Single Technology Appraisal

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408] Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

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 Leo Pharma:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

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

4. **Expert personal perspectives from:**

   a. Dr Philippa Cousen- clinical expert, nominated by the British Association of Dermatologists (see document 3b)
   b. Andrew Proctor, patient expert, nominated by National Eczema Society (see document 3a)

5. **External Assessment Report** prepared by BMJ Technology Assessment Group

6. **External Assessment Report – factual accuracy check**

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

Delgocitinib for treating moderate to severe chronic hand eczema in adults [ID6408]

Company evidence submission

File name	Version	Contains confidential information	Date
ID6408 – delgocitinib CHE – main submission v2.0[redacted].docx	2.0	No	19 March 2025

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 STA and highly specialised technologies evaluation: User guide for company evidence submission template.

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.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluations manual.

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

Highlighting in the template (excluding the contents list)

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’.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Contents

Tables

Figures

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

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

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	Adults with moderate to severe chronic hand eczema that has not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate	Adults with moderate to severe chronic hand eczema that have not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate	
Intervention	Delgocitinib	Delgocitinib	
Comparator(s)	• Alitretinoin (in severe hand eczema) • Topical calcineurin inhibitors (TCIs) • Ultraviolet light therapy (PUVA, narrowband UVB) • Systemic immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil)	• Alitretinoin (in severe hand eczema) • Ultraviolet light therapy (PUVA, narrowband UVB)	Feedback from clinical experts and real-world study data suggest that TCIs are used as part of a first line optimisation strategy alongside topical corticosteroids in the treatment of CHE, and not as a monotherapy for patients in the target patient population. TCIs have therefore been excluded as comparators in the presented decision problem due to their positioning and frequent use as first line treatment. Within the guidelines from the European Society of Contact Dermatitis (ESCD), systemic immunosuppressants are positioned in CHE patients who are refractory or contraindicated to first and second line options and are therefore positioned at a different point in the treatment pathway (third line+). Ciclosporin is a "suggested" treatment in the ESCD guidelines, so it has a higher grade of recommendation than the other systemic immunosuppressants; however, ciclosporin is also positioned as a third line treatment. Methotrexate and azathioprine have the lowest grade of recommendation and are positioned as third line treatments.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Mycophenolate mofetil is not included in the ESCD guidelines. Additionally, a survey of 194 UK dermatologists reported that mycophenolate mofetil is rarely used as the first, second or third choice of treatment for CHE, with the majority of those surveyed indicating that they would never or rarely use mycophenolate mofetil for the treatment of CHE. For these reasons, the decision problem addressed in this submission excludes azathioprine, ciclosporin, methotrexate and mycophenolate mofetil as comparators as they are used in a different line of therapy. In the absence of comparative evidence, PUVA was assumed to serve as a proxy for NBUVB. This assumption may be conservative given that the limited available evidence suggested that NBUVB may be less effective than PUVA though their unit costs in the UK NHS are the same.
Outcomes	The outcome measures to be considered include: • measures of disease severity • measures of symptom control, including improvement in itch • time to relapse/prevention of relapse • adverse effects of treatment • health-related quality of life.	The included outcome measures are: • measures of disease severity (Investigator's Global Assessment for Chronic Hand Eczema [IGA-CHE] treatment success [TS], Hand Eczema Severity Index [HECSI]-75, HECSI-90 and HECSI score reduction) • measures of symptom control, including improvement in itch (Hand Eczema Symptoms Diary [HESD]-PAIN and HESD-ITCH) • time to relapse/prevention of relapse (loss of response, measured as the time to first IGA-CHE score ≥2) • adverse effects of treatment • health-related quality of life (Dermatology Life Quality Index	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		[DLQI] >4-point improvement, change from baseline in DLQI, EQ-5D and HEIS)	
Subgroups to be considered	• Primary cause of hand eczema (atopic or contact) • Moderate vs severe disease • Inadequate response to topical corticosteroids vs topical corticosteroids inadequate or inappropriate	• Primary cause of hand eczema (atopic or non-atopic) • Moderate vs severe disease	In DELTA 1 and DELTA 2, the pivotal trials for delgocitinib versus cream vehicle, 99% of patients across both arms had an inadequate response to TCS in the last 12 months and 20.3% of patients across both treatment arms were inappropriate for treatment with TCS. This means that there is a significant overlap between these two populations within the key clinical studies. Additionally, the DELTA trials were not powered to look at efficacy differences in those subgroups. Therefore, subgroup analyses based on ineligibility for TCS versus inadequate response to TCS would not provide a meaningful comparison regarding the relative clinical efficacy of delgocitinib in these two subgroups.

DLQI, Dermatology Life Quality Index; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; HEIS, Hand Eczema Impact Scale; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PUVA, psoralen–UV A phototherapy.

1.2 Description of the technology being evaluated

Table 2 Technology being evaluated

UK approved name and brand name	• Delgocitinib (Anzupgo)
Mechanism of action	• Delgocitinib is a pan Janus kinase (JAK) inhibitor that targets the activity of all four members of the JAK family of enzymes consisting of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) in a concentration dependent manner
Marketing authorisation/CE mark status	• EU regulatory approval received 19th September 2024 • UK (MHRA) regulatory received 29th November 2024
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	• Delgocitinib is indicated for the treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate
Method of administration and dosage	• Delgocitinib cream contains 20 mg/g of delgocitinib • A thin layer of delgocitinib should be applied twice daily to clean and dry skin of the affected areas of the hands and wrists until the skin is clear or almost clear • It is recommended to apply the cream at regular intervals, approximately 12 hours apart • In the event of recurrence of the signs and symptoms of CHE (flares), twice daily treatment of the affected areas should be reinitiated as-needed • Treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment
Additional tests or investigations	• None
List price and average cost of a course of treatment	• £[redacted] per 60 g tube • The delgocitinib label instructs that it should be used until the skin is clear or almost clear and then as needed. Treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment. Within the model, the average time on treatment during Year 1 is approximately 24 weeks ([redacted]).
Patient access scheme (if applicable)	No patient access scheme or commercial access agreement is planned for delgocitinib in this indication

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

Summary

Overview of chronic hand eczema

- Hand eczema (HE) is a complex, multifactorial, non-infectious skin disease of the hands and wrists with a polymorphic clinical picture and painful, pruritic and inflammatory symptoms [1-3].
- Chronic HE (CHE) is defined as HE that lasts for more than 3 months or relapses at least twice per year [4, 5] – the core symptoms of CHE are itch and pain [5, 6].
- The most common aetiological subtypes of CHE are irritant contact dermatitis, allergic contact dermatitis and atopic HE; often, more than one aetiological factor plays a role in the development of CHE [5].

Epidemiology

- In a recent UK survey (CHECK), the point prevalence of self-reported, physician-diagnosed CHE in adults recruited from online general population panels (weighted to match the general population in terms of sex and age, region of residence, current employment status, urban/rural split, and race/ethnicity/origin) was 6.4% [7]. Based on data from CHECK, 52.62% of adults diagnosed with CHE in the UK have moderate/severe CHE confirmed by a physician.
- Approximately half of CHE is refractory to topical corticosteroids (TCS): in a recent chart review study (RWEAL), 49.68% of UK patients with moderate to severe CHE had experienced an inadequate response (defined as a history of failure to achieve and maintain a low disease activity state with a high or ultra-high potency TCS, or a history of adverse events experienced with a high or ultra-high potency TCS) or contraindication to TCS [8].

Burden of illness

- CHE has a persistent or fluctuating course with a poor prognosis, resulting in a substantial physical and psychological burden for patients [6, 9].
- The signs and symptoms of CHE have a substantial impact on patients' daily lives and physical functioning – the persistent itch, pain, blisters and fissures, together with the occupational nature of many CHE cases, may limit patients' ability to work, and constant itching can affect sleep [2, 6].
- CHE may be associated with a considerable psychological burden including anxiety and depression, while the appearance of CHE has a negative impact on personal relationships [4, 10-12].
- Overall, moderate to severe CHE has an impact on health-related quality of life (HRQoL) similar to or greater than that of moderate to severe atopic dermatitis (AD) or psoriasis [13].

Pathogenesis

- CHE is a complex, multifactorial disease with a polymorphic clinical picture [5].
- The immune signatures of the different CHE aetiological subtypes make CHE a distinct disease from AD, with atopic CHE being only one of the many recognised CHE subtypes (which can be overlapping).
- The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is a key therapeutic target in CHE because it mediates the activity of multiple inflammatory cytokine pathways involved in multiple mechanisms of inflammation that underly the different CHE subtypes [14].

Delgocitinib mechanism of action

- Delgocitinib is a topical pan-JAK inhibitor that targets the activity of all four members of the JAK family of enzymes, consisting of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), in a concentration dependent manner [15].
- Topical application of delgocitinib cream 20 mg/g twice daily results in minimal systemic absorption, thus minimal systemic pharmacological effect is expected [16].

Clinical pathway of care

- For CHE refractory to TCS, the European Society of Contact Dermatitis (ESCD) 2022 guidelines suggest phototherapy (for moderate to severe CHE) or recommend oral alitretinoin (for severe CHE only) as second-line therapies; however, these therapies have significant disadvantages [5]. NICE recommends alitretinoin for adults with severe CHE that has not responded to potent TCS [17].There are no recognised UK-specific treatment guidelines for CHE.
- Phototherapy can be inconvenient for patients to access, and it is associated with adverse events (AEs) such as erythema and burning of the skin, while long-term use increases the risk of premature skin ageing and non-melanoma skin cancer [5, 18].
- Oral alitretinoin is a systemic retinoid and a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects, and must be used with a strict pregnancy prevention programme [19]. Alitretinoin is also associated with AEs such as headache and nausea, and psychiatric disorders [19].
- Within ESCD guidelines systemic immunosuppressants are suggested as an option for patients refractory or contraindicated to first- and second-line therapies, but are mostly used off label in CHE. There is limited evidence for their efficacy in CHE and they can be associated with potentially serious AEs, hence requiring frequent monitoring [5].

Proposed positioning of delgocitinib

- The expected position of delgocitinib in the treatment pathway is as a second-line therapy for patients with moderate to severe CHE requiring long-term management, after TCS/topical calcineurin inhibitors (TCI) and before off label systemic therapy and biologics.

1.3.1 Disease overview

1.3.1.1 Clinical features

Hand eczema (HE) is a complex, multifactorial, non-infectious skin disease of the hands and wrists with a polymorphic clinical picture and painful, pruritic and inflammatory symptoms [1-3]. HE may involve the majority of the surface area of the hands and wrists or be limited to certain parts, for example palms, interdigital spaces, or fingertips [5].

Chronic HE (CHE) is defined as HE that lasts for more than 3 months or relapses at least twice per year [4, 5]. CHE is characterised by core symptoms of itch and pain, and patients may also experience dryness, cracking, thickened skin and bleeding; these signs and symptoms can fluctuate in severity over time [5, 6]. A large international chart review study (the Real-World trEatment & mAnagement of chronic hand eczema in cLinical practice [RWEAL study] [8, 20]) provides data on the clinical signs and symptoms recorded during patients' last clinic visit [8]. For inclusion, patients had to have moderate or severe CHE and to have been treated with topical corticosteroids (TCS) in the last 12 months, or to have a contraindication to TCS [8]. The most common signs reported for UK patients (n = 365) were

erythema (63.6%), pruritus 61.9%), scaling (50.7%) and fissures (45.2%) [8] (Appendix B.8, Table 160). Patients had a median of three signs or symptoms (interquartile range [IQR], 2–5) [8].

Similar results were seen in a recent retrospective review of medical records of adult patients receiving topical or systemic prescription treatment for moderate to severe CHE in countries including the UK [21].

1.3.1.2 Diagnosis and classification

The diagnosis of CHE is based on a potentially extensive array of assessments that include medical history, clinical examination, skin testing, histopathology and microbiology [2, 10, 22, 23]. However, the lack of a clear link between aetiology and morphology complicates diagnosis and makes the identification of effective treatments for each patient challenging [5, 24]. Patch testing is required to identify and classify allergic contact dermatitis [5], but there are inadequate numbers of patch testers available to test most patients with CHE [24]. A large prospective patient survey – Chronic Hand Eczema epidemiology, Care, and Knowledge of real-life burden (CHECK [25, 26]) – found that 16.1% of individuals with self-reported physician-diagnosed CHE in the UK underwent patch testing to confirm the diagnosis [7], while the RWEAL physician survey found that a mean of 41% of patients with moderate or severe CHE in UK practices underwent patch testing to confirm the diagnosis [8]. The clinical manifestations of CHE can overlap with other dermatoses, such as psoriasis, lichen planus, and tinea manuum [2], as well as scabies, mycosis fungoides, porphyria cutanea tarda, and hand-foot-and-mouth disease [10], which hinders diagnosis.

1.3.1.3 Overview of CHE aetiological subtypes

Multiple aetiological factors contribute to the development of HE and, for a given aetiological factor, there can be multiple clinical morphologies which may change with evolution of the condition [5]. The lack of a clear link between aetiology and morphology complicates diagnosis and makes the identification of effective treatments for each patient challenging [5, 24].

The most common aetiological subtypes are irritant contact dermatitis, allergic contact dermatitis and atopic HE; often, more than one aetiological factor plays a role in the development of CHE, and the clinical picture may also change over time, with the presence of one aetiological subtype leading to the development of another subtype [5]:

Irritant contact dermatitis – the most common type of hand dermatitis, a non-immunological, inflammatory skin reaction typically due to an irritant causing damage to keratinocytes and other skin cells. Hot, cold, dry or wet conditions can also cause irritant contact dermatitis on hands. This type of HE is common for people in certain types of jobs which involve contact with chemicals (e.g., acids and alkalis) or frequent hand washing [5, 10].
Allergic contact dermatitis – this is caused by a delayed-type reaction (type IV reaction) as an immunological response to contact with an allergen (e.g., perfume, metal [such as nickel], rubber or leather) in a sensitised individual [5, 24, 27]. It can occur independently or after

irritant contact dermatitis [5], which can cause the skin to become cracked, allowing allergens to penetrate and activating the immune system. With repeated, long-term exposure to allergens, the patient can develop allergic contact dermatitis. This type of HE can be more severe if exposure to the allergen continues [10].

Atopic HE – this is mainly caused by a person's immune system. Atopic HE can also be caused by genetic factors that affect the development of the skin outer layers, and by environmental factors that disrupt the skin barrier. Skin barrier disruption can lead to allergic reactions. As a result, if a patient has atopic HE, they may also develop allergic contact dermatitis and/or irritant contact dermatitis [10].

As a result, it is common for more than one underlying cause to play a role in the development of the disease, with irritant contact dermatitis often seen alongside allergic contact dermatitis and atopic HE. It is difficult to draw definitive conclusions about the underlying cause of an individual patient's HE, as this may evolve over time. This highlights the need for treatments that target the multifactorial nature of CHE.

1.3.1.4 Assessment of CHE severity

There is no consensus as to how the severity of CHE should be assessed. In clinical studies, CHE may be classified as mild, moderate or severe according to the Physician's Global Assessment (PGA), Investigator's Global Assessment (IGA), IGA for CHE (IGA-CHE) or Hand Eczema Severity Index (HECSI), combined with a photographic guide (Figure 43) (see also next section) [5, 28, 29]. However, in other cases a clinical judgement may be made that includes the functional impact of CHE on patients [30].

In practice, clinically validated scales are rarely used due to their complexity and the length of time needed for their completion. When UK clinicians in RWEAL were asked about the approaches employed to assess the severity of CHE in their patients, they reported relying on clinical judgement for 79% of their patient population, followed by psychosocial burden of the patient and/or the impact on their health-related quality of life (HRQoL; 49%), ability to work (46%) and CHE treatment history (41%) [8]. Only 24% used a scoring system for clinical assessment of HE [8]. Clinicians often do not distinguish between moderate and severe CHE and make treatment choices based on response to previous treatment rather than formal assessment of severity [31].

1.3.1.5 Measurement of treatment response

The PGA scale includes five levels (from 0 = 'clear' to 4 = 'severe disease'), based on the severity of each sign or symptom assessed with an outcome measure and photo guide. However, the definition of 'almost clear' is broad, which may make it difficult to differentiate between adjacent levels, potentially leading to inconsistent interpretation.

Authorities consider the PGA scale not to be a reliable/suitable primary outcome measure for the following reasons:

- The PGA scale is a global assessment of disease severity and could not accurately represent an evaluation of the smaller areas affected by CHE. Investigator's reliability to estimate the affected area was questioned.
- Treatment failure vs. treatment success was considered ill-defined. The category "almost clear" overlapped with the "mild" category. The "almost clear" category needed to include only residual erythema and no other signs of the disease in order to clearly distinguish treatment success from treatment failure.
- The PGA scale includes an assessment of itch and pain which were considered subjective symptoms not accurately assessed by the physician.

The IGA-CHE scale was created to address these issues and was further modified after the delgocitinib phase 2b trial following further regulatory and expert advice. Like the PGA, the IGA-CHE scale has five levels, but was developed specifically for CHE and uses detailed descriptions within a single scale to characterise each level (Appendix B.6.1, Table 154). The descriptions were defined carefully, with input from clinical experts and taking account of regulatory feedback, to ensure adjacent levels, in particular 'almost clear' and 'mild', are clearly distinct. The IGA-CHE score of 1 (barely perceptible erythema) is more strict than the PGA score of 1 and, in contrast to the PGA scale, the IGA-CHE scale does not include any subjective patient-reported outcomes such as itch and pain [29]. These inherent differences may lead to inconsistency when comparing results from trials that used the different scales, with possible lower estimates of efficacy expected when using the IGA-CHE scale, compared with the PGA scale. The IGA-CHE scale is used to define CHE severity in the inclusion criteria for the DELTA clinical trials described in section 1, and in the primary endpoint in the DELTA 1 and DELTA 2 trials. Validation of the IGA-CHE scale, including its content, is described in Appendix B.6.1.

For a heterogenous disease such as CHE, augmenting IGA-CHE results with other endpoints is the best way to achieve a comprehensive evaluation of severity in clinical trials. The HECSI is used by clinicians to rate the severity of six clinical signs of HE (erythema, infiltration/papulation, vesicles, fissures, scaling and oedema) at the time of evaluation [29]. The HECSI is calculated by dividing the patient's hand into five areas (fingertips, fingers, palms, back of hands and wrists) and measuring the intensity of each of the six clinical signs using a 4-point severity scale (0 = 'none/absent', 1 = 'mild', 2 = 'moderate' and 3 = 'severe'). For each location, the area score (total of both hands) is calculated by assigning a score of 0–4 based on the following criteria: 0 = '0%', 1 = '1–25%', 2 = '26–50%', 3 = '51–75%', 4 = '76–100%'. The score given for each location is multiplied by the total sum of the intensity of each clinical feature. The HECSI total ranges from 0 to 360 with higher scores indicating greater severity of CHE [29]. In clinical trials, treatment responses are often defined as HECSI-50, HECSI-75 or HECSI-90, representing ≥ 50%, ≥ 75% and ≥ 90% reductions in HECSI from baseline, respectively.

Patient-reported outcome (PRO) measures are valuable to support clinical endpoints in clinical trials of new therapies. Historically, PRO measures used in CHE were either not disease-specific (e.g., the Dermatology Life Quality Index [DLQI]) or primarily provided an

assessment of quality of life rather than a comprehensive assessment of the key signs/symptoms associated with CHE (e.g., Quality of Life in Hand Eczema). The Hand Eczema Symptom Diary (HESD) was therefore developed as a new, CHE-specific PRO measure assessing the severity of CHE signs and symptoms and designed for use in clinical trials of treatment interventions for CHE and in clinical practice for the management of CHE [32], which is aligned with regulatory guidance. The HESD is completed daily (eDiary), and its 24-hour recall period captures the fluctuating nature of CHE signs and symptoms. Validation of the HESD, including its six items, is described in Appendix B.6.2.

1.3.1.6 Epidemiology

Globally, the one-year prevalence of HE in the adult general population was estimated to be 9.7% in a meta-analysis of 19 studies, with a lifetime prevalence of 16% [33]. Risk factors associated with the development of HE include prior or current AD, wet work and exposure to irritants and allergens [10, 34]. The risk of developing HE is positively correlated to intensity of wet work, particularly among women [5, 35]. HE is more common in women than in men and has an earlier average age at onset in women than in men [5, 33]. This is explained by differences in exposure patterns between the sexes [10].

More than 50% of patients with HE have chronic disease, and patients often suffer from the disease for prolonged periods [33, 36, 37]. Among 858 UK patients in CHECK who self-reported having HE in the last 12 months, 89% reported having CHE (i.e., they reported that their HE lasted continuously for ≥ 3 months or that they had ≥ 2 disease flares) [7]. Among 10,014 UK respondents in CHECK overall (with or without HE), the point prevalence of self-reported CHE was 7.6% (95% confidence interval [CI], 7.1–8.1%). The point prevalence of self-reported physician-diagnosed CHE was 6.4% (95% CI, 6.0–6.9%) [7]. Based on data from CHECK, 52.62% of adults diagnosed with CHE in the UK have moderate or severe CHE confirmed by a physician.

