-line **azathioprine**	
Dupilumab (%)	10
Ciclosporin (%)	40
Methotrexate (%)	40
Mycophenolate mofetil (%)	
BSC (%)	10
Other (%)	

Source: Baricitinib technical engagement (stakeholder response); page 525 of committee papers (uploaded to NICE website 29 January 2021); available at https://www.nice.org.uk/guidance/ta681/documents/committee-papers (3)

A4. How many and what proportion of patients with moderate-to-severe atopic dermatitis in clinical practice in England have either an inadequate response to ciclosporin A or cannot receive it as it is not medically advised? Please provide appropriate references or sources to support your answer.

Company response: The resource impact report for NICE MTA TA814 included a prediction of the number of adults and adolescents who will have moderate-to-severe AD in England in 2026/7 with estimated patient numbers and proportions in the clinical pathway.(1)

Figure 1: Predicted number of adults and adolescents in England with moderate-to-severe AD in 2026/27



Key: AD, atopic dermatitis; MtS, moderate-to-severe
Source: TA814 resource impact report (1)

The 53% proportion (n=50,091) may be a suitable estimation for patients with moderate-to-severe atopic dermatitis in England that have either an inadequate response to ciclosporin A (and other first line systemics) or cannot receive them as they are not medically advised.

Company's systematic literature review

A5. Priority question: The ADhere-J (NCT04760314) and Adopt-VA trials (NCT04626297) are included in the NMA (CS, Appendix D.1.1, Table 91), but they are not listed in CS, Document B, Table 5, as among the relevant, identified clinical effectiveness evidence. The results of these studies are also

not presented in CS, Section B.2.6. Please clarify why these studies and their results are used in the NMA, but are not otherwise presented in the CS.

Company response: The NMA was developed at the Global level, which is why ADhere-J (carried out in Japan only) and ADopt-VA (carried out in the US only) are included. Summaries of these two studies are presented below. Please note that the evidence package to support EMA marketing authorisation didn't include ADhere-J, a study which was requested by Japanese authorities and conducted solely in Japan. Regarding the ADopt-VA, it was added to the EMA package during the approval process.

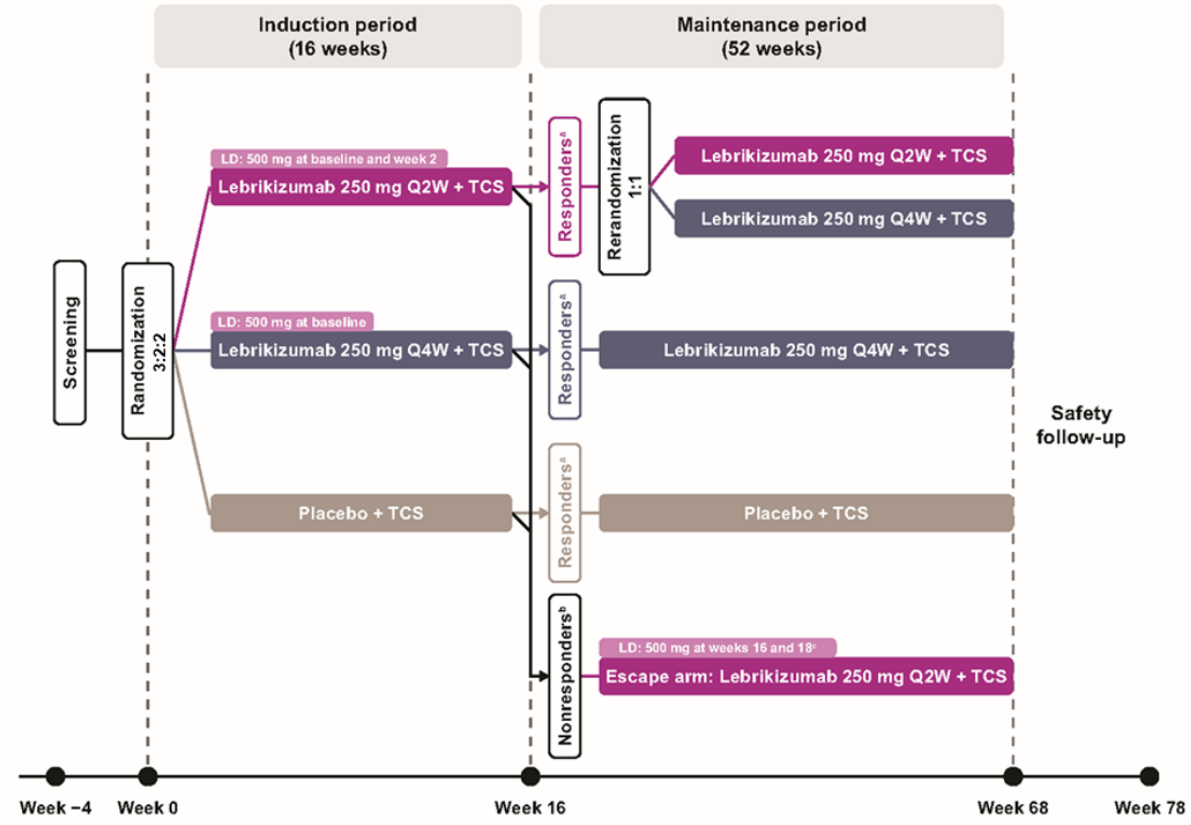
ADhere-J

Study design

ADhere-J was a randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of lebrikizumab in combination with topical corticosteroids (TCS) in Japanese patients with moderate-to-severe AD.(4-6)

The study design is shown in the figure below.

Figure 2: ADhere-J study design



[a]Responders were defined as patients who achieved IGA (0,1) and/or EASI 75 at week 16 without the use of rescue treatments. [b]Nonresponders were defined as patients who did not achieve IGA (0,1) and/or EASI 75 at week 16, and those who required high-potency topical or systemic rescue treatments during the induction period, and week 16 responders who did not maintain EASI 50 at weeks 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, and 64. For nonresponders who entered the escape arm from week 16, patients discontinued from the study if they did not achieve EASI 50 for 2 consecutive visits in the escape arm after week 32. For those who entered the escape arm after week 20, patients discontinued from the study if they did not achieve EASI 50 for 2 consecutive visits in the escape arm after 8 weeks of treatment. [c]LD of 500 mg at weeks 16 and 18 was administered only to patients who received placebo during the induction period.
Notes: All patients started on mid-potency TCS (and low-potency TCS and/or TCI for sensitive areas) ≥7 days before the baseline visit (week 0); patients could taper or stop TCS after baseline as needed based on treatment response, but not during screening.
Randomisation at Week 0 was 3:2:2 for Lebrikizumab Q2W+TCS, Lebrikizumab Q4W+TCS, and Placebo+TCS, respectively
Key: EASI 50, ≥50% improvement from baseline in Eczema Area and Severity Index; EASI 75, ≥75% improvement from baseline in Eczema Area and Severity Index; IGA (0,1), Investigator's Global Assessment score of 0 or 1; LD, loading dose; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors.
Source: ADhere-J draft manuscript (6)

The study consisted of a 16-week induction period followed by a 36-week maintenance period. At entry to the induction period, participants were randomised 3:2:2 to:

- 250 mg lebrikizumab Q2W (500 mg loading dose given at baseline and Week 2)
- 250 mg lebrikizumab Q4W (500 mg loading dose given at baseline)
- Placebo

Randomisation was stratified by age (adolescent vs adult) and disease severity (IGA 3 vs 4).

At Week 16, participants in the lebrikizumab 250 mg Q2W group who had responded to treatment (i.e. achieved an IGA score of 0 or 1 or a 75% reduction in EASI score [EASI 75]) were re-randomized 1:1 to receive 50 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W. Those who did not respond to treatment, or who used rescue therapy during the induction period were moved to an escape arm and received open-label lebrikizumab Q2W through Week 52.

Participants in the lebrikizumab Q4W group who had responded to treatment at Week 16 continued treatment at that dose level during the maintenance period; non-responders and those who had used rescue therapy during the induction period moved to the escape arm.

Participants in the placebo group who responded to treatment during the induction period continued to receive placebo during the maintenance period. Those who were non-responders or who use rescue therapy moved to the escape arm and received 250 mg lebrikizumab Q2W (with a loading dose of 500 mg lebrikizumab at Weeks 16 and 18).

A summary of the trial methods is shown in Table 3.

Table 3: Summary of trial design and methods (ADhere-J)

Study	**ADhere-J (NCT04760314)**
Study design	Phase 3, randomised, double-blind, placebo-controlled study
Location	Japan
Population	Adults and adolescents with moderate-to-severe atopic dermatitis
Intervention	Induction: Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q4W Maintenance: Lebrikizumab 250 mg Q2W Lebrikizumab 250 mg Q4W
Comparator	Placebo
Key eligibility criteria	Key inclusion criteria • Adult or adolescent (aged 12 to <18 years and weighing ≥40 kg) who is a candidate for systemic therapy • Diagnosis of chronic AD for ≥1 year before screening • Moderate-to-severe AD, defined as having all of the following at baseline: o EASI score ≥16 o IGA score ≥3 at the baseline visit o ≥10% BSA involvement • An inadequate response to existing topical medications or failure of systemic therapies Key exclusion criteria • Uncontrolled chronic disease requiring oral corticosteroids • Active chronic or acute infection • A history of immunosuppression • Known hepatitis B or C infection or test positive for hepatitis B virus or hepatitis C virus • Active or latent tuberculosis • A history of or positive HIV infection • Skin comorbidities that may interfere with study assessments • A history of malignancy • Prior or concomitant therapy not allowed • Abnormal screening laboratory tests

Primary outcomes	• Proportion of participants achieving EASI 75 at Week 16 • Proportion of participants achieving IGA (9,1) and a reduction of≥2 points from baseline to Week 16
Major secondary outcomes	• Percentage change in EASI score from baseline to Week 16 • Proportion of participants achieving EASI 90 at Week 16 • Proportion of participant with an itch NRS score of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Weeks 1, 2, 4 and 16 A full list of secondary outcomes is available at https://classic.clinicaltrials.gov/ct2/show/NCT04760314 (4)

Participants

Two hundred and eighty-six participants were randomised to treatment in the induction period: 82 to placebo, 81 to lebrikizumab Q4W and 123 to lebrikizumab Q2W. Of these, 282 completed the induction period, including 100% of participants receiving placebo, 98.8% of participants in the lebrikizumab Q4W treatment group, and 97.6% of participants in the lebrikizumab Q2W treatment group.

One hundred and fourteen participants entered the maintenance period as induction responders and were assigned to lebrikizumab Q2W or Q4W.

One hundred and sixty-eight participants entered the escape arm at Week 16 and continued treatment with lebrikizumab Q2W.

Baseline characteristics

Table 4 shows baseline demographic and disease characteristics for patients entering the induction period. Overall, these were well balanced across treatment groups.

Table 4: Baseline characteristics: ADhere-J

	PBO + TCS N = 82	LEB 250 Q4W + TCS N = 81	LEB 250 Q2W + TCS N = 123
Age (years), mean (SD)	34.8 (13.6)	37.8 (12.0)	35.5 (12.2)
Adults (≥18 years), n (%)	[redacted]	[redacted]	[redacted]
Adolescents (12-18 years), n (%)	[redacted]	[redacted]	[redacted]
Female, n (%)	24 (29.3)	25 (30.9)	41 (33.3)

Race, n (%)			
Asian	82 (100)	81 (100)	123 (100)
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]
Duration since AD onset (years), mean (SD)	[redacted]	[redacted]	[redacted]
IGA, n (%)			
3, moderate	[redacted]	[redacted]	[redacted]
4, severe	[redacted]	[redacted]	[redacted]
EASI, mean (SD)	[redacted]	[redacted]	[redacted]
Sleep-loss scale score, mean (SD)	[redacted]	[redacted]	[redacted]
Itch NRS, mean (SD)	[redacted]	[redacted]	[redacted]
DLQI, mean (SD)[a]	[redacted]	[redacted]	[redacted]
CDLQI, mean (SD)[b]	[redacted]	[redacted]	[redacted]
HADS total score, mean (SD)[c]	[redacted]	[redacted]	[redacted]
POEM, mean (SD)	[redacted]	[redacted]	[redacted]
SCORAD, mean (SD)	[redacted]	[redacted]	[redacted]

[a]DLQI scores for participants were calculated as follows: PBO, N = 77, LEB 250 mg Q4W, N = 77 LEB 250 mg Q2W, N = 116. [b]CDLQI scores for participants younger than 16 years of age were calculated as follows: PBO, N = 5, LEB 250 mg Q4W, N = 4, LEB 250 mg Q2W, N = 7. [c]HADS scores for adolescents were calculated as follows: PBO, N = 82, LEB 250 mg Q4W, N = 81, LEB 250 mg Q2W, N = 123

Key: AD, atopic dermatitis; BMI, body mass index; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, hospital anxiety depression scale; IGA, Investigator's global assessment; ITT, intent to treat; LEB, lebrikizumab; PBO, placebo; POEM, Patient Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; TCS, topical corticosteroid.

Source: Clinical Trials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04760314); ADhere-J clinical study report

Efficacy results – induction period

Table 5 summarises the key efficacy results for the induction period.

Table 5: Key efficacy results: induction period (ADhere-J)

Endpoint		PBO + TCS N = 82	LEB 250 Q4W + TCS N = 81	LEB 250 Q2W + TCS N = 123
Primary				
EASI 75 at Week 16	Response, n (%)	11 (13.4)	38 (47.2)	63 (51.2)
	P-value vs placebo	NA	<0.001	<0.001
IGA (0,1) at Week 16	Response, n (%)	5 (6.1)	24 (29.1)	41 (33.4)
	P-value vs placebo	NA	<0.001	<0.001
Major secondary				
EASI 90 at Week 16	Response, n (%)	8 (9.8)	23 (28.4)	42 (34.3)
	P-value vs placebo	NA	0.003	<0.001
% change in EASI from baseline	LSM (SE)	-25.3 (4.8)	-59.7 (4.9)	-64.2 (4.4)
	P-value vs placebo	NA	<0.001	<0.001
		PBO + TCS N = 60	**LEB 250 Q4W + TCS N = 59**	**LEB 250 Q2W + TCS N = 80**
Itch NRS ≥4-point reduction from baseline to Week 1[a]	Response, n (%)	[redacted]	[redacted]	[redacted]
	P-value vs placebo	[redacted]	[redacted]	[redacted]
Itch NRS ≥4-point reduction from baseline to Week 2[a]	Response, n (%)	0	1 (1.7)	3 (3.8)
	P-value vs placebo	NA	0.294	0.138
Itch NRS ≥4-point reduction from baseline to Week 4[a]	Response, n (%)	0	5 (8.5)	13 (16.3)
	P-value vs placebo	NA	0.013	0.001
Itch NRS ≥4-point reduction from baseline to Week 16[a]	Response, n (%)	2 (3.3)	14 (23.8)	26 (32.7)
	P-value vs placebo	NA	0.001	<0.001

Missing data were imputed using Markov Chain Monte Carlo multiple imputation
[a]In participants who had an itch NRS score ≥4 points at baseline
Key: EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; EASI 90 = 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least

squares mean; NA = not applicable; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error, TCS = topical corticosteroid.
Source: Clinical Trials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04760314); ADhere-J clinical study report.

Efficacy results - maintenance period

Table 6 summarises the key efficacy results for the maintenance period. Data are presented for the maintenance primary population (i.e. participants who had responded to lebrikizumab during the induction period and received at least one dose of study drug during the maintenance period).

Table 6: Key efficacy results: maintenance period (ADhere-J)

Endpoint		LEB 250 Q4W Res/LEB 250 Q4W + TCS	LEB 250 Q2W Res/LEB 250 Q4W + TCS	LEB 250 Q2W Res/LEB 250 Q2W + TCS
EASI 75 at Week 52 Response, n (%)	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]
IGA (0,1) at Week 16 Response, n (%)	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]
EASI 90 at Week 16 Response, n (%)	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]
% change in EASI from baseline Mean (SE)	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]
Itch NRS ≥4-point reduction from baseline to Week 52[a]	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]

% change in itch NRS score from baseline to Week 52	N	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]

Missing data were imputed using Markov Chain Monte Carlo multiple imputation
[a]In participants who had an itch NRS score ≥4 points at baseline
Key: EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; EASI 90 = 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least squares mean; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error, TCS = topical corticosteroid.
Source: ADhere-J clinical study report.

Safety

Table 7 gives an overview of adverse events (AEs) during the induction period. The proportion of participants who reported treatment-emergent adverse events (TEAEs) in the placebo treatment group and lebrikizumab Q4W treatment group was similar, but was higher in the lebrikizumab Q2W treatment group.

Table 7: Overview of AEs: induction period (ADhere-J)

	Number (%) of participants		
	PBO + TCS N = 82	LEB 250 Q4W + TCS N = 81	LEB 250 Q2W + TCS N = 123
Any TEAE	52 (63.4)	49 (60.5)	93 (75.6)
TEAEs by severity[a]			
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Deaths	0	0	0
SAEs	2 (2.4)	0	1 (0.8)
Treatment-related TEAEs[b]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]

Data are presented for the safety population. [a]Participants with multiple events with different severities were counted under the highest severity. [b]Relatedness as assessed by the investigator
Key: AE = adverse event; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.
Source: Clinical Trials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04760314); ADhere-J clinical study report.

Numerically higher frequencies of events were reported in the lebrikizumab treatment groups for several preferred terms, including conjunctivitis allergic, conjunctivitis, nasopharyngitis, and myalgia. Events in the conjunctivitis cluster were reported more frequently in the lebrikizumab treatment groups compared with placebo. No other clinically meaningful differences in the frequency of TEAEs were reported between lebrikizumab-treated participants and placebo participants.

Table 8 shows an overview of the AEs during the maintenance period.

Table 8: Overview of AEs: maintenance period (ADhere-J)

	Number (%) of participants		
	LEB 250 Q4W Res/LEB 250 Q4W + TCS N = 38	**LEB 250 Q2W Res/LEB 250 Q4W + TCS N = 33**	**LEB 250 Q2W Res/LEB 250 Q2W + TCS N = 32**
Any TEAE	30 (78.9)	22 (66.7)	28 (87.5)
TEAEs by severity[a]			
Mild	20 (52.6)	18 (54.5)	18 (56.3)
Moderate	9 (23.7)	4 (12.1)	10 (31.3)
Severe	1 (2.6)	0	0
Deaths	0	0	0
SAEs	1 (2.6)	0	1 (3.1)
Treatment-related TEAEs[b]	8 (21.1)	9 (27.3)	9 (28.1)
AEs leading to discontinuation	0	0	0

Data are presented for the safety population. [a]Participants with multiple events with different severities were counted under the highest severity. [b]Relatedness as assessed by the investigator
Key: AE = adverse event; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.
Source: Clinical Trials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04760314); ADhere-J clinical study report.

The most common TEAEs reported during the maintenance period were pyrexia, acne, allergic conjunctivitis and headache, which were each reported by 9.7% or more of the total population.

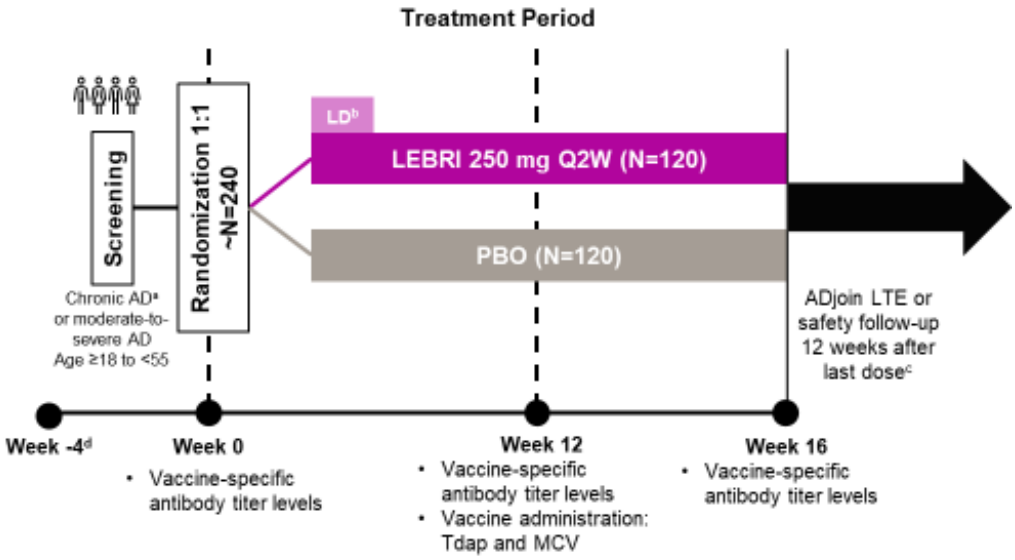
Further details of the safety results from ADhere-J are available at https://classic.clinicaltrials.gov/ct2/show/NCT04760314 (4) and in the clinical study report (which is supplied alongside the company responses).(5)

ADopt-VA

Study design

ADopt-VA was a randomised, double-blind, placebo-controlled 16-week study to evaluate the impact of lebrikizumab on vaccine responses in adult patients (aged 18 to 55 years) with moderate-to-severe AD. (7, 8) The study also addressed the efficacy and tolerability of lebrikizumab in this population. The study was carried out in the US only. The study design is shown in the figure below.

Figure 3: ADopt-VA study design



[a]According to American Academy of Dermatology Consensus Criteria. [b]500 mg loading dose was administered at Week 0 and Week 2. [c]Patients completing ADopt-VA were offered open-label treatment in ADjoin. [d]≤30-day screening period.
Source: ADopt-VA CSR.

Following screening, participants were randomised 1:1 to:

- 250 mg lebrikizumab Q2W (500 mg loading dose given at baseline and Week 2)
- Placebo

At Week 12, after pre-dose vaccine titres had been withdrawn, those participants who were still receiving lebrikizumab were given one dose of each of the following commercially-available vaccines:

- Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Tdap)
- Meningococcal (Groups A, C, Y and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine (MCV)

The co-primary endpoints of the study were:

- The percentage of participants who developed a booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine (i.e. at Week 16)

- The percentage of participants who had a positive antibody response to meningococcus C antigen of the MCV 4 weeks after the administration of the vaccine (i.e. at Week 16)

A summary of the trial design and methods is shown in Table 9.

Table 9: Summary of trial design and methods: ADopt-VA

Study	ADopt-VA (NCT04626297)
Study design	Phase 3, randomised, double-blind, placebo-controlled study
Location	US
Population	Adults (aged 18 to 55 years) with moderate-to-severe atopic dermatitis
Intervention	Lebrikizumab 250 mg Q2W
Comparator	Placebo

Key eligibility criteria	Key inclusion criteria
	• Adult (aged 18 to 55 years)
	• Diagnosis of chronic AD for ≥1 year before screening
	• Moderate-to-severe AD, defined as having all of the following at baseline:
	  ○ EASI score ≥16
	  ○ IGA score ≥3 at the baseline visit
	  ○ ≥10% BSA involvement
	• An inadequate response to existing topical medications or a determination that topical treatments are otherwise medically inadvisable
	• Had not received a tetanus-containing vaccine in the 5 years before randomisation
	• Had never received a meningococcal conjugate vaccine or had received no more than one prior MCV dose at least 4 years before randomisation, of a vaccine containing one or more meningococcal serogroups
	Key exclusion criteria
	• Treatment with the following before the baseline visit:
	  ○ TCS, calcineurin inhibitors or phosphodiesterase-4 inhibitors, such as crisabole, within 1 week
	  ○ Immunosuppressive/immunomodulating drugs within 4 weeks
	  ○ Phototherapy and photochemotherapy for AD within 4 weeks
	  ○ An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer
	  ○ B-cell-depleting biologics, including rituximab, within 6 months
	  ○ Other biologics within 5 half-lives (if known) or 8 weeks whichever is longer
	• Receiving a BCG vaccination or treatment within 12 months of screening, or treatment with a live (attenuated) vaccine within 12 weeks of the baseline visit or planned during the study
	• Contra-indication to the Tdap vaccine or MCV

Primary outcomes	• Develop a booster response to tetanus toxoid 4 weeks after administration of the Tdap vaccine

	• Have a positive antibody response to the meningococcus C antigen of the MCV 4 weeks after administration of the vaccine
Secondary outcomes	• Percentage of participants at Week 16: ○ with an IGA score of 0 or 1 and a reduction of ≥2 points from baseline ○ achieving EASI 75 ○ achieving EASI 90 ○ achieving a ≥4-point improvement form baseline in itch NRS score (participants who had itch NRS score ≥4 at baseline) • Percentage change from baseline to Week 16 in: ○ EASI ○ Itch NRS • Change from baseline to Week 16 in: ○ BSA ○ Sleep-loss scale

Source: Clinical Trials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04626297) (7)

Participants

Two hundred and fifty-four participants were randomised to treatment. However, following an audit, data from participant at two sites were excluded, resulting in in modified intention to treat population of 247 patients (122 in the placebo group and 125 in the lebrikizumab 250 Q2W. Of these, 202 completed the study: 89 (73%) in the placebo group and 113 (90.4%) in the lebrikizumab group. The higher frequency of withdrawal seen in the placebo group was driven mainly by participant who could no longer participate owing to schedule conflicts (work or personal reasons), moving out of the area, or were lost to follow-up.

Baseline characteristics

Table 10 shows participants' baseline demographic and disease characteristics. Overall, these were well balanced across treatment groups.

Table 10: Baseline characteristics: Adopt-VA

	PBO N = 122	LEB 250 Q2W N = 125
Age (years), mean (SD)	[redacted]	[redacted]
Adults (≥18 years), n[a] (%)	[redacted]	[redacted]
Adolescents (12-18 years), n[a] (%)	[redacted]	[redacted]
Female, n[a] (%)	[redacted]	[redacted]
Race, n[a] (%)		

	PBO N = 122	LEB 250 Q2W N = 125
American Indian or Alaska Native	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
White	[redacted]	[redacted]
Multiple	[redacted]	[redacted]
Other	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]
Duration since AD onset (years), mean (SD)	[redacted]	[redacted]
IGA, n (%)		
3, moderate	[redacted]	[redacted]
4, severe	[redacted]	[redacted]
EASI, mean (SD)	[redacted]	[redacted]
Sleep-loss scale score, mean (SD)	[redacted]	[redacted]
Itch NRS, mean (SD)	[redacted]	[redacted]
Skin pain NRS, mean (SD)[c]	[redacted]	[redacted]
POEM, mean (SD)	[redacted]	[redacted]

Data are shown for the modified intention to treat population. [a]Number of participant with non-missing data used as denominator. [b]Full date of birth not collected, only month and year. Calculated age of participant was 17 years old; however the participant was 18 years old when the ICF was signed
Key: AD = atopic dermatitis; ICF = informed consent form; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation.
Source: Adopt-VA clinical study report (8)

Efficacy results

Table 11 summarises the key efficacy results. Both primary endpoints were met.

Table 11: Key efficacy results: ADopt-VA

Endpoint		PBO	LEB 250 Q2W
Primary		**N = 81**	**N = 107**
Booster response to tetanus toxoid 4 weeks after administration of the Tdap vaccine (at Week 16)	Response, n/Nx (%) Difference (90% CI) vs placebo	53/79 (73.4) N/A	78/106 (73.6) 0.3 (-10.2, 11.2)
Positive antibody response to meningococcus C antigen of the MCV 4 weeks after administration of the vaccine (at Week 16)	Response, n/Nx (%) P-value vs placebo	60/80 (75.0) NA	86/99 (86.9) 12.2 (2.5, 22.0)
Secondary		**N = 122**	**N = 125**
IGA (0,1) and a reduction of ≥2 points from baseline at Week 16	Response, n (%) P-value vs placebo	23 (18.9) NA	51 (40.6) <0.001
EASI 75 at Week 16	Response, n (%) P-value vs placebo	40 (32.7) N/A	72 (58.0) <0.001
EASI 90 at Week 16	Response, n (%) P-value vs placebo	23 (18.9) N/A	49 (39.2) <0.001
% change in EASI from baseline to Week 16	LSM (SE) P-value vs placebo	-47.11 (4.347) N/A	-72.51 (3.813) <0.0001
Itch NRS ≥4-point reduction from baseline to Week 16[a]	Response, n/Nx (%) P-value vs placebo	31/93 (33.2) N/A	49/95 (51.7) 0.014
% change in itch NRS from baseline to Week 16	LSM (SE) P-value vs placebo	[redacted] [redacted]	[redacted] [redacted]
Change in BSA from baseline to Week 16	Nx LSM (SE) P-value vs placebo	85 -19.34 (1.882) N/A	110 -27.55 (1.719) <0.001
Change in Sleep-Loss Scale from baseline to Week 16	LSM (SE) P-value vs placebo	-0.87 (0.122) N/A	-1.35 (0.107) <0.05

Data are shown for the modified intention to treat population.
Key: AD = atopic dermatitis; ANCOVA = analysis of covariance; BSA = body surface area; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; EASI 90 = 90% reduction in EASI; IGA = Investigator's Global Assessment for AD; LEB = lebrikizumab; LSM = least squares mean; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); MMRM = mixed model for repeated measures; N = number of participants in the analysis population; n = number of participants in the specified group; NA = not applicable; NRI = participants who received topical or systemic rescue medication, withdrew from the study due to lack of efficacy, or any other missing values were set to non-response subsequent to this time through Week 16; NRS = numeric rating scale; Nx= number of participants with non-missing values; PBO = placebo; Q2W = every 2 weeks; SE = standard error; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).
Source: ClinicalTrials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04626297); ADopt-VA clinical study report

Safety results

Table 12 gives an overview of TEAEs in ADopt-VA. The incidence of TEAEs was higher in the lebrikizumab group than in the placebo group. Most TEAEs were mild or moderate in severity. The most common TEAEs included COVID-19, nasopharyngitis, headache, AD and conjunctivitis.

Table 12: Overview of TEAEs: ADopt-VA

	Number (%) of participants	
	PBO N = 122	LEB 250 Q2W N = 125
Any TEAE	42 (34.4)	48 (38.4)
Deaths	0	0
SAEs	1 (0.8)	1 (0.8)
Treatment-related TEAEs[b]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]

Data are presented for the modified safety population
Key: AE = adverse event; LEB = lebrikizumab; PBO = placebo; Q2W = every 2 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: ClinicalTrials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04626297); ADopt-VA clinical study report

Further details of the safety results are available from ClinicalTrials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT04626297) and the ADopt-VA clinical study report (which is supplied alongside the company responses).(8)

A6. Priority question: We are aware of the single-arm ADore study of lebrikizumab. Have any other single arm, observational or non-RCT studies of lebrikizumab been conducted? If so, please provide details, including trial registration number and the study population, intervention arms (i.e. doses of lebrikizumab assessed), comparator(s), outcomes and specific design. Please also provide reports (e.g. clinical study reports, journal publications etc) of the studies' results and summarise the EASI75 and EASI 50 + DLQI ≥4-point improvement composite results, where available, for each study.

Company response: ADore is the only single-arm study in the current data package.

For your information, a Phase 3b single-arm study (ADhope; NCT05990725) is due to start in the near future. This open-label study is designed to evaluate the effectiveness and safety of lebrikizumab over 24 weeks of treatment in adults and adolescents with moderate-to-severe atopic dermatitis. It is planned to enrol approximately 240 participants. Participants will receive lebrikizumab 250 mg Q2W up to Week 16, followed by lebrikizumab 250 mg Q4W up to Week 24. The study is expected to complete in May 2025. Details of the study are available at ClinicalTrials.gov website: https://classic.clinicaltrials.gov/ct2/show/NCT05990725 (9)

Lebrikizumab trials

A7. CS, Section B.2.2, states that maintenance period data are not yet available for the ADvantage study. Please clarify when the company expect these data to become available.

Company response: The last participant completed the ADvantage study on 5th October 2023. It is expected that the results will read out on 4th January 2024, with a clinical study report planned for April 2024.

A8. Priority question: CS, section B.2.2, states data in the CS from the ADjoin trial are based on an interim analysis. The clinical study report for the ADjoin trial included in the CS states that the analyses presented within it are based on a database lock date of [redacted]. Please confirm whether or not the data

presented in the CS from this study are from the [redacted] database lock (this is unclear to us from the text in the CS). Please also confirm whether or not any further interim analyses of the ADjoin trial data have been carried out since this date. If more up-to-date results are available, please provide these.

Company response: We can confirm that 6th July 2022 was the cut-off date for data which formed the interim analyses that are reported in the ADjoin CSR (provided in the submission reference pack as "Eli Lilly 2022_CSR report_ADjoin_Sept2022"). However, the company submission reports efficacy results (in CS section B.2.6.4) and safety results (in CS section B.2.10.5) from a more recent analysis (based on 14th April 2023 cut-off date data) that was presented by Guttman-Yassky *et al*. at the recent Fall Clinical Dermatology Conference (October 2023).(10) Please note that the ADjoin study has an expected completion date of September 2024 and final results are expected in Q3 2024.

A9. Please clarify whether or not the participants in the escape arm of the ADvocate 1 and 2 trials who did not achieve EASI 50 after 8 weeks were eligible for the ADjoin LTE (CS, section B.2.3.1).

Company response: Only participants who completed ADvocate 1 and 2 were eligible to enter ADjoin. Participants in the escape arm who did not achieve EASI 50 after 8 weeks were discontinued from the study and were therefore not eligible to enter ADjoin.

A10. CS, Tables 6 and 8, suggest that there were no UK trial centres or patients that took part in the ADvocate 1 and 2, ADhere and ADjoin trials. Please confirm if this was the case.

Company response: We confirm that there were no UK centres or participants in ADvocate 1, ADvocate 2 or ADhere.

A11. Please clarify how many UK centres and participants took part in the ADvantage trial (CS, Table 7).

Company response: Four UK centres (in Poole, Manchester, Southampton and Glasgow) took part in ADvantage, with a total of 10 participants.

A12. Please explain why participants were not eligible for the ADvocate 1 and 2 and ADhere trials if they had received previous treatment with dupilumab or tralokinumab (CS, Table 6). (Please note that there is an inconsistency in CS, Table 6, suggesting that all the key exclusion criteria mentioned for the ADvocate 1 and 2 trials – such as previous treatment with dupilumab or tralokinumab – also apply to the ADhere trial, but then an additional criterion for the ADhere trial is stated to be "Treatment with dupilumab in the last 8 weeks".)

Company response: It is common in pivotal (i.e. regulatory) Phase 3 trials to exclude patients with prior exposure to other drugs with a similar mechanism of action. This is done to avoid prior exposure to such drugs potentially affecting the results of a study. For this reason, patients with prior exposure to dupilumab or tralokinumab were excluded from the ADvocate 1 and ADvocate 2 trials.

We thank the EAG for highlighting the inconsistency in the ADhere exclusion criteria. Please find below an updated table listing the key eligibility criteria for the ADvocate studies and ADhere.

Table 13: Key eligibility criteria in the pivotal lebrikizumab trials

ADvocate 1	ADvocate 2	ADhere

Key inclusion 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
• Moderate-to-severe AD, 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
• Candidate for systemic therapy
		Key inclusion criteria:
		As for ADvocate 1 and 2
		
		Key exclusion criteria:
		• Previous participation in a lebrikizumab study
		• Treatment with TCS, calcineurin inhibitors or phosphodiesterase-4

Key exclusion criteria: • Previous enrolment in a lebrikizumab study • Previous treatment with dupilumab or tralokinumab • Treatment with TCS, calcineurin inhibitors or phosphodiesterase-4 inhibitors in the 7 days before the baseline visit • Treatment with immunosuppressants or immunomodulators in the 4 weeks before the baseline visit • Treatment with phototherapy or photochemotherapy in the 4 weeks before the baseline visit • Administration of an investigational drug in the last 8 weeks or within 5 half-lives (whichever is longer) • Treatment with B cell-depleting biologics in the last 6 months or other biologics within the last 16 weeks or 5 half-lives (whichever is longer) • Presence of skin comorbidities that may interfere with study assessments • Uncontrolled chronic disease that may require bursts of oral corticosteroids	inhibitors in the 7 days before the baseline visit • Treatment with immunosuppressants or immunomodulators in the 4 weeks before the baseline visit • Treatment with phototherapy or photochemotherapy in the 4 weeks before the baseline visit • Administration of an investigational drug in the last 8 weeks or within 5 half-lives (whichever is longer) • Treatment with B cell-depleting biologics in the last 6 months or other biologics within the last 16 weeks or 5 half-lives (whichever is longer) • Treatment with dupilumab in the last 8 weeks • Presence of skin comorbidities that may interfere with study assessments • Uncontrolled chronic disease that may require bursts of oral corticosteroids • Having had an important side effect to TCS, such as: o intolerance to treatment o hypersensitivity reactions o significant atrophy o systemic effects

Key: AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; TCS, topical corticosteroids

A13. What was the rationale for stratifying randomisation by dupilumab use in the ADvantage trial (CS, section B.2.3.1)?

Company response: The main objective of the ADvantage study was to study efficacy and safety of lebrikizumab in the population of patients who have failed prior CsA therapy or who were inadequate responders or not eligible for CsA.

However, dupilumab was (and still is) an available biological treatment. The company wanted to assess the response to lebrikizumab in both biological-naïve patients and biological prior-exposed patients like dupilumab use and, for this reason, the ADvantage trial stratified randomisation by dupilumab use.

A14. CS, section B.2.3, states that participants in Germany in the ADvantage study "could enter an extension period at the end of the study during which they received lebrikizumab Q4W for a minimum of 6 months". Please clarify why only participants in Germany could enter this.

Company response: Germany is one of the largest European healthcare systems. The company had the willingness to generate longer-term data in patients with prior CsA use or who were inadequate responders or not eligible for CsA; and with limited resources it was decided to invest in extending the ADvantage study in Germany only.

A15. To be eligible for the ADvocate 1 and 2 trials and the ADhere trial, participants needed to have a diagnosis of chronic AD defined by the AAD Consensus Criteria (CS, Table 6), and in the ADvantage trial this was defined by the Hanifin and Rajka Criteria (CS, Table 7). Please provide a reference for the Hanifin and Rajka criteria and clarify how reflective each of these sets of criteria are of those used to diagnose chronic AD in clinical practice in England.

Company response: The reference for the Hanifin and Rajka criteria is: Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1980:92:44-7, which is available at: https://www.medicaljournals.se/acta/content_files/files/pdf/60/92/924447.pdf (11)

Over the years, several sets of criteria have been developed to assist with the diagnosis of AD. The Hanifin-Rajka criteria are considered the gold standard for AD diagnosis, one of the earliest and more recognised sets of diagnostic criteria. The United Kingdom Working Party criteria are an abridged version of the Hanifin-Rajka criteria. The American Academy of Dermatology Consensus Criteria are also a streamlined version of the Hanifin-Rajka criteria.(12, 13) Both the Hanifin-Rajka and the AAD Consensus are therefore reflective of the criteria used in clinical practice in England

A16. Please clarify why the 'Addendum 1.1: Lebrikizumab open label 250 mg (US only)" group in the ADjoin study is not discussed further in the submission (CS, Figure 6).

Company response: This US only group was '*de novo'*: the participants had not previously taken part in one of the parent lebrikizumab trials, but otherwise met the eligibility criteria for the ADjoin study. The group was included in the study to allow collection of additional safety data. It is not discussed further in the submission because these *de novo* participants are not applicable to main analyses of the trial, and therefore we included only those participants who rolled over from the pivotal studies, ADvocate 1 & 2 or ADhere.

A17. Please clarify the number of participants enrolled in the ADjoin study who came from each of the ADore and Adapt-VA parent studies (CS, Table 8).

Company response: We can confirm that 149 patients from ADore enrolled in the ADjoin study. We can also confirm that ADopt-VA was still ongoing when the ADjoin trial cut off date for the interim CSR occurred and therefore no ADopt-VA participants were included in the ADjoin interim CSR.

We also want to point out that the trial name should be "ADopt-VA" and not "Adapt-VA" as stated by the EAG in Question A17 which could have been simply a typographical error.

A18. Priority question: Please provide the race or ethnicity baseline characteristics of the patients in each arm of the ADjoin LTE (number of participants and percentage, according to each race or ethnicity category). These data are not presented in CS, Table 12.

Company response: The baseline characteristics for race and ethnicity of the patients in each arm of the ADjoin LTE are as follows:

Table 14: Baseline characteristics: ADjoin LTE (race and ethnicity)

	ADvocate 1 & 2 → ADjoin		ADhere → ADjoin	
	LEB 250 Q4W (N = 99)	LEB 250 Q2W (N = 82)	LEB 250 Q4W (N = 29)	LEB 250 Q2W (N = 57)
Race, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]
Non-Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Key: Q2W = every two weeks; Q4W = every four weeks; SD = standard deviation
Source: Data on File 2023: ADjoin baseline characteristics (race and ethnicity) (14)

A19. Please clarify why in CS, Table 5, the ADvocate 1 and 2 maintenance comparator of placebo is referred in brackets to "lebrikizumab withdrawal". The EAG found this confusing, as it appears from CS, Figure 3, that responders to either lebrikizumab or placebo induction treatment could be re-randomised to either of the lebrikizumab maintenance arms or to maintenance placebo. Therefore, if our interpretation of CS, Figure 3, is correct, not all of

the participants receiving maintenance placebo would be withdrawing from lebrikizumab, unless there were no responders to induction placebo.

Company response: We apologise for any confusion caused. The EAG is correct in its interpretation of Figure 3, i.e. that not all of the participants receiving maintenance placebo would be withdrawing from lebrikizumab. As described in Section B.2.6.1 of the CS, the submission focuses on the 'maintenance primary population' of these studies, i.e. participants who responded to treatment with lebrikizumab during the induction period and were re-randomised at Week 16 to lebrikizumab Q2W, lebrikizumab Q4W or placebo. This is why the maintenance comparator of placebo has been referred to as 'lebrikizumab withdrawal' in Table 5.

Lebrikizumab trials' results

A20. Priority question: Regarding CS, Figure 8, which shows the maintenance of EASI 75 through to Week 52 in the pooled ADvocate study populations, please provide the corresponding results for participants who were responders to induction placebo.

Company response: As requested, we are able to provide the EAG with the EASI 75 results for the induction placebo responder patients out to Week 52. Participants who responded to placebo during the induction period were included in the maintenance secondary population (MSP). In ADvocate 1 & 2, 46 participants responded to placebo during the induction period and were re-randomised as follows: lebrikizumab 250 Q2W n = 20; lebrikizumab 250 Q4W n = 18; placebo n = 8. As can be seen from the figure below, the number of participants in the MSP out to Week 52 is very small, which limits interpretation of the data.

Figure 4: Maintenance EASI75 responders (Observed cases) by Week. ADvocate pooled, MSP

Key: Q2W = every two weeks; Q4W = every four weeks
Source: unpublished company analyses based on ADvocate 1 and ADvocate 2 findings. (15)

Note that in the company submission, data are presented for the maintenance primary population (i.e. those who responded to lebrikizumab during the induction period).

A21. Please state the number of patients with EASI 75 missing data for each of the trials and trial arms shown in CS, Tables 18 and 35.

Company response: The number of participants with EASI 75 missing data at Week 16 are shown in the tables below.

Table 15: Number of participants with EASI 75 missing data at Week 16: pivotal studies

	ADvocate 1		ADvocate 2		ADhere	
EASI 75 Week 16	**PBO (n = 141)**	**LEB 250 Q2W (n = 283)**	**PBO (n = 146)**	**LEB 250 Q2W (n = 281)**	**PBO + TCS (n = 66)**	**LEB + TCS (n = 145)**
Number of participants with missing data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADvocate 1 clinical study report (Table KGAB.8.23); ADvocate 2 clinical study report (Table KGAC.8.24); ADhere clinical study report (Table KGAD 8.13) (16-18)

Table 16: Number of participants with EASI 75 missing data at Week 16: ADvantage

	ADvantage	
EASI 75 Week 16	**PBO + TCS (N = 111)**	**LEB 250 Q2W + TCS (N = 220)**
Number of participants with missing data	[redacted]	[redacted]

Source: ADvantage clinical study report – final CSR dated 19 October 2023 (Table 14.2.1.1.1) (19)
Note: at the time of submission, an interim ADvantage CSR report was provided. The final ADvantage CSR is now provided alongside this company response

A22. Please state the number of patients with DLQI ≥4-point improvement missing data for each of the trials and trial arms shown in CS, Table 25, and for the interim analysis of the ADvantage trial.

Company response: The number of participants with DLQI ≥4-point improvement missing data at Week 16 are shown in the tables below.

Table 17: Number of participants with DLQI ≥4-point improvement missing data at Week 16: pivotal studies

	ADvocate 1		ADvocate 2		ADhere	
DLQI ≥4-point improvement Week 16	**PBO (n = 116)**	**LEB 250 Q2W (n = 226)**	**PBO (n = 115)**	**LEB 250 Q2W (n = 215)**	**PBO + TCS (n = 48)**	**LEB + TCS (n = 105)**
Number of participants with missing data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADvocate 1 clinical study report (Table KGAB.8.28); ADvocate 2 clinical study report (Table KGAC.8.30); ADhere clinical study report (Table KGAD 8.21) (16-18)

Table 18: Number of participants with DLQI 4-point improvement missing data at Week 16: ADvantage

	ADvantage	
DLQI ≥4-point improvement Week 16	**PBO + TCS (N = 90)**	**LEB 250 Q2W + TCS (N = 180)**
Number of participants with missing data	[redacted]	[redacted]

Source: ADvantage clinical study report – final CSR dated 19 October 2023 (Table 14.2.3.1.1) (19)
Note: at the time of submission, an interim ADvantage CSR report was provided. The final ADvantage CSR is now provided alongside this company response

A23. Please state the number of patients with EQ-5D-5L missing data for each of the trials and trial arms show in CS, Tables 30 and 31.

Company response: The number of participants with EQ-5D-5L missing data at Week 16 are shown in the table below.

Table 19: Number of participants with EQ-5D-5L missing data at Week 16: pivotal studies

	ADvocate 1		ADvocate 2		ADhere	
Change from baseline in EQ-5D-5L VAS and Health State Index (UK) scores	**PBO (n = 141)**	**LEB 250 Q2W (n = 282)**	**PBO (n = 145)**	**LEB 250 Q2W (n = 277)**	**PBO + TCS (n = 66)**	**LEB + TCS (n = 145)**
Number of participants with missing data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ADvocate 1 clinical study report (Table KGAB.8.55); ADvocate 2 clinical study report (Table KGAC.8.56); ADhere clinical study report (Table KGAD 8.33) (16-18)

A24. Priority question: CS, Section B.2.7.2, and CS, Appendix E. Please provide full numerical data for the post-hoc subgroup analyses of the composite endpoint (EASI 50 + (C)DLQI ≥4-point improvement) for all the lebrikizumab trials, for all the trial arms, for both the whole trial populations and the adult and adolescent subgroups at Week 16 and Week 52. Full data are not currently presented in the CS.

Company response: Data for the post-hoc subgroup analyses of the composite endpoint (EASI 50 + (C)DLQI ≥4-point improvement) are shown below for the lebrikizumab pivotal studies. We have presented data for the adult and adolescent subgroups in the pooled ADvocate 1 & 2 studies, ADhere and ADvantage. We have not provided data for the whole trial populations as this would mean mixing data collected using the DLQI (used in adults) and the CDLQI (used in adolescents). This would not be appropriate as the questionnaires contain different questions specific to the age group for which they are designed. It is also important to note that while the minimal clinically important difference is 4 points for DLQI (which correlates with the

≥4-point improvement in the composite endpoint), it is 6 points for the CDLQI (20) (21)

Please note that data from the pivotal studies and ADvantage are provided, thus, ADhere-J (Japan study) and ADopt (US study) are not included in these analyses. Furthermore EASI 50 and (C)DLQI ≥4-point improvement were not outcomes of the ADopt-VA studies.

Table 20: EASI50 and (c)DLQI ≥ 4-point improvement at Week 16 (n/N, %)

	Adults (≥ 18 y.o.) EASI 50 + DLQI ≥4-point improvement		**Adolescents** (>12 to <18 y.o.) EASI 50 + CDLQI ≥4-point improvement	
	Pbo	**Lebri 250mg Q2W**	**Pbo**	**Lebri 250mg Q2W**
ADvocate 1&2 pooled [1]	[redacted]	[redacted]	[redacted]	[redacted]
ADhere	[redacted]	[redacted]	[redacted]	[redacted]
ADvantage	[redacted]	[redacted]	[redacted]	[redacted]

***NOTE**: ADvocate 1 & 2 (pooled), mITT population. ADhere mITT population. ADvantage FAS population. Adults (≥ 18 y.o.) and adolescents (>12 to <18 y.o.). In the trials, adolescents aged 16 to 18 years should have completed the DLQI; however some completed the CDLQI. Here we report adolescents who completed CDLQI only. Non-Responder Imputation.*
***Key**: EASI= Eczema Area and Severity Index; (c)DLQI= (children's) Dermatology Life Quality Index; Lebri= Lebrikizumab; mITT= modified intended to treat population, N= number of patients in the analysis population; n = number of patients in the specified category; Pbo= placebo; Q2W= every two weeks; Q4W= every four weeks; y.o.= years old.*
Analyses restricted to patients with (c)DLQI score ≥ 4 points at Baseline. [1] There are 649 out of 749 adult patients with DLQI score ≥ 4 points at Baseline. There are 72 out of 102 adolescent patients with cDLQI score ≥ 4 points at Baseline.

Table 21: EASI50 and (c)DLQI ≥ 4-point improvement at Week 52 (n/N, %)

	Adults (≥ 18 y.o.) EASI 50 + DLQI ≥4-point improvement			**Adolescents** (>12 to <18 y.o.) EASI 50 + CDLQI ≥4-point improvement		
	Pbo	**Lebri 250mg Q2W**	**Lebri 250mg Q4W**	**Pbo**	**Lebri 250mg Q2W**	**Lebri 250mg Q4W**
ADvocate 1&2 pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***NOTE**: ADvocate 1 & 2 (pooled), mITT population. Adults (≥ 18 y.o.) and adolescents (>12 to <18 y.o.). In the trials, adolescents aged 16 to 18 years should have completed the DLQI; however some completed the CDLQI. Here we report adolescents who completed CDLQI only. Non-Responder Imputation.*

***Key**: EASI= Eczema Area and Severity Index; (c)DLQI= (children's) Dermatology Life Quality Index; Lebri= Lebrikizumab; mITT= modified intended to treat population, N= number of patients in the analysis population; n = number of patients in the specified category; Pbo= placebo; Q2W= every two weeks; Q4W= every four weeks; y.o.= years old.*
Analyses restricted to patients with (c)DLQI score ≥ 4 points at Baseline. There are 221 out of 253 adult patients in the maintenance period who had DLQI score ≥ 4 points at Baseline. There are 31 out of 38 adolescent patients in the maintenance period who had cDLQI score ≥ 4 points at Baseline.

Network meta-analysis and matching-adjusted treatment comparison (MAIC)

A25. Priority question: Please provide the results from all of the NMA models (currently only the company's favoured model is reported in the NMA technical report).

Company response: we apologise that the NMA technical report provided in PDF format (alongside the company submission) did not allow the EAG to open the various embedded Excel and Word files (including all the supplementary materials). As you may be aware, we uploaded the Microsoft Word versions of both the NMA full technical report and the NMA supplementary material documents to NICE Docs on 4th December 2023. Additionally (as aligned to question B4), we have supplied the key NMA input datasets presented in the full NMA technical report (pages 125–126) within the zipped folders entitled "NMA Combination therapy datasets – 22 Sept 2023" and "NMA Monotherapy datasets – 22 Sept 2023" that were also uploaded to NICE Docs on 4th December 2023.

A26. Priority question: Please provide the R/WinBUGs code and data for baseline risk models (fixed-effects and random-effects) including priors.