CHE is refractory to potent topical steroids in approximately half of patients [38]; among UK patients with moderate to severe CHE in RWEAL (n = 365), 49.68% reported an inadequate response (defined as a history of failure to achieve and maintain a low disease activity state with a high or ultra-high potency TCS, or a history of adverse events [AEs] experienced with a high or ultra-high potency TCS) or contraindication to TCS [8].

1.3.1.7 Prevalence of CHE subtypes

In the RWEAL study, the three most common CHE causes in the UK were atopic HE, irritant contact dermatitis and allergic contact dermatitis (Appendix B.8, Table 161) [8]. As described in section 1.3.1.3, it is common for patients with CHE to have more than one aetiological subtype. In RWEAL, one third of patients had either multiple CHE subtypes or CHE of unknown aetiology (Appendix B.8, Table 161) [8]. As noted in section 1.3.1.2, use of patch testing (which is required to identify and classify allergic contact dermatitis) is limited in clinical practice [8].

1.3.1.8 Burden of illness

Effect of CHE on patients

CHE has a persistent or fluctuating course with a poor prognosis, resulting in a major physical and psychological burden for patients [6, 9]. Inflammatory symptoms and signs (itch, pain, erythema, swelling and burning) are typically associated with flares of disease activity, and chronic features such as dry skin and flaking can persist between flares [6].

The signs and symptoms of CHE have a substantial impact on patients' daily lives and physical functioning, due to difficulty touching or gripping but also the need to avoid environmental triggers [6]. Persistent itch, blisters and fissures, together with the occupational nature of many CHE cases, may limit patients' ability to work [2]. Functional disturbance and pain can be disproportionate to the extent of hand eczema involvement; even a few isolated fingertip fissures can be disabling [2].

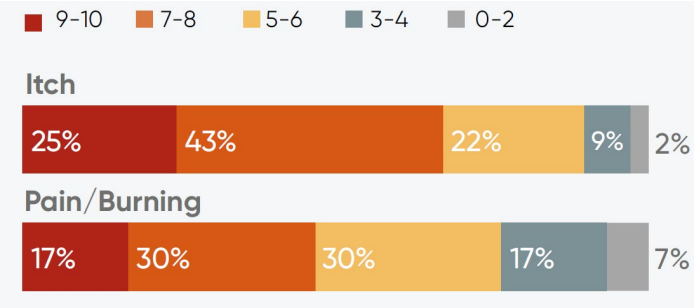
Constant itching can also affect sleep quality [6]. In the CHE Patient Impact Report, a research project undertaken by LEO Pharma with input from Allergy UK and healthcare professionals, 86% of surveyed patients (n = 152) had difficulty sleeping due to hand eczema during their last flare [12], whereas 75% of patients strongly agreed that having eczema on the hands was harder to deal with than other areas of the body due to that fact that they are in constant use [12].

Impact of itch and pain

As described in section 1.3.1.1, 62% of UK patients with moderate to severe CHE in RWEAL (n = 365) had itch (or pruritus), whereas 33% had pain (Appendix B.8, Table 160) [8]. At baseline in CHECK, most UK patients with moderate or severe CHE reported at least moderate levels of itch (Appendix B.8, Table 162), with 51% of patients with severe CHE reporting severe itch [7]. The majority of patients with moderate CHE (61%) and most patients with severe CHE (85%) had at least moderate pain. Similarly, moderate or severe sleep disturbance was reported by 58% of patients with moderate CHE and 74% of those with severe CHE [7].

In the CHE Patient Impact Report, participants rated an average itch score of 7.2 out of 10 and an average pain score of 6.2 out of 10 when assessing the impact on their lives; the distribution of itch and pain scores is shown in Figure 1. Around half of patients reported that experiencing itchy skin was a symptom that impacted them every day or most days. When asked about their future aspirations for treatment, the most frequent desire was for help with itching (75% of patients) [12].

Figure 1 Impact of CHE itch and pain on UK patients' lives



Patients were asked: 'On a scale of 0–10, to what extent does itch or pain/burning from your hand eczema impact on your life?', with 0 = 'not at all' and 10 = 'significant impact'.
Source: CHE Patient Impact Report [12].

Psychological impact of CHE

CHE may be associated with a considerable psychological burden including anxiety and depression [4] – one study found that 56% of patients with severe treatment-refractory CHE reported symptoms of anxiety or depression [11]. The visibility of the hands may contribute to the psychological burden of CHE [4]. A large observational study reported that HE was one of the three skin conditions associated with the highest likelihood of depression and anxiety, comparable to psoriasis [39]. In the CHE Patient Impact Report, 87% of patients agreed (45% strongly) that eczema on their hands is particularly hard to deal with because they are unable to hide it, with 71% agreeing to some extent that they try to hide their hand eczema as much as they can [12].

The appearance of CHE has a negative impact on personal relationships [10], causes embarrassment [6, 10] and can lead to self-isolation [10]. Almost two thirds of patients with CHE reported feeling anxious or stressed due to their condition and 55% felt angry or resentful towards their CHE, with 1 in 5 reported feeling low mood or depression frequently or every day [12]. Similarly, in a survey of 1023 people with HE, 89% of respondents were embarrassed or self-conscious about their eczema, and 74% reported that their condition affects the way they handle objects or touch people [40].

Overall impact of CHE on HRQoL

Overall, the burden of moderate to severe CHE on patients' lives is high, with patients consistently reporting HRQoL impairment [41], similar to or greater than that of moderate to severe AD or psoriasis [13]. In the CHE Patient Impact Report, 76% of respondents rated the impact of CHE on their HRQoL as high (30%) or moderate (46%) [12].

HRQoL impairment increases with disease severity. For example, in an Italian study, patients with severe CHE that was refractory to treatment reported utility scores similar to or worse than those reported in a study of treatment-refractory moderate to severe psoriasis [11, 42], with most patients reporting a moderate to extremely large effect as assessed with the DLQI [11]. A recent systematic literature review (SLR) found that mean DLQI increased in line with increasing disease severity (mean DLQI: mild CHE, 4.9–7.9; moderate CHE, 6.7–12.0; severe CHE, 11.1–17.3) [41].

Impact of CHE on work and education

CHE also has a significant cost burden. In addition to the costs of treatment and healthcare resource utilisation, the association of some occupations with an increased risk of CHE leads to a significant economic impact on both patients and society due to job losses and presenteeism [43].

Around half of patients in the CHE Patient Impact Report said that CHE has influenced their career choice to some extent, with 72% stating that they currently experience some impact on their work due to their condition. This impact was more notable in professions where wet work or the requirement to wash their hands is more frequent, with healthcare professionals (87%), those working in the service industry (77%) and those working in education (64%) reporting at least some impact of their condition on their work [12].

Studies in Europe and the USA indicate job loss/change owing to CHE ranging from 3% to 25% [43], whereas those who change profession or leave the job market are more likely to report complete healing [44]. In a one-year follow-up survey of 564 patients with occupational HE in Denmark [45], severe occupational HE, age ≥ 40 years and severe impairment of quality of life at baseline were found to predict prolonged sick leave and unemployment [45].

1.3.2 Pathogenesis and delgocitinib mechanism of action

1.3.2.1 Overview of CHE pathogenesis

CHE is a complex, multifactorial disease with a polymorphic clinical picture [5]. Guidelines identify a number of different aetiological and clinical subtypes of CHE [5]. There can also be mixed forms of CHE in which more than one aetiologic factor and clinical subtype are present. The clinical picture may also change over time [5], while, as described in section 1.3.1.3, the presence of one aetiological subtype can lead to the development of another subtype. Most cases of CHE are caused by an interaction of factors that trigger a cycle of skin barrier dysfunction and inflammation [4, 10]. Inflammation and immune responses can persist after environmental factors are removed, perpetuating the cycle [5].

1.3.2.2 Pathogenesis of CHE subtypes

CHE signs and symptoms arise from complex interactions between skin and immune cells that lead to a cycle of pro-inflammatory signalling; however, the precise immune signature depends on the underlying aetiology [1, 14].

AD is an established risk factor for CHE and the two conditions can occur concomitantly [5]. However, the immune signatures of the different CHE aetiological subtypes make CHE a distinct condition from AD (Table 3), with atopic CHE only one of the many recognised CHE aetiological subtypes. In contrast to AD, which is primarily driven by type 2 inflammation [46, 47], multiple immune profiles have been identified among patients with CHE. The underlying pathophysiology can include signalling cascades associated with type 1, type 2 and type 3 inflammation, with for example interferon gamma (IFNγ) involved in type 1, interleukin (IL)-4

and IL-13 in type 2, and IL-17 in type 3 inflammation [14, 48]. There are some characteristic variations across aetiologies [14] (Appendix B.8, Table 163).

Table 3 CHE versus atopic dermatitis: key characteristics

Disease Characteristics	CHE	Atopic dermatitis
Typical age of onset	Early to mid-twenties	< 5 years
Primary distribution	Hands and wrists	Widespread on flexural body surfaces
Population	Adults, workers exposed to occupational risk factors	Children commonly affected in addition to adults
Treatment considerations	Difficulty in avoiding irritants/allergens in daily routine Thicker skin of palms affects drug penetration Small body surface area affected (supporting targeted topical treatment)	Larger body surface area affected (may support systemic treatment)
Core symptoms	Pain, itch	Itch
Main aetiology	Irritant, allergic, atopic (often in combination)	Atopic
Immune profiles	Th1/Th17 and Th2/Th22 profiles	Th2/Th22 profile

CHE, chronic hand eczema; Th[X], type [X] T helper.
Source: Diepgen *et al*. 2015 [4].

Importance of JAK–STAT pathways

Skin barrier dysfunction is a key characteristic of CHE, irrespective of aetiology [9]. In healthy skin, the stratum corneum (outer layer) forms a protective barrier, but in CHE, activation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathways leads to downregulation of antimicrobial peptides and structural proteins, resulting in skin barrier dysfunction [1].

JAKs are intracellular enzymes associated with cytokine receptor chains that transmit signals from cytokines to regulate a broad range of physiological and pathological processes, including inflammatory responses [49]. Within the signalling pathways, JAKs are activated upon cytokine–receptor interaction and thereafter phosphorylate and activate STATs [49]. Activated STATs, in turn, activate the expression of cytokine-responsive genes to induce specific biological responses in target cells [49].

Therefore, the JAK–STAT pathways are a key therapeutic target in CHE because they mediate the activity of multiple inflammatory cytokine pathways involved in all of the types of inflammation that underly the different CHE subtypes [14].

1.3.2.3 Delgocitinib mechanism of action

Inhibition of JAK activity with delgocitinib prevents the phosphorylation and activation of STATs [15], thus blocking the signalling of multiple pro-inflammatory cytokines [50] driving disease severity in CHE.

Delgocitinib is a topical pan-JAK inhibitor that targets the activity of all four members of the JAK family of enzymes, consisting of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), in a concentration dependent manner [15]. In human cells, inhibition of the JAK–STAT pathway by delgocitinib attenuates the signalling of several pro-inflammatory cytokines, including IL-2, IL-4, IL-6, IL-13, IL-21, IL-23, GM-CSF and IFNα, downregulating the immune and inflammatory responses in cells of relevance to CHE pathology [15]. Consequently,

delgocitinib is expected to be efficacious across all CHE aetiologies. As delgocitinib is applied topically, it is associated with a low risk of systemic side effects due to its minimal systemic absorption (see section 2.11.3.8).

1.3.3 Clinical pathway of care for CHE

1.3.3.1 Overview of treatment guidelines

Treatment guidelines for HE, based on a 2019 Cochrane systematic review [51], were published in 2022 by the European Society of Contact Dermatitis (ESCD) Guideline Development Group [5]. The treatment of HE is also described in a British Association of Dermatologists (BAD) information leaflet published in 2023 [27]. NICE has published guidance only on alitretinoin for severe CHE (TA177) [17] and a Clinical Knowledge Summary on contact dermatitis [52]; however, there are no UK-specific recognised treatment guidelines for CHE.

1.3.3.2 Summary of ESCD guidelines

Current ESCD guidelines are summarised in Appendix B.8, Figure 44 [5].

ESCD guideline recommendation strength

ESCD recommendations are graded as: **A**, strong recommendation/'we recommend'; **B**, weak recommendation/'we suggest'; **0**, open (high level of uncertainty)/'may be considered'.

First-line therapy

For patients whose CHE remains inadequately controlled following use of emollients and reduction of exposure to substances causing skin reactions, the first-line treatments are TCS with or without topical calcineurin inhibitors (TCIs) [grade of recommendations: short-term TCS, **A**; long-term TCS, **0**; short-term TCIs, **B**] [5].

International and European guidelines suggest use of TCIs in milder cases of CHE and primarily as part of a steroid-sparing regimen following flare resolution with TCS, or when fear of side effects of TCS exist [5, 22, 53].

Second-line therapy

Phototherapy (psoralen–UV A phototherapy [PUVA] or ultraviolet B [UVB]) may be used for moderate to severe CHE refractory to TCS [grade of recommendation, **B**] [5].

Alitretinoin is the only treatment recommended as second-line treatment for patients with severe CHE [grade of recommendation, **A**] [5]. In TA177, NICE recommends alitretinoin for adults with severe CHE that has not responded to potent TCS [17].

For the ALPHA trial (commissioned by the National Institute for Health and Care Research [NIHR]), PUVA was identified as the most relevant comparator for alitretinoin based on published clinical trials and on feedback from 194 UK dermatologists and the UK Dermatology Clinical Trials Network [54].

Third line therapy

Ciclosporin is suggested for patients with CHE refractory to first- and second-line treatment or with a contraindication for first- and second-line treatment; this is off label except for atopic HE [grade of recommendation, **B**] [5].

Azathioprine, methotrexate and acitretin may be considered for patients with CHE refractory to first- and second-line treatment or with a contraindication for first- and second-line treatment, although evidence for their efficacy is limited [grade of recommendations, **0**] [5].

No biological treatments are specifically approved for CHE. The biologic dupilumab is also mentioned in the ESCD guidelines, but without specific treatment recommendations [5]. Dupilumab is approved for AD and thus, use in atopic HE is within label; however, it targets only the type 2 inflammation associated with AD [47].

The ESCD guidelines state that pan-JAK inhibitors may benefit all types of CHE, but without providing specific treatment recommendations [5].

1.3.3.3 Treatment of different CHE aetiological subtypes

Aetiology and clinical features of CHE can vary considerably between patients [5]. As described in sections 1.3.1.3 and 1.3.2.2 above and Appendix B.8 (Table 163), the three main aetiological subtypes of CHE have different causes and immunological signatures [1, 14].

For irritant contact dermatitis and allergic contact dermatitis, removal of the trigger is the primary objective and may benefit a large proportion of patients [5]. However, as occupational hazards may be unavoidable and new allergies may develop over time (see section 1.3.1.3), treatment of the underlying pathophysiology may be needed for many patients.

Optimal treatment for atopic HE differs from that for AD affecting the rest of the body, due to the relative body surface area affected, the multifactorial nature of CHE and the possibility that atopic HE can lead to the development of irritant contact dermatitis and allergic contact dermatitis [10]. In the ESCD guidelines, it is hypothesised that pan-JAK inhibitors (e.g., delgocitinib) may benefit all subtypes [5].

1.3.3.4 Treatment use in clinical practice

In general, there are limited published clinical data on the treatment of CHE, with the 2019 Cochrane review noting that the evidence base for CHE treatments was lacking in guidelines published up to that time [51]. The limited clinical data and limited approved second-line treatments for moderate and severe CHE lead to inconsistent treatment strategies. A survey of 194 UK dermatologists likewise found that it was uncertain which treatment could provide best short and long-term outcomes for severe CHE, with both alitretinoin and PUVA being commonly used treatments regardless of CHE subtype. Oral steroids were also frequently used for vesicular HE, but the adverse events associated with their long-term repeated use caused concerns among the dermatologists surveyed. Similar concerns were raised for ciclosporin.

The RWEAL study investigated current treatment use in the UK for a population of patients with moderate to severe CHE who had been treated by dermatologists with TCS in the last 12 months or for whom TCS were not medically advisable (Appendix B.8, Table 164). Data as to which line of treatment (i.e., first, second or later lines of treatment) each therapy was used in were not captured and multiple responses were possible. The most commonly used therapy was TCS (use of TCS in the last 12 months or a contraindication to TCS were required for inclusion in the study). A total of 4.7% of patients had used a TCI therapy (pimecrolimus and/or tacrolimus) in combination with other treatments [8], whereas 1.1% had used it as monotherapy (data not shown). Alitretinoin was used by 11% of patients [8]. Despite NICE guidance for the use of alitretinoin being restricted to the severe population only, it had been used to treat 5% of patients with moderate CHE (compared with 18% of those with severe CHE) [8]. Clinicians often do not distinguish between moderate and severe CHE and make treatment choices based on substantial impact of the disease or response to previous treatment rather than formal assessment of severity [31]. Some treatment guidelines suggest patients should be treated "as severe" after failure on topicals or PUVA [2, 55]. The use of PUVA and ultraviolet B therapy was similar (both 5%) [8], with both treatments being used for patients with moderate or severe CHE.

Methotrexate and ciclosporin had been used in the treatment of 9.8% and 8.2% of patients, respectively. Azathioprine use in the UK was rare (2.2% of patients), and no use of mycophenolate was identified [8]. As described above, no data were captured in RWEAL as to in which line of therapy each treatment was used. The use of systemic therapies with limited evidence of efficacy in the treatment of CHE and a risk of serious adverse events (SAEs) is notable and highlights the lack of efficacious topical therapies for patients for whom TCS is insufficiently effective or unsuitable.

1.3.3.5 Limitations of current second-line treatments

Phototherapy

Usually, ultraviolet B phototherapy is given three times weekly and PUVA is given two times weekly [56]. In the NIHR-commissioned ALPHA trial, PUVA phototherapy was scheduled twice weekly for 12–24 weeks; each session involved immersion of hands in a Meladinine® solution for 15 minutes followed by a delay of up to 30 minutes before exposure to ultraviolet A radiation according to standard practice at the participating site [54]. A limitation of phototherapy is that it can be inconvenient and costly to access [57]. Patients may live too far away from the hospital or the opening times of a local unit may not fit in with their work and home commitments [56]. In the NIHR-commissioned ALPHA trial, 22% of patients who did not consent to participate in the study gave the inconvenience of the PUVA schedule or travel as the reason [54]. Phototherapy (especially PUVA) is also associated with AEs such as erythema and burning of the skin, and long-term use increases the risk of premature skin ageing and non-melanoma skin cancer [5, 27]. These factors contribute to a low level of compliance with phototherapy.

Alitretinoin

For patients with severe CHE not adequately treated by TCS therapy, the only specifically licensed product is alitretinoin, a systemic retinoid [5]. Alitretinoin is a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects [19]. Consequently, pregnancy is an absolute contraindication to treatment with alitretinoin; in women of childbearing age alitretinoin must be used with a strict pregnancy prevention programme extending 1 month after the end of treatment [19], which can lead to tokophobia (fear of becoming pregnant). Alitretinoin also requires additional visits in case of treatment reinitiation, and has a number of further contraindications, including use in patients with hypersensitivity to peanuts or soya, as the capsule filling contains soya-bean oil [19]. Additional monitoring is required in patients to assess lipid metabolism and potential hepatobiliary disorders [19] and for signs of depression [19]. Alitretinoin is associated with AEs including headache in 24% of patients and nausea in 5.1% of patients [19]. As such, given the restricted label and various safety limitations and contraindications, alitretinoin is unsuitable for a significant proportion of patients with CHE [51].

1.3.3.6 Later lines of therapy for CHE

Off label systemic treatments

Ciclosporin is licensed for the treatment of severe atopic eczema but not specifically CHE. Patients who are prescribed ciclosporin require careful monitoring, since treatment can be associated with potentially serious AEs, including risks of malignancy, nephrotoxicity and hypertension, and an increased risk of infection [5].

Other conventional systemic treatments (acitretin, azathioprine, methotrexate and oral corticosteroids) may be considered for patients with CHE refractory to first- and second-line therapies, or for whom these therapies are contraindicated [5]. However, none of these are licensed for the treatment of eczema and the evidence for their efficacy in the treatment of CHE is limited, with very limited randomised controlled trial (RCT) evidence available (Appendix B.1) and no health technology assessments (HTA) having been conducted. In addition, they can be associated with potentially serious AEs, requiring frequent monitoring [5]:

- Acitretin is highly teratogenic (a strict pregnancy prevention programme extending 3 years after the end of treatment is required) [5, 58].
- Azathioprine is hepatotoxic, can lead to bone marrow depression and may be teratogenic (pregnancy prevention is advised when either partner is receiving azathioprine, and for at least three months after the end of azathioprine therapy) [59].
- Methotrexate treatment can be hepatotoxic and teratogenic, is associated with severe reactions to sun exposure (which limits patients' ability to carry out daily activities or work outside), and can lead to susceptibility to infection [60, 61].
- Oral corticosteroids can only be used short-term, as long-term or repeated use is associated with long-term AEs (in RWEAL, UK patients who had used oral corticosteroids had a median treatment duration of 24 days) [5, 8].

Biologics

Although there are no licensed biologics for non-atopic CHE, some patients may be treated with biological therapies when earlier lines of therapy have failed. Dupilumab, which is licensed for AD for patients whose disease has not responded to at least one systemic immunosuppressant, has shown efficacy and good tolerability in patients with severe CHE in a phase 2b placebo-controlled proof-of-concept study [62]. In a phase 3 RCT, dupilumab was shown to be statistically significantly more efficacious than placebo in the treatment of atopic hand and foot dermatitis [63].

However, dupilumab, an inhibitor of IL-4 and IL-13, targets only the type 2 inflammation associated with AD [46, 47]. Given the lack of a clear link between CHE aetiology and morphology [5, 24], dupilumab may be a relevant treatment option only for patients with atopic CHE who have failed at least one conventional systemic, as per the current NICE recommendation for dupilumab for moderate to severe AD [64].

In the UK, data from RWEAL showed that only 3.8% of patients with CHE received biologics in the past 12 months [8]. Furthermore, local requirements for prescribing mean many patients with just CHE will not meet the threshold for biologics.

Oral JAK inhibitors

Use of the oral JAK inhibitor (JAKi) baricitinib, which is on label only for the treatment of moderate to severe AD for patients who likewise have not responded to conventional systemic immunosuppressants, has been described in case reports involving patients with severe CHE [65] or chronic hand and foot eczema [66], whereas abrocitinib was assessed in a head-to-head RCT with dupilumab evaluating their effects in patients with moderate to severe AD with coexisting HE [67]. However, oral JAK inhibitors carry a black box warning of an increased risk of serious heart-related events [68], potentially leading to an unfavourable risk–benefit profile specifically for the treatment of CHE.

1.3.3.7 Comparators to delgocitinib

As described above (see also section 1.1, Table 1) there are limited suitable comparators to delgocitinib for the treatment of moderate to severe CHE. For adults with moderate CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate, the only available second-line treatment suggested is phototherapy. For those with severe CHE, alitretinoin is also approved and recommended by treatment guidelines.

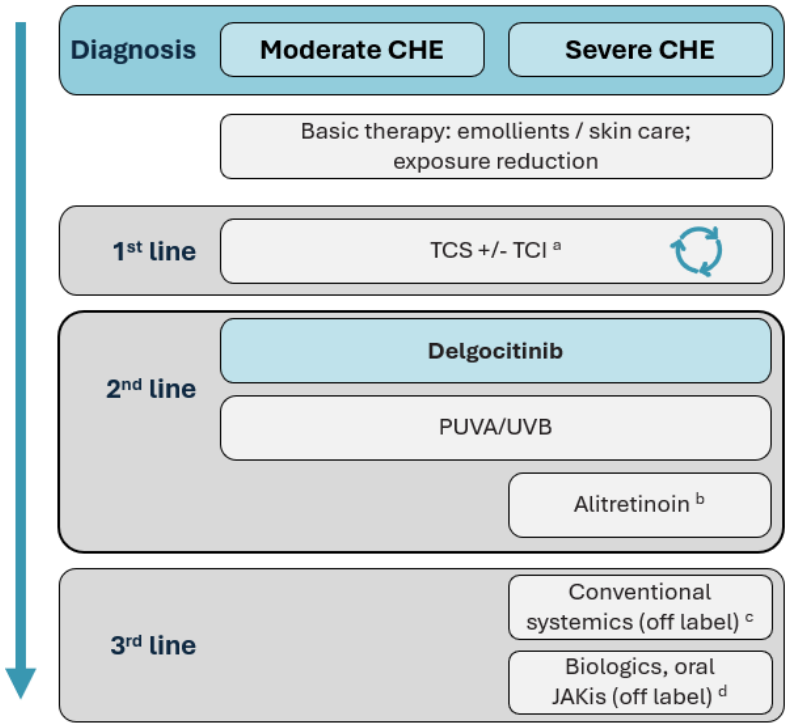
For the ALPHA trial (commissioned by the NIHR), PUVA was identified as the most relevant comparator for alitretinoin based on published clinical trials and on feedback from UK dermatologists and the UK Dermatology Clinical Trials Network [54]. Accordingly, the relevant comparators for delgocitinib in this submission are phototherapy (for moderate and severe CHE) and alitretinoin (for severe CHE only).

1.3.4 Proposed positioning of delgocitinib in the treatment pathway

The indication of delgocitinib approved by the MHRA is the treatment of moderate to severe CHE in adults for whom TCS are inadequate or inappropriate. Delgocitinib is the first treatment with a licence for both moderate and severe CHE.

The expected position of delgocitinib in the treatment pathway, as shown in Figure 2, is as a second-line therapy for patients with moderate to severe CHE requiring long-term management, after TCS/TCI.

Figure 2 Anticipated position of delgocitinib in treatment pathway



Positioning is based on ESCD guidelines [5] and NICE scope (section 1.1).
[a] TCI are not indicated for non-atopic subtypes of CHE and are used as a steroid-sparing option.
[b] Alitretinoin is licensed in the UK only for severe CHE. Guidelines position alitretinoin as initial 2nd line therapy based on weight of evidence.
[c] Conventional systemics are off label, with the exception of ciclosporin which is registered in some countries for use in AD but not specifically for HE (and is thus off label in HE of other aetiologies).
[d] Biologics and oral JAKis are off label; they are registered in some countries for use in atopic dermatitis but not specifically for HE (and are thus off label in HE of other aetiologies).
AD, atopic dermatitis; CHE, chronic hand eczema; JAKi, Janus kinase inhibitors; PUVA, psoralen–UV A phototherapy; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UVB, ultraviolet B.

1.4 Equality considerations

CHE may disproportionately affect certain groups, while the availability and suitability of existing therapies is not equal across the patient population.

CHE disproportionately impacts people in some job roles that require long lasting or repeated contact with water or other substances which can trigger CHE symptoms. This may include trade workers and people who work in the service industry, healthcare industry or

education [10]. CHE is more common in women than in men, as a result of differences in exposure patterns between the sexes [5, 33].

There may be racial differences in susceptibility to CHE. An intrinsically thinner stratum corneum and higher density of eccrine glands means that Asian people may have skin that is more sensitive to exogenous chemicals [69]. Skin type may also affect assessment of the severity of CHE, which can be more difficult in people with brown and black skin. For example, reddening of skin (erythema) is more difficult to determine by visual assessment in people with brown and black skin. This means that some potential CHE patients with brown and black skin may be undiagnosed, which could lead to undertreatment.

Some diagnostic tools, such as patch testing for allergic contact dermatitis, are not available in some locations. This results in inequality of diagnoses across different geographical locations within the UK. Some patients may be unable to access PUVA treatment due to the time and travel required to attend specialist healthcare settings, e.g., if they are unable to get time off from work. This may exclude some people from treatment with PUVA.

The only licensed treatment for severe CHE is alitretinoin, which is a teratogen. This means that patients who are able to become pregnant, would either be unsuitable for treatment with alitretinoin or would have to be involved in a pregnancy prevention programme [19]. As a precautionary measure, it is preferable to avoid the use of delgocitinib during pregnancy [70], but no pregnancy prevention programme is required. Therefore, the potential adoption of delgocitinib could provide women of childbearing age with an alternative licensed treatment for CHE.

Alitretinoin is contraindicated in patients with hypersensitivity to peanuts or soya, which limits treatment options for patients with peanut or soya allergies. Alitretinoin also requires additional monitoring when used to treat patients with diabetes, which may make it less suitable for these individuals [19]. The potential for hepatotoxicity means that similar monitoring requirements exist for ciclosporin, particularly for elderly patients [71].

Alitretinoin and ciclosporin can cause visual disturbances resulting in patients with CHE who operate machinery or drive being disproportionately affected by the lack of available treatments [71, 72].

CHE may disproportionately affect patients who have comorbidities, such as human immunodeficiency virus or other conditions that require antivirals as a primary treatment option. Antivirals are known to have many severe interactions which can increase the risk of drug toxicity or reduce the efficacy of a drug, when given in combination with systemic immunosuppressants [73]. As a result, patients with moderate to severe CHE who require antivirals to treat a condition have limited treatment options after TCS.

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a negative impact on people protected by equality legislation, compared with the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

2 Clinical effectiveness

Summary

Clinical trial evidence

- The efficacy and safety of delgocitinib cream for the treatment of moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate have been investigated in the phase 3 vehicle-controlled RCTs DELTA 1 and DELTA 2, together with their open-label extension study DELTA 3, and have been compared with oral alitretinoin for the treatment of severe CHE in the phase 3 active-controlled RCT DELTA FORCE.

Efficacy

- Both DELTA 1 and DELTA 2 met their primary endpoints, the proportion of patients achieving Investigator's Global Assessment for chronic hand eczema (IGA-CHE) treatment success (TS) at week 16 (defined as IGA-CHE scores of 0/1 and an improvement from baseline of ≥ 2 points).
- In addition, delgocitinib cream was statistically significant compared with cream vehicle for all key secondary endpoints, including 75% and 90% reduction in Hand Eczema Severity Index from baseline (HECSI-75, HECSI-90), patient-reported itch and pain, and HRQoL assessed with the DLQI or 5-dimension, 3-level EuroQol questionnaire (EQ-5D-3L).
- In DELTA 3, patients used delgocitinib cream on an as-needed basis, with levels of treatment success maintained during the 36-week study period; DELTA 3 also demonstrated that patients who lost response (defined as an IGA-CHE score ≥ 2) while off-treatment were able to regain their IGA-CHE TS response after a median of 8 weeks of retreatment with delgocitinib cream.
- In DELTA FORCE, delgocitinib cream was statistically significant compared with oral alitretinoin in reducing the mean HECSI score at week 12 from baseline (primary end point) and at week 24 (secondary endpoint).
- Delgocitinib cream showed statistically significance compared with oral alitretinoin for all key secondary endpoints, including IGA-CHE TS, HECSI-90, itch, pain and DLQI, as well as HECSI-75 (which was an exploratory endpoint).
- Subgroup analysis by disease severity from DELTA 1 and DELTA 2 demonstrated [redacted], with a similar efficacy observed across the two different subgroups for the primary endpoint. In DELTA 3, treatment success [redacted] at baseline of the parent trial, with [redacted] response after retreatment with delgocitinib cream by the end of treatment.
- Additional subgroup analyses for DELTA 1 and DELTA 2 showed that [redacted].
- In DELTA FORCE, results were [redacted].

Safety

- Overall, the results of the safety analyses show that delgocitinib cream has a favourable safety profile, with a low rate of AEs, a low rate of discontinuation due to AEs and no new safety issues during long-term use in DELTA 3.

- Pharmacokinetic data from DELTA 2 suggest that minimal systemic pharmacological effect is expected with delgocitinib cream 20 mg/g dosing in patients with moderate to severe CHE; the safety issues associated with use of oral JAK inhibitors were not identified in the RCTs as safety concerns for delgocitinib cream.

Network meta-analysis

- In the absence of head-to-head RCT data comparing delgocitinib and PUVA, a network meta-analysis (NMA) was performed to compare delgocitinib, PUVA and alitretinoin.
- Analyses were conducted using data from 16 weeks (the primary endpoint) and 12 weeks in DELTA 1, DELTA 2 and the Worm *et al.* 2022 phase 2 delgocitinib trial, compared with week 12 (primary endpoint) data from all other studies (DELTA FORCE, ALPHA, BACH).
- At both timepoints, patients treated with delgocitinib cream were [redacted].
- An NMA of discontinuation due to AEs found that patients treated with delgocitinib cream [redacted].

2.1 Identification and selection of relevant studies

See appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

Included clinical trials

The main sources of evidence in this submission are the DELTA 1 and DELTA 2 pivotal phase 3 cream vehicle-controlled trials and the DELTA 3 open-label extension study, as well as the DELTA FORCE head-to-head trial of delgocitinib and oral alitretinoin (Table 4).

DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101) are identical 16-week phase 3 randomised, double-blind, cream vehicle-controlled, parallel-group, multi-site clinical trials conducted in adult patients with moderate to severe CHE who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable [74, 75]. DELTA 1 and DELTA 2 provide evidence of the clinical efficacy and safety of continuous treatment with delgocitinib cream 20 mg/g twice daily (BD), compared with cream vehicle (see section 2.13.2 for discussion of how this regimen compares with the delgocitinib label).

DELTA 3 (NCT04949841) is a phase 3 open-label multi-site extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of twice-daily treatment with delgocitinib cream 20 mg/g as-needed for up to 36 weeks [76]. DELTA 3 provides evidence of the safety and efficacy of delgocitinib cream 20 mg/g BD up to 1 year of treatment using an as-needed regimen.

DELTA FORCE (NCT05259722) is a 24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3 trial to compare the efficacy and safety of delgocitinib cream 20 mg/g BD with alitretinoin capsules once daily (QD) in adult patients with severe

CHE (IGA-CHE score of 4; Table 4) who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable [77]. This population is in line with the licensed indication for alitretinoin. Delgocitinib cream and oral alitretinoin were used continuously for 16 and 12 weeks, respectively, and then as-needed [77].

Additional evidence from a phase 2b study of delgocitinib versus placebo (NCT03683719) was also identified in the systematic review [78]. Because phase 3 trial data are available, the phase 2b results are summarised in section 2.6.12.1, but are not described in detail in this submission. For completeness, data for patients who were allocated to the licensed delgocitinib dose and vehicle cream, who had moderate to severe CHE at baseline, are included in the network meta-analysis (NMA) described in section 2.10.

Subgroup analyses of clinical efficacy

Subgroup analyses are presented in section 2.8. For DELTA 1, DELTA 2 and DELTA 3, key trial outcomes were analysed for patients with moderate or severe CHE (IGA-CHE scores of 3 or 4, respectively) at baseline of the parent trial [79]. For both the pooled DELTA 1 and DELTA 2 moderate and severe CHE population and DELTA FORCE, additional subgroup analyses were conducted for aetiological subtypes (patients with atopic and contact CHE), and previous use of TCIs [79-81].

NMA inputs

In the absence of head-to-head RCT data comparing delgocitinib and PUVA, NMAs were performed. Analyses were conducted using data from 16 weeks (the primary endpoint) and 12 weeks in DELTA 1, DELTA 2 and the Worm *et al.* 2022 phase 2 delgocitinib trial, compared with week 12 (primary endpoint) data from DELTA FORCE and the ALPHA trial (see section 2.10.3).

The outcomes assessed in NMAs are IGA-CHE/PGA 0/1 endpoint response (i.e., the proportion of patients who had achieved a response at a specific timepoint); IGA-CHE 0/1 cumulative response (i.e., the proportion of patients who had ever achieved a response throughout the assessment period); HECSI-90 endpoint response; and discontinuation due to AEs.

Economic model inputs

The base-case economic model reflects the patient characteristics of the DELTA 1 and DELTA 2 trial populations. Health states in the economic model are based on the IGA-CHE results of the NMAs and DELTA trials at week 12 and of the DELTA 3 and DELTA FORCE studies beyond week 12. AE data from the DELTA trial programme are incorporated into the model, and 5-dimension, 3-level EuroQol questionnaire (EQ-5D-3L) data from DELTA 1 and DELTA 2 are used to estimate health state utilities.

Data sources used

Clinical data in this submission are taken from the DELTA 1 and DELTA 2 publication [82], four DELTA trial protocols [83-86], the corresponding clinical study reports (CSRs) [87-90], six conference presentations [16, 91-95], and four statistical appendices [79-81, 96].

Results presented in main submission

The DELTA trial results presented in section 2 of this submission correspond to the pre-specified trial outcomes and timepoints. In addition, week 12 data are presented for IGA-CHE TS and HECSI endpoints. Data for *post hoc* analyses used in the economic model are shown in Appendix B.7.1.

Table 4 Clinical effectiveness evidence

Study	**DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101)**		
Study design	16-week phase 3 randomised, double-blind, cream vehicle-controlled, parallel-group, multi-site clinical trials		
Population	Adult patients with moderate to severe CHE who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable due to important side effects or safety risks that outweigh the potential treatment benefit		
Intervention(s)	Continuous treatment with delgocitinib cream 20 mg/g BD		
Comparator(s)	Continuous treatment with cream vehicle BD		
Indicate if study supports application for marketing authorisation	**Yes**	**Indicate if trial used in the economic model**	**Yes**
Reported outcomes specified in the decision problem	Clinical response: **IGA-CHE TS, HECSI-50,[a] HECSI-75, HECSI-90** and percentage change in HECSI Symptom control: HESD total, HESD itch and **HESD pain** scores HRQoL: DLQI, **EQ-5D-3L** and HEIS Adverse events		

Outcomes in **bold** are incorporated into the economic model.

[a] *Post hoc* analysis; HECSI-50 was not a predefined outcome in the DELTA 1 and DELTA 2 trials.

BD, twice daily; CHE, chronic hand eczema; TCS, topical corticosteroids.

Study	**DELTA 3 (NCT04949841)**		
Study design	36-week phase 3 open-label multi-site extension to DELTA 1 and DELTA 2		
Population	Adult patients with moderate to severe CHE who had completed the DELTA 1 or DELTA 2 trials		
Intervention(s)	As-needed treatment with delgocitinib cream 20 mg/g BD (initiated or reinitiated if patients had an IGA-CHE score ≥ 2; stopped when IGA-CHE 0/1 was achieved)		
Comparator(s)	None		
Indicate if study supports application for marketing authorisation	**Yes**	**Indicate if trial used in the economic model**	**Yes**
Reported outcomes specified in the decision problem	Clinical response: **IGA-CHE TS,** mean HECSI, HECSI-50,[a] HECSI-75 and HECSI-90 Symptom control: HESD total, HESD itch and HESD pain scores HRQoL: DLQI, EQ-5D-3L and HEIS Adverse events **Time to loss of response:** IGA-CHE score ≥2		

Outcomes in **bold** are incorporated into the economic model.

[a] *Post hoc* analysis: HECSI-50 was not a predefined outcome in the DELTA 3 trial.

BD, twice daily; CHE, chronic hand eczema; IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

Study	DELTA FORCE (NCT05259722)		
Study design	24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3 trial The primary endpoint was assessed at week 12, reflecting the initial continuous treatment period for alitretinoin		
Population	Adult patients with severe CHE (IGA-CHE score of 4 at baseline) who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable due to important side effects or safety risks that outweigh the potential treatment benefit		
Intervention(s)	Delgocitinib cream 20 mg/g BD; continuous for 16 weeks, then as-needed		
Comparator(s)	Alitretinoin capsules, 30 mg QD, with an option to reduce to 10 mg QD; continuous for 12 weeks, then as-needed		
Indicate if study supports application for marketing authorisation	**No**	**Indicate if trial used in the economic model**	**Yes**
Reported outcomes specified in the decision problem	Clinical response: **IGA-CHE TS, HECSI-50,[a] HECSI-75 [a], HECSI-90**, mean change in HECSI Symptom control: HESD total, itch and pain scores HRQoL: DLQI and **EQ-5D-3L** **Adverse events** **Time to loss of response [a]**		

Outcomes in **bold** are incorporated into the economic model.

[a] *Post hoc* analysis: outcomes were not predefined analyses in the DELTA FORCE trial.

BD, twice daily; CHE, chronic hand eczema; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; QD, daily; TCS, topical corticosteroids.

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Methodology

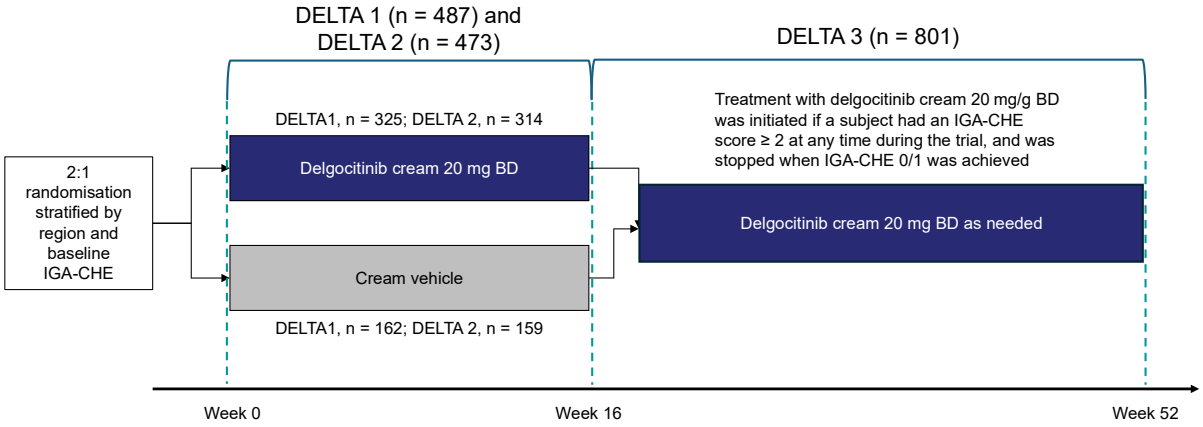
2.3.1.1 Study design and interventions

DELTA 1 and DELTA 2

DELTA 1 and DELTA 2 were identical phase 3 randomised, double-blind, vehicle-controlled, parallel-group, multi-site clinical trials designed to assess the efficacy and safety of continuous delgocitinib cream 20 mg/g BD compared with continuous cream vehicle [82, 87, 88]. Eligible patients were adults with moderate to severe CHE (an IGA-CHE score of 3 or 4), who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable (due to important side effects or safety risks that outweigh the potential treatment benefit).