Company response: Analyses were conducted using the software OpenBUGS version 3.2.3, using the statistical software R version 4.2.2, through the R package 'R2OpenBUGS'. The OpenBUGS codes are now provided in Section 9.2 of the Word NMA full technical report ("Almirall 2023_Data on file_NMA report_Word_3Oct2023").

Please also refer to Section 4.7 of the full NMA technical report for information related to prior distributions.

We have provided the Clinical SLR report as a Data on File source ("Eli Lilly 2023_Data on File_Clinical SLR_25 Sept 2023") with this company response.(22) Please refer to the following tables from the Clinical SLR report for the following data:

- Clinical SLR Table 18: Efficacy Outcomes: Adults and Adolescents, Monotherapy
- Clinical SLR Table 34: Efficacy Outcomes: Adults and Adolescents, Combination Therapy.

A27. Priority question: We note the exclusion of non-placebo-controlled studies which may have contributed indirect evidence to the evidence network. This exclusion means the Heads Up (upadacitinib vs dupilumab) and JADE DARE (abrocitinib vs dupilumab) trials were absent from the monotherapy and combination therapy networks, respectively, where they would have contributed additional evidence for dupilumab which the company describes as the 'most relevant clinical comparator'. Please provide (i) the rationale underpinning this decision (i.e. to exclude non-placebo controlled studies), and (ii) the NMA results including these studies.

Company response: At the outset, the company considered the recommendations from previous HTAs across different country markets as well as other published NMAs, for example the recently published Silverberg et al. (2023) NMA that also omitted head-to-head trial data. (23)As a result, the company took the approach of including studies with a common comparator in order to remove bias arising from the absence of a placebo control arm. The available studies allowed the connection between all relevant comparators in the CS. The number of studies, the sample size of these studies and the homogeneity of the study-specific estimated informed the decision on proceeding to include placebo-controlled studies and reduce complexity of the analyses.

Non-placebo trials cannot be included in the baseline-adjusted NMA (which requires placebo). Therefore, as stated during the 28 November clarification call, it is not

technically possible for us to provide an NMA that includes the non-placebo-controlled studies. Please note that the Heads Up study was a monotherapy setting trial so we would not expect there to be impact on the overall results of lebrikizumab in combination with TCS setting.

A28. Please clarify why dupilumab was the only comparator considered for population matching? Was this the only study reporting Week 52 data?

Company response: Dupilumab was chosen as the comparator for population matching due it being the most established and commonly used second-line systemic for the treatment of moderate-to-severe AD.

Additionally, dupilumab's SOLO-CONTINUE (monotherapy in adults) trial covers weeks 16-52 for dupilumab responder patients enrolled after 16 weeks of treatment in the SOLO trial for whom EASI 75 or IGA 0/1 was achieved by week 16. This study thus provides comparable data against lebrikizumab responder patients (from ADvocate 1 and ADvocate 2) and providing responder data out to week 52.

A29. Please provide the results of the population matching sensitivity analysis.

Company response: The results of the sensitivity analysis are available in the recently published Rand K et al. (2023) supplementary material document that was submitted in the reference pack at the time of submission.(24) There are 9 different sensitivity analyses provided to test various combinations of matching variables.

In sensitivity analysis 1–3, mean and SD for EASI score at week 16 were substituted by corresponding scores for IGA, DLQI, and POEM, respectively. In sensitivity analysis 4–8, a single baseline severity variable was used rather than two, i.e., % BSA, EASI, IGA, DLQI, and POEM. In the final sensitivity analysis, age, proportion male, and proportion white were included for matching, illustrating the impact of baseline score adjustment.

A30. For the matching, please provide before and after statistics for those factors not matched on.

Company response: Regarding changes to baseline variables after propensity score weighting, re-weighting impacts not only the distribution of the variables used in weighting, but all variables in the matching dataset. Table 22 below displays the reported aggregate data from the SOLO-CONTINUE trial, the unweighted statistics from the SOLO-like cohort, and the corresponding statistics for each of the scenarios. The unweighted and weighted distributions for all binary baseline variables can be considered as acceptable.

Table 22: Unweighted and weighted distributions for all binary baseline variables

Source: Almirall 2023 Data on file (updated MAIC technical report, 1 December 2023)
Note: the MAIC technical report has now been updated to include this information and is provided as an updated Data on File item

Section B: Clarification on cost-effectiveness data

Published cost-effectiveness and HRQoL studies

B1. The searches for published cost-effectiveness studies and health-related quality of life (HRQoL) studies are slightly out-of-date (10 and 11 months, respectively). Please clarify if any relevant cost-effectiveness or HRQoL studies have been published in the intervening period.

Company response: To our knowledge, no relevant studies have been published in the intervening period. To maintain as much consistency as possible with the recent NICE MTA, model parameters have been sourced, where possible, from that appraisal. The health state utility data, in line with NICE's preferred methods, are sourced directly from the lebrikizumab clinical studies and multiple alternative values from past NICE HTAs are also provided in the model.

Model population

B2. Priority question: For the baseline characteristics of the model population, the company have used data from patients with a "*moderate-to-severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable*" (from the ADvantage study), as these were considered the closest to the population of interest (CS page 142). For best supportive care (BSC) baseline responses, you used data from "*patients who had received prior systemic therapy, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors, or biologics in with combination TCS*" as this is the most relevant subgroup to provide baseline responses (CS, page 144). Please clarify why you use two different populations for baseline inputs.

Company response: Baseline demographics (age, proportion adults vs. adolescent and % female) were indeed sourced from ADvantage, which recruited "moderate-to-severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable". The model shows little sensitivity to baseline demographics, hence for simplicity we used those from the overall population of the most generalisable lebrikizumab trial rather than carrying out *post-*

hoc analyses of demographics for subgroups that matched those used for baseline effectiveness.

B3. It is our understanding that the clinical inputs in the model come from the overall population (adults and adolescents) in the trials. Please clarify whether or not this is correct.

Company response: The baseline absolute treatment effectiveness in the base case was sourced from the NICE MTA EAG report for consistency. The baseline response rates in the MTA were from the pooled adult and/or adolescent subgroups from upadacitinib Measure UP 1 & 2 trials (monotherapy) or AD UP (combo therapy). Scenario analyses are also available in the model for the following placebo response rates from the lebrikizumab studies (submission Table 57): Please note that the responses from the below *post-hoc* analyses only included those for adults, as the majority of adolescents had completed the cDLQI rather than the DLQI (please see response to question A24 for information regarding the proportions of patients completing the two types of measure). The absence of adolescent data informing response rates for the composite endpoint should be considered within the context of the NICE MTA, where the appraisal committee considered the clinical evidence in adults to be generalisable to adolescents.

Monotherapy:

- Response rates in the pooled subgroup of patients who failed prior systemic therapy in ADvocate 1 and 2, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors and biologics.

Combination therapy:

- Response rates in the pooled subgroup of patients who failed prior systemic therapy in ADhere and ADvantage, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors and biologics (“ADhere and ADvantage 1” scenario).

- Response rates in the subgroup of patients who failed prior systemic therapy in ADhere, including CsA, MMF, methotrexate, azathioprine, JAK inhibitors and biologics, pooled with the ADvantage FAS ("ADhere and ADvantage 2" scenario).

- Response rates in the subgroup of patients who failed prior systemic therapy in ADhere (CsA, MMF, methotrexate, azathioprine, JAKs, biologics) pooled with the subgroup of patients in ADvantage who had failed prior systemic therapy (CsA, MMF, methotrexate, azathioprine EXCLUDING JAKs & biologics) ("ADhere and ADvantage 3" scenario).

The relative effectiveness data in the base case came from the following:

Monotherapy:

- Random effects, baseline-adjusted NMA that included the overall population from ADvocate 1 and 2

Combination therapy:

- Random effects, baseline-adjusted NMA that included the overall population from ADhere.

Treatment effectiveness

B4. Priority question: Please provide the NMA input datasets presented in the full NMA technical report (pages 125-126).

Company response: These have been uploaded to NICE Docs on 4th December 2023 as data on file within the zipped folders entitled "NMA Combination therapy datasets – 22 Sept 2023" and "NMA Monotherapy datasets – 22 Sept 2023".

B5. The baseline BSC response at Week 16 for monotherapy was sourced from NICE TA814 (Table 39). Table 39 in NICE TA814 presents response estimates

for both adults and adolescents. Please clarify why you have opted to use the adults estimates only.

Company response: For the monotherapy baseline response rate, it was unclear from the EAG Table 39 whether the adolescent value was for the 2nd line systemic therapy population, hence why the adult population was used. We have updated the model to provide an average response rate weighted by the proportion adult vs adolescent. This only reduces the baseline response from [redacted] due to the small proportion of adolescents. Note that monotherapy data are not used in the base case, hence this amendment does not impact the base case ICER.

For combination therapy, no adolescent value was provided in Table 39, but it should be noted that the appraisal committee in the NICE MTA considered that clinical trial results for adults who have tried systemic immunotherapy are likely to be generalisable to young people.

B6. Priority question: The baseline BSC responses at Week 16 for the combination therapy used in scenario analysis in the company submission (CS, section B.3.3.2, Table 58) do not match the modelled inputs ('NMA inputs_combo'!B16:E20). Please clarify which values should be considered in the model.

Company response: The model values are correct. We have updated CS Table 58 with the values for combination therapy in Table 23 below:

Table 23: Updated combination therapy baseline effectiveness estimates

Population	Baseline response (95% CI)	Base case/Scenario	Source
Combination therapy - second-line systemic treatment	[redacted]	Base case	AD UP – [redacted] patients responded to placebo at Week 16
	[redacted]	Scenario 1	Pooled placebo response data from ADhere and ADvantage prior

			systemic therapy subgroup
	[redacted]	Scenario 2	Pooled placebo response data from ADhere prior systemic therapy subgroup and ADvantage full analysis set (FAS)
	[redacted]	Scenario 3	Pooled placebo response data from ADhere prior systemic therapy subgroup and ADvantage prior systemic therapy subgroup excluding JAKs and biologics

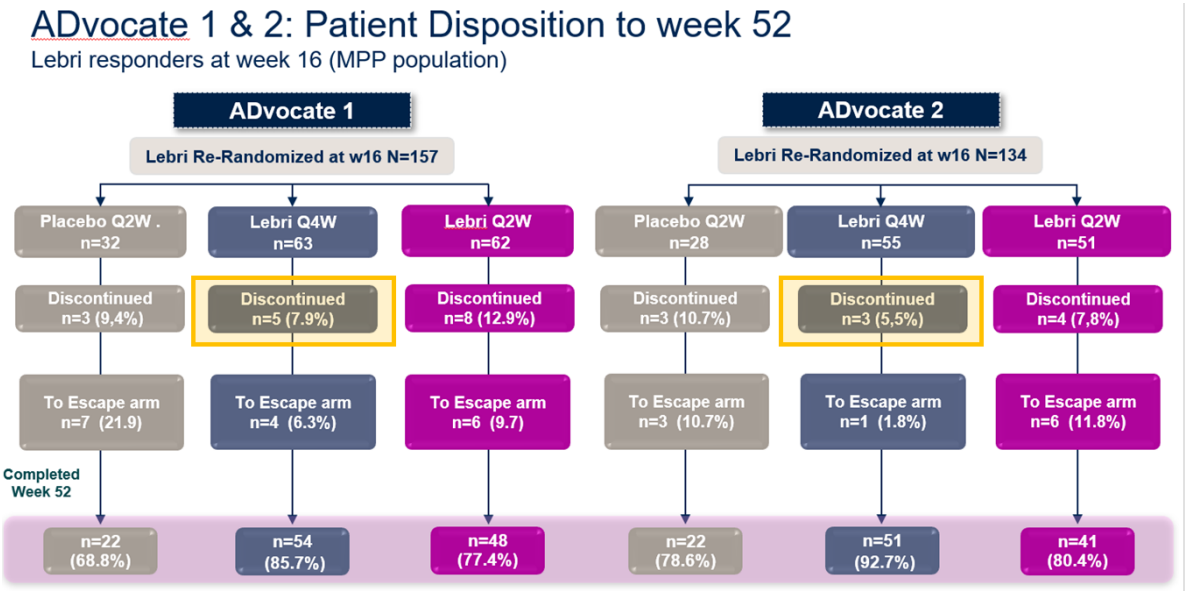
B7. Conditional treatment discontinuation.

(a) Priority question: Please provide a clear description of how the conditional treatment discontinuation (response at Week 52) was derived from the trial data for lebrikizumab monotherapy and combination therapy (CS, Table 59).

Company response: For monotherapy composite endpoint responders, this was estimated from a *post-hoc* analysis of the pooled ADvocate studies. [redacted] patients who had achieved the EASI50 and ≥4pts improvement at week 16 on lebrikizumab were re-randomised to Q4W maintenance, of which [redacted] discontinued before week 52.

For monotherapy EASI75 responders, the discontinuation rate was calculated from the patients re-randomised to lebrikizumab Q4W at week 16 who discontinued before week 52, as depicted in Figure 5 below (sum of the orange boxes).

Figure 5: Source of lebrikizumab monotherapy discontinuation rates, EASI75 responders



For combination therapy, discontinuation rates were obtained from a *post-hoc* analysis of patients who had achieved the relevant endpoint in ADhere and had rolled over into ADjoin. However, in checking these data we have noticed some discrepancies between the patient numbers and what was implemented in the model. The patient numbers are presented in Table 24 below and we have updated the conditional discontinuation rates for combination therapy to [redacted] and [redacted] for the EASI75 and composite endpoint, respectively, derived from those patients who rolled over onto Q4W.

Table 24: Disposition of responders who rolled over from ADhere to ADjoin

EASI 75	**ADjoin treatment arm**		
Study disposition	**Lebrikizumab Q2W N(%)**	**Lebrikizumab Q4W N(%)**	**Total**
Total assigned	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]
Continuing Study	[redacted]	[redacted]	[redacted]
EASI50 and ≥4pts improvement	**ADjoin treatment arm**		
Study disposition	**Lebrikizumab Q2W N(%)**	**Lebrikizumab Q4W N(%)**	**Total**
Total assigned	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]

Continuing Study	[redacted]	[redacted]	[redacted]

(b) Tralokinumab monotherapy conditional treatment discontinuation was based on the percentage dosed in the maintenance phase of ECZTRA 1 and 2 who discontinued, as presented in the Wollenberg et al. 2021 publication (Figure S3). Figure S3 in Wollenberg et al. 2021, in particular part b) and d), shows various stages where patients discontinue treatment within the trial. Why did you not include all these patients instead of only including the patients that discontinue out of the percentage dosed?

Company response: The parameter of interest is the proportion of patients who respond to 16 weeks of induction treatment who go on to discontinue after 36 weeks of maintenance. The most clinically realistic values to use are therefore the proportion of patients who achieved a response on tralokinumab during the induction period who remained on treatment over the maintenance period. Using discontinuation from all dosed patients would ignore the impact of treatment efficacy and prior treatment experience on propensity to discontinue.

The majority of patients re-randomised and not dosed in the CONSORT diagram did so due to being assigned to open-label treatment. These patients were not counted as being at risk of discontinuation since they exit the disposition chart. One patient in ECZTRA 1 discontinued after re-randomisation to Q2W and before dosing (figure S3(b)) and this patient could reasonably be counted as a true discontinuation. We have therefore updated the number at risk of discontinuation from Q2W in the model to 91+69 (re-randomised dosed patients, plus the patient who was not dosed but was known to discontinue) and added an additional discontinuation to the numerator, that is, 9+4 discontinuations (see cell **Clinical Inputs!D63**). This increases the proportion discontinuing Q2W tralokinumab from 7.5% to 8.1%.

Similarly, one patient in ECZTRA 1 discontinued after re-randomisation to Q4W, We have therefore updated the number at risk of discontinuation from Q4W in the model to 89+77 (re-randomised dosed patients, plus the patient who was not dosed but was known to discontinue) and added an additional discontinuation to the numerator,

that is, 13+6 discontinuations (see cell **Clinical Inputs!D64**). This increases the proportion discontinuing Q4W tralokinumab from 10.71% to 11.45%.

(c) The conditional treatment discontinuation for tralokinumab Q4W combination therapy was based on the study by Silverberg et al. 2021 (Figure S2). Figure S2 in Silverberg et al. 2021 does not show data for tralokinumab Q4W. Please explain how you calculated the conditional treatment discontinuation for tralokinumab Q4W based on Figure S2.

Company response: The Silverberg study included a Q4W maintenance arm. We assumed that there was a typographical error in the re-randomisation part of Figure S2 and that the second Tralokinumab Q2W + TCS box should have instead read Tralokinumab Q4W + TCS (the N=68 plus the N = 66 in these two boxes add up to the 134 patients re-randomised to Q2W or Q4W tralokinumab referred to in the main body and align with Table 4 of the manuscript).

B8. Rates of adverse events.

(a) Please provide a rationale for including these six specific adverse events – injection site reaction, allergic conjunctivitis, infectious conjunctivitis, oral herpes, upper respiratory tract infection and acne – in the model and not others.

Company response: As lebrikizumab's AE profile does not include any that are distinct from other biologics, we included the same AEs as those considered in the NICE MTA for consistency. These were selected by the EAG in that MTA because they were "in line with those included in TA534 and TA681 and were considered the most important to include by the EAG's clinical experts".

(b) We note that Simpson et al. 2020 reports AEs for baricitinib monotherapy for upper respiratory tract infection, herpes and conjunctivitis. Please clarify why you assumed the same rate of AEs for

baricitinib monotherapy as for the combination therapy with baricitinib in the CS economic model (CS, Table 60) and why you have not used the AE rates from Simpson et al. 2020.

Company response: For consistency with the MTA, all comparator AE rates were sourced from Table 42 of the MTA EAG report, other than those of tralokinumab, which were redacted in their report. These included “serious AEs with an incidence of >5% in any treatment arm”. Note that when considering these values, a “serious” AE was found not to be synonymous with a “severe” AE and presumably pertained to those AEs which were considered important to include by clinicians advising the EAG.

(c) Wollenberg et al. 2021 and Silverberg et al. 2021 report AEs for tralokinumab monotherapy (upper respiratory tract infection and conjunctivitis) and combination therapy (injection site reaction, upper respiratory tract infection and conjunctivitis), respectively. As above, please clarify why you assumed the same rate of AEs for tralokinumab as for dupilumab (CS, Table 60) and have not used the rates from the Wollenberg et al. 2021 and Silverberg et al. 2021 studies.

Company response: As these values were redacted in the MTA report, we had assumed that they were not available. We have updated the relevant model AEs with the extracted values in Table 25 below (only updated values are presented):

Table 25: Updated 16 week AE rates for tralokinumab

	Injection site reaction	Allergic conjunctivitis	Infectious conjunctivitis	Upper respiratory tract infection
Tralokinumab monotherapy		5.11%	0.00%	5.70%
Tralokinumab combination therapy	6.75%	11.11%	0.00%	7.54%

Note: where only ‘conjunctivitis’ was listed, this was allocated to allergic conjunctivitis and infectious conjunctivitis was set to zero. Viral upper respiratory tract infection was not included.

Note that we have also updated the values for baricitinib monotherapy in the model, which were not provided in the NICE MTA report. These have been sourced from the BREEZE-AD1 and AD2 trials(25) and are updated as yellow cells in the model (but do not inform the combination therapy base case).

(d) The rate of allergic conjunctivitis for upadacitinib 15mg monotherapy reported in CS (CS, section B.3.3.7, Table 60) and used in the model ('Adverse events'!B9:H32) is 2.10%, while the rate reported in the source (NICE TA814 Assessment Report, Table 42) is 0.21%. Please clarify which of these values is correct.

Company response: The incidence of allergic conjunctivitis is not tabulated in the MEASURE UP 1 and 2 Guttman-Yassky 2021 publication, however the body text states “In both studies, no differences in overall incidence of ocular events, including conjunctivitis, were observed between the upadacitinib treatment groups (2–3%) and the placebo group (3%).” We therefore consider 2.1% to be the more realistic figure, as this would generate a total incidence of 2.72% for both allergic and infectious conjunctivitis combined.

(e) The rate of acne for lebrikizumab combination therapy reported in CS (CS, section B.3.3.7, Table 60) and used in the model ('Adverse events'!B9:H32) is 1.40%, while the rate reported in the source (ADhere CSR, Table KGAD 8.41) is 0.70%. Please clarify which of these values is correct.

Company response: The 1.4% represented the sum of acne (0.7%) plus dermatitis acneform (0.7%). However, on consultation with our medical team, we have removed the proportion attributable to dermatitis acneform in our updated base case.

Health-related quality of life

B9. Priority question: Please provide the raw data for EQ-5D-5L from the ADvocate 1 & 2 and ADhere trials (i.e. the aggregated data presented by trial arm and for each timepoint – baseline, Week 16 and Week 52) and provide a clear description of how the utilities in the model were derived from the trial EQ-5D-5L data. Alternatively, if this information is available in the CS, please clarify where it is reported (the EAG have been unable to find this information).

Company response: This information was provided in section B.3.4.2 of our submission. Further information was also provided in a standalone utility analysis report "*Almirall 2023_Lebrikizumab EQ-5D Utility mapping Report v0.2_Sept2023*" provided as data on file, as well as an Excel spreadsheet "*Almirall 2023_Lebrikizumab EQ-5D utility mapping Excel data analyses_Sept 2023*".

- The "*Contents*" tab of the spreadsheet includes hyperlinks to individual tabs.
- The "*Utility summary*" tab presents the summary statistics of the EQ-5D values by trial, arm, timepoint and responder status.
- The preferred models were mixed model for repeated measures (MMRM) model 2.1 for monotherapy and ordinary least squares (OLS) model 2.2 for combination therapy. The models were run using pooled data from the ADvocate 1 & 2 studies and from the ADhere study, respectively. These models, along with the health state utility calculations generated from them and the baseline utility values, are found under tabs "*MM_2.1*" and "*OLS_2.2*", respectively.

Note that all utility analyses were carried out on observed data only.

B10. Please clarify how the disutility of oral herpes (0.05) was derived from the source (Fisman, 2005; CS, Table 64) and provide a rationale for using this

disutility, as the Fisman study presents TTO values for genital herpes and not oral herpes.

Company response: We could not identify any disutilities in the literature for oral herpes. Values are widely available for herpes zoster (shingles) which is significantly more severe. The disutility was calculated as the difference between asymptomatic oral herpes (0.76) and symptomatic oral herpes (0.71) from the Fisman paper.

It should be noted that the results are insensitive to this disutility, with removal of it altogether having little impact on results.

B11. Priority question: CS, Table 65, presents the utility values used in the cost-effectiveness model. It presents different responder and non-responder utilities for the active treatments (from lebrikizumab arm) and BSC (from placebo arm). Please a) provide the pooled utility data (from the lebrikizumab and placebo arms) for baseline, responders and non-responders; and, (b) please run a scenario analysis using the pooled utility data for both patients in the active treatments and BSC health states in the model.

Company response:

(a) We have re-run our preferred regression models MMRM 2.1 (for monotherapy) and OLS 2.2 (for combination therapy), removing the covariates for active treatment arm. The utility values generated from this approach are shown in Table 26 and Table 27.

Table 26: Utility values by health state, monotherapy

Health state	Mean	Lower CI	Upper CI
Baseline	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; BSC, best supportive care

Table 27: Utility values by health state, combination therapy

Health state	Mean	Lower CI	Upper CI
Baseline	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; BSC, best supportive care

However, it should be noted that the “on treatment” coefficient was significant in almost all regression models and the interaction term with responder significant in a large proportion (as expected, as power is lower for the interaction term). This result aligns with differences in the magnitude of response between responders on placebo vs. lebrikizumab in the clinical studies, as illustrated in Table 28 below from ADhere (the study informing the base case combination therapy utility values). It is evident that the absolute EASI score of EASI 50 non-responders to lebrikizumab is substantially lower than the EASI score of non-responders to placebo and that the % reduction from baseline was larger for both responders and non-responders. The differences are more apparent with the DLQI, where a 12.5-point (78%) reduction from baseline was observed for responders to lebrikizumab vs. a 10.4-point (69%) reduction for responders to placebo and a 4.6-point (26%) reduction from baseline was observed for non-responders to lebrikizumab vs. a 2-point (4%) reduction for non-responders to placebo. There is therefore a good clinical rationale for having separate utility values for patients on active treatments vs. BSC in the economic model.

Table 28: EASI50 and DLQI ≥ 4-point improvement responders* (Observed cases) at Baseline and Week 16, by arm. ADhere, Lebrikizumab 250mg Q2W from Baseline to Week 16 (mITT)

	Placebo (N=47)		Lebrikizumab (N=104)	
	Responder (N=18)	**Non-responder** (N=22)	**Responder** (N=72)	**Non-responder** (N=27)
Baseline EASI score mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 EASI score mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]

Change from baseline EASI mean (% change from baseline) (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DLQI score mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 16 DLQI score mean(SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline DLQI mean (% change from baseline) (SD)	[redacted]	[redacted]	[redacted]	[redacted]

* Analysis restricted to adult patients with DLQI score ≥ 4 points at Baseline. DLQI only includes patients ≥ 18 years old, adolescent patients from ≥12 to < 18 years old not included. Analysis from observed cases only.

(b) A list box has been incorporated into the model cell **QoL!G10**. Lebrikizumab remains cost effective when the same utility values are used for responder and non-responders on active treatments vs. BSC (Table 29).

Table 29: Cost-effectiveness results with the same health state utility by treatment

Comparator	ICER company base case	NMB at £20k WTP company base case	ICER EAG scenario	NMB at £20k WTP EAG scenario
Dupilumab	£1,408,755	£35,762	£8,646,449	£36,193
Baricitinib	Lebrikizumab dominates	£8,159	Lebrikizumab dominates	£6,405
Upadacitinib	£366,436	£27,476	£1,536,606	£28,684
Abrocitinib	£568,504	£17,549	£2,361,734	£18,035
Tralokinumab	Lebrikizumab dominates	£21,176	Lebrikizumab dominates	£20,727

*Denotes an ICER in the southwest quadrant. NMB, net monetary benefit. WTP, willingness to pay.
Note: the company base case includes the corrections made to the baseline response, discontinuation, AE rates and AE cost applied in questions B5, B7(b), B8(c) and (e) and B12.