DELTA 1 and DELTA 2 were conducted over a 16-week treatment period (Figure 3) [82, 87, 88]. Following a 4-week washout period, patients were randomised 2:1 to continuous delgocitinib cream 20 mg/g BD or cream vehicle BD. Patients were instructed to apply the investigational medicinal product (IMP) to clean, dry hands, fingers, fingertips and wrists in a thin layer twice daily, approximately 12 hours apart. Patients were instructed not to change their usual skin care routine but were asked not to use emollients within 2 hours before or after application of the IMP.

Figure 3 DELTA 1, DELTA 2 and DELTA 3 trial design



BD, twice daily; IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

DELTA 3

DELTA 3 was a phase 3 open-label multi-site extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of as-needed delgocitinib 20 mg/g BD for up to a further 36 weeks [89] as the primary endpoint, with efficacy measured as secondary endpoints. Patients who had completed 16 weeks of treatment in DELTA 1 or DELTA 2 (with either delgocitinib cream 20 mg/g BD or cream vehicle BD) were eligible for inclusion in DELTA 3 [89].

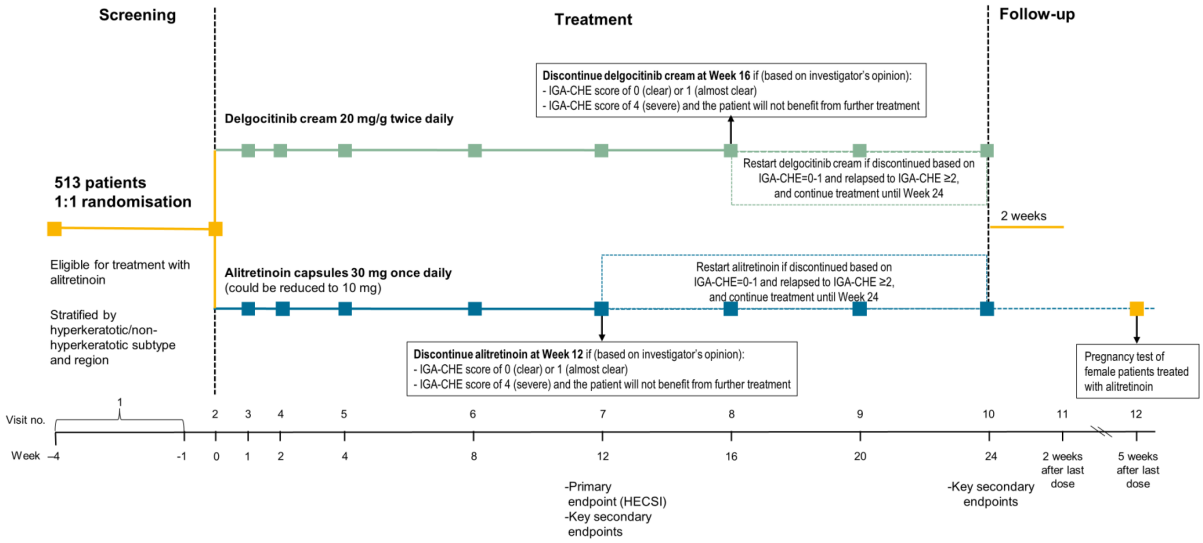
During DELTA 3, all patients were treated on an as-needed basis with delgocitinib cream 20 mg/g BD over 36 weeks [89]. Patients started DELTA 3 on delgocitinib cream 20 mg/g BD if they had not achieved IGA-CHE TS at week 16 in DELTA 1 or DELTA 2; those who had achieved IGA-CHE TS at week 16 in DELTA 1 or DELTA 2 started DELTA 3 off-treatment. During DELTA 3, treatment with delgocitinib cream 20 mg/g BD was initiated if a patient had an IGA-CHE score ≥ 2 at any time during the trial, and was stopped when an IGA-CHE score of 0 (clear) or 1 (almost clear) was achieved, then restarted if worsening occurred. If needed, unscheduled visits could be performed to initiate or stop treatment with delgocitinib cream 20 mg/g BD [89].

DELTA FORCE

DELTA FORCE was a 24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3 trial to compare the efficacy and safety of delgocitinib cream 20 mg/g BD with oral alitretinoin QD in adult patients with severe CHE [90]. Eligible patients were adults with severe CHE (an IGA-CHE score of 4) at baseline who had a recent history of inadequate response to treatment with TCS or for whom TCS were medically inadvisable (due to important side effects or safety risks that outweigh the potential treatment benefit) [90].

DELTA FORCE participants were randomised 1:1 to receive topical administration of delgocitinib cream 20 mg/g BD, or oral administration of alitretinoin capsules 30 mg QD with an option to reduce to 10 mg QD in participants with unacceptable adverse reactions (Figure 4). Patients in both trial arms were allowed to use their normal and preferred emollient throughout the trial in line with standard care of CHE [86].

Figure 4 DELTA FORCE trial design



For participants treated with medications requiring a 28-day washout period prior to baseline, the duration of the screening period could be extended up to 31 days to ensure appropriate washout. For women of childbearing potential, the duration of the screening period could be extended up to 42 days to ensure compliance with contraceptive and pregnancy prevention programme requirements.
BD, twice daily; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; QD, daily.
Source: Giménez-Arnau *et al.*, 2024 [95].

The recommended duration of treatment in the alitretinoin label is 12–24 weeks depending on response [17]. Therefore, in order to ensure comparable evaluation in the two arms, the primary endpoint in the DELTA FORCE trial was assessed at week 12 to reflect the initial continuous treatment period for alitretinoin.

Treatment with delgocitinib cream 20 mg/g BD was continuous until week 16, as in the pivotal phase 3 trials. After week 16, treatment was as-needed. At week 16 or subsequent visits, patients in the delgocitinib cream 20 mg/g BD arm discontinued treatment (based on the investigator's opinion) if they had an IGA-CHE score of 0 or 1. Patients who had an IGA-CHE score of 4 and, in the opinion of the investigator, would not benefit from further treatment permanently discontinued treatment [90]. Patients who discontinued with an IGA-CHE score of 0 or 1 were at risk of loss of response (i.e., relapse to an IGA-CHE score of 2 or higher), in which case they were required to restart treatment with delgocitinib cream 20 mg/g BD [29, 90].

Treatment with oral alitretinoin capsules was continuous until week 12, after which alitretinoin was used as-needed (per its label and at the investigator's discretion). At week 12 or subsequent visits, patients in the oral alitretinoin capsule arm discontinued treatment (based on the investigator's opinion) if they had an IGA-CHE score of 0 or 1. Patients who had an IGA-CHE score of 4 and, in the opinion of the investigator, would not benefit from further treatment, permanently discontinued treatment [90]. Patients who discontinued with an IGA-CHE score of 0 or 1 were at risk of loss of response (i.e., relapse to an IGA-CHE score of 2 or higher), in which case they could restart treatment with oral alitretinoin capsules [29, 90].

2.3.1.2 Randomisation and blinding

DELTA 1 and DELTA 2

Participants were randomised in a 2:1 ratio using interactive response technology. Randomisation was stratified by region (Europe or North America) and baseline IGA-CHE score (3 or 4) [82, 87, 88].

DELTA 1 and DELTA 2 were double-blind trials. The packaging and labelling of the IMP contained no evidence of the identity of the product, and it was not considered possible to differentiate between delgocitinib cream 20 mg/g and cream vehicle by sensory evaluation [82, 87, 88].

DELTA 3

DELTA 3 was conducted as an open-label extension with no randomisation or blinding. To maintain the blinding of DELTA 1 and DELTA 2, patients' treatment assignments were not revealed on entering DELTA 3 [85].

DELTA FORCE

Participants were randomised in a 1:1 ratio using interactive response technology [86]. Randomisation was stratified by region (Europe or North America) and CHE subtype (hyperkeratotic/non-hyperkeratotic) [86]. Due to the different administration routes for delgocitinib and alitretinoin, participants and investigators were not blinded to treatment assignment [86]. A double-dummy design was not considered feasible because it was considered that addition of the cream vehicle to alitretinoin-treated participants might increase the clinical effect in the alitretinoin arm; a further consideration was the requirement for mental health monitoring of patients in the alitretinoin arm [86]. However, the evaluation of efficacy (IGA-CHE and HECSI) was performed by a blinded assessor [86].

2.3.1.3 Eligibility criteria

All DELTA trials

Participants were required to be aged 18 years or older, to have a diagnosis of CHE, defined as HE that has persisted for more than 3 months or returned twice or more within the last 12 months [82-86]. In addition, participants were required to have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for TCS to have been documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks).

Inadequate response to TCS was defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score of ≤ 2) despite treatment with a daily regimen of TCS of class III–IV (potent to very potent) for Europe and class IV–I (medium potency to very/ultra-high potency) for Canada, applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter [83-86].

Important side effects or safety risks were defined as those that outweigh the potential treatment benefits, and include intolerance to treatment, hypersensitivity reactions, and significant skin atrophy, as assessed by the physician [83-86].

The main inclusion and exclusion criteria are shown in Table 5; full criteria are presented in Appendix B.5.1, Table 150 and Table 151.

Table 5 Key inclusion and exclusion criteria common to all DELTA trials

Key inclusion criteria
• Age 18 years or above at screening • Diagnosis of CHE, defined as HE that has persisted for more than 3 months or returned twice or more within the last 12 months • Documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks) • Adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens • Women of childbearing potential were required to use birth control (see Appendix B.5.1, Table 150 and Table 151 for details)
Key exclusion criteria
• Concurrent skin diseases on the hands • Active AD requiring medical treatment in regions other than the hands and feet • Active psoriasis on any part of the body • Hyperkeratotic HE in combination with a history of psoriasis on any part of the body • Clinically significant infection (e.g., impetiginised HE) on the hands • Receiving other treatment for CHE, or any immunosuppressive, immunomodulating or biological therapies (see Appendix B.5.1, Table 150 and Table 151 for details)

AD, atopic dermatitis; CHE, chronic hand eczema; HE, hand eczema; TCS, topical corticosteroids.
Source: Bissonette *et al.,* 2024 [82]; LEO Pharma [83-86].

DELTA 1 and DELTA 2

In addition to the criteria above, participants were required to have 1) an IGA-CHE score of 3 or 4 at screening and baseline, and 2) a HESD itch score (weekly average) of ≥ 4 points at baseline [83, 84].

DELTA 3

Patients who completed the treatment period in DELTA 1 or DELTA 2 were offered the opportunity to participate in the DELTA 3 extension trial [85].

DELTA FORCE

In addition to the inclusion criteria described above (Table 5), participants were required to have an IGA-CHE score of 4 at screening and baseline [86].

As alitretinoin is highly teratogenic, it is strictly contraindicated in pregnant women. Accordingly, the DELTA FORCE trial imposed stricter birth control requirements for women of childbearing potential than the DELTA 1 and DELTA 2 trials – these are described in Appendix B.5.1, Table 151.

Additional alitretinoin contraindications include patients with severe or end-stage renal insufficiency, hepatic insufficiency, uncontrolled hypercholesterolaemia, uncontrolled hypertriglyceridaemia, uncontrolled hypothyroidism and hypervitaminosis A (see section 1.3.3.5 and Appendix B.5.1, Table 151).

2.3.1.4 Settings and locations

DELTA 1, DELTA 2 and DELTA 3

DELTA 1 was conducted at 53 sites in Canada, France, Germany, Italy, Poland and the UK (6 UK sites and 24 UK participants) [74, 82, 87]. In total, 80.1% of participants (390/487) were in Europe and 19.9% in Canada [87].

DELTA 2 was conducted at 50 sites in Belgium, Canada, Denmark, Germany, the Netherlands, Poland and Spain [75, 82]. In total, 79.5% of participants (376/473) were in Europe and 20.5% in Canada [88].

A total of 801 patients from DELTA 1 and DELTA 2 (including 23 in the UK) participated in DELTA 3 [89].

DELTA FORCE

DELTA FORCE was conducted at 103 sites in Austria, Canada, France, Germany, Italy, Norway, Poland, Slovakia, Spain and the UK (2 UK sites and 6 UK participants) [77, 90]. In total, 89.5% of participants (459/513) were in Europe and 10.5% in Canada [90].

2.3.1.5 Outcome measures

Outcome definitions, which were consistent across the DELTA trials, are summarised in Table 6.

Table 6 Outcome measures used in the DELTA trials

Outcome	Definition
Efficacy	
HECSI	The HECSI is an instrument used in clinical trials to rate the severity of six clinical signs of HE (erythema, infiltration/papulation, vesicles, fissures, scaling and oedema) at the time of evaluation. Total score ranges from 0 to 360 with higher scores indicating greater severity [97].
HECSI-50[a] HECSI-75 HECSI-90	HECSI-50 is defined as a ≥ 50% improvement in HECSI from baseline. HECSI-75 is defined as a ≥ 75% improvement in HECSI from baseline. HECSI-90 is defined as a ≥ 90% improvement in HECSI from baseline.
IGA-CHE	The IGA-CHE is an instrument used in the phase 2b trial of delgocitinib (NCT03683719) and revised for the DELTA trials. The IGA-CHE rates the severity of a patient's global disease on a 5-point scale ranging from 0 (clear) to 4 (severe). A 2-point change is considered a conservative meaningful change threshold [29]. The development of the IGA-CHE is described in more detail in Appendix B.6.1.
IGA-CHE TS	IGA-CHE TS is defined as an IGA-CHE score of 0 or 1 with an improvement from baseline of ≥ 2 points.
Loss of IGA-CHE TS response (relapse)	In DELTA 3 and DELTA FORCE, patients who discontinued treatment following an IGA-CHE TS response could experience loss of response, defined as an IGA-CHE score of ≥ 2, while off-treatment.
Daily diary endpoints	
HESD	The 6-item HESD was developed from an 11-item version used in the phase 2b trial of delgocitinib (NCT03683719). Patients assess the worst severity over the past 24 hours of six individual signs and symptoms of CHE (itch, pain, cracking, redness, dryness and flaking) using an 11-point numeric rating scale ranging from 0 (no) to 10

Outcome	Definition
	(severe) [32]. The development of the HESD is described in more detail in Appendix B.6.2.
Patient-reported outcomes	
DLQI	The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL [98]. Scores range from 0 to 30, with higher scores indicating worse HRQoL [98]. A 4-point improvement is defined as an minimal clinically important difference (MCID) among patients with baseline scores ≥ 4 [99].
EQ-5D-3L/EQ-5D-5L	The EQ-5D is a standardised instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D questionnaire is used to calculate a utility score based on a descriptive profile, or 'health state'. Data in the DELTA trials were collected using the 5-level version (EQ-5D-5L) [100], and mapped from the 5-level system to the 3-level system using the EQ-5D-5L crosswalk value set [101], as recommended by NICE [102]. The index score ranges from −0.594 to 1.0 (based on the UK-specific value set), with a higher score indicating a better health status.
EQ VAS	The EQ VAS records the patient's self-rated health on a 0–100 scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement [103].
HEIS	The HEIS addresses nine items within the following domains: PDAL, embarrassment with the appearance of the hands, frustration with CHE, sleep, work and physical functioning. Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely). The HEIS score is the average of the nine items. The HEIS was used in the delgocitinib phase 2b trial.

[a] *Post hoc* analysis; HECSI-50 was not a predefined outcome in the DELTA trials.
CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; EQ, EuroQol; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; HE, hand eczema; HECSI, Hand Eczema Severity Index; HEIS, Hand Eczema Impact Scale; HESD, Hand Eczema Symptom Diary; HRQoL, health-related quality of life; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; MCID, minimal clinically important difference; NICE, National Institute of Health and Care Excellence; PDAL, proximal daily activity limitations; TS, treatment success; VAS, visual analogue scale.

IGA-CHE validation

The IGA-CHE was used in the phase 2b trial of delgocitinib (NCT03683719) and revised for the DELTA trials [29]. Psychometric validation of the IGA-CHE was recently conducted using data from DELTA 1; the results showed that the IGA-CHE scale has strong reliability, construct validity, and ability to detect change, supporting its use as an endpoint in CHE clinical trials and clinical practice (see Appendix B.6.1) [29, 94]. A 2-point change was considered a conservative meaningful change threshold, although a 1-level change can reflect a clinically meaningful improvement for patients [29]. This means that the definition of IGA-CHE treatment success (TS) used in the DELTA trials (a score of 0 [clear] or 1 [almost clear] with an improvement from baseline of ≥ 2 points) can be interpreted with confidence as a clinically meaningful improvement [29]. A more detailed description of the IGA-CHE validation study is presented in Appendix B.6.1.

HESD validation study

The HESD is the first CHE-specific PRO measure of CHE signs/symptoms developed and validated in line with regulatory guidance [32]. The HESD was developed based on the

literature and concept elicitation interviews and used in the phase 2b trial of delgocitinib (NCT03683719) [32]. Item properties and dimensionality analyses in the phase 2b data supported removal of additional items, resulting in the 6-item HESD included in the DELTA trials [32]. Psychometric validation of the HESD was recently conducted using data from the first 280 participants in DELTA 1 [32]. The results demonstrate strong content validity and psychometric validity and show that improvements of ≥ 4 points on 7-day average HESD scores represent clinically meaningful, important changes [32]. A more detailed description of the HESD validation study is presented in Appendix B.6.2.

2.3.1.6 Assessment schedule

DELTA 1 and DELTA 2

The primary endpoint analysis was conducted at week 16 [82, 87, 88]. IGA-CHE and HECSI were assessed during all trial visits, which took place at weeks 0, 1, 2, 4, 8, 12 and 16. Patients completed the DLQI, the 5-dimension, 5-level EuroQol questionnaire (EQ-5D-5L) and the EuroQol (EQ) visual analogue scale (VAS) during all trial visits except week 2. Patients also completed HESD e-diaries daily during the screening and treatment period [82, 87, 88].

DELTA 3

The primary endpoint analysis (safety) was assessed up to week 38 [89]. IGA-CHE and HECSI were assessed at week 0 then every 4 weeks until week 36. Patients completed the DLQI, the EQ-5D-5L and the EQ VAS at week 0 then every 8 weeks until week 32, as well as at week 36. HESD e-diaries were completed daily as in the parent trials [89].

DELTA FORCE

The primary endpoint analysis was conducted at week 12 (see section 2.3.1.1) [90]. IGA-CHE and HECSI were assessed during all trial visits, which took place at weeks 0, 1, 2, 4, 8, 12, 16, 20 and 24. Patients completed the DLQI during all visits and the EQ-5D-5L and EQ VAS at weeks 0, 4, 8, 12, 16 and 24. Patients also completed HESD e-diaries daily during the screening and treatment period [90].

2.3.1.7 Study endpoints

DELTA 1 and DELTA 2

The primary objective of the DELTA 1 and DELTA 2 trials was to confirm the efficacy of twice-daily delgocitinib cream 20 mg/g, compared with cream vehicle. Secondary objectives were to evaluate the HRQoL improvements and safety profile associated with delgocitinib cream 20 mg/g [82, 87, 88].

The primary endpoint of the DELTA 1 and DELTA 2 trials was the proportion of patients with IGA-CHE TS, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2-step improvement from baseline, at week 16 [82, 87, 88].

Key secondary endpoints for the primary objective were: for IGA-CHE TS, the proportion of patients with IGA-CHE TS (week 4, week 8); for HECSI, the proportions of patients with

HECSI-75 (week 8, week 16), with HECSI-90 (week 16), and the percentage change in HECSI from baseline to week 16 [82, 87, 88].

For the secondary objective, key secondary endpoints included: for HESD, the proportions of patients with a reduction in weekly average HESD itch and pain scores and HESD total scores as well as a reduction of ≥ 4 points (from baseline to weeks 2, 4, 8, 16); for DLQI, total score change as well as a reduction of ≥ 4 points from baseline to week 16; for HEIS, change from baseline to week 16 to total and PDAL score [82, 87, 88].

Secondary endpoints for the secondary objective included the number of treatment-emergent AEs (TEAEs) from baseline up to week 16 (or week 18, for patients not participating in DELTA 3) [82, 87, 88].