Costs and Resource Use

B12. Please explain why the consultation costs used for adverse events in the model, and reported in CS, Table 75 (for injection site reaction and infectious

conjunctivitis), are not the same as calculated in the model in the Data store sheet cell I89 and I102.

Company response: For infectious conjunctivitis, we used the same weighting and references as per the NICE MTA "GP per surgery consultation lasting 9.22 minutes. £39.23 (80% weight from TA681) National Schedule of NHS Costs - Year 2020/21 - NHS trusts and NHS foundation trusts. Service code 130, ophthalmology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D. £110.66 (20% weight from TA681)". The consultation cost in I102 from the data store sheet is used but only 20% of patients are assumed to incur this cost.

For injection site reaction, this is an error, the ERG is correct, it should be linked to cell I89 from sheet "*Data store*" i.e. the AE cost is in fact £171.93 and has been updated in the new company base case.

B13. Priority question: Please provide instructions on how to run the scenario analysis: Source of baseline (placebo) response (CS, Table 89).

Company response: Row 16 of the "*NMA inputs_mono*" and "*NMA inputs_combo*" tabs show the "live" BSC composite response rates used in the model. The "ADhere and ADvantage 1" scenario (and other scenarios not described in the submission; patient numbers in "*prior Tx combo*" tab) is selected using the blue list box in **NMA inputs_combo!B16**. The "ADhere and ADvantage 1" scenario selects the placebo response from the subgroup of patients in ADhere and ADvantage with prior systemic therapy (any of CsA, MMF, methotrexate, azathioprine, JAKs, biologics).

B14. CS, page 166, states: "*Almirall will provide training on the self-administration of lebrikizumab to the NHS free of charge, thus no administration costs are applied to the intervention arm*". Does this mean that Almirall will provide training to patients directly or only to the NHS staff?

Company response: Training will be provided to NHS staff only. It should be noted that training on treatment administration would be required for patients taking any

injectable treatment and these costs, if implemented in the model, would therefore cancel out between lebrikizumab, dupilumab and tralokinumab.

Results

B15. For CS, Figures 38-42, and CS, Tables 84-88, please provide either the input parameters names written in full or a footnote with the abbreviations explained.

Company response: A parameter description has been incorporated into the model. Updated tornado diagrams, including parameter descriptions, are provided in Appendix A (at the end of this document).

Section C: Textual clarification and additional points

C1. In CS, Table 2, in the row for the 'List price and average cost of a course of [the intervention] treatment', it is stated: "Approximately 71 units over 5 years of treatment (for patients who achieve response at 16 weeks." Please confirm whether or not the EAG is correct in understanding that the latter is the expected average course of lebrikizumab treatment.

Company response: Lebrikizumab for the treatment of moderate-to-severe AD would be an ongoing treatment and therefore there is no expected average course of treatment. However, based on the anticipated indication and dosing regimen, approximately 71 units of treatment are expected over 5 years for patients who achieve response at 16 weeks. For patients who do not achieve a response at week 16, approximately 11 units of treatment would be incurred.

C2. Please provide the EAG with copies of the clinical study reports for the ADhere-J (NCT04760314) and Adopt-VA trials (NCT04626297), if these are available.

Company response: As requested, the CSR reports for ADhere-J and ADopt-VA are now provided.

References

1. National Institute for Health and Care Excellence (NICE). Resource impact report: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814). 2022.
2. National Institute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe atopic dermatitis (TA534 committee papers). 2018.
3. National Institute for Health and Care Excellence (NICE). Baricitinib for treating moderate to severe atopic dermatitis (TA681 committee papers). 2021.
4. ClinicalTrials.gov. A Study of Lebrikizumab (LY3650150) in Combination With Topical Corticosteroids in Japanese Participants With Moderate-to-Severe Atopic Dermatitis (ADhere-J) 2021 [Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04760314.
5. Almirall. [Data on File: ADhere-J CSR] A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When Used in Combination with Topical Corticosteroid Treatment in Japanese Patients with Moderate-to-Severe Atopic Dermatitis. Clinical study report. 2023.
6. Katoh N, Tanaka A, Takahashi H, Shimizu H, Kataoka Y, Torisu-Itakura H, et al. [Data on file: ADhere-J draft manuscript] Efficacy and Safety of Lebrikizumab Combined With Topical Corticosteroids in Japanese Patients With Moderate to Severe Atopic Dermatitis. 2023.
7. ClinicalTrials.gov. A Study of Lebrikizumab (LY3650150) on Vaccine Response in Adults With Atopic Dermatitis (ADopt-VA) (NCT04626297) 2020 [updated 17 October 2023. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04626297.
8. Almirall. [Data on File: ADopt-VA CSR] A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis. 2023.
9. ClinicalTrials.gov. Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents With Moderate-to-Severe Atopic Dermatitis (ADhope) (NCT05990725) 2023 [updated 14 August 2023. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05990725.
10. Guttman-Yassky E, Weidinger S, Simpson E, Gooderham M, Irvine A, Spelman L, et al., editors. Efficacy and safety of lebrikizumab is maintained to two years in patients with moderate-to-severe atopic dermatitis. Oral presentation given at the Fall Clinical Dermatology Conference; 2023; Las Vegas, NV, USA.
11. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatovener (Stockholm) Suppl. 1980;92:44-7.
12. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338-51.
13. Fishbein AB, Silverberg JI, Wilson EJ, Ong PY. Update on Atopic Dermatitis: Diagnosis, Severity Assessment, and Treatment Selection. J Allergy Clin Immunol Pract. 2020;8(1):91-101.
14. Eli Lilly and Company. [Data on File: ADjoin LTE race ethnicity baseline characteristics. 2023.
15. Almirall. Data on file: ADvocate 1 & 2 EASI 75 responders (observed cases) by week; MSP population. 2023.

16. Eli Lilly and Company. [Data on File: ADvocate 1 (KGAB) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 1). Clinical study report.; 2022.
17. Eli Lilly and Company. [Data on File: ADvocate 2 (KGAC) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 2). Clinical study report.; 2022.
18. Eli Lilly and Company. [Data on File: ADhere (KGAD) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroid treatment in patients with moderate-to-severe atopic dermatitis (ADhere). Clinical study report.; 2022.
19. Almirall. [Data on File: ADvantage CSR final 19Oct2023] A randomised, double-blind, placebo-controlled phase 3 clinical trial to assess the efficacy and safety of lebrikizumab in combination with topical corticosteroids in adult and adolescent patients with moderate-to-severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable (ADvantage). Clinical study report. 2023.
20. Simpson EL, Blauvelt A, Silverberg JI, Cork MJ, Katoh N, Mark T, et al. Tralokinumab Provides Clinically Meaningful Responses at Week 16 in Adults with Moderate-to-Severe Atopic Dermatitis Who Do Not Achieve IGA 0/1. Am J Clin Dermatol. 2023.
21. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial. JAMA Dermatology. 2020;156(1):44-56.
22. Eli Lilly and Company. [Eli Lilly Data on FIle: Clinical SLR] Systematic Literature Review to Evaluate the Efficacy and Safety of Treatments for Adult, Adolescent, and Paediatric Patients With Moderate-to-Severe Atopic Dermatitis: Update 3 Final Report. 2023 25 September 2023.
23. Silverberg JI, Hong HC, Calimlim BM, Lee WJ, Teixeira HD, Collins EB, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis without Topical Corticosteroids: An Updated Network Meta-analysis. Dermatol Ther (Heidelb). 2023;13(10):2247-64.
24. Rand K, Ramos-Goñi JM, Akmaz B, Solé-Feu L, Armario-Hita JC. [Supplementary material] Matching-Adjusted Indirect Comparison of the Long-Term Efficacy Maintenance and Adverse Event Rates of Lebrikizumab versus Dupilumab in Moderate-to-Severe Atopic Dermatitis Dermatol Ther (Heidelb). 2023.
25. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol. 2020;183(2):242-55.

Appendix A: Updated cost effectiveness results

Table 30 provides an updated company base case including the minor corrections made to the baseline response, discontinuation and AE rates applied in questions B5, B7(b), B8(c) and (e) and B12. The life years gained are not included as these have not changed from the original company submission.

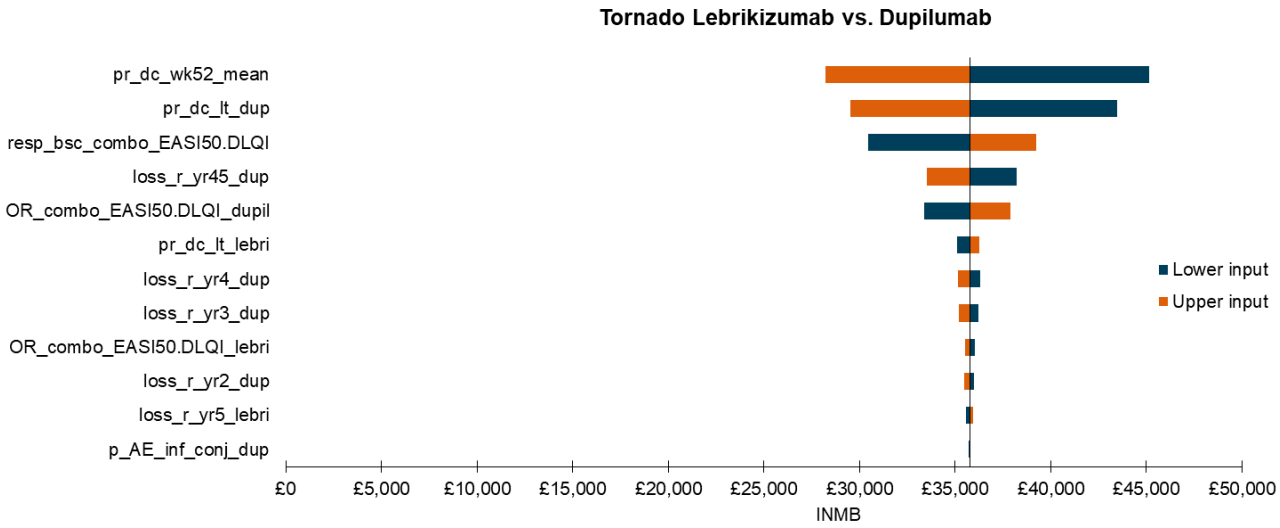
Updated tornado diagrams, including key, are provided in Figure 6 to Figure 10.

Table 30: Updated company base case results

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

Key: Ext, extendedly

Figure 6: Dupilumab tornado

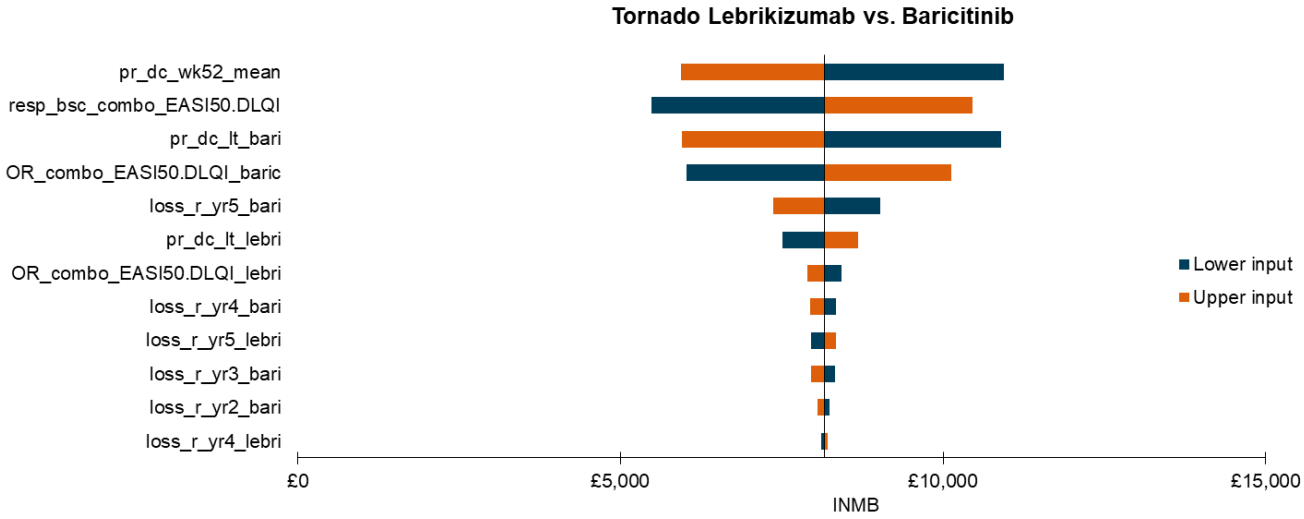


Key:

Parameter	Description
pr_dc_wk52_mean	Conditional discontinuation at week 52, Average
pr_dc_lt_dup	Long-term treatment discontinuation (> week 52), Dupilumab
resp_bsc_combo_EASI50.DLQI	BSC response, composite - combotherapy
loss_r_yr45_dup	Treatment waning (year 5), Dupilumab
OR_combo_EASI50.DLQI_dupil	NMA OR combotherapy overall - EASI 50 & DLQI, Dupilumab
pr_dc_lt_lebri	Long-term treatment discontinuation (> week 52), Lebrikizumab
loss_r_yr4_dup	Treatment waning (year 4), Dupilumab
loss_r_yr3_dup	Treatment waning (year 3), Dupilumab
OR_combo_EASI50.DLQI_lebri	NMA OR combotherapy overall - EASI 50 & DLQI, Lebrikizumab
loss_r_yr2_dup	Treatment waning (year 2), Dupilumab
loss_r_yr5_lebri	Treatment waning (year 5), Lebrikizumab
p_AE_inf_conj_dup	dupi AE rate, Infectious conjunctivitis

OR, odds ratio; NMA, network meta-analysis; iNMB, incremental monetary benefit at £20,000 per QALY

Figure 7: Baricitinib tornado

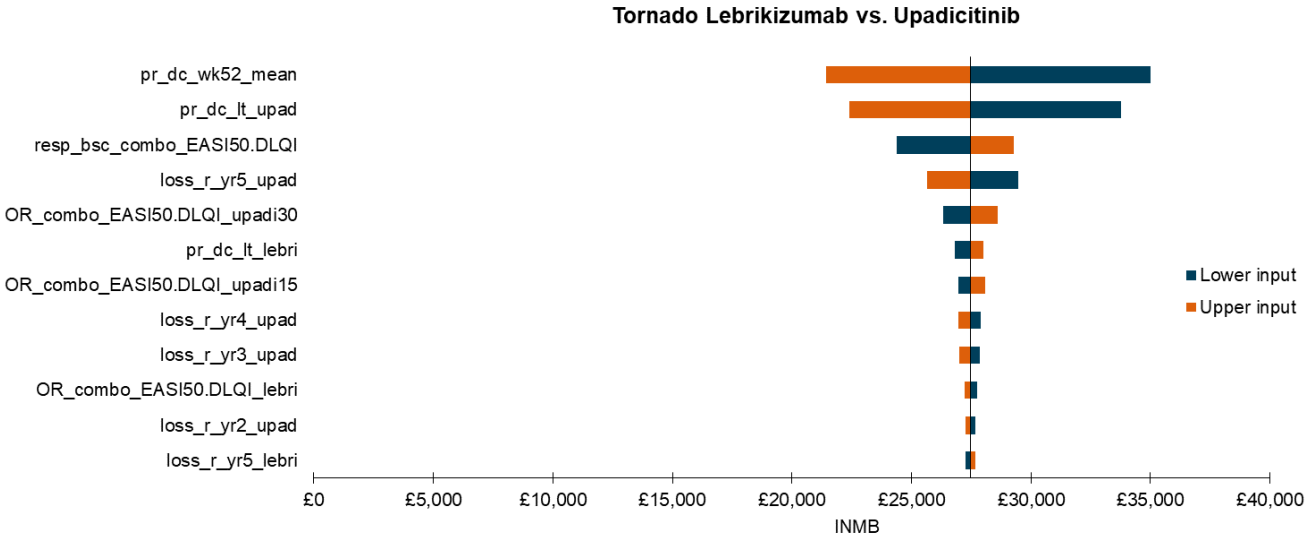


Key:

Parameter	Description
pr_dc_wk52_mean	Conditional discontinuation at week 52, Average
resp_bsc_combo_EASI50.DLQI	BSC response, composite - combotherapy
pr_dc_lt_bari	Long-term treatment discontinuation (> week 52), Baricitinib
OR_combo_EASI50.DLQI_baric	NMA OR combotherapy overall - EASI 50 & DLQI, Baricitinib
loss_r_yr5_bari	Treatment waning (year 5), Baricitinib
pr_dc_lt_lebri	Long-term treatment discontinuation (> week 52), Lebrikizumab
OR_combo_EASI50.DLQI_lebri	NMA OR combotherapy overall - EASI 50 & DLQI, Lebrikizumab
loss_r_yr4_bari	Treatment waning (year 4), Baricitinib
loss_r_yr5_lebri	Treatment waning (year 5), Lebrikizumab
loss_r_yr3_bari	Treatment waning (year 3), Baricitinib
loss_r_yr2_bari	Treatment waning (year 2), Baricitinib
loss_r_yr4_lebri	Treatment waning (year 4), Lebrikizumab

OR, odds ratio; NMA, network meta-analysis; iNMB, incremental monetary benefit at £20,000 per QALY

Figure 8: Upadacitinib tornado

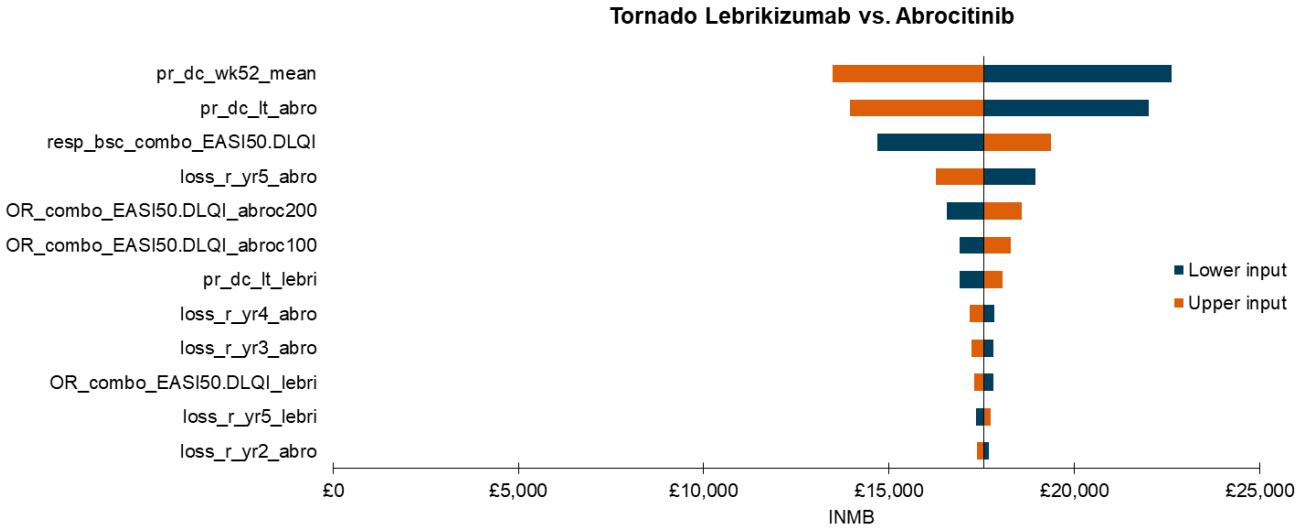


Key:

Parameter	Description
pr_dc_wk52_mean	Conditional discontinuation at week 52, Average
pr_dc_lt_upad	Long-term treatment discontinuation (> week 52), Upadacitinib
resp_bsc_combo_EASI50.DLQI	BSC response, composite - combotherapy
loss_r_yr5_upad	Treatment waning (year 5), Upadacitinib
OR_combo_EASI50.DLQI_upadi30	NMA OR combotherapy overall - EASI 50 & DLQI, Upadicitinib - 30 mg
pr_dc_lt_lebri	Long-term treatment discontinuation (> week 52), Lebrikizumab
OR_combo_EASI50.DLQI_upadi15	NMA OR combotherapy overall - EASI 50 & DLQI, Upadicitinib - 15 mg
loss_r_yr4_upad	Treatment waning (year 4), Upadacitinib
loss_r_yr3_upad	Treatment waning (year 3), Upadacitinib
OR_combo_EASI50.DLQI_lebri	NMA OR combotherapy overall - EASI 50 & DLQI, Lebrikizumab
loss_r_yr2_upad	Treatment waning (year 2), Upadacitinib
loss_r_yr5_lebri	Treatment waning (year 5), Lebrikizumab

OR, odds ratio; NMA, network meta-analysis; iNMB, incremental monetary benefit at £20,000 per QALY

Figure 9: Abrocitinib tornado

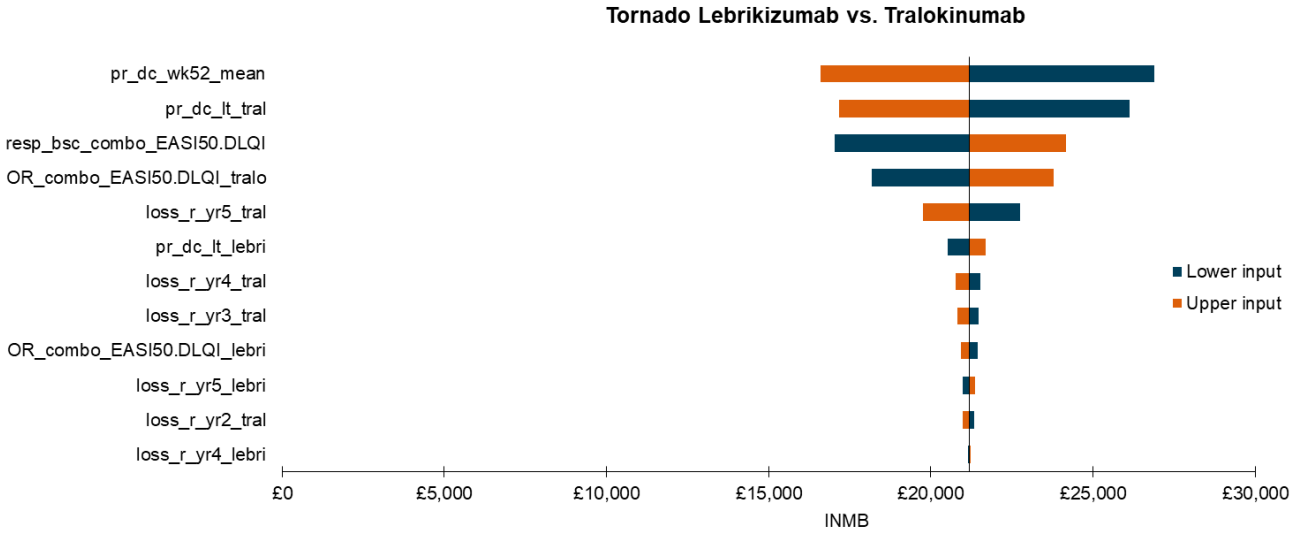


Key:

Parameter	Description
pr_dc_wk52_mean	Conditional discontinuation at week 52, Average
pr_dc_lt_abro	Long-term treatment discontinuation (> week 52), Abrocitinib
resp_bsc_combo_EASI50.DLQI	BSC response, composite - combotherapy
loss_r_yr5_abro	Treatment waning (year 5), Abrocitinib
OR_combo_EASI50.DLQI_abroc200	NMA OR combotherapy overall - EASI 50 & DLQI, Abrocitinib - 200 mg
OR_combo_EASI50.DLQI_abroc100	NMA OR combotherapy overall - EASI 50 & DLQI, Abrocitinib - 100 mg
pr_dc_lt_lebri	Long-term treatment discontinuation (> week 52), Lebrikizumab
loss_r_yr4_abro	Treatment waning (year 4), Abrocitinib
loss_r_yr3_abro	Treatment waning (year 3), Abrocitinib
OR_combo_EASI50.DLQI_lebri	NMA OR combotherapy overall - EASI 50 & DLQI, Lebrikizumab
loss_r_yr5_lebri	Treatment waning (year 5), Lebrikizumab
loss_r_yr2_abro	Treatment waning (year 2), Abrocitinib

OR, odds ratio; NMA, network meta-analysis; iNMB, incremental monetary benefit at £20,000 per QALY

Figure 10: Tralokinumab tornado



Key:

Parameter	Description
pr_dc_wk52_mean	Conditional discontinuation at week 52, Average
pr_dc_lt_tral	Long-term treatment discontinuation (> week 52), Tralokinumab
resp_bsc_combo_EASI50.DLQI	BSC response, composite - combotherapy
OR_combo_EASI50.DLQI_tralo	NMA OR combotherapy overall - EASI 50 & DLQI, Tralokinumab
loss_r_yr5_tral	Treatment waning (year 5), Tralokinumab
pr_dc_lt_lebri	Long-term treatment discontinuation (> week 52), Lebrikizumab
loss_r_yr4_tral	Treatment waning (year 4), Tralokinumab
loss_r_yr3_tral	Treatment waning (year 3), Tralokinumab
OR_combo_EASI50.DLQI_lebri	NMA OR combotherapy overall - EASI 50 & DLQI, Lebrikizumab
loss_r_yr5_lebri	Treatment waning (year 5), Lebrikizumab
loss_r_yr2_tral	Treatment waning (year 2), Tralokinumab
loss_r_yr4_lebri	Treatment waning (year 4), Lebrikizumab

OR, odds ratio; NMA, network meta-analysis; iNMB, incremental monetary benefit at £20,000 per QALY

Almirall company responses to EAG additional clarification aspects

Revised 16 May 2024 (original submitted 19th February 2024)

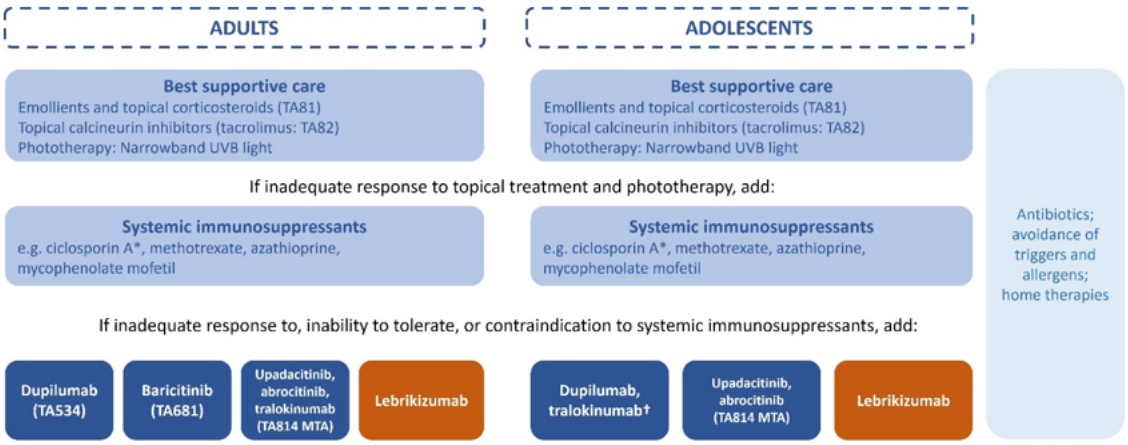
Key issue 7: Positioning of lebrikizumab

1. Can you confirm that the company is positioning lebrikizumab treatment for people with atopic dermatitis in whom conventional, first-line systemic therapies (that is, azathioprine, ciclosporin, methotrexate or mycophenolate mofetil) have been inadequately effective, not tolerated or contraindicated?

COMPANY RESPONSE: Yes, we can confirm that we intend to position lebrikizumab for patients who have failed on, cannot tolerate or are unsuitable for **any** of the first-line systemic therapies (azathioprine, ciclosporin A, methotrexate or mycophenolate mofetil). This is in line with the other currently available second-line systemic therapies for moderate-to-severe atopic dermatitis (i.e. biological therapies and JAK inhibitors).

The following schematic (provided as Figure 2 in our company submission) shows the intended positioning of lebrikizumab for the treatment of moderate-to-severe atopic dermatitis after **any** of the first-line systemic therapies.

Figure 1: The anticipated position of lebrikizumab in the clinical pathway of care for moderate-to-severe AD [Note: this is Figure 2 in the company submission]



*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 (58)
NICE TA82: Tacrolimus and pimecrolimus for atopic eczema (59)
NICE TA534: Dupilumab for treating moderate to severe atopic dermatitis (1)
NICE TA681: Baricitinib for treating moderate to severe atopic dermatitis (2)
NICE TA814: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (3)

2. In table 1 of the company's submission, there is a statement about a sub-population of patients who have had an inadequate response to ciclosporin A or in whom ciclosporin A is not medically advised. The EAG are unclear what this means. Please can you confirm if either of the descriptions below is what the company intends:
    a. the company are positioning lebrikizumab specifically in people who have had an inadequate response to or who are unsuitable for ciclosporin A **only**.
    b. or alternatively, 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.

COMPANY RESPONSE: In the company submission Table 1 (The decision problem) for comparators, the company had included this statement about the ciclosporin A sub-population of patients with the intention of clarifying that we were submitting data from ADvantage as part of the evidence package. No further intent was implied.

We can confirm that statement 2b is correct (statement 2a is incorrect). As stated in the response above, we can confirm that we intend to position lebrikizumab for patients who have failed on, cannot tolerate or are unsuitable for **any** of the first-line systemic therapies (azathioprine, ciclosporin A, methotrexate or mycophenolate mofetil). This is in line with the other currently available second-line systemic therapies for moderate-to-severe atopic dermatitis (i.e. biological therapies and JAK inhibitors).

Of note, only ciclosporin A is licensed in the UK (for treatment of severe AD only); while methotrexate, azathioprine and mycophenolate mofetil are used off-label. Therefore, with regards to statement (2b), we confirm that the following statement would better capture our thoughts "the company are suggesting that evidence from the ciclosporin A population **may reflect** the wider population of patients who have failed on or are unsuitable for first-line systemic therapies, and thus available data from the ADvantage study were submitted as part of the company submission."

We apologise for the ongoing confusion related to lebrikizumab's positioning and hope that this now clarifies the company's views.

Key issue 3: Average conditional discontinuation rates for all treatments

1. Please provide a rationale for why you chose to use the average conditional discontinuation rate for all treatments? Previous TA's in this area have used the individual treatment conditional discontinuation rates.

COMPANY RESPONSE: The original company submissions and/or EAG models in previous TAs in this area have indeed applied individual treatment conditional discontinuation rates. However, this does not necessarily appear to have been accepted as the final modelling assumption by the appraisal committees, as noted by the EAG in NICE TA814, *'short-term conditional treatment discontinuation data is subject to a substantial amount of uncertainty'.* Furthermore, as can be seen in our response to part 2 of this query, some of the 'individual'

treatment condition discontinuation rates that have been applied in previous TAs are actually informed by the conditional discontinuation rates for other treatments, or, these conditional discontinuation rates rely heavily on assumptions. For instance, in NICE MTA (TA814), the conditional discontinuation rates for abrocitinib were assumed equal to those for upadacitinib. The population from which the conditional discontinuation rates were obtained varied (in some instances including systemic therapy naïve patients, in other instances systemic therapy experienced patients only from post-hoc analyses). Furthermore, the discontinuation rates did not consistently come from patients who had achieved the EASI 50 and DLQI ≥4pt improvement, in some cases being substituted by the EASI 75 or IGA 0/1. Finally, in some instances the trial was of shorter duration. Conditional discontinuation rates stratified by treatment are therefore highly likely to be biased.

This issue was also noted by AbbVie in the consultation on the appraisal consultation document for TA814, (committee 2 papers), who stated that applying individual treatment conditional discontinuation rates may bias the results. Under the EAG's preferred approach, conditional discontinuation is derived from each trial without adjustment for differences, whereas expanding the assumption of responder-derived values (as has been done for the utility values) to also cover conditional discontinuation is consistent and removes a potential bias where the evidence-base for differences remains unclear. As noted by AbbVie, more recent clinical trials, such as AD UP, were conducted at a time when treatment choice in clinical practice and the clinical trial setting had drastically improved. Clinical expert opinion suggests that availability of alternative treatments is likely to influence patient discontinuation. Furthermore, demographics and disease characteristics of the various treatments and their respective studies may vary slightly, with a progressively more moderate population participating in studies of more recent drugs and thus these patients would be more likely to discontinue than more severe patients. Therefore, extending the assumption of responder values for health state utility values to also cover conditional discontinuation is a reasonable approach when considering disease-specific utilities. In the present appraisal, patients with a response to treatment were assumed to have similar risk of discontinuing treatment.

Given the substantial uncertainty associated with short-term conditional treatment data, advice was sought from attendees at a UK HTA advisory board (which was conducted to inform the development of the company submission) who advised that equal discontinuation rates across treatment arms should be applied. Based on the advisory board feedback, Almirall believes that this was also the approach taken in the final base-case in TA814.

2. Provide further details on how the conditional discontinuation rates for each treatment were derived from their respective trials.

COMPANY RESPONSE: The conditional discontinuation rates for each treatment were sourced from the NICE MTA (TA814) where available. Assumptions regarding conditional discontinuation rates were also taken from TA814, such as assuming that conditional discontinuation rates for abrocitinib were equal to those of upadacitinib. Details regarding the source of discontinuation rates are provided in the table below, with further details of the methods used previously provided in our clarification responses.

Table 1: Conditional discontinuation data and assumptions

Treatment		Source/assumptions
Monotherapy – Adults		
Lebrikizumab	[redacted]	Discontinuation rate between week 16 and week 52 in pooled ADvocate 1 & ADvocate 2, conditional on achieving EASI 50 & DLQI ≥4
Abrocitinib	[redacted]	As per NICE TA814, assumed to be the same as upadacitinib
Baricitinib	[redacted]	As per NICE TA814, for abrocitinib and baricitinib, the EAG assumed the same conditional discontinuation as upadacitinib as they are all JAK inhibitors
Dupilumab	3.70%	As per NICE TA814, assumed to be the same as dupilumab combination therapy
Tralokinumab Q2W	8.1%	Pooled data from ECZTRA 1 and ECZTRA 2: % dosed in maintenance phase who discontinued, Figure S3 from Wollenberg et al., 2021
Tralokinumab Q4W	11.45%	Pooled data from ECZTRA 1 and ECZTRA 2: % dosed in maintenance phase who discontinued, Figure S3 from Wollenberg et al., 2022
Upadacitinib	[redacted]	As per NICE TA814, pooled data from Measure UP 1 (n/N = 1/28) and Measure UP 2 (n/N = 1/52) in 15mg upad arm. Pooled data from Measure UP 1 (n/N = 1/25) and Measure UP 2 (n/N = 2/43) in 30mg upad arm. Only second-line systemic treatment reported.
Combination therapy – Adults		
Lebrikizumab	[redacted]	Discontinuation rate between week 16 and week 52 in ADhere-ADjoin, conditional on achieving EASI 50 & DLQI ≥4
Abrocitinib	[redacted]	As per NICE TA814, assumed to be the same as upadacitinib
Baricitinib	[redacted]	As per NICE TA814, for abrocitinib and baricitinib, the EAG assumed the same conditional discontinuation as upadacitinib as they are all JAK inhibitors
Dupilumab	3.70%	As per NICE TA814, source from TA534. Estimate accepted by the committee. Data based on annual discontinuation in CHRONOS, defined as non-completers in the 52-week treatment period among responders at week 16.
Tralokinumab Q2W	1.45%	ECZTRA 3, figure S2, Silverberg et al., 2021
Tralokinumab Q4W	4.35%	ECZTRA 3, figure S2, Silverberg et al., 2021
Upadacitinib	[redacted]	As per NICE TA814, AD UP. Data are based on second-line systemic treatment subgroup only (n/N = [redacted]) in 15mg arm & (n/N = [redacted]) in 30mg arm

3. Explain why the conditional discontinuation rate for lebrikizumab is much higher than the discontinuation rates of the other comparators (EAG report section 4.2.6.2)

COMPANY RESPONSE: The conditional discontinuation data for all individual treatments is very heterogenous. One possible reason why the conditional discontinuation rate for lebrikizumab is higher than that for other comparators is that for the combination therapy setting, this rate was informed by a patient population who rolled over from one study (ADhere) to another (ADjoin), whereas for other treatments, conditional discontinuation rates were sourced from single studies. In the case of lebrikizumab, patients had to transition from ADhere to ADjoin, and not all patients decided to roll over.

The ADhere sample size was low (211), and patients were randomised 2:1 to lebrikizumab +TCS vs. placebo + TCS. In the ADhere study, only patients who received lebrikizumab Q2W + TCS and were per protocol responders at week 16 were invited to transition to ADjoin; only 86 patients decided to roll-over to the extension study (ADjoin). Once in the extension study, these patients were re-randomised 2:1 to either lebrikizumab Q2W (57 patients) or lebrikizumab Q4W (29 patients). For all these reasons, the population we are focusing on is small and thus even a few discontinuations have a significant impact on the percentage of the discontinuation rate.

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

- EAG report comment on the expected effect of the CE estimates: "*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*."

COMPANY RESPONSE: Almirall would like to provide a proactive response to this point raised as part of Issue 1 as we believe this to be helpful to the EAG at this time.

Almirall does not have access to the comparator data to be able to state whether the inclusion of people naïve to systemic treatment might have biased the NMA results overall. However, we are able to provide evidence from subgroup analyses from our own clinical studies demonstrating that response to lebrikizumab does not differ between systemic therapy naïve and systemic therapy experienced patients (with the limitation that prior systemic therapy was not a pre-specified stratification factor).

Please see below pooled data from ADvocate 1 and ADvocate 2 for the week 16 outcomes of EASI 50 (Table 2), EASI 75 (Table 3) and EASI 50 and DLQI ≥ 4 point reduction (Table 4). A forest plot is also presented (**Figure 2**). The data show that there is no statistical difference between 'prior systemic' and 'no prior systemic' patients in ADvocate 1 and ADvocate 2 (pooled data). Please note that prior systemic patients were defined as those who received prior CsA, methotrexate, azathioprine or MMF.

Table 2: EASI 50 at Week 16 (NRI). Pooled mITT (ADvocate 1 and ADvocate 2)

Table 3: EASI 75 at Week 16 (NRI). Pooled mITT (ADvocate 1 and ADvocate 2)

Table 4: EASI 50 and DLQI ≥ 4 Point Reduction at Week 16 (NRI). Pooled mITT (ADvocate 1 and ADvocate 2)

[redacted]

Figure 2: Parameters by Prior Systemic or No Prior Systemic at Week 16 (NRI). Pooled mITT (ADvocate 1 and ADvocate 2)

Presently, we can also provide you with post-hoc findings from the ADvantage study for EASI 75 response at week 16 regarding prior systemic use (see Table 5). Again the data show that there is no statistical difference associated with any prior systemic treatment. We are currently working to generate more results stratifying by those who received prior ciclosporin, methotrexate, azathioprine and MMF only. These results can be made available to the EAG once complete.

Table 5: ADvantage (Post Hoc): EASI 75 at Week 16, Efficacy by prior systemic therapy (MCMC-MI)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Patient Organisation Submission

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

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

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

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Eczema Outreach Support
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Eczema Outreach Support provides practical and emotional support to over 4,000 children with eczema living across the UK and their families. We currently have 4,012 member families. We are funded through grants from trusts and foundations, Medical Industry partners, private companies and through donations from our members and the general public. A full list of our funders is available in our annual accounts: Annual Report – Eczema Outreach Support (eos.org.uk) Medical industry partners include: - Sanofi - AbbVie - Leo Pharma - Pfizer - Pierre Fabre
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12	We have not received any funding from Almirall in the last 12 months or prior to this. We have received funding from the following companies in the last 12 months: 1. AbbVie: £15K towards EOS's charitable activities 2. Leo Pharma: £7,500 to support the running of EOS charitable activities in 2023 3. Pfizer: £19,790 to deliver a health inequalities research project with a health consultancy firm

months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	4. Sanofi: £35K to support EOS's charitable activities, ultimately supporting patient care 5. Pierre Fabre: £12k towards educational support to the families struggling with eczema across the UK
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	One to one support calls Peer support sessions EOS Closed Facebook Group EOS Youth Panel

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Eczema is vastly misunderstood as “a bit of itchy skin” by so many, including the people that children expect to help them. GPs, teachers and friends can all regularly minimise the condition and tell children that they’ll grow out of it. Children and young people feel ashamed for struggling, avoid asking for help and then withdraw. Children as young as four tell us that they are bullied at school for looking different and that no-one will hold their hand in case they “catch” their eczema. These experiences have a fundamental impact on a child or young person’s self-esteem and their ability to trust and make connections with others at the time and in the future. Furthermore, eczema is a complex disease shaped by genetic, immunologic and environmental factors, which makes its management unique to each individual and based on a long process of trial and error. There is no cure for eczema, only treatments to manage the symptoms, however they don’t always work. Carers of a child with eczema report despair, loss and frustration as they struggle to help their child. Sleepless nights have an enormous impact on the whole family and carers report strained family relationships as a result. Caring for a child with moderate to severe eczema can significantly affect the mental wellbeing of carers who often have no-where to turn and feel isolated and alone. Carers struggle to access support from friends and extended family who can’t understand how a skin condition could have such a negative impact on a family. Some carers need professional mental health support, however, accessing this can be impossible depending on a person’s location, availability of services and cost due to lack of NHS provision. In summary, uncontrolled eczema has a huge psycho-social impact on patients, their families and society. "*Eczema is far more than dry skin or a bit of an itch. Eczema can demand an all-consuming lifestyle and coping techniques which need to be embraced by not only the sufferer, but their family as well. Only when people fully understand the far-reaching impact of this relentlessly itchy, intolerable skin condition, can we hope for better treatment and acceptance.”* Mother of a child with eczema.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There are concerns from many young people and their carers who feel topical steroids are not safe and want other options. However, they are not often aware that most other treatment options are not available to everyone and there are guidelines and criteria as to who and when they can be used. Many initially expect to be able to access all treatments and are confused and disappointed when they cannot. Our members share the struggles they face to access mental health support for their child or young person citing long NHS waiting lists and the impact of eczema on mental wellbeing being unrecognised by some clinicians. As eczema can have a significant impact on mental wellbeing, access to psychological support is essential to ensure that young people can thrive. Currently, many families are not receiving the care that they need. Our members share the need for clearer instructions and support on how to use treatments safely and effectively, especially from Primary Care clinicians. Many families also express concern over being prescribed topical corticosteroids which they believe to be unsafe and want to access alternative steroid-free treatments. Many families have experienced a lack of understanding about the complex and individual nature of eczema from Primary Care clinicians and that they often need to fight very hard to get a referral to Dermatology despite their child's eczema remaining uncontrolled. They also report that there can be an inconsistent approach to treating eczema amongst different healthcare professionals treating the same patient. Carers that have been advised by Dermatology teams that calcineurin inhibitors or immunosuppressants are the next treatments for their child can feel frightened of their potential side effects and the long-term impacts. Many don't feel they receive enough information to make an informed decision about whether to use them or not.
8. Is there an unmet need for patients with this condition?	Delays in being able to access Dermatology teams are becoming a real issue for many families, especially when the condition is severe. A growing number of our members are seeking advice from private dermatologists due to waiting times to see NHS Dermatology teams, however, many private dermatologists don't have referral pathways into more advanced treatments and families are referred back into the NHS. As eczema management is so unique to each individual, a diverse range of treatments are required to ensure that there are options for everyone experiencing it. Many families we work with report that their child's eczema is undertreated, and they struggle to access the treatment and support they need to manage the condition. Eczema is overall not seen as a priority for the NHS in comparison to other conditions, such as cancer, as it is not life ending. However, eczema can cause huge misery, isolation and distress for whole family units. Eczema must be recognised for the impacts it can have on patients and their families across the NHS and in wider society. Many families are seeking a cure for eczema and the treatment that would provide this.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	If Lebrikizumab can be used as a monotherapy and patients can cease using topical steroids whilst accessing it, this could have an advantage for those who are concerned about using steroids (particularly those concerned about topical steroid withdrawal) and could improve treatment adherence. New treatment options can increase the psychological wellbeing of family units. At the point a young person would be eligible to receive this technology, they and their carers have often felt hopeless and that nothing is working. To bring in another option for over 12s can bring hope, motivation and a higher rate of treatment adherence as the family feel more positive that something will work. In comparison to phototherapy which can be effective for many patients, Lebrikizumab could provide another treatment option that may require less travel and attendance in hospital reducing the financial burden on families and the emotional impacts of missed school/college to attend appointments. However, we need further information on how it will be administered and monitored to establish this.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and their carers often have concerns when treatments are new on the market as the long-term side effects might be unknown. Other concerns include: - Whether the technology will mean that their young person will be immunocompromised - Whether they will still need to use topical treatments in conjunction with this technology to control their eczema and the impact of introducing and managing another treatment on the young person and carer - Whether a patient will need to be on the treatment for a significant amount of time before they see improvements/know if it is effective. It must also be understood that by the time patients are able to access this technology, they may be exhausted from trying a range of other treatments that haven't worked and may feel scepticism about using this one. More detail on how the technology would be administered and monitored is needed to provide more feedback on the disadvantages patients/carers would feel it had. For example, would there be a need to access therapists if a young person had a fear of needles and required support to be able to use the technology?

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As we previously stated, consideration should be given to adolescents as a specific group as they may require higher levels of support and education to successfully manage their eczema and engage with this technology effectively. Consideration must be taken over whether this technology will be available in all units or whether patients will have to be transitioned to regional centres to access it. If it is only available in regional centres, this may limit who can access the treatment due to funding streams and availability of clinicians with the expertise to administer. Some young people may also be unable to travel to central sites due to costs of carer support.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As previously stated, consideration should be given to patient groups living in rural areas or those on low incomes if the treatment requires frequent hospital visits, particularly to central sites. Families may be unable to cover travel costs making the treatment inaccessible for them. Consideration must be given for young people and their carers where English is not their first language as information is often provided in English meaning side effects may not be fully understood and a patient/carer may not be able to give informed consent. Consideration must also be given to young people whose developmental stage does not reflect their chronological age and the additional support needs that they might have to enable them to access the technology.

Other issues

13. Are there any other issues that you would like the committee to consider?	We previously mentioned red as a term that did not cover all skin tones and you removed the term. Looking again, the below could be included (or similar) to acknowledge the diversity of skin types: "It is characterised by a dry, itchy, erythematous (red in light skin tones and purple grey in skin of colour) rash". The recent publication of the TREAT study should be considered within the NICE guidance: https://doi.org/10.1093/bjd/ljad281 We would stress again that the NICE guideline should be updated to included recent research relating to eczema and treatment options.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The impact of eczema on patient and their families continues to be underestimated and families continue to suffer without the right treatment and support • Patients and their carers should be made fully aware of where this technology would fit in their eczema journey and of what the criteria would be to access it • The individual support needs of young people should be considered if this technology was to be offered to them to ensure adherence • There could be a potential inequity of service provision for young people with eczema if this technology wasn't made widely available due to a patient's locations and/or income • Eczema management is unique to each individual, so a diverse range of treatment options is required.

Thank you for your time.

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Please select YES if you would like to receive information about other NICE topics - **YES**

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Single Technology Appraisal

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	National Eczema Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	National Eczema Society is the UK charity for people of all ages living with eczema, and those who care for them. We support people with information and advice about eczema and its management and treatment, which we deliver through our website, social media platforms, publications and nurse-supported Helpline. We are the campaigning voice for people with eczema and raise awareness of their needs with healthcare professionals, the Medicines and Healthcare products Regulatory Agency (MHRA) and other relevant organisations, and the government. We are funded by membership fees, donations from the public and organisations, and our corporate partners (pharmaceutical and emollient companies that sell products or services for people with eczema). We have approximately 2,000 members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Yes, the manufacturer Almirall has been a corporate member of National Eczema Society since January 2023 and the corporate membership agreement complies with the ABPI code of practice. The annual corporate membership fee paid by the company is £20,000 plus VAT. The Corporate Membership Scheme allows company partners to demonstrate public support for the important work of the Society. The funding helps pay for the charity's core operating costs with the purpose of helping the Society achieve its overall objective of supporting people living with eczema. Almirall has also provided project-specific funding to National Eczema Society of £4,620 (including VAT), to part-fund a series of educational podcasts about living with eczema. Regarding manufacturers of comparator products: Eli Lilly is a corporate member of National Eczema Society and pays an annual fee for this of £20,000 plus VAT. Eli Lilly has also provided funding of £6,000 (including VAT) for support of the company's #GOALS

amount, and purpose of funding.	eczema awareness campaign, and £4,620 (including VAT) to part-fund a series of educational podcasts about living with eczema. AbbVie is a corporate member of National Eczema Society and pays an annual fee for this of £20,000 plus VAT. AbbVie also provided project-specific funding of £4,620 (including VAT), to part-fund a series of educational podcasts about living with eczema, plus a £340 speaker fee. Sanofi was a corporate member of National Eczema Society, but this ceased in March 2023. Sanofi has provided project-specific funding of £9,140 to produce an educational video about eczema, and provided an educational grant of £36,000 to fund the production and distribution of the charity's eczema information booklets, plus a £431 speaker fee. Leo Pharma is a corporate member of National Eczema Society and pays an annual fee for this of £10,000 plus VAT.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	National Eczema Society operates a dermatology nurse-supported Helpline service, responding to telephone, email and social media enquiries from people affected by eczema who are seeking advice either on their own behalf or for a loved one. The calls and messages we receive give us a valuable insight into the experiences of people living with eczema and the many challenges they face. In 2022 we responded to over 1,500 Helpline enquiries. We also gain insights from the conversations and comments shared by people with eczema on our busy social media platforms. We carried out a survey with over 1,000 patients and carers in the UK in 2020, which revealed further insights into the lived experience of eczema and how it affects physical health, mental health, quality of life and people's life chances. In 2023 we carried out a survey with nearly 600 adults with eczema in the UK to learn more about the mental health impacts of the condition. More than three quarters of respondents to this survey reported that eczema reduced their quality of life in certain ways; for example, by making it difficult for them to sleep, making them feel self-conscious, and causing them to worry.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Atopic eczema is a chronic skin condition characterised by dry skin and often unpredictable flare-ups, involving inflammation and itchiness. Even when eczema is mild to moderate (not severe), if it's not well managed, it can significantly affect a person's quality of life. In the UK, about one in five children and one in ten adults has eczema. The symptom of itch, which can be intense and relentless, is one of the most challenging aspects of eczema. People who are constantly itchy and/or have eczema on visible areas of their body can feel extremely self-conscious about their condition and appearance, and reluctant to leave their home. This can put a strain on relationships. Itchiness also makes it difficult to sleep, affecting concentration and the ability to carry out tasks effectively during the day. Frequent scratching can lead to skin damage and increase the risk of infection. Managing eczema takes a lot of time. Applying treatments multiple times a day is necessary, and people who scratch and bleed overnight may need to wash their bedding every day. Children and young people may feel embarrassed by frequent emollient applications at school. Some individuals with eczema also struggle with mental health conditions, and find it particularly demanding and stressful to keep up with an eczema care regimen. Even those without diagnosed mental health issues can find daily eczema management burdensome. Recent reports and surveys show that eczema has significant psychosocial impacts on children and young people, including low self-confidence, friendship difficulties, and school attendance problems. Parents sometimes have to cancel family activities due to their child's eczema, and some feel it strains their relationships with their other children. Caring for someone with eczema can be physically and emotionally draining. Caregivers need to apply treatments frequently, provide emotional support, and accompany the person to medical appointments. Caregivers are also likely to be affected by the sleep difficulties of the person in their care, and suffer from a lack of sleep themselves.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	While the number of treatments available on the NHS for atopic eczema has increased in recent years, many patients with moderate to severe symptoms and their carers still consider eczema treatments to be limited in number and effectiveness. Many patients are reluctant to use topical steroids regularly to manage their symptoms due to concerns about potential side effects, particularly those related to topical steroid withdrawal, which has been the subject of numerous (often sensationalist) news stories in recent years. Access to topical calcineurin inhibitors is limited, generally being prescribed for areas of delicate skin only. Phototherapy and immunosuppressant drugs (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil) are usually the next options in the treatment pathway. Phototherapy, which requires a significant time commitment of two or three hospital appointments per week over several months, can be impractical for many individuals. Immunosuppressant drugs have the potential for significant long-term harm from severe adverse side effects, causing concern for patients. Biologic drugs have fewer potential side effects than immunosuppressants, but are currently only available to patients for whom immunosuppressants have not proven effective and those who would not be eligible to take them. In addition, they are not effective for everyone who tries them, or suitable for people with certain co-morbidities. The MHRA's warning for JAK-inhibitors has made some patients and dermatologists worried about using/prescribing these treatments.
8. Is there an unmet need for patients with this condition?	While five new treatments have been made available for people with moderate to severe atopic eczema in recent years, these treatments are not effective for everyone who tries them. Atopic eczema is a heterogeneous condition, and patients will respond differently to different treatments. This being the case, making more treatments available for long-term eczema management will increase the likelihood that all patients with moderate to severe atopic eczema will eventually find a treatment or combination of treatments that works effectively for them. Biologic drugs appear to have a better safety profile than immunosuppressants, so having more types of biologic drugs available is a positive step for people with eczema.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The effectiveness of lebrikizumab and its rapid onset of action are advantages of the treatment. Phase 3 clinical trials of lebrikizumab (ADvocate1 and ADvocate2) have shown that it significantly improves atopic eczema symptoms in adults and adolescents in terms of skin clearance and itch compared with placebo, and that improvements occur soon after starting treatment. In the phase 3 clinical trial ADhere, lebrikizumab used alongside topical steroids was compared with placebo used alongside topical steroids in adults and adolescents with moderate to severe atopic eczema. This trial showed that using topical steroids in combination with lebrikizumab to treat eczema flares has a positive effect. Lebrikizumab has a good, consistent safety profile. The side effects of lebrikizumab in clinical trials have tended to be non-serious, mild or moderate in severity. Patients are likely to need fewer visits to outpatient clinics for observation and monitoring on lebrikizumab than for immunosuppressant drugs, which would be welcomed by patients and desirable in terms of NHS resource use.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	One disadvantage of lebrikizumab is the side effect of conjunctivitis, which has been identified in clinical trials as a common side effect. Even when conjunctivitis is mild or moderate, dealing with a visible and sometimes uncomfortable eye condition can cause embarrassment or self-consciousness, and affect self-esteem and social interactions. We have heard from a number of patients in real-life clinical settings who have had to discontinue dupilumab because of eye-related side effects. This may also occur with lebrikizumab. Lebrikizumab is unlikely to work effectively for everyone eligible to use it. Some patients may start treatment and not receive sufficient benefit to warrant continuing, which would be demoralising and result in a longer period of poorly controlled symptoms. The fact that lebrikizumab comes as an injection rather than a tablet will make it less appealing to some patients. Patients and carers, especially adolescent patients, tend to prefer oral over injectable drugs.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with atopic eczema affecting the face and/or hands might benefit more from lebrikizumab. The ADvocate1, ADvocate2 and ADhere trials showed that lebrikizumab was effective in clearing and improving hand and facial eczema in most people with moderate to severe atopic eczema at week 16, both with and without concomitant topical steroid use. Both facial and hand eczema tend to have a significant impact on patients' mental health as well as their physical health, as they affect such a visible and/or frequently used part of the body. If the evidence for its efficacy in these areas is sufficiently strong, perhaps lebrikizumab should be offered to patients with hand and/or facial eczema before immunosuppressants or alitretinoin (in the case of hand eczema). Patients with a history of conjunctivitis may be less likely to experience an overall benefit from lebrikizumab if this increases the likelihood of their experiencing conjunctivitis as a side effect of lebrikizumab. If this side effect is moderate to severe, it may cause patients to discontinue the treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues

13. Are there any other issues that you would like the committee to consider?	N/A

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Since atopic eczema is a heterogeneous condition, with different treatments working effectively for different people, the introduction of lebrikizumab would increase the likelihood that patients with moderate to severe eczema would find a long-term treatment that is effective for them. • Trial data results show that lebrikizumab can not only improve, but rapidly improve, the symptom of itch (and other symptoms), which many people with eczema report as being the most debilitating. • Given patients' concerns about the potential side effects of immunosuppressants, a treatment with a better safety profile will be welcomed. Adverse events in lebrikizumab trials were mainly non-serious, mild or moderate. • Lebrikizumab appears to be effective in clearing and improving facial and hand eczema, which are challenging areas of the body to manage, and often present specific difficulties for patients.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists (the BAD)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? **Yes** A specialist in the treatment of people with this condition? **Yes** A specialist in the clinical evidence base for this condition or technology? **Yes**
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To successfully treat the skin of people living with moderate-to-severe atopic dermatitis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Investigators' Global Assessment (IGA) score of 0 or 1 which represents clear or nearly clear skin, a 75% or 90% reduction in the Eczema Activity and Severity Index (EASI), a reduction in Dermatology Life Quality Index (DLQI) score of at least 4 points, a Patient-Oriented Eczema Measure (POEM) score of 0 to 2 which represents clear or nearly clear skin
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need, albeit not as urgent, as there are multiple treatment options available to NHS patients with atopic dermatitis including conventional systemic treatments such as ciclosporin, methotrexate and azathioprine, biologics such as dupilumab and tralokinumab, and Janus kinase (JAK) inhibitors such as baricitinib, abrocitinib and upadacitinib. However, there are people who do not respond adequately to or are unable to tolerate existing treatments outlined above, and they will need to have access to a range of safe and effective systemic treatments.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is a treatment ladder or stepped-care approach to managing people with atopic dermatitis. 1. Emollients +/- topical corticosteroids +/- topical calcineurin inhibitors would be advised in virtually all patients, with light-based or systemic treatments added on to topical treatments. 2. Phototherapy. 3. Conventional systemic therapy such as ciclosporin, methotrexate or azathioprine. 4. Systemic therapy that has become available more recently such as biologics (dupilumab and tralokinumab) or Janus kinase inhibitors (baricitinib, abrocitinib and upadacitinib).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are NICE guidelines on the diagnosis and management of eczema in the under 12s published in 2007 and Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of atopic eczema in primary care published in 2011. The European guidelines on atopic eczema published in 2022 (https://doi.org/10.1111/jdv.18345) might be most relevant currently and includes systemic therapy appraised by NICE from 2018 to 2022 such as dupilumab, baricitinib, abrocitinib, tralokinumab and upadacitinib.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is some variation in the pathway of care across England, but it is more marked in Scotland where Health Boards may define their own policies. Therefore, according to NICE recommendations, people with moderate-to-severe atopic dermatitis are eligible to have treatment with newer systemic treatment options such as dupilumab, baricitinib, abrocitinib, tralokinumab and upadacitinib if their disease has not responded to at least one systemic immunosuppressant, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or if these are not suitable. However, in some parts of Scotland, these patients need to have failed to respond to or be unsuitable to have at least two immunosuppressive treatments.
9c. What impact would the technology have on the current pathway of care?	This technology would add to the treatments available for people who require biological treatment to manage their moderate-to-severe atopic dermatitis. It will be especially important as an alternative to other biologics available for managing people with moderate-to-severe atopic dermatitis and may be used in primary or secondary failure to the previously available biologics and Janus kinase inhibitors used in the management of these patients.
10. Will the technology be used (or is it already used) in the same way as current	Yes.

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	No significant difference – lebrikizumab would be used as an alternative to previously NICE-approved biologics for managing people with moderate-to-severe atopic dermatitis.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary and tertiary care.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant investment as other similar drugs are already being used.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Having a variety of drugs will be useful because atopic dermatitis is a complex and diverse disease with different pathogenic mechanisms in different individuals. This is reflected in inter-individual variation between people's responses to dupilumab and tralokinumab. Lebrikizumab will extend this choice.
11a. Do you expect the technology to increase length of life more than current care?	No.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, for people who experience primary or secondary failure to previously available biologics and Janus kinase inhibitors used in the management of moderate-to-severe atopic dermatitis. Lebrikizumab may have superiority over previously available biologics in this group.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Evidence is not yet available to know this, but with the advent of personalised medicine and better prediction algorithms we may find such patient groups.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Same as current care.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that dermatologists will adopt a process of identifying and managing people on lebrikizumab similarly to the processes identified in the NICE TA guidance published so far, e.g. dupilumab and tralokinumab EASI and DLQI responses at 16 weeks.
15. Do you consider that the use of the technology will result in any	Yes, there is emerging evidence that lebrikizumab may improve health-related quality of life outcomes in people living with moderate-to-severe atopic dermatitis (https://pubmed.ncbi.nlm.nih.gov/33333295/,

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	https://pubmed.ncbi.nlm.nih.gov/37318750/, https://pubmed.ncbi.nlm.nih.gov/36630140/ and https://pubmed.ncbi.nlm.nih.gov/37266844/).
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is one of several innovative novel biologic treatments for atopic dermatitis.
16a. Is the technology a 'step-change' in the management of the condition?	This technology will be used alongside previously identified biologics and Janus kinase inhibitors used for managing people with moderate-to-severe atopic dermatitis.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, those whose atopic dermatitis is not controlled by other drugs.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There is evidence that this new technology may have fewer side effects (especially with reference to the ocular side effects of dupilumab) compared to some other agents identified above. There is not (according to current evidence) an increased safety signal with the new technology compared to previously assessed technologies identified above. However, further research will help ascertain this.

Sources of evidence

18. Do the clinical trials on the technology reflect	Yes

current UK clinical practice?	
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	EASI and DLQI; HOME initiative: EASI, POEM, NRS-11, RECAP or ADCT, DLQI http://www.homeforeczema.org/
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 814 [TA814]?	No.

21. How do data on real-world experience compare with the trial data?	Not known yet.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Treatment which adds to the range available for managing people with moderate-to-severe atopic dermatitis. • Useful because of the heterogeneity in atopic dermatitis as a complex trait.

Thank you for your time.

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Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5:00pm** on **Wednesday 13 March 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Treating severe atopic dermatitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Richard Weller
2. Name of organisation	NHS Lothian, and University of Edinburgh
3. Job title or position	Professor of Medical Dermatology and Honorary Consultant Dermatologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with severe atopic dermatitis? ☒ A specialist in the clinical evidence base for severe atopic dermatitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for severe atopic dermatitis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Reduction of disease severity and symptoms in a safe manner

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction of disease severity to mild or less.
10. In your view, is there an unmet need for patients and healthcare professionals in severe atopic dermatitis?	Yes. We now have a number of effective treatments for severe eczema (2 biologics and 3 JAKis), but not all patients respond and MHRA has put out a warning about potential side effects for JAKis. Further choice in biologics offers treatment options for Dupi/Tralo non-responders/intolerant patients
11. How is severe atopic dermatitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	European guidelines here: European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy - Wollenberg - 2022 - Journal of the European Academy of Dermatology and Venereology - Wiley Online Library Pathway of care defined for other biologics/JAKis which would be analogous to letbrikizumab patients. In Scotland/England Topical treatment->phototherapy (if available)->systemic treatment with Ciclosporin/MTX/Azathioprine->Biologics/JAKis. Stepping up treatment level on failure to respond/intolerance of that level of Rx. Move to biologics/JAKis following failure/intolerance of one systemic agent (usually Ciclosporin) in England, but usually 2 or 3 in Scotland. Lebrikizumab would fit in at same level as Dupilumab.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	Yes- exactly analogous to Dupilumab. Secondary care, specialist eczema clinic. No change in healthcare resource use needed. No investment needed to introduce

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	No effect on lifespan, but may increase quality of life compared to existing benchmark Dupilumab
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No difference from dupilumab
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Same as dupilumab. Start with mod to severe eczema not responding to systemic Rx. Assess at 16 weeks. Continue if >EASI 75
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Improved general wellbeing- working ability- sleep.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Not a step change on Dupilumab, but potentially an incremental improvement.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No different from Dupilumab. Conjunctivitis is main possible side effect- as Dupi.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In trials, patients did not need to have tried/failed an existing systemic but this has been the same for most trials of existing biologic eczema treatments. Best outcome measures are EASI 75, IGA and DLQI. All were measured in trials. No unexpected adverse events that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA814?	No
23. How do data on real-world experience compare with the trial data?	Don't know yet.
24. Would people who fail on methotrexate or ciclosporin A respond less well to lebrikizumab and other novel systemic therapies than patients naïve to systemic therapies?	Don't know.
25. Is it plausible that all treatments would have the same discontinuation rate at 52 weeks?	Discontinuation rates much lower with biologics than existing systemic treatments at one year. I expect them to be comparable with Lebri and Dupi
26. What are the most commonly used first line systemic therapies in clinical practice?	Cyclosporine then MTX. Azathioprine third
27. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	Eczema severity harder to assess with dark skin types. This may lead to undertreatment.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Highly effective treatment for severe eczema.

A competitor for Dupilumab

Safety of biologics seems higher than JAK inhibitors and higher than existing systemics.

Click or tap here to enter text.

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with severe atopic dermatitis or caring for a patient with severe atopic dermatitis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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Patient expert statement

Part 1: Living with this condition or caring for a patient with severe atopic dermatitis

Table 1 About you, severe atopic dermatitis, current treatments and equality

1. Your name	Stephen Pugh
2. Are you (please tick all that apply)	☒ A patient with severe atopic dermatitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with severe atopic dermatitis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	National Eczema Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with severe atopic dermatitis? **If you are a carer (for someone with severe atopic dermatitis) please share your experience of caring for them**	I have had serious eczema all life – over sixty years. I have used emollients and steroids (topical and sometimes oral) over that time. I have been an occasional hospital outpatient for eczema.
7a. What do you think of the current treatments and care available for severe atopic dermatitis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I was an early user of steroids for eczema when they started being used and they are helpful if used carefully, but are far from properly dealing with eczema when severe. I am aware that there are other treatments, notably immunosuppressants, but they have side effects and I have not used them. I am aware of those who have serious reservations about steroids and possible withdrawal effects. I have not experienced this.
8. If there are disadvantages for patients of current NHS treatments for severe atopic dermatitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I can only comment on steroids as I have not used other treatments. I found myself as a teenager using increasing amounts of strong steroid on my face when guidance on this was not clear. It failed to clear the problem and has left me with a face that often looks very red.
9a. If there are advantages of Lebrikizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Lebrikizumab help to overcome or address any of the listed disadvantages of current treatment**	I have not used Lebrikizumab, but I am highly supportive of other eczema treatments that may improve quality of life for sufferers and have fewer side effects than other treatments.

that you have described in question 8? If so, please describe these	
10. If there are disadvantages of Lebrikizumab over current treatments on the NHS please describe these. For example, are there any risks with Lebrikizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I cannot comment, on risks, but I am not conscious of any serious side effects of Lebrikizumab.
11. Are there any groups of patients who might benefit more from Lebrikizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I cannot comment.
12. Are there any potential equality issues that should be taken into account when considering severe atopic dermatitis and Lebrikizumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	I am conscious that eczema manifests in different ways with different skin colour, but I am not aware that Lebrikizumab's effectiveness varies according to skin colour.

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I feel that treatment options for moderate to severe eczema are very limited and not always effective, and some have serious side effects. The arrival of new treatments is very much to be welcomed, but it is important that the treatments are readily available to patients and so prescription by GPs and not just consultants is important.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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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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Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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Declared competing interests of the authors and advisors

The authors report none. Professor Carsten Flohr reports being paid in May 2022 by Almirall (travel costs and an honorarium) to make a presentation at a non-promotional Almirall-sponsored meeting where he spoke about the management of severe atopic dermatitis, using systemic medications, and in particular a living network meta-analysis and European treatment guideline for atopic dermatitis, both of which he leads. Prof Flohr also reports the following non-financial interests in the health technologies included in this appraisal within the previous 12 months: he was the Chief Investigator of an NIHR-funded trial (TREAT), which compared methotrexate with ciclosporin in children with severe atopic eczema, and, as mentioned above, Prof Flohr also leads the European treatment guideline and the living network meta-analysis.

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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Contributions of authors

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.

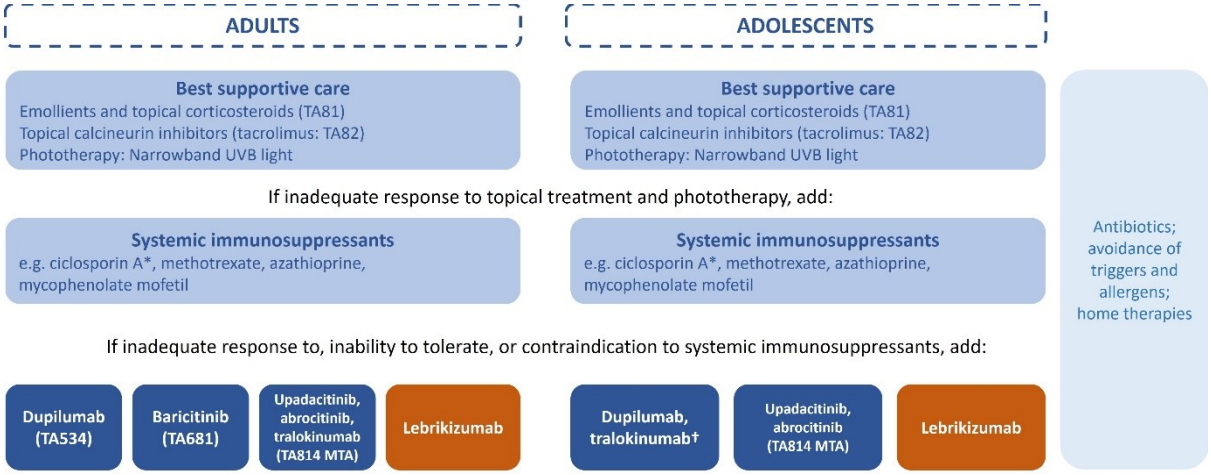
The CS describes the clinical pathway of care in CS section B.1.3.5 with the anticipated position of lebrikizumab shown in CS Figure 2 which we have reproduced below as Figure 1.

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.

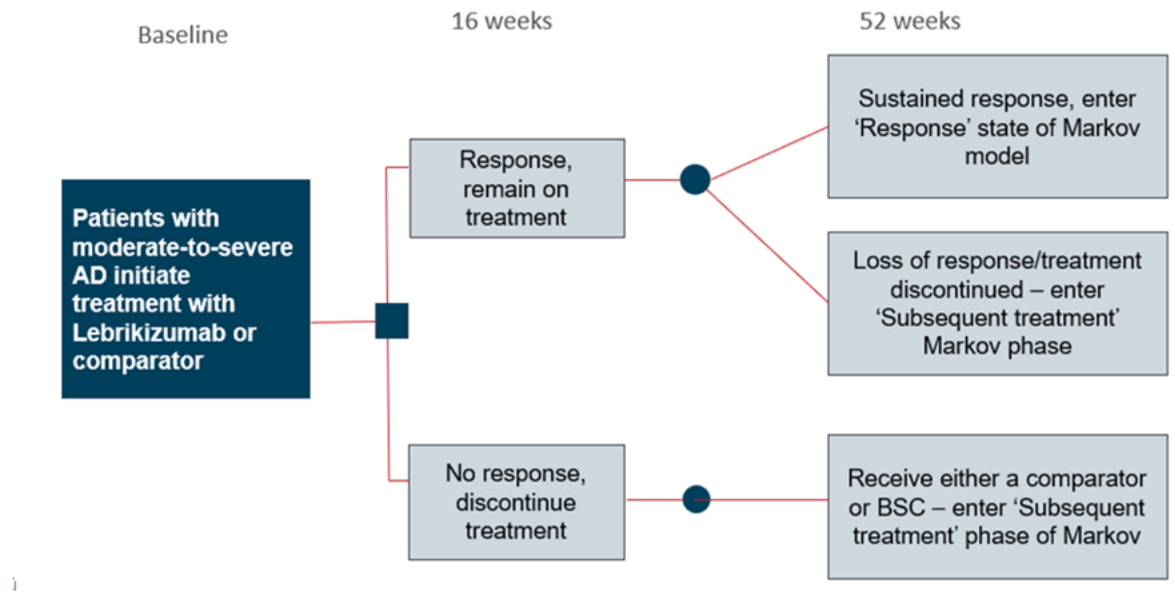


Figure 2 Decision-tree diagram

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

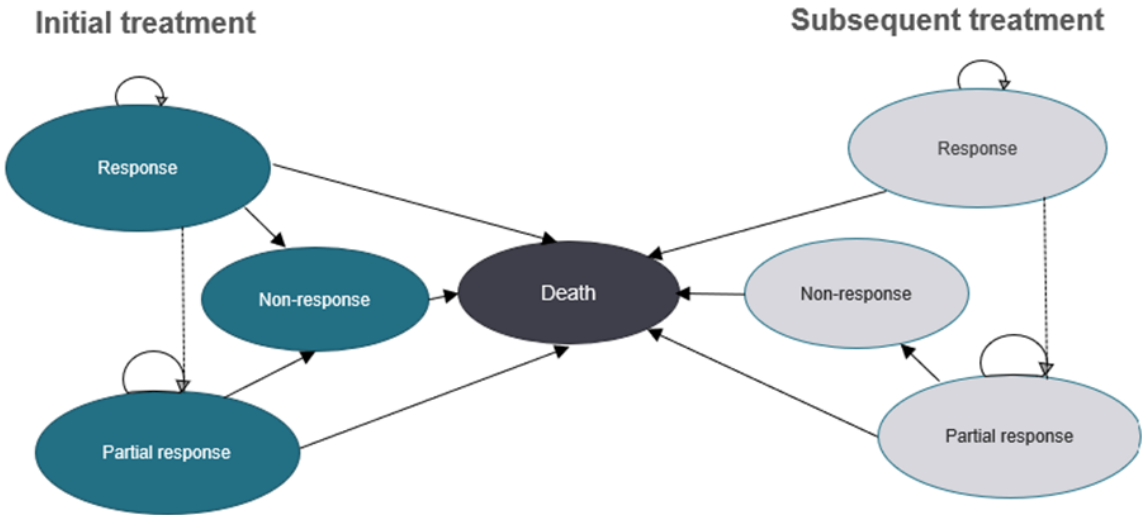


Figure 3 Markov model diagram

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.

8 REFERENCES

1. HOME. Harmonising Outcome Measures for Eczema (HOME). http://www.homeforeczema.org/about/about.aspx (accessed 12/12/2023).

2. Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. J Allergy Clin Immunol 2014;134(4):800-7.

3. Gooderham MJ, Bissonnette R, Grewal P, et al. Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document. Section II: Tools for Assessing the Severity of Atopic Dermatitis. J Cutan Med Surg 2018;22(1_suppl):10s-16s.

4. Rehal B, Armstrong AW. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. PLoS One 2011;6(4):e17520.

5. Futamura M, Leshem YA, Thomas KS, et al. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. J Am Acad Dermatol 2016;74(2):288-94.

6. National Institute for Health and Care Excellence. Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis (TA814), 2022.

7. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. Br J Dermatol 2017;177(5):1316-21.

8. Kleyn CE, McKenzie R, Meeks A, et al. Prevalence and treatment patterns of adult atopic dermatitis in the UK Clinical Practice Research Datalink. Skin Health Dis 2023;3(4):e232.

9. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy 2018;73(6):1284-93.

10. Chan LN, Magyari A, Ye M, et al. The epidemiology of atopic dermatitis in older adults: A population-based study in the United Kingdom. PLoS One 2021;16(10):e0258219.

11. National Institute for Health and Care Excellence. Frequency of application of topical corticosteroids for atopic eczema (TA81 final guidance), 2004.

12. National Institute for Health and Care Excellence. Tacrolimus and pimecrolimus for atopic eczema (TA82 final guidance), 2004.

13. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis (TA534 final guidance), 2018.

14. National Institute for Health and Care Excellence. Baricitinib for treating moderate to severe atopic dermatitis (TA681 final guidance), 2021.

15. Edwards S, Karner C, Jhita T, et al. Upadacitinib, abrocitinib and tralokinumab for treating moderate-to-severe atopic dermatitis (MTA assessment report for TA814), 2021.

16. European Medicines Agency. Lebrikizumab: Summary of Product Characteristics: EMA, 2023.

17. ClinicalTrials.gov. A study of lebrikizumab (LY3650150) in participants with moderate-to-severe atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT03443024?term=NCT03443024&draw=2&rank=1 (accessed 1st December 2023).

18. Stein Gold L, Thaçi D, Thyssen JP, et al. Safety of Lebrikizumab in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: An Integrated Analysis of Eight Clinical Trials. Am J Clin Dermatol 2023:1-13.

19. ClinicalTrials.gov. A study to evaluate the safety of lebrikizumab compared to topical corticosteroids in adult patients with atopic dermatitis. https://clinicaltrials.gov/ct2/show/NCT02465606?term=NCT02465606&draw=2&rank=1 (accessed 2 June).

20. Paller AS, Flohr C, Eichenfield LE, et al. Safety and efficacy of lebrikizumab in adolescent patients with moderate-to-severe atopic dermatitis: A 52-week, open-label, phase 3 study. Dermatology and Therapy 2023;13:1517-34.

21. Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. New England Journal of Medicine 2023.

22. Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere). JAMA Dermatology 2023.

23. Guttmann-Yassky E, Weidinger S, Silverberg, et al. Maintenance of efficacy and safety with lebrikizumab up to one year of treatment in patients with moderate-to-severe atopic dermatitis with or without topical corticosteroids. Oral presentation given at the World Congress of Dermatology, Singapore; 2023.

24. Almirall. [Data on File: ADvantage CSR] A randomised, double-blind, placebo-controlled phase 3 clinical trial to assess the efficacy and safety of lebrikizumab in combination with topical corticosteroids in adult and adolescent patients with moderate-to-severe atopic dermatitis that are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable (ADvantage). Clinical study report, 2023.

25. Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. Br J Dermatol 2023.