DELTA 3

The primary objective of DELTA 3 was to evaluate the long-term safety of delgocitinib cream 20 mg/g. Secondary objectives were to evaluate long-term efficacy and the effect of delgocitinib cream 20 mg/g on HRQoL and work productivity [89].

The primary endpoint of DELTA 3 was the number of TEAEs from baseline up to week 38 [89].

Secondary endpoints were IGA-CHE score, IGA-CHE TS, HECSI, HECSI-75 and HECSI-90 at each scheduled visit up to week 36 [89].

DELTA FORCE

The primary objective of DELTA FORCE was to demonstrate the superiority of delgocitinib cream 20 mg/g over oral alitretinoin capsules in the treatment of severe CHE [90].

The primary endpoint of DELTA FORCE was the mean change in HECSI from baseline to week 12 [90].

Key secondary endpoints were: HECSI-90 at week 12; IGA-CHE TS at week 12; the change in weekly average HESD itch and pain scores from baseline to week 12; the area under the curve (AUC) of HECSI-90 from baseline to week 24; the AUC of change from baseline in DLQI to week 24; and the mean change in HECSI from baseline to week 24 [90]. Secondary objectives for the safety assessment were TEAEs and treatment-emergent SAEs up to week 26; and the number of AEs leading to IMP discontinuation up to week 24 [90].

2.3.2 Comparative summary of trial methodology

Table 7 Comparative summary of trial methodology

Trial acronym (trial registry number)	DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101)	DELTA 3 (NCT04949841)	DELTA FORCE (NCT05259722)
Location	DELTA 1: 53 sites in Canada, France, Germany, Italy, Poland and the UK DELTA 2: 50 sites in Belgium, Canada, Denmark, Germany, the Netherlands, Poland and Spain	DELTA 1 and DELTA 2 sites	103 sites in Austria, Canada, France, Germany, Italy, Norway, Poland, Slovakia, Spain and the UK
Trial design	16-week phase 3 randomised, double-blind, cream vehicle-controlled, parallel-group, multi-site clinical trials	36-week phase 3 open-label multi-site extension to DELTA 1 and DELTA 2	24-week phase 3 randomised, assessor-blinded, active-controlled, parallel-group, multisite clinical trial The primary endpoint was assessed at week 12, reflecting the initial continuous treatment period for alitretinoin
Eligibility criteria for participants	Adult patients with moderate to severe CHE (IGA-CHE score of 3 or 4 and HESD itch score [weekly average] of ≥4 points at baseline) who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable due to important side effects or safety risks that outweigh the potential treatment benefit	Adult patients with moderate to severe CHE who had completed the DELTA 1 or DELTA 2 trials	Adult patients with severe CHE (IGA-CHE score of 4 at baseline) who had a documented recent history of inadequate response to treatment with TCS, or for whom TCS were medically inadvisable due to important side effects or safety risks that outweigh the potential treatment benefit
Settings and locations where the data were collected	Data were collected during scheduled visits to study centres and via daily e-diaries (HESD)		
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	Continuous delgocitinib cream 20 mg/g BD, DELTA 1, n = 325; DELTA 2, n = 314	As-needed delgocitinib cream 20 mg/g BD (initiated if patients had an IGA-CHE score ≥ 2; stopped when IGA-CHE 0/1 was achieved), n = 801	Continuous delgocitinib cream 20 mg/g BD for 16 weeks, followed by as-needed delgocitinib cream 20 mg/g BD, n = 254

Trial acronym (trial registry number)	DELTA 1 (NCT04871711) and DELTA 2 (NCT04872101)	DELTA 3 (NCT04949841)	DELTA FORCE (NCT05259722)
Permitted and disallowed concomitant medication	Continuous cream vehicle BD, DELTA 1, n = 162; DELTA 2, n = 159		Continuous oral alitretinoin capsules, 30 mg QD for 12 weeks, with an option to reduce to 10 mg QD, followed by as-needed oral alitretinoin capsules, n = 259 From week 16/12, patients permanently discontinued treatment if they had IGA-CHE 4 (and were considered not to benefit from further treatment); if they had IGA-CHE 0 or 1 they discontinued treatment and restarted if they had IGA-CHE ≥ 2 at a subsequent visit.
	If medically necessary, rescue treatment for CHE could be prescribed at the discretion of the investigator. In DELTA FORCE, alitretinoin could not be used as rescue treatment. Following rescue treatment, patients were required to discontinue IMP and could not restart.		
Primary outcomes (including scoring methods and timings of assessments)	The proportion of patients with IGA-CHE TS	The number of TEAEs from baseline up to week 38	The mean change in HECSI from baseline to week 12
Other outcomes used in the economic model	IGA-CHE TS, HECSI, HECSI-50,[a] HECSI-75, HECSI-90, HESD pain, EQ-5D-3L	IGA-CHE TS, maintenance of response, time to loss of response, discontinuation	IGA-CHE TS, HECSI-50,[a] HECSI-75,[b] HECSI-90, TEAEs, maintenance of response, time to loss of response, discontinuation
Subgroups described in submission	Moderate vs severe CHE Atopic vs non-atopic CHE Contact vs non-contact CHE Prior TCI use, yes vs no	Moderate vs severe CHE [c]	Atopic vs non-atopic CHE Contact vs non-contact CHE Prior TCI use, yes vs no

[a] *Post hoc* analysis: HECSI-50 was not a predefined outcome in the DELTA 1 and DELTA 2 trials.

[b] *Post hoc* analysis: HECSI-75 was not a predefined outcome in the DELTA FORCE trial.

[c] At baseline of parent trial (i.e., DELTA 1 or DELTA 2).

BD, twice daily; CHE, chronic hand eczema; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IMP, investigational medicinal product; NA, not applicable; QD, daily; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event; TS, treatment success.

2.3.3 Baseline characteristics

2.3.3.1 DELTA 1, DELTA 2 and DELTA FORCE baseline characteristics

DELTA 1 and DELTA 2

In both DELTA 1 and DELTA 2, there were no differences between treatment groups in demographic variables or baseline characteristics that would affect the interpretation of efficacy and safety results (Table 8) [82, 87, 88].

Most characteristics were similar between the two trials. However, DELTA 1 had more patients with severe CHE than DELTA 2 [82, 87, 88]. There was also a difference in the distribution of CHE subtypes: DELTA 1 included more patients with atopic HE and allergic contact dermatitis, and fewer patients with other CHE subtypes, than DELTA 2 [82, 87, 88].

DELTA 3

The characteristics of DELTA 3 trial participants at baseline in the parent trials are shown in Appendix B.5.2, Table 152, and are similar to those in the overall DELTA 1 and DELTA 2 populations [89].

There were no differences between parent trial treatment groups in demographic variables or other parent trial baseline characteristics that would affect the interpretation of efficacy or safety results [89].

DELTA FORCE

In DELTA FORCE, there were no differences between treatment groups in demographic variables or baseline characteristics that would affect the interpretation of efficacy and safety results (Table 8) [90, 95].

Baseline characteristics of UK patients

Baseline characteristics of the UK patients in DELTA 1 and DELTA FORCE are summarised in Appendix B.5.2, Table 153 [79], and were generally consistent with the overall trial populations.

Table 8 Baseline characteristics of participants in the DELTA trials

	DELTA 1		DELTA 2		DELTA FORCE	
	Delgocitinib cream 20 mg/g (n = 325)	Cream vehicle (n = 162)	Delgocitinib cream 20 mg/g (n = 314)	Cream vehicle (n = 159)	Delgocitinib cream 20 mg/g (n = 254)	Oral alitretinoin capsules (n = 259)
Demographics						
Age (years), median (range)	45 (19–87)	42.5 (20–73)	46 (18–83)	42 (18–86)	46 (18–77)	44 (18–75)
Female, n (%)	202 (62.2)	104 (64.2)	204 (65.0)	108 (68.0)	167 (65.7)	167 (64.5)
Baseline characteristics						
IGA-CHE, n (%)						
Moderate	218 (67.1)	109 (67.3)	239 (76.1)	121 (76.1)	0	0
Severe	107 (32.9)	53 (32.7)	75 (23.9)	38 (23.9)	254 (100)	259 (100)
HECSI, median (range)	66 (10–275)	61.5 (12–280)	59 (7–272)	59 (8–213)	80 (13–320)	80 (8–306)
DLQI						
Median (range)	12.0 (0–30)	12.0 (2–30)	11.0 (1–28)	11.0 (2–30)	12 (0–28)	12 (0–30)
≥ 4, n (%)	305 (95.0)	148 (93.7)	308 (98.7)	153 (97.5)	219 (86.2)	229 (88.4)
CHE characteristics						
Median (range) age at onset of CHE, years	33 (0–87)	30 (0–72)	35 (0–83)	32 (0–77)	37.5 (0–72)	36 (0–72)
Median (range) duration of CHE, years	6 (0–61)	5.5 (0–53)	4 (0–59)	5 (0–52)	4 (0–50)	4 (0–48)
CHE subtype, main diagnosis, n (%)						
Hyperkeratotic eczema	57 (17.5)	20 (12.3)	86 (27.0)	43 (27.0)	31 (12.2)	32 (12.4)
Atopic hand eczema	143 (44.0)	74 (45.7)	82 (26.0)	46 (29.0)	66 (26.0)	57 (22.0)
Irritant contact dermatitis	49 (15.1)	26 (16.0)	75 (24.0)	38 (24.0)	75 (29.5)	76 (29.3)
Vesicular HE (pompholyx)	25 (7.7)	9 (5.6)	44 (14.0)	9 (6.0)	22 (8.7)	36 (13.9)
Allergic contact dermatitis	51 (15.7)	33 (20.4)	27 (9.0)	22 (14.0)	58 (22.8)	54 (20.8)
Contact urticaria/protein contact dermatitis	0	0	0	1 (1.0)	0	0
Previous CHE treatments						
TCS, n (%)						
Inadequate response last 12 months	323 (99.4)	161 (99.4)	311 (99.0)	155 (97.5)	250 (98.4)	258 (99.6)
Medically inadvisable	79 (24.3)	39 (24.1)	48 (15.3)	29 (18.2)	29 (11.4)	23 (8.9)
TCI, n (%)	121 (37.2)	53 (32.7)	113 (36.0)	62 (39.0)	77 (30.3)	80 (30.9)
Phototherapy and other procedures, n (%)	65 (20.0)	27 (16.7)	60 (19.1)	39 (24.5)	30 (11.8)	35 (13.5)
Oral retinoids, n (%)	45 (13.8)	22 (13.6)	52 (16.6)	24 (15.1)	7 (2.8)	7 (2.7)
Oral corticosteroids, n (%)	46 (14.2)	13 (8.0)	50 (15.9)	28 (17.6)	39 (15.4)	37 (14.3)
Oral methotrexate, n (%)	9 (2.8)	5 (3.1)	26 (8.3)	10 (6.3)	7 (2.8)	3 (1.2)
Oral ciclosporin, n (%)	5 (1.5)	4 (2.5)	15 (4.8)	7 (4.4)	5 (2.0)	5 (1.9)
Oral azathioprine, n (%)	0	0	6 (1.9)	2 (1.3)	0	0
Other previous CHE treatments, n (%)	91 (28.0)	41 (25.3)	53 (16.9)	27 (17.0)	50 (19.7)	73 (28.2)

CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; HE, hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids. Source: Bissonette *et al*. 2024 [82]; DELTA 1, DELTA 2 and DELTA FORCE CSRs [87, 88, 90]; Giménez-Arnau *et al*. 2024 [95].

2.3.3.2 Disease severity at baseline in DELTA 3

CHE severity at DELTA 3 baseline was lower in the previous delgocitinib cream group than in the previous cream vehicle group

At baseline in DELTA 3 (i.e., for patients continuing in the extension study at DELTA 1 and DELTA 2 week 16), patients who had been treated with delgocitinib cream BD typically had less severe disease than those who had previously been receiving cream vehicle (Table 9) [89].

Table 9 Disease severity at baseline in DELTA 3

	Previous delgocitinib cream 20 mg/g (n = 560)	Previous cream vehicle (n = 241)
IGA-CHE, n (%)		
Clear (0)	70 (12.5)	7 (2.9)
Almost clear (1)	68 (12.1)	15 (6.2)
Mild (2)	256 (45.7)	89 (36.9)
Moderate (3)	145 (25.9)	98 (40.7)
Severe (4)	21 (3.8)	32 (13.3)
HECSI		
Mean (SD)	23.9 (29.1)	46.8 (46.0)
Median (Q1–Q3)	13 (4–33)	36 (14–62)

HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; Q, quartile; SD, standard deviation. Source: DELTA 3 CSR [89].

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

2.4.1.1 Analysis populations

DELTA 1, DELTA 2 and DELTA FORCE

All patients randomised and exposed to the IMP were included in the full analysis set (FAS) [83, 84, 86]. The safety analysis set (SAS) was defined as all patients exposed to IMP [83, 84, 86].

DELTA 3

The SAS was defined as all enrolled patients and used for the analysis of all endpoints [85].

2.4.1.2 Management of intercurrent events and missing data

DELTA 1, DELTA 2 and DELTA FORCE

The intercurrent events considered to affect the interpretation of the estimated treatment effects were initiation of rescue treatment (at the discretion of the investigator), following which patients stopped treatment with IMP immediately and did not restart, and permanent discontinuation of IMP [83, 84].

The primary analysis in DELTA 1, DELTA 2 and DELTA FORCE was conducted using a composite estimand. For binary endpoints, missing data and data following an intercurrent event were imputed as non-response. For continuous endpoints, missing data and data following an intercurrent event were imputed using worst observation carried forward (WOCF) [83, 84, 86].

DELTA 3

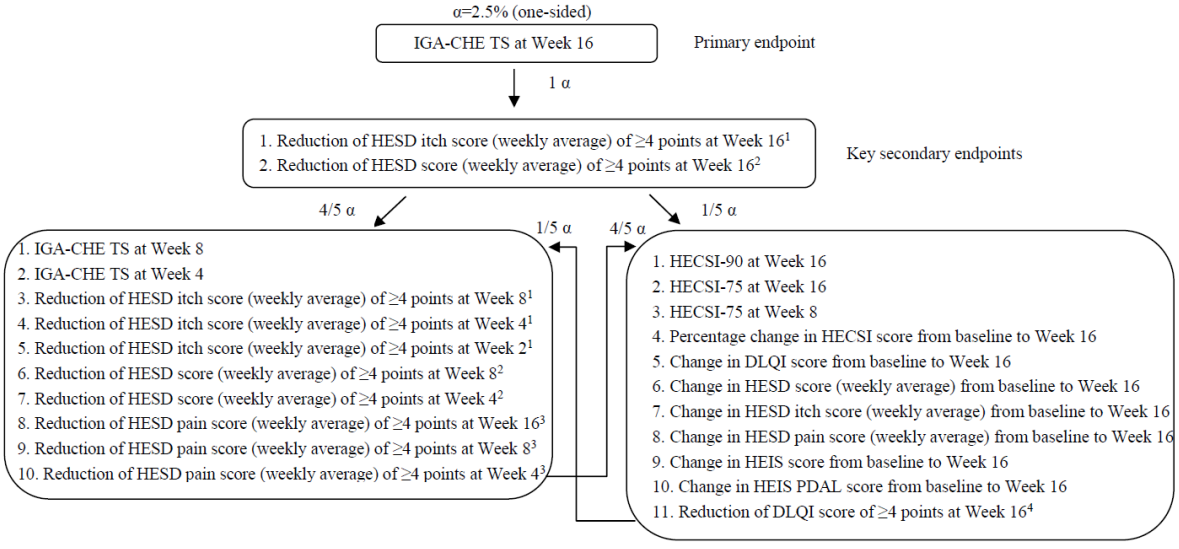
For binary endpoints, patients experiencing discontinuation of IMP, initiation of rescue treatment or withdrawal from the trial were imputed as non-responders [85]. Otherwise, an observed-case approach was used, and missing values were not imputed [85].

2.4.1.3 Statistical testing procedure

DELTA 1 and DELTA 2

For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream 20 mg/g versus cream vehicle [83, 84]. A closed testing procedure with hierarchical tests, alpha splitting and alpha recycling was used to control the overall type I error at a nominal one-sided 2.5% level. The one-sided (superiority) hypotheses were evaluated by deriving the two-sided *p* value, with the null hypothesis being rejected if the *p* value was smaller than 5% and if the point estimate was in favour of the alternative hypothesis [82]. The primary endpoint of IGA-CHE TS at week 16 was tested first, followed by the key secondary endpoints (reduction in weekly average HESD itch scores and HESD total scores of ≥ 4 points). Secondary endpoints were then tested as shown in Figure 5 [83, 84].

Figure 5 Sequential testing procedure in DELTA 1 and DELTA 2



1) From baseline among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) From baseline among subjects with a baseline HESD score (weekly average) of ≥4.
3) From baseline among subjects with a baseline HESD pain score (weekly average) of ≥4.
4) From baseline among subjects with a baseline DLQI score of ≥4.

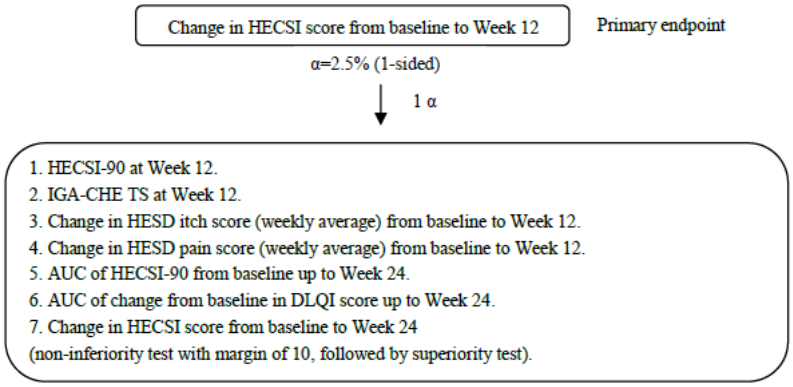
DLQI, Dermatology Life Quality Index; HECSI, Hand Eczema Severity Index; HECSI-75, at least 75% improvement in HECSI from baseline; HECSI-90, at least 90% improvement in HECSI from baseline; HEIS, Hand Eczema Impact Scale; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IGA-CHE TS, IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2-step improvement from baseline; PDAL, Proximal Daily Activity Limitations.
Source: DELTA 1 and DELTA 2 protocols [83, 84].

DELTA FORCE

For the primary endpoint and for the key secondary endpoints, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream 20 mg/g versus oral alitretinoin

30 mg capsules [86]. A closed testing procedure with hierarchical tests was used to control the overall type I error at a nominal one-sided 2.5% level. The primary endpoint of the change in HECSI from baseline to week 12 was tested first, followed by the key secondary endpoints in the order shown in Figure 6. Change in HECSI from baseline to week 24 was tested last, first using a non-inferiority test (margin of 10), then using a superiority test [86].

Figure 6 Sequential testing procedure in DELTA FORCE



AUC, area under the curve; DLQI, Dermatology Life Quality Index; HECSI, Hand Eczema Severity Index; HECSI-90, at least 90% improvement in HECSI from baseline; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IGA-CHE TS, IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥ 2-step improvement from baseline.
Source: DELTA FORCE protocol [86].

2.4.1.4 Participant flow

DELTA 1 and DELTA 2

Patient disposition in DELTA 1 and 2 is presented in Appendix B.3, Figures 36 and 37, and Tables 145 and 146 [82, 87, 88]. In both trials, most participants completed the trial without the need for rescue treatment (DELTA 1: delgocitinib cream, 93.8%; cream vehicle, 88.9%; DELTA 2, delgocitinib cream, 93.3%; cream vehicle, 75.5%).

Discontinuation was less common in the delgocitinib cream groups than in the cream vehicle groups (DELTA 1: delgocitinib cream, 6.2%; cream vehicle, 13.0%; DELTA 2, delgocitinib cream, 7.0%; cream vehicle, 23.3%) [82, 87, 88].

In total, 87.7% of participants in DELTA 1 (delgocitinib cream, 90.2%; cream vehicle, 82.7%) and 79.1% of those in DELTA 2 (delgocitinib cream, 85.0%; cream vehicle, 67.3%) transferred to the DELTA 3 open-label extension study.

DELTA 3

Patient disposition in DELTA 3 is shown in Appendix B.3, Figure 38 and Table 147. Most patients completed the trial without the need for rescue treatment (total, 82.5%; without rescue treatment, 80.4%) [89].

DELTA FORCE

Patient disposition in DELTA FORCE is shown in Appendix B.3, Figure 39 and Table 148 [90]. In the delgocitinib cream arm, [redacted]% of patients completed the trial without the need for rescue treatment; the corresponding figure in the alitretinoin arm was [redacted]% [90].

Overall, discontinuation was less common in the delgocitinib cream group than in the alitretinoin group (13.4% vs 35.9%) [90]. Discontinuations specifically due to AEs (0.8% vs 9.3%) and due to lack of efficacy (3.1% vs 10.0%) were also less common in the delgocitinib cream group than in the alitretinoin group [90].

2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for the DELTA trials is shown in Table 10.

Table 10 Quality assessment results for DELTA trials

Trial ID	Random sequence generation	Allocation conceal-ment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
DELTA 1	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DELTA 2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DELTA FORCE	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

The quality of the included trials was assessed using the Cochrane Risk of Bias tool [104].

2.6 Clinical effectiveness results of the relevant studies

2.6.1 Summary of statistical significance of primary and secondary endpoints

DELTA 1 and DELTA 2

In both DELTA 1 and DELTA 2, all of the primary and secondary endpoints in the statistical testing hierarchy (section 2.4.1.3, Figure 5) showed statistically significantly greater efficacy with delgocitinib cream than with cream vehicle [82, 87, 88].

DELTA FORCE

Results for all primary and secondary endpoints in the DELTA FORCE statistical testing hierarchy (section 2.4.1.3, Figure 6) demonstrated statistically significantly greater efficacy with delgocitinib cream than with alitretinoin capsules [90].

2.6.2 DELTA 1 and DELTA 2 clinical endpoints

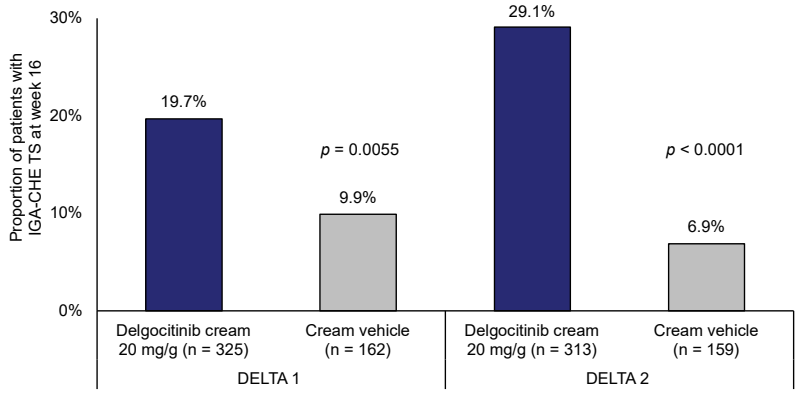
2.6.2.1 Primary endpoint: IGA-CHE TS at week 16

Statistically significantly more patients achieved IGA-CHE TS at week 16 with delgocitinib cream than with cream vehicle

The primary endpoint of IGA-CHE TS was achieved in both studies, with 19.7% and 29.1% of patients treated with delgocitinib cream in DELTA 1 and DELTA 2, respectively, having IGA-CHE scores of 0 or 1 at week 16 and an improvement from baseline of ≥ 2 points, compared with 9.9% and 6.9% of patients in the corresponding cream vehicle groups ($p = 0.0055$ and $p < 0.0001$, respectively; Figure 7) [82].

At week 12, 25.8% and 33.2% of patients treated in the DELTA 1 and DELTA 2 delgocitinib cream groups, respectively, had IGA-CHE TS, compared with 14.8% and 11.3% in the cream vehicle groups ($p = 0.006$ and $p < 0.001$, respectively; Figure 8) [87, 88].

Figure 7 IGA-CHE TS at week 16 in DELTA 1 and DELTA 2



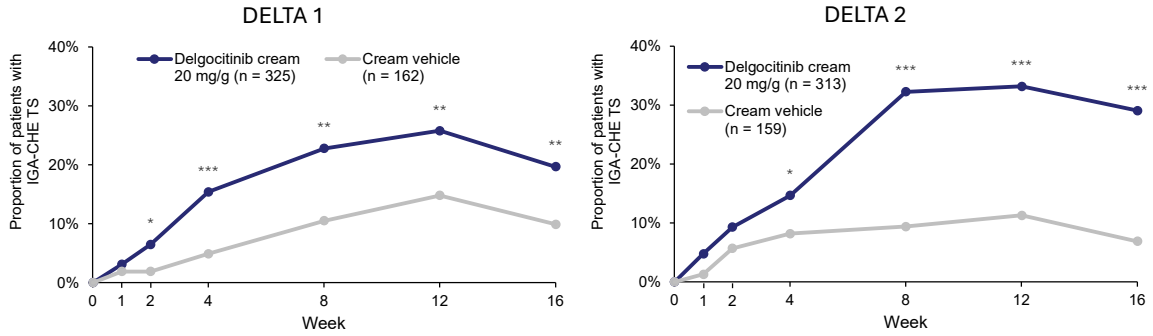
IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success.
Sources: Bissonnette *et al.* 2024 [82].

2.6.2.2 Time to IGA-CHE TS response

A significant difference in the proportion of patients with IGA-CHE TS was already seen between delgocitinib cream and cream vehicle at weeks 4 and 8

In both DELTA 1 and DELTA 2, statistically significantly more patients treated with delgocitinib cream achieved IGA-CHE TS at week 4, compared with cream vehicle (DELTA 1, 15.4% vs 4.9%; $p = 0.0007$; DELTA 2, 14.7% vs 8.2%; $p = 0.043$; Figure 8) [82]. In DELTA 1, the difference between the delgocitinib cream and cream vehicle arms was statistically significant as early as week 2 (Figure 8) [87]. Statistically significant differences between the arms were seen at week 8 in DELTA 1 (22.8% vs 10.5%; $p = 0.001$) and DELTA 2 (32.3% vs 9.4%; $p < 0.0001$; Figure 8) [82].

Figure 8 Proportion of patients with IGA-CHE TS to week 16 in DELTA 1 and DELTA 2



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success.
Sources: Bissonnette *et al.* 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

2.6.2.3 HECSI-75 and HECSI-90

Patients treated with delgocitinib cream were more likely to achieve HECSI-75 and HECSI-90 at week 16 than those receiving cream vehicle

In DELTA 1 and DELTA 2, respectively, 49.2% and 49.5% of patients treated with delgocitinib cream achieved HECSI-75 at week 16, compared with 23.5% and 18.2% of patients in the two cream vehicle groups (both $p < 0.0001$; Table 11) [82, 91, 93].

HECSI-90 at week 16 was achieved by 29.5% and 31.0% of patients in the DELTA 1 and DELTA 2 delgocitinib cream groups, respectively, compared with 12.3% and 8.8% of those in the corresponding cream vehicle groups (both $p < 0.0001$; Table 11) [82, 91, 93].

In addition, the proportions of patients with HECSI-75 and HECSI-90 were statistically significantly higher with delgocitinib cream than with cream vehicle at week 8 and week 12 (Table 11) [82, 87, 88].

Table 11 HECSI-75 and HECSI-90 in DELTA 1 and DELTA 2

	DELTA 1			DELTA 2		
	Delgocitinib cream 20 mg/g (n = 325)	Vehicle cream (n = 162)	*p* value	Delgocitinib cream 20 mg/g (n = 313)	Vehicle cream (n = 159)	*p* value
HECSI-75, n (%)						
Week 8	163 (50.2)	42 (25.9)	< 0.0001	158 (50.5)	31 (19.5)	< 0.0001
Week 12	168 (51.7)	46 (28.4)	< 0.001	163 (52.1)	31 (19.5)	< 0.001
Week 16	160 (49.2)	38 (23.5)	< 0.0001	155 (49.5)	29 (18.2)	< 0.0001
HECSI-90, n (%)						
Week 8	104 (32.0)	16 (9.9)	< 0.001	87 (27.8)	12 (7.5)	< 0.001
Week 12	114 (35.1)	20 (12.3)	< 0.001	103 (32.9)	15 (9.4)	< 0.001
Week 16	96 (29.5)	20 (12.3)	< 0.0001	97 (31.0)	14 (8.8)	< 0.0001

HECSI, Hand Eczema Severity Index.

Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

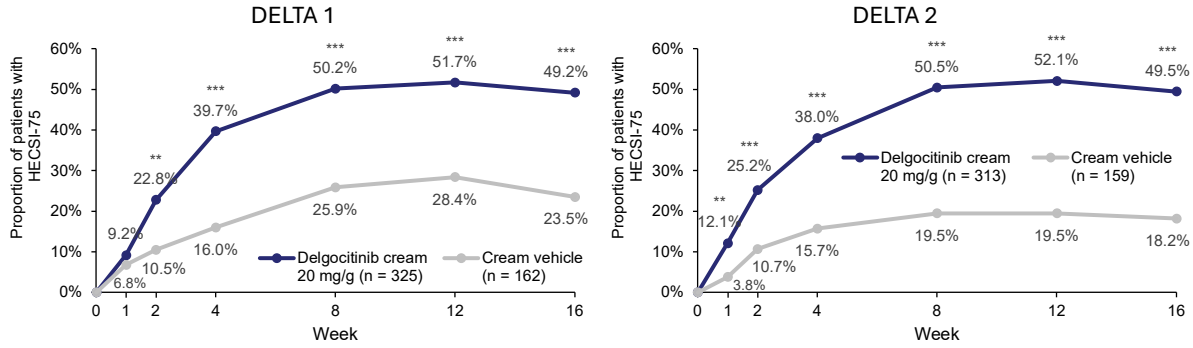
The results of a *post hoc* analysis of HECSI-50 responses are shown in Appendix B.7.1, Table 157.

2.6.2.4 Time to HECSI-75 and HECSI-90 response

Statistically significant differences in the proportion of patients with HECSI-75 on delgocitinib cream compared with cream vehicle were seen as early as week 2 in DELTA 1 and week 1 in DELTA 2

As shown in Figure 9, the proportion of patients achieving HECSI-75 was statistically significantly higher with delgocitinib cream than with cream vehicle from week 2 (DELTA 1) or week 1 (DELTA 2) [87, 88] Statistically significant differences were maintained up to week 16 [87, 88, 91, 93].

Figure 9 Proportion of patients with HECSI-75 to week 16 in DELTA 1 and DELTA 2

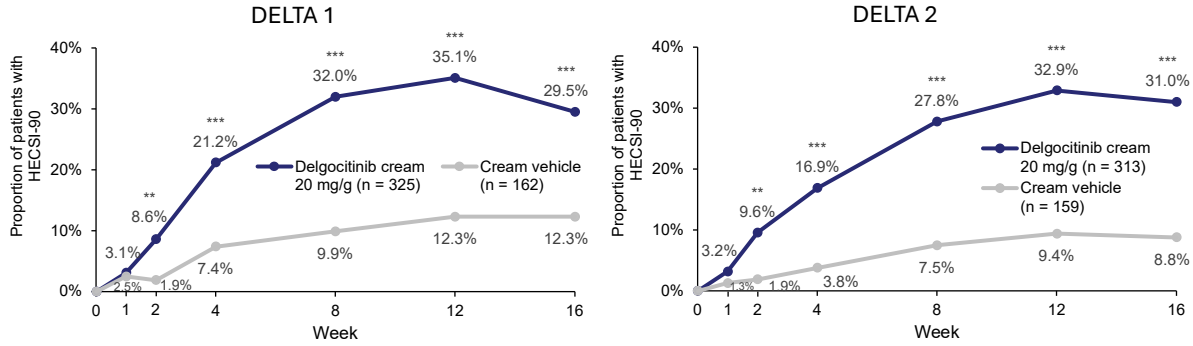


* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 8 and week 16 p values are reported as < 0.0001 in Bissonette *et al*. [82]. HECSI, Hand Eczema Severity Index.
Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

Significant differences in the proportion of patients with HECSI-90 were already seen at week 2 in DELTA 1 and DELTA 2

From week 2, statistically significantly more patients had HECSI-90 responses in the DELTA 1 and DELTA 2 delgocitinib cream groups than in the corresponding cream vehicle groups (Figure 10) [87, 88]. Statistically significant differences in HECSI-90 response rates continued up to week 16 in both trials [87, 88, 91, 93].

Figure 10 Proportion of patients with HECSI-90 to week 16 in DELTA 1 and DELTA 2



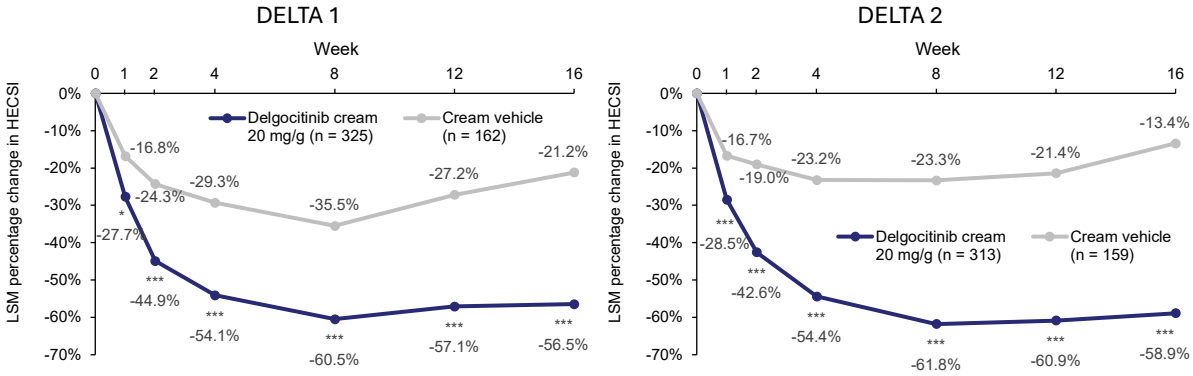
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 16 p values are reported as < 0.0001 in Bissonette *et al*. [82]. HECSI, Hand Eczema Severity Index. Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

2.6.2.5 Percentage change in HECSI

Treatment with delgocitinib cream led to improvements in mean HECSI, with statistically significant differences between groups from week 1 onward

In both DELTA 1 and DELTA 2, the least squares mean (LSM) decrease (improvement) in HECSI was statistically significantly greater in the delgocitinib cream groups than in the cream vehicle groups at week 1, with significant differences maintained up to week 16 (Figure 11) [82, 87, 88].

Figure 11 LSM percentage change in HECSI from baseline to week 16 in DELTA 1 and DELTA 2



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 16 p values are reported as < 0.0001 in Bissonette *et al*. [82].
ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline HECSI.
ANCOVA, analysis of covariance; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean.
Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

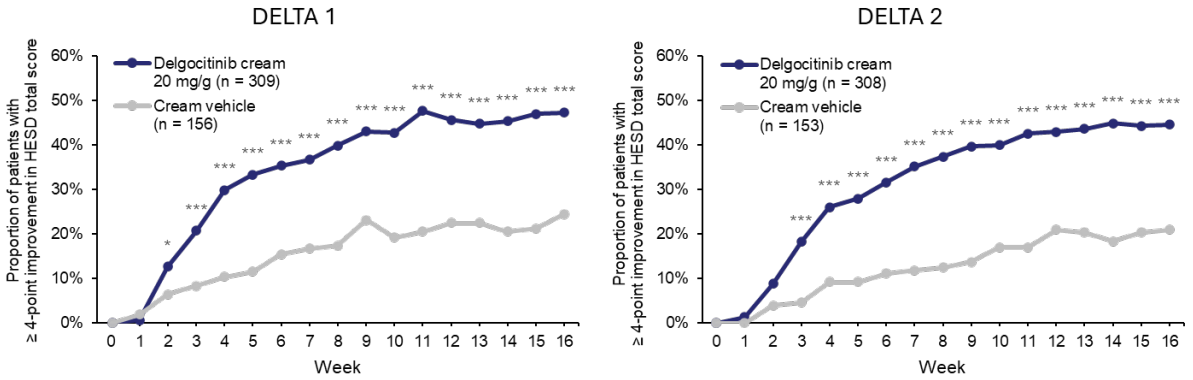
2.6.3 DELTA 1 and DELTA 2 daily diary endpoints

2.6.3.1 HESD total score

Patients treated with delgocitinib cream were statistically significantly more likely than those using cream vehicle to have a clinically meaningful improvement in HESD total score

In both DELTA 1 and DELTA 2, statistically significantly more patients had ≥ 4-point reductions (improvements) in weekly average HESD total score at week 16 (see Appendix B.6.2 for details of HESD) in the delgocitinib cream group than in the vehicle cream group from week 2 (DELTA 1) and week 3 (DELTA 2); the differences between groups were statistically significant at week 4 and week 8, and remained significant up to week 16 (Figure 12) [82, 87, 88].

Figure 12 Proportion of patients with ≥ 4-point improvement in HESD total score to week 16 in DELTA 1 and DELTA 2



n = number of patients with HESD total score ≥ 4 at baseline. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 4, 8 and 16 p values are reported as < 0.0001 in Bissonette *et al*. [82]. HESD, Hand Eczema Symptom Diary.
Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

The mean improvement in weekly average HESD total score at week 16 was statistically significantly greater among patients treated with delgocitinib cream, compared with the cream vehicle group, in both DELTA 1 and DELTA 2 (Table 12) [82].

Table 12 LSM improvement in HESD total score from baseline to week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib cream 20 mg/g (n = 324)	Cream vehicle (n = 162)	Delgocitinib cream 20 mg/g (n = 312)	Cream vehicle (n = 157)
LSM improvement in HESD total score (SE)	−3.4 (0.1)	−1.7 (0.2)	−3.2 (0.1)	−1.4 (0.2)
LSM difference (95% CI)	−1.7 (−2.2, −1.2)		−1.9 (−2.4, −1.4)	
p value	< 0.0001		< 0.0001	

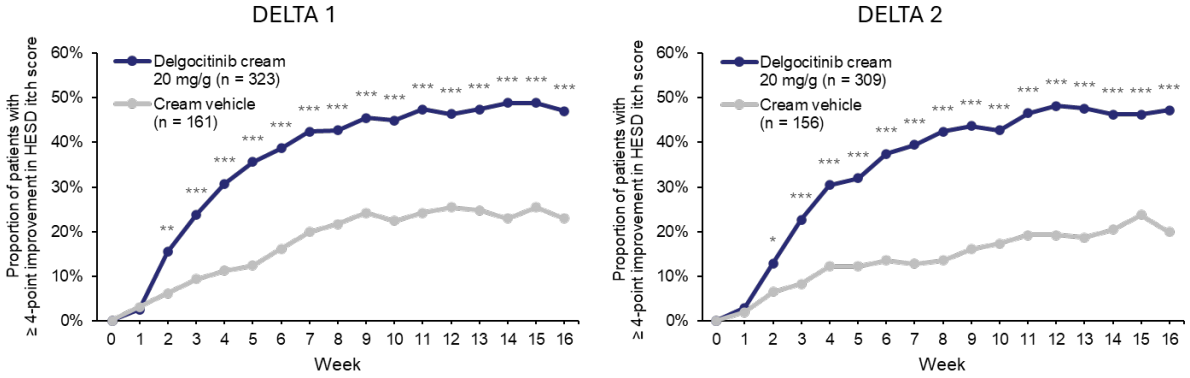
n = number of patients with HESD total score ≥ 4 at baseline. ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline HESD total score. ANCOVA, analysis of covariance; CI, confidence interval; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; SE, standard error. Sources: Bissonnette *et al*. 2024 [82].

2.6.3.2 HESD itch score

Statistically significantly higher rates of clinically meaningful improvements in HESD itch score were seen among patients treated with delgocitinib cream, compared with those receiving cream vehicle, as early as week 2

In both DELTA 1 and DELTA 2, statistically significantly more patients had a ≥ 4-point reductions (improvements) in weekly average HESD itch score (a key secondary endpoint) at week 16 in the delgocitinib cream group than in the vehicle cream group from week 2; the difference between groups remained significant up to week 16 (Figure 13) [82, 87, 88].

Figure 13 Proportion of patients with ≥ 4-point improvement in HESD itch score to week 16 in DELTA 1 and DELTA 2



n = number of patients with HESD itch score ≥ 4 at baseline. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ week 2, 4, 8 and 16 *p* values are reported as < 0.0001 in Bissonette *et al*. [82]. HESD, Hand Eczema Symptom Diary. Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

Delgocitinib cream was associated with a statistically significantly greater improvement in HESD itch score at week 16, compared with cream vehicle

The mean reduction (improvement) in weekly average HESD itch score at week 16 was statistically significantly greater among patients treated with delgocitinib cream, compared with the cream vehicle group, in both DELTA 1 and DELTA 2 (Table 13) [82, 87, 88].