26. Warren RB, de Bruin-Weller M, Tsianakas A, et al. Lebrikizumab improves signs and symptoms of moderate-to-severe atopic dermatitis in patients inadequately controlled or ineligible for cyclosporine: a placebo-controlled, randomized phase 3 clinical study (ADvantage). (Oral presentation) EADV 2023 (European Academy of Dermatology and Venereology), Berlin; 2023.

27. Guttmann-Yassky E, Weidinger S, Simpson E. Efficacy and safety of lebrikizumab is maintained two years in patients with moderate-to-severe atopic dermatitis. Oral presentation given at the Fall Clinical Dermatology Conference, Las Vegas, NV, USA.

28. Eli Lilly Company. [Data on File: ADvocate 1 (KGAB) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 1). Clinical study report, 2022.

29. Eli Lilly Company. [Data on File: ADvocate 2 (KGAC) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADvocate 2). Clinical study report, 2022.

30. Eli Lilly Company. [Data on File: ADhere (KGAD) CSR] A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab when used in

combination with topical corticosteroid treatment in patients with moderate-to-severe atopic dermatitis (ADhere). Clinical study report, 2022.

31. Eli Lilly Company. [Data on File: ADjoin (KGAA) CSR] A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (ADjoin). Abbreviated clinical study report, 2022.

32. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatovener (Stockholm) 1980;Suppl. 92:44-47.

33. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.

34. Bowers M, Pickering R, Weatherall M. Design, objectives, execution and reporting of published open-label extension studies. Journal of Evaluation in Clinical Practice 2012;18(2):209-15.

35. EuroQol Research Foundation. EQ-5D-5L. https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/ (accessed 9 January 2024).

36. Oakley A. SCORAD. https://dermnetnz.org/topics/scorad (accessed 13 December 2023).

37. Eli Lilly Company. Statistical Analysis Plan Version 4. J2T-DM-KGAB (DRM06-AD04): A Randomised Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients with Moderate-To-Severe Atopic Dermatitis. NCT04146363, 2022.

38. Eli Lilly Company. Statistical Analysis Plan Version 5. J2T-DM-KGAC (DRM06-AD05): A Randomised Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab in Patients with Moderate-To-Severe Atopic Dermatitis. NCT04178967, 2022.

39. Eli Lilly Company. Statistical Analysis Plan Version 4. J2T-DM-KGAD (DRM06-AD06): A Randomised Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When Used in Combination with Topical Corticosteroid Treatment in Patients with Moderate-To-Severe Atopic Dermatitis. NCT04250337, 2021.

40. Almirall. Data on file: ADvocate 1, ADvocate 2 and ADhere post-hoc analyses, 2023.

41. Almirall. Data on file: Full technical report, Network meta-analysis of outcomes at Week 16, 2023.

42. Silverberg JI, Hong HC, Calimlim BM, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate-to-Severe Atopic Dermatitis without Topical Corticosteroids: An Updated Network Meta-analysis. Dermatol Ther (Heidelb) 2023;13(10):2247-64.

43. Wollenberg A, Howell MD, Guttman-Yassky E, et al. Treatment of atopic dermatitis with tralokinumab, an anti–IL-13 mAb. Journal of Allergy and Clinical Immunology 2019;143(1):135-41.

44. Riley RD, Dias S, Donegan S, et al. Using individual participant data to improve network meta-analysis projects. BMJ Evidence-Based Medicine 2023;28:197-203.

45. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.

46. Hodgson R, Sharif S, Beresford L, et al. Baricitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis. University of York: CRD and CHE Technology Assessment Group, 2020.

47. Edwards HA, McMeniman EK. The cost of dupilumab treatment for severe atopic dermatitis is largely offset by broader health-care savings and improvement in quality of life. Australas J Dermatol 2020;61(2):e273-e75.

48. ClinicalTrials.gov. Tralokinumab in Combination With Topical Corticosteroids in Japanese Subjects With Moderate-to-severe Atopic Dermatitis (ECZTRA 8). https://classic.clinicaltrials.gov/ct2/show/NCT04587453 (accessed 18 October).

49. Worm M, Simpson EL, Thaçi D, et al. Efficacy and Safety of Multiple Dupilumab Dose Regimens After Initial Successful Treatment in Patients With Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156(2):131-43.

50. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

51. Dias S, Welton NJ, Sutton AJ, et al. NICE Decision Support Unit Technical Support Document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials [Internet]. London: National Institute for Health and Care Excellence (NICE), 2011.

52. Turner RM, Jackson D, Wei Y, et al. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med 2015;34(6):984-98.

53. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE).

54. Achana FA, Cooper NJ, Dias S, et al. Extending methods for investigating the relationship between treatment effect and baseline risk from pairwise meta-analysis to network meta-analysis. Stat Med 2013;32(5):752-71.

55. Thom H, Cheng V, Keeney E, et al. Matching-Adjusted Indirect Comparison of Crisaborole Ointment 2% vs. Topical Calcineurin Inhibitors in the Treatment of Patients with Mild-to-Moderate Atopic Dermatitis. Dermatol Ther (Heidelb) 2022;12(1):185-94.

56. Almirall. Data on file: Technical report, MAIC and STC for w16-w52, 2023.

57. Wailoo A, Hernandez Alava M, Pudney, S. NICE DSU Technical Support Document 22 Mapping to estimate health state utilities. NICE, 2023.

58. National Institute for Health and Care Excellence. Final scope for the evaluation of Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over. 2023.

59. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE, London 2013.

60. Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397(10290):2169-81.

61. Silverberg JI, Toth D, Bieber T, et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol 2021;184(3):450-63.

62. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol 2022;158(5):523-32.

63. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021;184(3):437-49.

64. van Hout B, Jansse MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012;15:708-15.

65. National Institute for Health and Care Excellence. British National Formulary (BNF). https://bnf.nice.org.uk/ (accessed 1st December 2023).

66. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

67. NHS England. 2020/21 National Cost Collection Data Publication. https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ (accessed 1st December 2023).

68. Personal Social Services Research U. Unit Costs of Health and Social Care 2022 Manual. Personal Social Services Research Unit (PSSRU), 2022.

69. Schneider P, McNamara S, Love-Koh J, et al. QALY Shortfall Calculator. 2021.

70. Clinicaltrials.gov. A study of lebrikizumab in participants with persistent moderate to severe atopic dermatitis. https://clinicaltrials.gov/study/NCT02340234 (accessed 2nd January 2024).

71. Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol 2020;156(4):411-20.

72. Dermira Inc. J2T-DM-KGAD-A1 Protocol: A Randomised Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Lebrikizumab When Used in

Combination with Topical Corticosteroid Treatment in Patients with Moderate-To-Severe Atopic Dermatitis. NCT04250337, 2020.

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

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5:00pm on Thursday 1 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 7, Issue 6 heading The current heading for issue 6 is “Use of treatment-specific utility values”. The EAG states that the company used treatment-specific utilities in their base case, i.e. utility values conditional on response but also different for active treatments and best supportive care.	We suggest that the title is updated to “Use of treatment-specific utility values (active treatment vs. BSC)” to make it clear that this treatment-specific utility relates only to active treatments vs. BSC, and does not imply that different utility values were applied for all the different second-line systemic treatments (i.e. JAK inhibitors and biological treatments). The current heading is somewhat misleading. We suggest that this is updated throughout the EAG report where the utilities are mentioned, for example section 4.2.7.	To provide clarity to the heading for Issue 6	Amended as suggested.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 9, third paragraph	The sentence should read “The incremental cost-effectiveness results are shown in Table 4 and Table 5.”	Typographical error	Amended as suggested.

There should be an “and” in between “Table 4” and “Table 5”.			

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10 Final sentence at the bottom of page 10, commencing “Modelling errors identified…” has an incorrect section number at the end of the sentence.	Update the current “section 0” to read “section 6”. This would then read: “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.”	Typographical error	Amended as suggested.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Section 2.2.2, end of first paragraph that commences “The company’s	Include “signs and” so that the sentence reads:	Clinical accuracy	Amended as suggested.

description of lebrikizumab…" The end of the first paragraph highlights signs and symptoms of atopic dermatitis. The text would benefit from the inclusion of "signs" as well as symptoms.	"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."		

Issue 5

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 13, Section 2.2.2, second paragraph that commences "Marketing authorisation was granted…" The date of marketing authorisation is incorrect and should be amended to 16th November 2023 (instead of 21st November) to reflect the date that marketing authorisation for	The revised text should read: "Marketing authorisation was granted in the European Union on 16th November 2023 and MHRA approval was received on 19th December 2023".	Date of marketing authorisation correction	Amended as suggested.

lebrikizumab was issued by the EMA.			

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Section 2.2.2, third paragraph that commences "The lebrikizumab SmPC…" It would be beneficial to add the word "both" before "week 0 and 2 of treatment" for added clarity on the dosing, this would reflect lebrikizumab's SmPC.	The revised text would read: "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."	Clinical clarity to reflect lebrikizumab SmPC	Amended as suggested.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13, Section 2.2.2, third paragraph that commences "The lebrikizumab SmPC…"	Revised sentence to read: "When clinical response has been achieved, the SmPC states that	Clinical accuracy	We agree that this sentence needs to be revised to improve accuracy. However,

The final sentence of this paragraph currently states that “it is recommended that patients received a maintenance dose of 250 mg every four weeks.” We feel that the SmPC content clearly dictates, rather than recommends this, and therefore the sentence would be accurately improved by use of “the SmPC states” instead of “it is recommended”.	patients receive a maintenance dose of 250 mg every four weeks.”		rather than using the company’s suggested re-wording, we have revised this sentence as follows: “When clinical response has been achieved, the SmPC states that the recommended maintenance dose of lebrikizumab is 250 mg every four weeks.”

Issue 8

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 15, figure 1 legend TA814 is missing from the legend for figure 1	Include TA814 in the legend for Figure 1: “NICE TA814: Abrocitinib, tralokinumab or upadacitinib for treating moderate to severe atopic dermatitis”	Omission of content from the legend	Amended as suggested, with corresponding reference number added.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, middle of last paragraph. Sentence that commences “The company responded that ciclosporin A is the only first-line treatment licensed in the UK, and that one of the lebrikizumab pivotal trials…” Please note that the ADvantage study (which this sentence refers to) was not part of the submission package to EMA and is therefore not a lebrikizumab pivotal study. Please note that the pivotal trials for lebrikizumab (that formed the clinical evidence submitted to EMA) include ADvocate 1, ADvocate 2, ADhere, ADopt-VA. Of note, ADopt-VA was added to the EMA package during the	Please delete the word “pivotal” from this sentence so that it reads: “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).”	Inaccuracy	Amended as suggested.

approval process at Day 120 of the process.			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 8, Issue 7 table We apologise for the unresolved confusion regarding the intended population and positioning of lebrikizumab. The EAG's assumption is correct. We can confirm that we intend to position lebrikizumab for patients who have failed on or are unsuitable for ANY of the first-line systemic therapies. This is in line with the other currently available second-line systemic therapies.	In the row for "What additional evidence or analyses might help to resolve this issue?", the EAG may wish to include the company's confirmation that we intend to position lebrikizumab for patients who have failed on or are unsuitable for any of the first-line systemic therapies.	To address this unresolved inaccuracy and query from the EAG in order to avoid further confusion	We thank the company for this clarification, but we have not altered Issue 7, as this was not a factual inaccuracy.

The last row (at the bottom of the Issue 7 table) would benefit from inclusion of this confirmation in order to avoid further confusion and correct this unresolved inaccuracy.			

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, Table 7 Summary of decision problem, Outcomes row, Rationale if different column	The reference to “TA914 MTA” is indeed a typographical error from the company and this can be corrected to “TA814 MTA” if the EAG wishes, and the relevant footnote under the table deleted.	Typographical error	Again, we thank the company for this clarification, but we have not made this suggested change as we accurately reported what was stated in the company submission (CS) and inserted an appropriate footnote to explain that this was likely an error.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25, fifth paragraph commencing “CS section B.2.2. states…” There are a couple of typos in the sentence “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 data of 14th April 2023	Replace “data” with “date” and change the date from “14th April” to “18th April”, so that the sentence reads: “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.”	Typographical error	The company’s response to clarification question A8 states that the cut-off date was 14th April 2023. We therefore accurately reported what was stated in the clarification response. However, we have amended the text as suggested by the company to reflect the 18th April 2023 date supplied here and have corrected the “data” typographical error.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, end of second paragraph In the final sentence of the second paragraph it states "pivotal lebrikizumab trials". However, please note that the ADvantage study was not part of the submission package to EMA and is therefore not a lebrikizumab pivotal study.	We suggest replacing the word "pivotal" with "key" to read: "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."	Inaccuracy	Amended as suggested.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 29, second paragraph There is a typo in the sentence "In response to clarification question A7 the	Please remove the word "be" so that this reads: "In response to clarification question A7 the company said that they anticipate that the findings from the maintenance phase will "*read out*"	Typographical error	Amended as suggested.

company said that they anticipate that the findings from the maintenance phase will be "*read out*" (clarification response A7) on 4th January 2024."	(clarification response A7) on 4th January 2024."		

Issue 15

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 29, fourth paragraph We suggest replacing the word "could" with "had to" in the sentence "If lesions re-occurred, then participants could resume mid- to low-potency TCS" to match the CS.	The revised text should read: "If lesions re-occurred, then participants had to resume mid- to low-potency TCS" to match the CS."	Accuracy to reflect CS	Amended as suggested.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 30, Table 8, Intervention row, ADhere column The induction text has a typo as it states "TCS Q2W" when it should read "TCS": "Lebrikizumab 250 mg Q2W + TCS Q2W (participants received a loading dose of lebrikizumab 500mg at weeks 0 and 2)"	Please remove Q2W after TCS so that it reads: "Lebrikizumab 250 mg Q2W + TCS (participants received a loading dose of lebrikizumab 500mg at weeks 0 and 2)"	Typographical error	Amended as suggested.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31, Table 8, Key eligibility row, ADvantage column	Revised text to read: "No previous CsA exposure and not a candidate for it as it is not medically advisable, or previously discontinued CsA (due to intolerance, unacceptable	For accuracy	Amended as suggested.

For completeness, we suggest the addition of “and duration” following the word “dose” in the following text: “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 needed outside of prescribing information, or inadequate response)”	toxicity, dose or duration needed outside of prescribing information, or inadequate response)”		

Issue 18

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 32, footer point ‘c’ Please note that not all drugs were administered as subcutaneous injections since TCS are topical treatments, therefore this footer point is inaccurate	Removal of footer point “c All study drugs were administered as subcutaneous injections” from the table footer	For accuracy	We have removed this footnote as suggested by the company, and have amended other footnote lettering within and below the table in response to this change.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 34, end of second paragraph There is a date error in the sentence: "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 March 2024) (CS Table 53)." Of note, March 2024 is the expected study completion date for ADapt, not the expected date for results.	Please replace March 2024 with October 2024 so that it reads: "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)."	For accuracy	Amended as suggested.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 34, section 3.2.1.2 Please note that the EAG report makes 3 references to pivotal lebrikizumab trials in this section: • The company summarised participant baseline characteristics from the pivotal ADvocate 1 and 2, ADhere, ADvantage and ADjoin trials in CS section B.2.3.3 (in CS Tables 10, 11 and 12, respectively). • 3.2.1.2.1 Balance of baseline characteristics within the pivotal lebrikizumab trials • 3.2.1.2.2 Balance of baseline	For accuracy, we suggest removal of the word “pivotal” and/or replace with “key” trials so that these read as follows: • 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). • 3.2.1.2.1 Balance of baseline characteristics within the key lebrikizumab trials • 3.2.1.2.2 Balance of baseline characteristics between the key lebrikizumab trials	For accuracy	Amended as suggested.

characteristics between the pivotal lebrikizumab trials Please note that the pivotal trials for lebrikizumab (that formed the clinical evidence submitted to EMA) include ADvocate 1, ADvocate 2, ADhere, ADopt-VA. Of note, ADopt-VA was added to the EMA package during the approval process at Day 120 of the process. ADvantage and ADjoin are not lebrikizumab pivotal trials.			

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36, EAG comment on included studies The comment begins with "Of the five pivotal trials of lebrikizumab included in the CS…"	We suggest deleting the word "pivotal" so that it reads "Of the five trials of lebrikizumab included in the CS…"	For accuracy	We have amended this by replacing "pivotal" with "key", as the CS contains more than five trials of lebrikizumab.

Please note that ADvantage is not a lebrikizumab pivotal trial.			

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 36, Risk of bias assessment section In the fourth line down, there is a typo in the trial name Advocate 1 and 2, which should have an uppercase D.	Please replace “Advocate” with “ADvocate” to ensure the trial name is displayed correctly	Typographical error	Amended as suggested.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 37, paragraph 3	Please replace “recue” with “rescue” so this reads: “…ii) although intention-to-treat (ADvocate 1) or modified intention-to-treat (ADvocate 2)	Typographical error	Amended as suggested.

In the eighth line down, there is a typo: "…ii) although intention-to-treat (ADvocate 1) or modified intention-to-treat (ADvocate 2) analyses were conducted the assumption that patients who received topical recue therapy were non-responders…"	analyses were conducted the assumption that patients who received topical rescue therapy were non-responders…"		

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 40, fifth paragraph down There is a typo and the word outcomes should be singular: "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 outcomes	Amend "outcomes" to "outcome" so that this reads: "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."	Typographical error	Amended as suggested.

was not used in the economic model."			

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 44-46, Table 11 There are several incidences where the trial name Advocate is presented without an uppercase D: • EAG comment at the bottom of page 44: Advocate 1: True ITT population and only one participant missing from the lebrikizumab arm of the safety population. • Top of page 35: Advocate 2: the 18 patients excluded because they may not have met the trial entry criteria represent 4% of	Please replace "Advocate" with "ADvocate" to ensure the trial name is displayed correctly	Typographical error	Amended as suggested.

the 445 enrolled (ITT) population. • Half way down on page 46: Advocate 1&2 and ADhere: Appropriate procedures			

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, section 3.2.5 There is a typo in the sentence "Consequently, we focus on 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."	Delete the initial "on" so that this reads: "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."	Typographical error	Amended as suggested.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 50, section 3.2.5.1 The word “of” is missing from the sentence “The percentage [MISSING] 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.”	Add the word “of” so that this reads: “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.”	Typographical error	Amended as suggested.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 51, second paragraph following the table For accuracy, we would recommend the addition of the following text into this paragraph:	The revised text would read as follows: “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	For accuracy	Amended as suggested.

"Participants who received either of the lebrikizumab maintenance doses had a similar EASI 75 [ADD: maintenance of] response at week 52 (lebrikizumab 250mg every 4 weeks 82% versus lebrikizumab 250mg every 2 weeks 78%) whereas the EASI 75 [ADD: maintenance of] response at week 52 was lower at 66% for the group of [ADD: lebrikizumab] 16-week responders re-randomised to placebo maintenance.	maintenance of response at week 52 was lower at 66% for the group of lebrikizumab 16-week responders re-randomised to placebo maintenance.		

Issue 29

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 51, final paragraph "Participants who completed either of the ADvocate RCTs could enrol	The revised text to read: "Participants who completed either of the ADvocate RCTs could enrol in the ADjoin long-term extension study"	For accuracy	Amended as suggested.

in the open label ADjoin long-term extension study” For accuracy, we recommend deleting the term “open label” since the trial was blinded until the cut off for regulatory purposes, after which it became open label.			

Issue 30

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 52, bottom of page, Section 3.2.5.3 There is a typo in the sentence: “In the ADvocate 1 and 2 pooled population a post-hoc analyses were conducted for participants who had previously been exposed to ciclosporin…”	Remove the word “a” so that it reads: “In the ADvocate 1 and 2 pooled population post-hoc analyses were conducted for participants who had previously been exposed to ciclosporin…”	Typographical error	Amended as suggested.

Issue 31

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 52, bottom of page, Section 3.2.5.3 For accuracy, please add "≥" to the sentence "For the four outcomes analysed (EASI 75, IGA 0,1, NRS itch [ADD: ≥] 4-point improvement and EASI 90 at week 16) the proportion of participants…"	The revised text should read: "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…"	For accurate representation of outcome	Amended as suggested.

Issue 32

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, Table 14 footer	"Advocate" in the Table 14 footer to be updated to "ADvocate"	Typographical error	Amended as suggested.

Typo in trial name Advocate, should have an uppercase D			

Issue 33

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 53, bottom of page final sentence Regarding the sentence: "The company do not comment on the high placebo[MISSING: +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."	We suggest the EAG report can be updated to say: "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 (triamcinolone as for ADhere) up to 16 weeks, switching to a low-potency TCS for seven days when lesions were under control."	For accuracy	We have added "+ TCS" after "placebo" as suggested by the company. We thank the company for confirming that triamcinolone acetonide 0.1% cream was provided in the induction period of ADvantage, but on checking the ADvantage clinical study report (CSR), the CS, CS appendices and the Warren EADV 2023 reference, we cannot find any information about what specific mid- or low-potency topical corticosteroid (TCS) products were used in

We confirm that the ADvantage CSR provided at clarification includes use of triamcinolone acetonide 0.1% cream (a mid-potency TCS) as well as hydrocortisone 1% cream (a low-potency TCS, for use on sensitive skin areas). These were provided by the sponsor in the ADvantage induction period. Also for completion, we would suggest addition of "+TCS" after the placebo.			Advantage. We therefore believe that this is not a factual inaccuracy. Consequently, we have not amended the report as suggested by the company.

Issue 34

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 54, final paragraph "Participants who completed the ADhere study could enrol in the open label ADjoin long-term extension study."	The revised text to read: "Participants who completed the ADhere study could enrol in the ADjoin long-term extension study."	For accuracy	Amended as suggested.

For accuracy, we recommend deleting the term “open label” since the trial was blinded until the cut off for regulatory purposes, after which it become open label.			

Issue 35

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 55, top of the page There are errors in the sentence: “Long-term data for participants from the ADvantage RCT who joined the ADhere long-term extension study are not yet available (clarification response A7).”	We suggest this sentence is rephrased as: “Long-term (week 52) data for participants from the ADvantage RCT are not yet available (clarification response A7).”	Inaccuracies	Amended as suggested.

Please note that ADvantage patients did not progress to the ADjoin extension study so this is inaccurate (the mention of “ADhere long term extension” is also incorrect as the long term extension study is ADjoin). What is not yet available is the ADvantage week 52 data that will read out imminently.			

Issue 36

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 56, section 3.2.6.3 The word “of” is missing from the sentence: “The percentage [MISSING] participants achieving an IGA score of zero or one (corresponding to clear or almost clear skin in atopic dermatitis…”	Add the word “of” so that this reads: “The percentage of participants achieving an IGA score of zero or one (corresponding to clear or almost clear skin in atopic dermatitis…”	Typographical error	Amended as suggested.

Issue 37

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 57, final paragraph "Participants who completed the ADhere study could enrol in the open label ADjoin long-term extension study." For accuracy, we recommend deleting the term "open label" since the trial was blinded until the cut off for regulatory purposes, after which it become open label.	The revised text to read: "Participants who completed the ADhere study could enrol in the ADjoin long-term extension study."	For accuracy	Amended as suggested.

Issue 38

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59, section 3.2.6.5	Update text to read "Participants in the ADhere study reported days where	Typographical error	Amended as suggested.

There is a typo in the word “used”, this should be “use” “Participants in the ADhere study reported days where they did not used TCS or topical calcineurin inhibitor (CS section B.2.6.1).”	they did not use TCS or topical calcineurin inhibitor (CS section B.2.6.1).”		

Issue 39

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, paragraph below table 21 “CS Figure 21, right hand panel shows the percentage of participants [MISSING: with a ≥4-point improvement in DLQI from baseline] at ADhere study visits from baseline to week 16.”	For accuracy, we suggest adding “with a ≥4-point improvement in DLQI from baseline” after the word “participants”. This would then read: “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.”	For accuracy	Amended as suggested.

Issue 40

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65, table 23 footer In the table footer, there is a typo in the trial name “Advocate” which should have an uppercase D. “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”	Please replace “Advocate” with “ADvocate” to ensure the trial name is displayed correctly	Typographical error	Amended as suggested.

Issue 41

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65, paragraph under Table 23 For accuracy, please add "≥" to the sentence "The CS presents results for three outcomes up to week 16: EASI 75, IGA (0,1) and 2-point improvement from baseline, itch NRS [MISSING: ≥4-point improvement from…"	The revised text should read "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…"	For accurate representation of outcome	Amended as suggested.

Issue 42

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, 3.2.6.10 Subgroup analyses section	Replace "Pruritis" with "Pruritus" so that it reads: "Results are shown for four outcomes (IGA 0,1; Pruritus NRS ≥4-point improvement; EASI 75 and EASI 90)."	Typographical error	Amended as suggested.

The second sentence has a typo: "Results are shown for four outcomes (IGA 0,1; Pruritis NRS ≥4-point improvement; EASI 75 and EASI 90)."			

Issue 43

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, Safety outcomes section 11th line down into the section: "Results of an analysis of safety in the placebo-controlled induction period (ADvocate 1 and 2 and ADhere trials only) and an analysis of the long-term safety of lebrikizumab (all eight trials) are presented."	For accuracy and clarity, please add "phase 2b dose-ranging study" before "ADvocate 1 and 2 and ADhere trials only)" so that it reads: "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."	Accuracy and clarity	Amended as suggested.

Issue 44

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, section 3.2.6.9, half way through first paragraph of this section For accuracy we suggest adding "≥" into the following sentence: "Among the ciclosporin-A exposed subgroup, the proportions who achieved IGA 0,1, NRS [MISSING: ≥] 4-point improvement and EASI 90…"	The revised text would read: "Among the ciclosporin-A exposed subgroup, the proportions who achieved IGA 0,1, NRS ≥4-point improvement and EASI 90…"	For accuracy	Amended as suggested.

Issue 45

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 64, section 3.2.6.9, half way through first paragraph of this section	The revised text should read: "… proportion of lebrikizumab patients in the prior ciclosporin A subgroup	Typographical error	Amended as suggested.