Table 13 LSM improvement in HESD itch score from baseline to week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib cream 20 mg/g (n = 324)	Cream vehicle (n = 162)	Delgocitinib cream 20 mg/g (n = 312)	Cream vehicle (n = 157)
LSM improvement in HESD itch score (SE)	−3.6 (0.2)	−1.9 (0.2)	−3.4 (0.2)	−1.4 (0.2)
LSM difference (95% CI)	−1.7 (−2.3, −1.2)		−2.0 (−2.5, −1.4)	
p value	< 0.0001		< 0.0001	

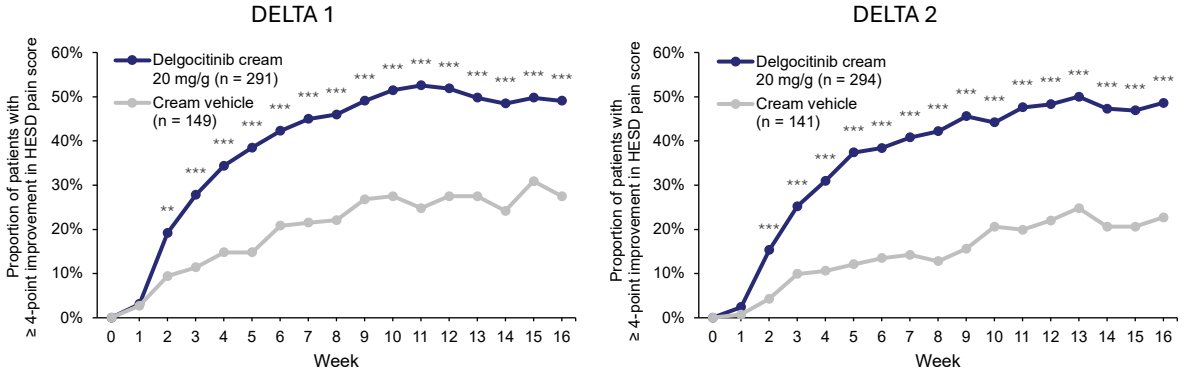
n = number of patients with HESD itch score ≥ 4 at baseline. ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline HESD itch score. ANCOVA, analysis of covariance; CI, confidence interval; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; SE, standard error. Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

2.6.3.3 HESD pain score

Statistically significantly higher rates of clinically meaningful improvements in HESD pain score were seen among patients treated with delgocitinib cream, compared with those receiving cream vehicle, as early as week 2

In both DELTA 1 and DELTA 2, statistically significantly more patients had ≥ 4-point reductions (improvements) in weekly average HESD pain score in the delgocitinib cream group than in the vehicle cream group from week 2; the difference between groups remained significant up to week 16 (Figure 14) [82, 87, 88].

Figure 14 Proportion of patients with ≥ 4-point improvement in HESD pain score to week 16 in DELTA 1 and DELTA 2



n = number of patients with HESD itch score ≥ 4 at baseline. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 4, 8 and 16 *p* values are reported as < 0.0001 in Bissonette *et al*. [82]. HESD, Hand Eczema Symptom Diary. Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

The mean reduction (improvement) in HESD pain score at week 16 was statistically significantly greater among patients treated with delgocitinib cream, compared with the cream vehicle group, in both trials (Table 14) [82, 87, 88].

Table 14 LSM improvement in HESD pain score from baseline to week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib cream 20 mg/g (n = 324)	Cream vehicle (n = 162)	Delgocitinib cream 20 mg/g (n = 312)	Cream vehicle (n = 157)
LSM improvement in HESD pain score (SE)	−3.4 (0.2)	−1.8 (0.2)	−3.3 (0.2)	−1.3 (0.2)
LSM difference (95% CI)	−1.6 (−2.1, −1.0)		−2.0 (−2.6, −1.5)	
p value	< 0.0001		< 0.0001	

n = number of patients with HESD pain score ≥ 4 at baseline.

ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline HESD pain score.

ANCOVA, analysis of covariance; CI, confidence interval; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; SE, standard error.

Sources: Bissonnette *et al*. 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88]

2.6.4 DELTA 1 and DELTA 2 patient-reported outcomes

2.6.4.1 DLQI

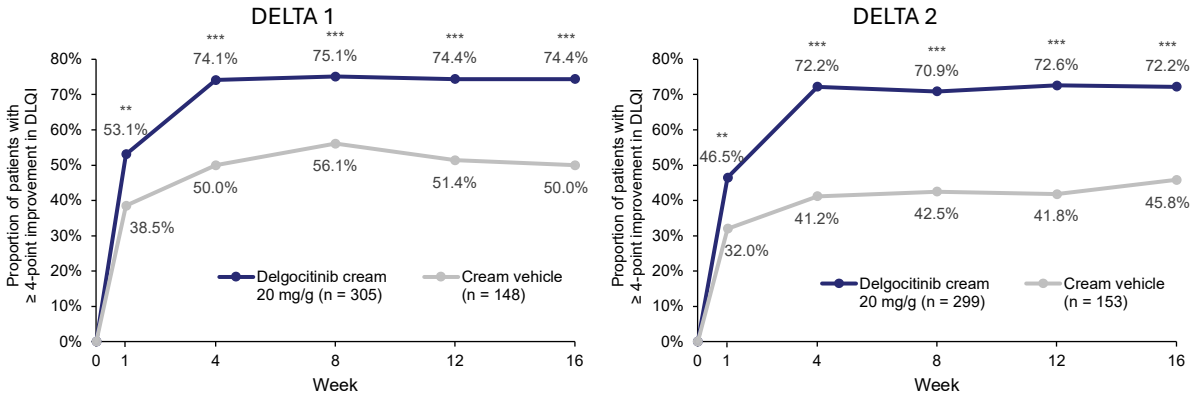
Patients were statistically significantly more likely to achieve a ≥ 4-point improvement in DLQI at week 16 in the delgocitinib cream group, compared with the cream vehicle group

A 4-point reduction (improvement) from baseline is defined as a clinically meaningful change in DLQI [99]. Among patients treated with delgocitinib cream in DELTA 1 and DELTA 2, respectively, who had DLQI ≥ 4 at baseline, 74.4% and 72.2% had a ≥ 4-point improvement at week 16, compared with 50.0% and 45.8% of patients in the corresponding cream vehicle groups (both $p < 0.0001$; Figure 15) [82]. Statistically significant differences were seen between the groups from week 1 onward in both trials; at week 4, 74.1% and 72.2% of patients with DLQI ≥ 4 at baseline in DELTA 1 and DELTA 2, respectively, achieved a 4-point improvement, compared with 50.0% and 41.2% in the corresponding vehicle cream groups (both $p < 0.001$) [82, 87, 88].

Patients treated with delgocitinib cream had statistically significantly larger mean improvements in DLQI than those receiving cream vehicle already from week 1

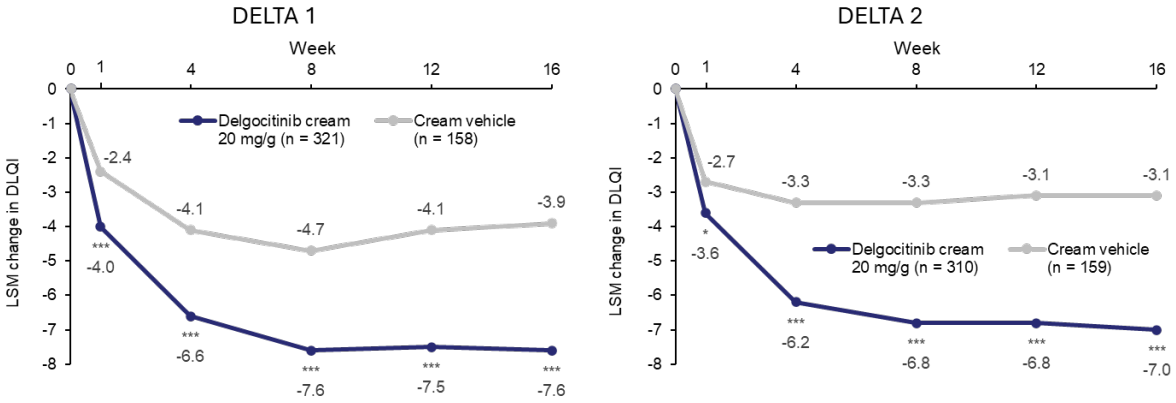
In both DELTA 1 and DELTA 2, mean reductions (improvements) in DLQI were statistically significantly larger in the delgocitinib cream groups than in the cream vehicle groups at week 1 (DELTA 1, −4.0 vs −2.4 [$p < 0.001$]; DELTA 2, −3.6 vs −2.7 [$p < 0.05$]) [87, 88]. Statistically significant differences were maintained at all study visits (Figure 16); at week 16, reductions in the DELTA 1 and DELTA 2 delgocitinib cream groups were −7.6 and −7.0, respectively, versus −3.9 and −3.1 in the corresponding cream vehicle groups (both $p < 0.0001$) [82].

Figure 15 Proportion of patients with ≥ 4-point improvement in DLQI to week 16 in DELTA 1 and DELTA 2



n = number of patients with DLQI ≥ 4 at baseline. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 16 p values are reported as < 0.0001 in Bissonette *et al*. [82]. DLQI, Dermatology Life Quality Index. Sources: Bissonnette *et al.* 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

Figure 16 LSM change in DLQI from baseline to week 16 in DELTA 1 and DELTA 2



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; week 16 p values are reported as < 0.0001 in Bissonette *et al*. [82]. ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline DLQI.
ANCOVA, analysis of covariance; DLQI, Dermatology Life Quality Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean. Sources: Bissonnette *et al.* 2024 [82]; DELTA 1 and DELTA 2 CSRs [87, 88].

2.6.4.2 EQ-5D-3L and EQ VAS

Patients treated with delgocitinib cream had larger improvements from baseline to week 16 in EQ-5D-3L index and EQ-5D VAS than those receiving vehicle cream

The mean (SD) EQ-5D-3L index at baseline was 0.626 (0.249) and 0.667 (0.212) in the DELTA 1 and DELTA 2 delgocitinib cream groups, respectively, and 0.644 (0.228) and 0.632 (0.246) in the corresponding cream vehicle groups (EQ-5D-5L data were cross-walked to the EQ-5D-3L in accordance with NICE recommendations [102], as described in section 2.3.1.7, Table 6) [87, 88].

In both DELTA 1 and DELTA 2, treatment with delgocitinib cream resulted in a significantly greater increase (improvement) in EQ-5D-3L index from baseline to week 16, compared with cream vehicle (both $p < 0.001$; Table 15).

Similarly, increases (improvements) in EQ VAS scores were statistically significantly larger in the delgocitinib cream groups than in the cream vehicle groups (Table 15).

Table 15 Improvement in EQ-5D-3L index and EQ VAS from baseline to week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib cream 20 mg/g (n = 321)	Cream vehicle (n = 158)	Delgocitinib cream 20 mg/g (n = 310)	Cream vehicle (n = 159)
EQ-5D-3L index				
Baseline, mean (SD)	0.626 (0.249)	0.644 (0.228)	0.667 (0.212)	0.632 (0.246)
LSM improvement (SE)	0.176 (0.011)	0.073 (0.015)	0.157 (0.011)	0.049 (0.015)
LSM difference (95% CI)	0.103 (0.067–0.140)		0.108 (0.071–0.145)	
p value [a]	< 0.001		< 0.001	
EQ VAS				
Baseline (SD)	71.0 (18.6)	70.2 (17.9)	71.5 (17.5)	69.1 (20.1)
LSM improvement (SE)	8.3 (0.9)	0.8 (1.2)	8.3 (0.9)	3.6 (1.3)
LSM difference (95% CI)	7.5 (4.6–10.5)		4.8 (1.7–7.8)	
p value [a]	< 0.001		0.002	

[a] Nominal *p* values; EQ-5D-3L index and EQ VAS are not included in the DELTA 1 and DELTA 2 statistical testing hierarchy (see section 2.4.1.3).

EQ-5D-5L data were cross-walked to the EQ-5D-3L in accordance with NICE recommendations [102], as described in section 2.3.1.7, Table 6.

ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline EQ-5D-5L index/EQ VAS score.

ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; SD, standard deviation; SE, standard error; VAS, visual analogue scale. Sources: DELTA 1 and DELTA 2 CSRs [87, 88].

2.6.4.3 HEIS

Improvements in HEIS scores were statistically significantly larger with delgocitinib cream than with cream vehicle

In both DELTA 1 and DELTA 2, a statistically significant difference in LSM decrease (improvement) in HEIS score from baseline to week 16 was seen with delgocitinib, compared with the cream vehicle group (both $p < 0.0001$; Table 16) [82]. Similar results were seen for HEIS proximal daily activity limitations (PDAL) scores (Table 16) [82].

Table 16 LSM improvement in HEIS total score and PDAL score from baseline to week 16 in DELTA 1 and DELTA 2

	DELTA 1		DELTA 2	
	Delgocitinib cream 20 mg/g (n = 321)	Cream vehicle (n = 158)	Delgocitinib cream 20 mg/g (n = 310)	Cream vehicle (n = 159)
HEIS total score				
LSM improvement (SE)	−1.5 (0.1)	−0.8 (0.1)	−1.5 (0.1)	−0.7 (0.1)
LSM difference (95% CI)	−0.6 (−0.8, −0.5)		−0.8 (−1.0, −0.6)	
p value	< 0.0001		< 0.0001	
HEIS PDAL score				
LSM improvement (SE)	−1.5 (0.1)	−0.9 (0.1)	−1.5 (0.1)	−0.7 (0.1)
LSM difference (95% CI)	−0.6 (−0.8, −0.4)		−0.8 (−1.0, −0.6)	
p value	< 0.0001		< 0.0001	

ANCOVA adjusting for treatment, region, baseline IGA-CHE score and baseline HEIS total/PDAL score.

ANCOVA, analysis of covariance; CI, confidence interval; HEIS, Hand Eczema Impact Scale; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; PDAL, proximal daily activity limitations; SE, standard error. Sources: Bissonnette *et al.* 2024 [82].

2.6.5 DELTA 3 clinical endpoints

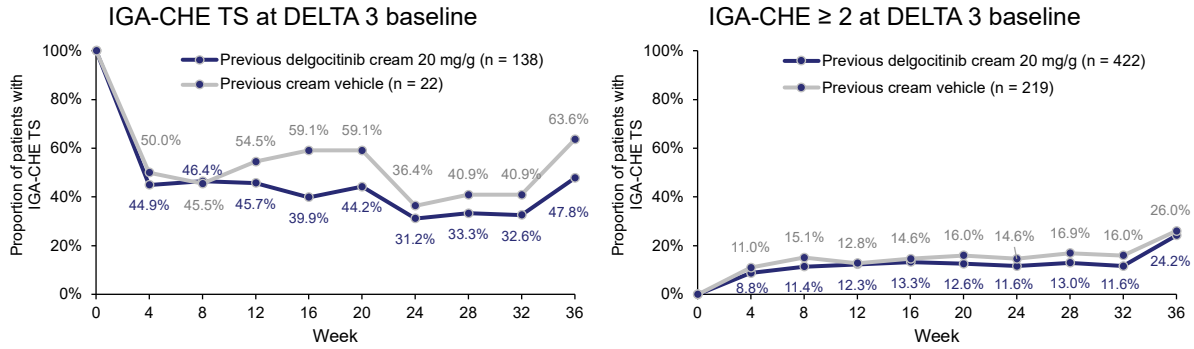
2.6.5.1 IGA-CHE TS over time

Among patients with IGA-CHE TS at baseline, the proportion with IGA-CHE TS fell initially while off-treatment, and was then maintained up to week 36

As described above, among patients starting DELTA 3 off-treatment (regardless of treatment with delgocitinib cream or cream vehicle in the parent trials), the median time to losing IGA-CHE TS (i.e., no longer having an IGA-CHE score of 0 or 1) was 4 weeks. From week 4 onward, the proportion of patients with IGA-CHE TS while using delgocitinib cream as-needed was consistent throughout DELTA 3 (Figure 17) [89].

Among patients starting DELTA 3 on-treatment (i.e., with IGA-CHE scores ≥ 2), 50.3% achieved IGA-CHE TS at some point during DELTA 3 (previous delgocitinib cream, 48.1%; previous cream vehicle, 54.4%), and 29.8% had IGA-CHE TS at week 36 (Table 17) [89].

Figure 17 Proportion of patients with IGA-CHE TS to week 36 in DELTA 3, by baseline response and parent trial treatment



IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Source: DELTA 3 CSR [89].

Table 17 IGA-CHE TS at baseline and week 36 in DELTA 3

	N	Proportion of patients with IGA-CHE TS, n (%)	
		Baseline	Week 36
Previous delgocitinib cream 20 mg/g	560	138 (24.6)	168 (30.0)
IGA-CHE TS at DELTA 3 baseline	138	138 (100.0)	66 (47.8)
IGA-CHE ≥ 2 at DELTA 3 baseline	422	0	102 (24.2)
Previous cream vehicle	241	22 (9.1)	71 (29.5)
IGA-CHE TS at DELTA 3 baseline	22	22 (100.0)	14 (63.6)
IGA-CHE ≥ 2 at DELTA 3 baseline	219	0	57 (26.0)
Overall	801	160 (20.0)	239 (29.8)
IGA-CHE TS at DELTA 3 baseline	160	160 (100.0)	80 (50.0)
IGA-CHE ≥ 2 at DELTA 3 baseline	641	0	159 (24.8)

IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success.
Source: DELTA 3 CSR [89].

2.6.5.2 Loss of IGA-CHE TS response while off-treatment

Among patients treated with delgocitinib cream in DELTA 1 and DELTA 2 who had an IGA-CHE TS response at the start of DELTA 3, the estimated median time to loss of response while off-treatment was 4 weeks

Among the 138 patients who received delgocitinib cream 20 mg/g in the parent trial and who had achieved IGA-CHE TS at the DELTA 3 baseline, the estimated median time to loss of response (i.e., no longer having an IGA-CHE score of 0 or 1) while being off-treatment was 4 weeks (Table 18). The cumulative proportion of patients with an IGA-CHE score ≥ 2 (or permanently discontinuing or initiating rescue treatment) was estimated as 59.4% (95% CI, 51.4–67.6%) at week 4 and 71.7% (95% CI, 64.1–79.0%) at week 8 (i.e., 28.3% of patients retained IGA-CHE TS for at least 8 weeks while off-treatment) [89].

Table 18 Time to loss of IGA-CHE TS off-treatment in DELTA 3, previous delgocitinib cream group with IGA-CHE TS at DELTA 3 baseline

	Previous delgocitinib cream and IGA-CHE 0/1 at DELTA 3 baseline (n = 138)
Cumulative incidence of IGA-CHE ≥ 2	
Week 4	59.4% (51.4–67.6%)
Week 8	71.7% (64.1–79.0%)
Week 12	77.5% (70.3–84.1%)
Week 16	84.1% (77.5–89.6%)
Week 20	89.1% (83.3–93.6%)
Week 24	90.6% (85.0–94.7%)
Week 28	90.6% (85.0–94.7%)
Week 32	92.0% (86.8–95.8%)
Week 36	93.5% (88.5–96.8%)
Median (25^{th}–75^{th} percentile) time to IGA-CHE ≥ 2	4 weeks (4–12 weeks)

IGA-CHE, Investigator's Global Assessment for chronic hand eczema. Source: DELTA 3 CSR [89].

2.6.5.3 Time to regain IGA-CHE TS response after treatment re-initiation

Among patients who had an IGA-CHE TS response on delgocitinib cream in DELTA 1 and DELTA 2 and who reinitiated treatment after a loss of response while off-treatment, the median time to achieving IGA-CHE TS again was 8 weeks

Among the 138 patients who received delgocitinib cream 20 mg/g in the parent trial and who had achieved IGA-CHE TS at the DELTA 3 baseline, 124 reinitiated treatment following a loss of response during an off-treatment period. The estimated median time to IGA-CHE TS following first re-initiation of treatment was 8 weeks. The estimated cumulative proportion of patients who regained IGA-CHE TS by the end of the treatment period after having reinitiated treatment was 80.7% (95% CI, 72.5–87.7%) [89].

Of the 422 patients previously treated with delgocitinib cream who did not have IGA-CHE TS at the DELTA 3 baseline, 137 subsequently achieved IGA-CHE TS, stopped treatment, but later reinitiated treatment due to an IGA-CHE score of ≥ 2. Among these patients, the median time to IGA-CHE TS following treatment re-initiation was 12 weeks; the estimated cumulative proportion regaining IGA-CHE TS by the end of the treatment period was 94.5% (95% CI, 80.0–99.5%) [89].