There are a couple of mentions of ciclosporin; these are typos and should read “ciclosporin A”. “… proportion of lebrikizumab patients in the prior ciclosporin [MISSING “A”] subgroup achieved EASI 75 than in the overall ADhere lebrikizumab trial arm but for placebo arm participants the proportion achieving EASI 75 was ….in the prior ciclosporin [MISSING “A”] subgroup than in the overall ADhere placebo trial arm (Table 23).”	achieved EASI 75 than in the overall ADhere lebrikizumab trial arm but for placebo arm participants the proportion achieving EASI 75 was ….in the prior ciclosporin A subgroup than in the overall ADhere placebo trial arm (Table 23).”		

Issue 46

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 64, last sentence of the page	Updated text to read:	Typographical error	Amended as suggested.

"EASI75" is a typo and should read "EASI 75" "CS Appendix E Table 107 also provides proportions of patients achieving EASI75 at week 16…"	"CS Appendix E Table 107 also provides proportions of patients achieving EASI 75 at week 16…"		

Issue 47

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 64, last sentence of the page For accuracy and completeness, the percentage value at the end of this page should read [redacted] instead of [redacted]. "….instead of [redacted]% for the placebo+TCS dupilumab exposed group)."	Please update last part of the sentence to read: "….instead of [redacted]% for the placebo+TCS dupilumab exposed group)."	Accuracy and completeness since all other values in this sentence include the decimal figure	Amended as suggested.

Issue 48

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 65, Table 23 For accuracy and completeness, the percentage value for dupilumab previous exposure, PBO+TCS column, % of participants row should read [redacted] instead of [redacted]. "[redacted])[a]"	Please update the figure to show 42.9 instead of 42	Accuracy and completeness	Amended as suggested.

Issue 49

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 66, Safety outcomes section, last two points on the page For the penultimate point on this page, there is an error	For the penultimate point, state Section "B.2.10.4" instead of "B.2.10.5" so that it reads: "Adverse events data from the 16-week induction period of the ADvantage trial (combination therapy	Error in signposting to CS sections	Amended as suggested.

in section naming, this should read CS Section “B.2.10.4” instead of “B.2.10.5” “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.2.10.5).” For the final point on this page, this should only say “CS Section B.2.10.5”, it should not include “Section B.2.10.6”. “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	in the failed CsA or CsA not medically advisable population) (CS section B.2.10.4).” For the final point on this page, remove “sections B.2.10.5 and B.2.10.6” and replace with “CS Section B.2.10.5” so that it reads: “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 section B.2.10.5).”		

1 and 2 or ADhere trials (CS sections B.2.10.5 and B.2.10.6)."			

Issue 50

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 68, second paragraph, second half of the paragraph For clarity and accuracy, we feel that the summary on the eosinophilia rates and injection site reaction rates would benefit from the context that the incidence was still low. "As is noted in the lebrikizumab SmPC, rates of eosinophilia were [redacted] in lebrikizumab-treated than placebo-treated patients. Injection site reactions (another adverse event of special interest) were	We suggest adding a short contextual sentence (e.g. "Of note, the incidence of eosinophilia and injection site reactions associated with lebrikizumab treatment were still low" to follow the current text; this would then read: "As is noted in the lebrikizumab SmPC, rates of eosinophilia were [redacted] in lebrikizumab-treated than placebo-treated patients. Injection site reactions (another adverse event of special interest) were [redacted] in the lebrikizumab than placebo arms in the ADvocate 2, ADhere and ADvantage trials and in the integrated safety analysis. Of note, the incidence of eosinophilia and injection site reactions associated with lebrikizumab treatment were still low."	Accuracy and contextualisation of findings	We agree with the company that it would be beneficial to contextualise the rates of these adverse events. Rather than adding the company's suggested statement that the incidence was low, we have contextualised the findings by adding the specific rates of the adverse events found in the studies mentioned. To additionally improve this paragraph, we have deleted the reference to the Summary of Product Characteristics (SmPC) ("As is noted in the

[redacted] in the lebrikizumab than placebo arms in the ADvocate 2, ADhere and ADvantage trials and in the integrated safety analysis."			lebrikizumab SmPC,[16]…"), as the results presented are from the CS and the reference to the SmPC may be confusing for the reader. Additionally, we have added "generally" to the following sentence: "Rates of eosinophilia were [generally] … in lebrikizumab-treated than …", to better reflect the findings.

Issue 51

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 68, third paragraph, line 3 For accuracy, the number of adverse events reported in the lebrikizumab arms of the	Please update to read: "Of the 11 serious adverse events reported in the lebrikizumab arms of the monotherapy trials, [redacted] were considered to be [redacted]	For accuracy	Amended as suggested.

monotherapy trials needs amending from eight to 11 (six SAEs were reported in ADvocate 1 and five in ADvocate 2). "Of the eight serious adverse events reported in the lebrikizumab arms of the monotherapy trials, [redacted] were considered to be [redacted] lebrikizumab ([redacted] and [redacted])."	lebrikizumab ([redacted] and [redacted])."		

Issue 52

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 68, end of fifth paragraph, just above section 3.2.6.12 The final sentence of the fifth paragraph, the 1.4% treatment discontinuation rate is an error and should be corrected to 1.8%.	Please replace 1.4% with 1.8%; furthermore, we feel this sentence would be more simply depicted as follows: "1.8% of patients in the lebrikizumab 250 mg Q2W + TCS arm and 0.9% in the placebo + TCS arm discontinued due to an adverse event."	Error and simplification of content	We have re-visited the data in CS Table 48 and note that the 1.8% rate applies to the placebo + TCS arm, while the 0.9% figure relates to the lebrikizumab 250 mg Q2W + TCS arm. We have therefore amended the rates accordingly in

"In the ADvantage combination therapy trial of the ciclosporin A failed or not medically advisable population, there were 1.4% treatment discontinuations due to an adverse event in the lebrikizumab 250 mg Q2W + TCS arm and 0.9% in the placebo + TCS arm (CS Table 48)."			our report. We have also clarified that these were treatment discontinuations due to a *treatment-emergent* adverse event (as this was not clear originally). This sentence now reads as follows: "In the ADvantage combination therapy trial of 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)."

Issue 53

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 70, Table 25, nasopharyngitis row, ADvocate 2 column, lebrikizumab arm data We apologise but there is an error in the 21 (7.5) data for nasopharyngitis in ADvocate 2, lebrikizumab arm. This is incorrect. This was a direct copy from the CS Table 43 which included this error. The correct value should be 14 (5.0).	Please replace “21 (7.5)” with “14 (5.0)”.	Error in figures from original CS Table 43	Amended as suggested.

Issue 54

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 71, bottom of the page, last 2 points Final 2 bullets currently state: • pruritus numerical rating scale at week 4, • pruritus numerical rating scale at week 16 (CS section B.2.9.1). These outcomes would be more accurately depicted by adding "≥4-point improvement" to the pruritus NRS	Update final 2 bullets to state upfront the "≥4-point improvement", so that they read: • ≥4-point improvement pruritus numerical rating scale at week 4, • ≥4-point improvement pruritus numerical rating scale at week 16 (CS section B.2.9.1).	Accurate representation of outcomes	Amended as suggested.

Issue 55

Description of problem	Description of proposed amendment	Justification for amendment	
Page 73, second paragraph, fifth line down in the second paragraph There is a typo and it should read “CS Appendix D” and not “CA Appendix D”	Replace “CA Appendix D” with “CS Appendix D”	Typographical error	Amended as suggested.

Issue 56

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 77, third point from the bottom of the page There is a typo and BREZE-AD7 should read BREEZE-AD7: “Five included participants who had had an inadequate response to either topical or systemic therapies (JADE TEEN, JADE COMPARE,	Replace BREZE-AD7 with BREEZE-AD7 so that this reads: “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)”	Typographical error	Amended as suggested.

BREZE-AD7, I4V-MC-JAHG and LIBERTY AD CHRONOS)”			

Issue 57

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 80, section 3.3.3 MAIC There is a typo at the start of the second paragraph of the MAIC section, this should say “MAIC” not “MIAC” “In the MIAC, 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).”	Replace “MIAC” with “MAIC” so that the text reads: “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).”	Typographical error	Amended as suggested.

Issue 58

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 82, section 3.4.1 Data inputs to the NMA First sentence of this section reads: "The NMA included 28 studies in the monotherapy analysis, and 16 in the combination therapy analysis." There is an error in the number of included studies for monotherapy; this should be 22 studies, not 28. Additionally, there is a typo in the third sentence whereby Abrocitinib should be represented with a lower case "a", and pruritis is incorrectly spelt.	Please replace 28 studies with 22 so that it reads: "The NMA included 22 studies in the monotherapy analysis, and 16 in the combination therapy analysis." Please replace "Abrocitinib" with "abrocitinib" and "pruritis" with "pruritus" so that the third sentence reads: "Data for abrocitinib improvement in pruritus used 12-week rather than 16-week data."	Typographical errors	Amended as suggested.

Issue 59

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 83, second from last paragraph from the bottom of the page There is a typo in the sentence [redacted]	Replace “pruritis” with “pruritus” so that this reads: “[redacted]”.	Typographical error	Amended as suggested.

Issue 60

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88, first paragraph, third line down	Remove the bracketed text as this is inaccurate so that the text reads:	Factual accuracy	Amended as suggested.

"Statistically significant improvements in itch in both combination therapy trials, and sleep-loss due to itch (measured in ADhere only) were also…" Please note that sleep loss due to itch was also measured in the ADvantage study.	"Statistically significant improvements in itch in both combination therapy trials, and sleep-loss due to itch were also…"		

Issue 61

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92, "Similarly, the EAG noticed that no patients occupy the non-response health state for the "initial treatment" phase. Patients in the initial treatment response health state move directly to the "subsequent treatment" or death health states upon non-response or	Please remove this paragraph	This paragraph is factually incorrect. Patients in the initial treatment phase do occupy the non-response health state, this is captured in the discontinuation rates shown in columns H to L of the Markov traces within the company's economic model. In other words, non-response is captured via discontinuation,	Amended as suggested.

other discontinuation reasons.”		which may be due to loss of response or any other reason.	

Issue 62

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 102, “Moreover, we note that some of the rates are very low, leading to a better response rate at week 52, as is the case for tralokinumab. Based on the results of an NMA by Drucker et al. (2022),62, which shows that tralokinumab and baricitinib are the least effective drugs when assessing response at week 16, our clinical expert did not expect tralokinumab to have a better response at week 52 than all the other drugs.”	We would request that the EAG please consider removing these sentences from the report.	These sentences are misleading as it is not the response rate that is measured at week 52, it is the conditional discontinuation rate. Whilst the response rates for tralokinumab may be lower than the comparators, this does not necessitate that of those patients who do manage to achieve response at week 16 with tralokinumab, would be more likely to discontinue treatment compared to the other drugs included in the analysis.	We agree with the company’s point that these sentences might be misleading and therefore we have edited the text to make it clearer. We have also edited Table 44.

Issue 63

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 103 “The company developed a model to estimate the cost-effectiveness of lebrikizumab compared to dupilumab, tralokinumab, abrocitinib, upadacitinib and baricitinib for patients with atopic dermatitis.”	“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.”	Accuracy to reflect CS	Amended as suggested (in the first paragraph of section 6.3).

Issue 64

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 134 “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.”	We will propose inclusion of the following text: “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. It should be noted that the high ICERs are due to lower costs in the lebrikizumab arm but also slightly	Provides clarity to readers and a more accurate representation of outcomes. This will aid in helping readers understand why the ICERs are so high	We thank the company for their suggestion, but we have not included the proposed text, as this was not a factual inaccuracy.

	lower QALYs compared to other treatments excluding baricitinib. In this situation where the intervention is less costly but there is a very minimal loss in QALYs, the ICERs can be misleading as they are very high, but this is purely due to the minute difference in QALYs between the two treatments."		

Issue 65

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 148, first sentence "In the CS, three other placebo-controlled lebrikizumab RCTs were identified for inclusion in the company's NMA in addition to the pivotal ADvocate 1 and 2, ADhere, ADvantage and ADjoin clinical trials, but were not otherwise presented in the CS…"	Please delete the word "pivotal" from this sentence so that it reads: "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…"	Inaccuracy	Amended as suggested.

Please note that the ADvantage and ADjoin studies were not part of the submission package to EMA and are therefore not lebrikizumab pivotal studies. Please note that the pivotal trials for lebrikizumab (that formed the clinical evidence submitted to EMA) include ADvocate 1, ADvocate 2, ADhere, ADopt-VA. Of note, ADopt-VA was added to the EMA package during the approval process at Day 120 of the process.			

Issue 66

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 148, second paragraph, 7th line down	"Evidence-based" is a typo and should be corrected to "evidence base", and "the" should be removed so that it reads:	Typographical errors	Amended as suggested.

A few typos are highlighted in red in the following sentence: "ADhere-J was not part of the evidence based used to support the EMA marketing authorisation, and ADopt-VA was added to the evidence-based for the marketing authorisation part the way through the approval process."	"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."		

Issue 67

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 150, table 51, ADhere-J (Japan only study) column, Intervention row We suggest that for clarity, the "Induction (16 weeks)" and "Maintenance (52 weeks)" lines be formatted to remove the bullet points.	Minor error, the induction and maintenance points should be unbulleted and the lebrikizumab Q2W induction arm should also include "+TCS" so that it reads as follows: Induction (16 weeks): • Lebrikizumab 250mg Q2W (500mg LD at baseline and week 2) + TCS	Formatting error and omission/typographical error	We thank the company for pointing this out. We have added "+ TCS" to the lebrikizumab every two weeks (Q2W) induction arm. We have also adjusted the bullet point formatting.

Also the induction lebrikizumab Q2W arm should include TCS. • Induction (16 weeks): • Lebrikizumab 250mg Q2W (500mg LD at baseline and week 2) • 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	• 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		

Issue 68

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 150, table 51, ADhere-J (Japan only study) column, Comparator row We suggest that for clarity, the “Maintenance (52 weeks)” line be formatted to remove the bullet point. Induction (16 weeks): • Placebo + TCS • Maintenance (52 weeks): [b] • Responders to placebo received: • Placebo + TCS	Minor error, the induction and maintenance points should both be unbulleted as follows: Induction (16 weeks): • Placebo + TCS Maintenance (52 weeks): [b] • Responders to placebo received: • Placebo + TCS	Formatting error	We have amended the bullet point formatting.

Issue 69

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 150, table 51, ADhere-J (Japan only study) column, Primary outcome row We suggest that for clarity, the “proportion of participants…” line should also be bulleted. Additionally, there is a typo and the primary outcomes should read “IGA (0,1)” not “IGA (9,1)” • % achieving EASI 75 at week 16 Proportion of participants achieving IGA (9,1) [c] and a reduction of≥2 points from baseline to week 16	Bullet the second primary endpoint and correct it to say “IGA (0,1)”; this should read: • % 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	Typographical error and formatting	The “Proportion of participants…” line is showing as a bullet point in the report when we view it, so we have not amended this. We have amended the “IGA (9,1)” typographical error to “IGA (0,1)”.

Issue 70

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 152, Table 52, Study locations row: "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)."	Please correct "Advocate" with "ADvocate" (with upper case D) to provide correct depiction of the trial name. This should read: 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).	Typographical errors	Amended as suggested.

Issue 71

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 152, Table 52, Comparator row: Maintenance: Placebo (described by the company as *"lebrikizumab withdrawal"* in CS Table 5 [d])	For added clarity and to avoid any misinterpretation, we would suggest the following alternative description to follow Placebo: Maintenance: Placebo (described as "*lebrikizumab withdrawal*" when referring to the maintenance primary population [i.e. patients who received lebrikizumab during induction, responded at week 16 without using TCS and were re-randomised to placebo at maintenance])	For accuracy and clarity	We thank the company for this suggestion, but on reviewing how we have described this arm in Table 52 and the associated footnote 'd', we believe we have accurately represented the descriptions of this arm and the maintenance primary population that were provided in the CS and the company's response to clarification question A19.

Issue 72

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 153, Table 52, table footer, point d	Please amend table footer point d to "placebo week 16 responders" instead	Error relating to data request for clarification question A20	Amended as suggested.

Please note that the provided results for clarification question A20 relates to placebo week 16 responders (not non-responders) as currently stated in the table footer ‘d’: [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 non-responders in response to the EAG’s request for these	of “placebo non-responders”; this would then read: [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).		

data (clarification question and response A20).			

Issue 73

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 153, Table 53, top of page 153 company response There is a typo in the company response to the question “Were the care providers, participants and outcome assessors blind to treatment allocation?” The highlighted text below should read “the duration”: **“Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments, and blinding integrity was maintained for the62urationn of both trials”	Please correct the typo so that it reads “the duration”: **“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 both trials”	Typographical error	Amended as suggested.

Issue 74

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 157, Table 54, company response to the question “Were the care providers, participants and outcome assessors blind to treatment allocation?” As with the above issue, the highlighted text below should read “the duration”: **“Yes.** The sponsor, investigators, trial-site personnel, and patients were unaware of the trial-group assignments, and blinding integrity was maintained for the63urationn of the trial”	Please correct the typo so that it reads “the duration”: **“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”	Typographical error	Amended as suggested.

Issue 75

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 157, Table 54, company response to the question “Were there any unexpected imbalances in drop-outs between groups?” “Aes” is a typo and should be corrected to “AEs” with upper case E. “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	Please correct the “Aes” typo so that it reads as follows: “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%]).”	Typographical error	Amended as suggested.

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%]).”			

Issue 76

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26, first sentence “Of the five pivotal lebrikizumab trials the company includes in the CS…” Please note that the ADvantage study (which this sentence refers to) was not part of the submission package to EMA and is therefore not a lebrikizumab pivotal study. Please note that the pivotal trials for lebrikizumab (that	Please replace the word “pivotal” with “key” in this sentence so that it reads “Of the five key lebrikizumab trials the company includes in the CS…”	Inaccuracy	Amended as suggested.

formed the clinical evidence submitted to EMA) include ADvocate 1, ADvocate 2, ADhere, ADopt-VA. Of note, ADopt-VA was added to the EMA package during the approval process at Day 120 of the process.			

CONFIDENTIALITY MARK UP AMENDMENTS

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	
Page 35, fourth paragraph **In the sentence commencing "In ADvantage, [redacted] of the participants in each arm**	The text "over half" **does not** require confidential markup; however we would ask that the bracketed percentages that follow remain marked academic in confidence.	"In ADvantage, over half of the participants in each arm had previously received ciclosporin A"	Amended as suggested.

had previously received ciclosporin A…"			
Page 48, top entry for ADvocates and ADhere shows confidential markup: **"Induction period, supportive estimands:** [redacted]**."** **And also:** **"ADvocate 1 & 2 maintenance period, supportive estimand:** [redacted]	The content "For categorical endpoints, participants who received rescue medication or discontinued treatment due to lack of efficacy or had missing data for another reason were considered as non-responders." **does not** require confidential mark up The content "participants who received any rescue medication, discontinued treatment for any reason, or transferred to the escape arm were considered as non-responders. Intermittent missing data were also considered as non-response." **does not** require confidential mark up	"Induction period, supportive estimands: For categorical endpoints, participants who received rescue medication or discontinued treatment due to lack of efficacy or had missing data for another reason were considered as non-responders." "ADvocate 1 & 2 maintenance period, supportive estimand: participants who received any rescue medication, discontinued treatment for any reason, or transferred to the escape arm were considered as non-responders. Intermittent missing data were also considered as non-response."	Amended as suggested.

[redacted]			
Page 64, section 3.2.6.9 **“Due to the** [redacted] **.”**	The content “small numbers of ciclosporin-exposed participants in this trial the results must be interpreted cautiously.” **does not** require confidential mark up	“Due to the small numbers of ciclosporin-exposed participants in this trial the results must be interpreted cautiously.”	Amended as suggested.

Page 65, paragraph under Table 23, end of the paragraph **"…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."**	The word "[redacted]" is not currently marked up in the EAG report as confidential information and we would like to request that it is please, in keeping with the CS:	"…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."	Amended as suggested.
Page 161, Table 57, EAG assessment of ADjoin long-term extension study **Content has been marked up as confidential in 2 parts of this table. These include the content in the 2nd and 3rd rows:** **Partly**. Those enrolled in ADjoin are drawn from five different parent studies[redacted]	The EAG assessment content for ADjoin does **not** require confidential mark up.	**"Partly**. Those enrolled in ADjoin are drawn from five different parent studies and a small cohort (n=100) directly enrolling who had not taken part in a parent study. The level of TCS use permitted differed slightly depending on the parent study (CS Table 8)." **"Yes.** Blinding was maintained by the use of	Amended as suggested.

[redacted]. The level of TCS use permitted differed slightly depending on the parent study (CS Table 8). **Yes.** Blinding was maintained by the use of placebo injections (CS section B.2.3.1). [redacted]		placebo injections (CS section B.2.3.1). Participants who entered from the escape arm of ADvocate 1 or 2 continued to receive open label treatment.”	

23/02/2024

Single Technology Appraisal

Lebrikizumab for treating moderate to severe atopic dermatitis in people 12 years and over [ID4025]

Dear NICE technical team,

Following Almirall's most recent correspondence with the EAG via NICE, where the EAG requested further clarification for the discontinuation rates applied in the company submission, Almirall have taken a further look into this data. The company has realised that the discontinuation rates for combination therapy with lebrikizumab that were provided in table 59 of Document B of the company submission had not been calculated following the same criteria as the comparator treatments considered in the submission. Initially, the company had calculated the discontinuation rates for combination therapy for a total follow-up period of 68 weeks (16 weeks in the ADhere study and 52 weeks in the ADjoin long-term extension study), whereas the discontinuation rates for comparators were based on varying maintenance periods that were shorter than 68 weeks. Furthermore, the original discontinuation rates considered patients on both Q2W and Q4W maintenance arms instead of Q4W alone, which is the approved treatment posology after an induction phase of 16 weeks. To allow for a fair comparison with the comparators, the discontinuation data should come from one maintenance regimen only, as this was what was done for the comparators. Finally, Almirall had only considered responders based on NICE's recommended composite endpoint (EASI 50 and DLQI ≥4 points improvement) but not EASI 75 responders like some of the comparators.

To enable a 'like for like', equal comparison between the discontinuation rates of the different treatments listed in table 59, Almirall would like to take this opportunity to provide two new post-hoc analyses. The new post hoc analyses aim to substitute the Table 59 lebrikizumab combination therapy discontinuation rate and use similar criteria to other advanced systemic drugs that have been appraised by NICE.

- In table 1 below, the company has calculated the proportion of patients who were EASI 75 responders at week 16 of ADhere, who were treated with lebrikizumab Q4W during the ADjoin long-term extension study and had discontinued at week 52.
- In table 2 below, the company has calculated the proportion of patients who were EASI 50 and DLQI≥4 points improvement responders at week 16 of ADhere, who were treated with lebrikizumab Q4W during the ADjoin long-term extension study and had discontinued at week 52.

The company has also detected a transcription error in Table 59 of the submission document. The correct discontinuation rate for dupilumab based on Table 123 of TA814 is 5.1%, not 3.70%.

Individual patient data from the above-mentioned studies and post-hoc analyses can be provided upon request.

Table 1: Discontinuation data for week 16 (EASI 75) responders

Treatment		Source/assumption
Combination therapy – Adults (EASI 75)		
Lebrikizumab (Q4W)	6.9%	Discontinuation rate between week 16 and week 52 in ADhere going to ADjoin in Q4W arm, conditional on achieving EASI 75 at week 16

Table 2: Discontinuation data for week 16 composite endpoint (EASI 50 and DLQI ≥4) responders

Treatment		Source/assumption
Combination therapy – Adults (EASI 50 and DLQI ≥4)		
Lebrikizumab (Q4W)	6.25%	Discontinuation rate between week 16 and week 52 in ADhere going to ADjoin in Q4W arm, conditional on achieving EASI 50 and DLQI ≥4

In conclusion, these new post-hoc analyses consider a total treatment period of 52 weeks and lebrikizumab Q4W dosing beyond week 16. They demonstrate the robustness of the discontinuation rates for Lebrikizumab (Q4W) subject to various endpoints. They also show there were no relevant differences with the discontinuation rates considered for other treatments, despite the different assumptions used for those competitors' discontinuation rates.

EAG response to company updated discontinuation data

We have reviewed the company's letter with their update to their submission. The new conditional discontinuation rate for lebrikizumab supplied by the company will not have an impact in terms of the EAG model conclusions. Please may I refer you to Table 48 within our EAG report, where we supplied EAG scenario analyses using alternative values for the week 16-52 lebrikizumab discontinuation rate – specifically the 'Lebrikizumab discontinuation rate week 16-52' scenarios 2 and 3. As the company's new estimate falls between the two values in scenarios 2 and 3, the results will be similar to those results.

Additionally, we noted the following in relation to the company's letter:

- Due to the letter wording, it is unclear if the new conditional discontinuation rates provided by the company are based on 36 or 52 weeks of maintenance treatment in ADjoin. We assume that given that the values inform the week 16-52 lebrikizumab discontinuation rates used in the model and the company refer to a total treatment period of 52 weeks at the end of the letter, that the data are based on 36 weeks of maintenance treatment.

- The company state they detected a transcription error in Table 59 of the CS and thus state that "the correct discontinuation rate for dupilumab based on Table 123 of TA814 is 5.1%, not 3.70%". However, Table 123 in TA814 is an appendix table (Appendix 10.7.1) showing the conditional discontinuation rates based on EASI 75, while Table 41 of TA814 shows the conditional discontinuation rates used in the TA814 base case and are based on EASI 50 + DLQI>4. Table 41 reports a conditional discontinuation rate for dupilumab of 3.7% for the combination therapy patients. We believe the conditional discontinuation rates should be based on achieving the composite outcome rather than achieving EASI 75, if data are available, so use of the 3.7% figure is correct.

- In our EAG model we used the lebrikizumab discontinuation rate provided in the company's response to clarification question B7 (Table 24 of the clarification response document) for the patients from ADhere who went onto the Q4W dosing regimen of the ADjoin trial. That is, data were supplied separately for patients on the Q2W or Q4W regimens at the clarification response stage. We are just noting this for completeness.