2.6.5.4 HECSI-75 and HECSI-90

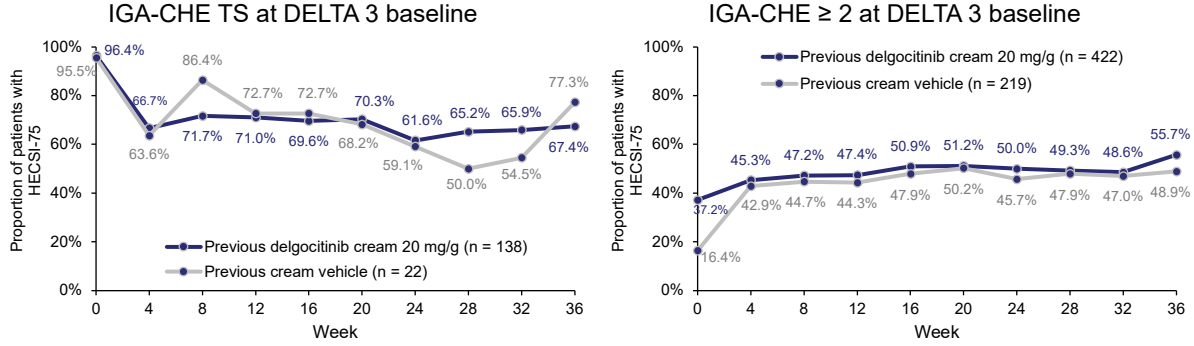
Among patients with IGA-CHE TS at baseline, the proportions with HECSI-75 and HECSI-90 fell initially while off-treatment, and were then maintained up to week 36

As shown in Figure 18, among patients who started DELTA 3 off-treatment (i.e., with IGA-CHE TS), the proportion with HECSI-75 responses dropped between baseline and week 4 (i.e., some patients' CHE worsened while off-treatment; similar reductions were seen both for patients treated with delgocitinib cream in the parent trials and for those who had received cream vehicle), and was then generally stable throughout the trial period [89].

Among patients who did not have IGA-CHE TS at the DELTA 3 baseline and started the extension study on-treatment, the proportion with HECSI-75 responses increased during the first 16 weeks of the trial and then remained stable [89].

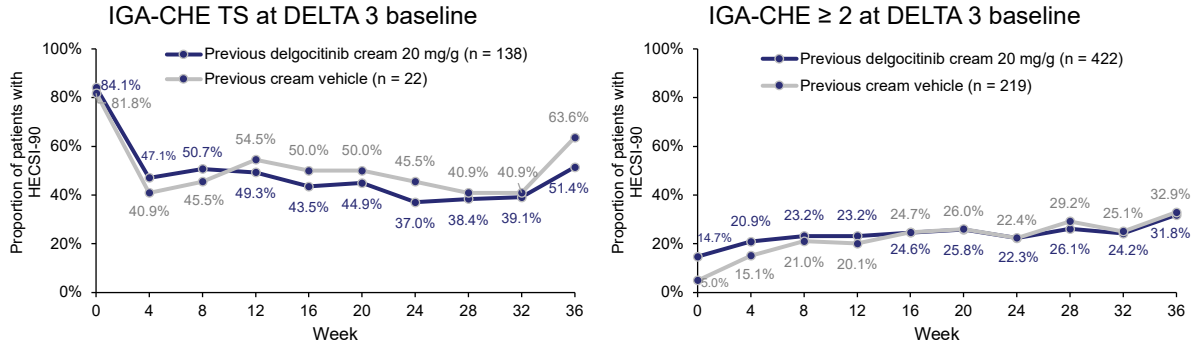
A similar pattern was seen for the proportion of patients with HECSI-90 responses (Figure 19) [89].

Figure 18 Proportion of patients with HECSI-75 to week 36 in DELTA 3, by baseline response and parent trial treatment



HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Source: DELTA 3 CSR [89].

Figure 19 Proportion of patients with HECSI-90 to week 36 in DELTA 3, by baseline response and parent trial treatment



HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Source: DELTA 3 CSR [89].

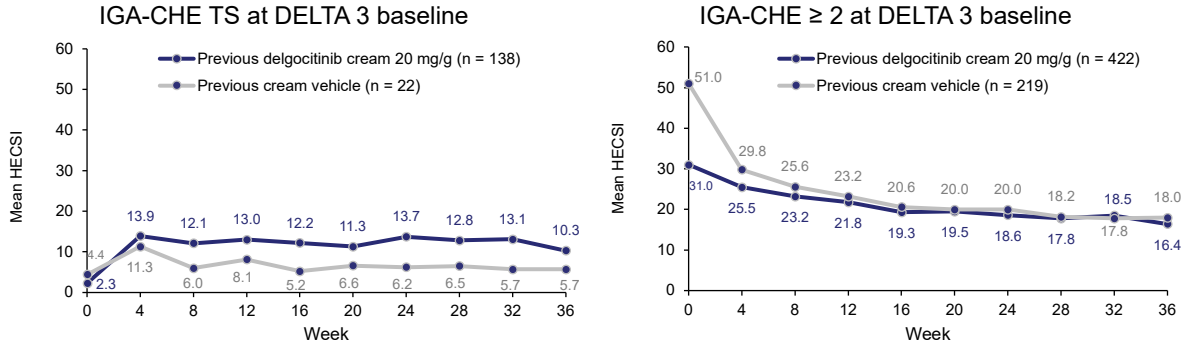
2.6.5.5 Mean HECSI

Among patients with IGA-CHE ≥ 2 at baseline, mean HECSI improved during DELTA 3

Among patients who did not have IGA-CHE TS at the DELTA 3 baseline and started the extension study on-treatment, mean HECSI decreased (improved) up to week 16 and then remained stable (Figure 20) [89].

For patients who started DELTA 3 off-treatment, mean HECSI increased (worsened) over the first 4 weeks of the trial (consistent with the loss of IGA-CHE TS for some patients during this period, as described above; similar changes were seen both for patients treated with delgocitinib cream in the parent trials and for those who had received cream vehicle), and was then stable for the remainder of the extension study (Figure 20) [89].

Figure 20 Mean HECSI to week 36 in DELTA 3, by baseline response and parent trial treatment



Data are as observed; n reflects total number of patients at DELTA 3 baseline.
HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Source: DELTA 3 CSR [89].

2.6.6 DELTA 3 daily diary endpoints

2.6.6.1 HESD total score

In the overall group of patients treated with delgocitinib cream in DELTA 1 and DELTA 2, mean HESD total score improved during DELTA 3

Patients who received delgocitinib cream in the parent trials and started DELTA 3 on-treatment (i.e., with IGA-CHE ≥ 2) had reductions (improvements) in mean HESD total score during the extension study (Table 19) [89].

For patients treated with delgocitinib cream in the parent trials who started DELTA 3 off-treatment (i.e., who had IGA-CHE TS at DELTA 3 baseline), mean HESD total score increased over the first 4 weeks of the trial (consistent with the loss of IGA-CHE TS for some patients during this period, as described above), and was then stable for the remainder of the extension study (Table 19) [89].

Patients who received cream vehicle in the parent trials had reductions in mean HESD total score during DELTA 3 regardless of IGA-CHE response status at baseline (Table 19) [89].

Table 19 Weekly average HESD score at baseline and week 36 in DELTA 3

	Baseline		Week 36	
	N	Mean (SD)	N	Mean (SD)
Previous delgocitinib cream 20 mg/g	541	3.34 (2.67)	441	2.49 (2.23)
IGA-CHE TS at DELTA 3 baseline	136	1.52 (1.89)	119	1.81 (1.97)
IGA-CHE ≥ 2 at DELTA 3 baseline	405	3.95 (2.62)	322	2.74 (2.26)
Previous cream vehicle	233	4.91 (2.59)	175	3.04 (2.61)
IGA-CHE TS at DELTA 3 baseline	20	2.30 (2.33)	17	1.89 (2.39)
IGA-CHE ≥ 2 at DELTA 3 baseline	213	5.16 (2.48)	158	3.16 (2.61)
Overall population	774	3.81 (2.74)	616	2.65 (2.35)

HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; SD, standard deviation; TS, treatment success. Source: DELTA 3 CSR [89].

2.6.6.2 HESD itch

In the overall group of patients treated with delgocitinib cream in DELTA 1 and DELTA 2, mean HESD itch score improved during DELTA 3

Patients who received delgocitinib cream in the parent trials and started DELTA 3 on-treatment (i.e., with IGA-CHE ≥ 2) had reductions (improvements) in mean HESD itch score during the extension study (Table 20) [89].

For patients treated with delgocitinib cream in the parent trials who started DELTA 3 off-treatment (i.e., who had IGA-CHE TS at DELTA 3 baseline), mean HESD itch score increased over the first 4 weeks of the trial (consistent with the loss of IGA-CHE TS for some patients during this period, as described above), decreased slightly to week 6, and was then stable for the remainder of the extension study (Table 20) [89].

Patients who received cream vehicle in the parent trials had reductions in mean HESD itch score during DELTA 3 regardless of IGA-CHE response status at baseline (Table 20) [89].

Table 20 Weekly average HESD itch score at baseline and week 36 in DELTA 3

	Baseline		Week 36	
	N	Mean (SD)	N	Mean (SD)
Previous delgocitinib cream 20 mg/g	541	3.2 (2.7)	441	2.4 (2.3)
IGA-CHE TS at DELTA 3 baseline	136	1.5 (2.1)	119	1.9 (2.1)
IGA-CHE ≥ 2 at DELTA 3 baseline	405	3.7 (2.7)	322	2.5 (2.3)
Previous cream vehicle	233	4.8 (2.8)	175	2.9 (2.8)
IGA-CHE TS at DELTA 3 baseline	20	2.3 (2.5)	17	1.7 (2.3)
IGA-CHE ≥ 2 at DELTA 3 baseline	213	5.0 (2.7)	158	3.0 (2.8)
Overall population	774	3.6 (2.8)	616	2.5 (2.5)

HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; SD, standard deviation; TS, treatment success. Source: DELTA 3 CSR [89].

2.6.6.3 HESD pain

In the overall group of patients treated with delgocitinib cream in DELTA 1 and DELTA 2, mean HESD pain score improved during DELTA 3

Patients who received delgocitinib cream in the parent trials and started DELTA 3 on-treatment (i.e., with IGA-CHE ≥ 2) had reductions (improvements) in mean HESD pain score during the extension study (Table 21) [89].

For patients treated with delgocitinib cream in the parent trials who started DELTA 3 off-treatment (i.e., who had IGA-CHE TS at DELTA 3 baseline), mean HESD pain score increased over the first 4 weeks of the trial (consistent with the loss of IGA-CHE TS for some

patients during this period, as described above) and then remained stable for the remainder of the extension study (Table 21) [89].

Patients who received cream vehicle in the parent trials had reductions in mean HESD pain score during DELTA 3 regardless of IGA-CHE response status at baseline (Table 21) [89].

Table 21 Weekly average HESD pain score at baseline and week 36 in DELTA 3

	Baseline		Week 36	
	N	Mean (SD)	N	Mean (SD)
Previous delgocitinib cream	541	3.0 (2.9)	441	2.1 (2.4)
IGA-CHE TS at DELTA 3 baseline	136	1.2 (1.9)	119	1.4 (2.1)
IGA-CHE ≥ 2 at DELTA 3 baseline	405	3.6 (2.9)	322	2.4 (2.5)
Previous cream vehicle	233	4.4 (2.9)	175	2.7 (2.8)
IGA-CHE TS at DELTA 3 baseline	20	1.8 (2.4)	17	1.7 (2.6)
IGA-CHE ≥ 2 at DELTA 3 baseline	213	4.7 (2.9)	158	2.8 (2.9)
Overall population	774	3.4 (3.0)	616	2.3 (2.6)

HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; SD, standard deviation; TS, treatment success. Source: DELTA 3 CSR [89].

2.6.7 DELTA 3 patient-reported outcomes

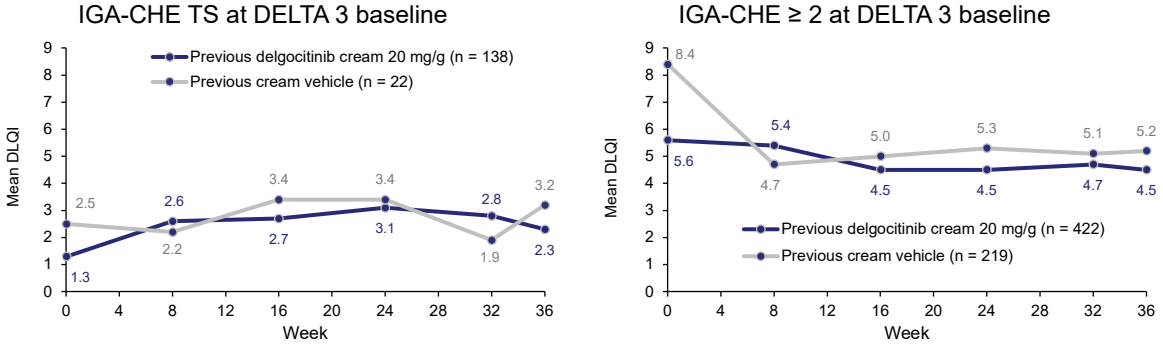
2.6.7.1 DLQI

In the overall study population, mean DLQI improved during DELTA 3

Across all patients in DELTA 3, the mean (SD) DLQI decreased (improved) from 5.5 (5.7) at baseline to 4.2 (4.7) at week 36 (data not shown) [89].

Mean DLQI scores over time are shown in Figure 21. From baseline to week 8, mean DLQI increased (worsened) among patients treated with delgocitinib cream in DELTA 1 and DELTA 2 who were off-treatment (i.e., who had IGA-CHE TS at DELTA 3 baseline; this increase in mean DLQI is consistent with the loss of IGA-CHE TS for some patients during this period, as described above). In the same period, mean DLQI decreased (improved) in both groups of patients using delgocitinib cream (i.e., those who did not have IGA-CHE TS at the end of DELTA 1 and DELTA 2). From week 8 onward, mean DLQI was generally stable in all groups [89].

Figure 21 Mean DLQI to week 36 in DELTA 3, by baseline response and parent trial treatment



DLQI, Dermatology Life Quality Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Source: DELTA 3 CSR [89].

2.6.7.2 EQ-5D-3L and EQ VAS

In the overall study population, mean EQ-5D-3L index and EQ VAS increased slightly from baseline to week 36 in DELTA 3

EQ-5D-5L data were cross-walked to the EQ-5D-3L in accordance with NICE recommendations [102], as described in section 2.3.1.7, Table 6. Mean EQ-5D-3L index and EQ VAS scores in DELTA 3 are shown in Table 22; for both measures, scores increased (improved) slightly from baseline to week 36 in the overall trial population. Mean EQ-5D-3L index decreased among patients starting the trial off-treatment (i.e., with IGA-CHE TS at DELTA 3 baseline), regardless of treatment in the parent trial. In addition, mean EQ VAS decreased (worsened) among patients who received delgocitinib cream in the parent trial and started DELTA 3 off-treatment (i.e., with IGA-CHE TS at DELTA 3 baseline). Patients starting DELTA 3 on-treatment had increases in both mean EQ-5D-3L index and mean EQ VAS during the study, regardless of treatment in the parent trial (Table 22) [89].

Table 22 Mean EQ-5D-3L index and EQ VAS at baseline and week 36 in DELTA 3, by parent trial treatment and baseline IGA-CHE TS

Parent trial treatment	Previous delgocitinib cream 20 mg/g		Previous vehicle		Total (n = 801)
IGA-CHE at DELTA 3 baseline	IGA-CHE 0/1 (n = 138)	IGA-CHE ≥ 2 (n = 422)	IGA-CHE 0/1 (n = 22)	IGA-CHE ≥ 2 (n = 219)	
EQ-5D-3L index					
Baseline, mean (SD)	0.94 (0.10)	0.80 (0.18)	0.90 (0.16)	0.72 (0.20)	0.80 (0.19)
Week 36, mean (SD)	0.91 (0.13)	0.84 (0.17)	0.86 (0.29)	0.80 (0.20)	0.84 (0.18)
EQ VAS					
Baseline, mean (SD)	86.2 (11.6)	78.9 (16.3)	82.4 (13.6)	74.3 (18.2)	79.0 (16.5)
Week 36, mean (SD)	84.9 (12.0)	80.9 (15.6)	84.7 (13.4)	79.8 (16.9)	81.5 (15.4)

EQ-5D-5L data were cross-walked to the EQ-5D-3L, as described in section 2.3.1.7, Table 6.
EQ, EuroQol; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; SD, standard deviation; VAS, visual analogue scale. Source: DELTA 3 CSR [89].

2.6.7.3 HEIS

In the overall study population, mean HEIS total and PDAL scores improved from baseline to week 36 in DELTA 3

Mean HEIS total and PDAL scores in DELTA 3 are shown in Table 23. In the overall population, mean scores decreased (improved) between baseline and week 36. Increases (worsening) were seen for patients starting DELTA 3 off-treatment (i.e., with IGA-CHE TS at DELTA 3 baseline). By contrast, mean HEIS total and PDAL scores improved among patients starting DELTA 3 on-treatment (i.e., who did not have IGA-CHE TS at DELTA 3 baseline), regardless of treatment in the parent trial [89].

Table 23 Mean HEIS total and PDAL scores at baseline and week 36 in DELTA 3, by parent trial treatment and baseline IGA-CHE TS

Parent trial treatment	Previous delgocitinib cream 20 mg/g		Previous vehicle		Total (n = 801)
IGA-CHE at DELTA 3 baseline	IGA-CHE 0/1 (n = 138)	IGA-CHE ≥ 2 (n = 422)	IGA-CHE 0/1 (n = 22)	IGA-CHE ≥ 2 (n = 219)	
HEIS total score					
Baseline, mean (SD)	0.23 (0.32)	1.11 (0.90)	0.67 (0.95)	1.61 (1.04)	1.08 (0.99)
Week 36, mean (SD)	0.48 (0.63)	0.93 (0.84)	0.67 (1.10)	1.05 (1.00)	0.87 (0.88)
HEIS PDAL score					
Baseline, mean (SD)	0.3 (0.5)	1.2 (1.0)	0.7 (1.0)	1.7 (1.1)	1.2 (1.1)
Week 36, mean (SD)	0.6 (0.7)	1.0 (1.0)	0.8 (1.1)	1.1 (1.1)	0.9 (1.0)

HEIS, Hand Eczema Impact Scale; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PDAL, proximal daily activity limitations; SD, standard deviation. Source: DELTA 3 CSR [89].

2.6.8 DELTA 3 on- and off-treatment periods

Patients who had an IGA-CHE TS response at the start of DELTA 3 spent a larger proportion of the trial period with a response than those with IGA-CHE ≥ 2 at the start of the trial

The proportion and total number of days with IGA-CHE TS in DELTA 3 by parent trial treatment and IGA-CHE TS at DELTA 3 baseline are shown in Table 24 [89]. Among patients treated with delgocitinib cream in DELTA 1 and DELTA 2, those who started DELTA 3 with a treatment response (and therefore off-treatment) had a response for a mean of 46% of days during DELTA 3, compared with 10% of days for those who started the trial on-treatment and with IGA-CHE ≥ 2 [89].

Table 24 Proportion and number of days in response in DELTA 3, by parent trial treatment and baseline IGA-CHE TS

Parent trial treatment	Previous delgocitinib cream 20 mg/g		Previous vehicle		Total (n = 799)
IGA-CHE at DELTA 3 baseline	IGA-CHE 0/1 (n = 138)	IGA-CHE ≥ 2 (n = 421)	IGA-CHE 0/1 (n = 22)	IGA-CHE ≥ 2 (n = 218)	
Proportion of days in response					
Mean (SD) proportion of days	46.45% (29.61%)	9.87% (17.72%)	59.15% (33.30%)	12.13% (18.03%)	18.16% (25.78%)
Median (Q1–Q3) proportion of days	43.50% (21.70–66.00%)	0.00% (0.00–11.10%)	53.15% (33.20–100.00%)	0.00% (0.00–21.10%)	4.30% (0.00–31.60%)
Min–max proportion of days	3.9–100.0%	0.0–88.2%	10.7–100.0%	0.0–88.5%	0.0–100.0%
Number of days in response					
Mean (SD) number of days	111.3 (72.0)	24.9 (44.9)	136.3 (80.7)	30.0 (44.8)	44.3 (62.7)
Median (Q1–Q3) number of days	110 (52–155)	0 (0–28)	121 (83–216)	0 (0–52)	10 (0–80)
Min–max number of days	7–259	0–217	27–274	0–224	0–274

Proportion of days in response is calculated as number of days in response (i.e. IGA-CHE score of 0 or 1) divided by total number of days in the treatment period.
IGA-CHE, Investigator's Global Assessment for chronic hand eczema; Q, quartile; SD, standard deviation. Source: DELTA 3 CSR [89].

Among patients treated with delgocitinib cream in DELTA 1 and DELTA 2, those who had an IGA-CHE TS response at the start of DELTA 3 had shorter on-treatment periods during the trial than those who did not

The number and duration of on-treatment periods in DELTA 3 were similar for patients who were treated with delgocitinib cream in the parent trials and for those who received cream vehicle (Table 25) [89]. Overall, patients had a mean of 1.5 (median, 1) periods on-treatment, with each on-treatment period lasting a mean of 121.5 (median, 86) days [89].

Patients who had an IGA-CHE TS response at the start of the DELTA 3 trial had a similar number of on-treatment periods to those who did not. However, on-treatment periods were on average shorter among those with IGA-CHE TS at DELTA 3 baseline, compared with those without IGA-CHE TS at baseline (Table 25) [89].

Table 25 Number and duration of on-treatment periods in DELTA 3, by parent trial treatment and baseline IGA-CHE TS

Parent trial treatment	Previous delgocitinib cream 20 mg/g		Previous vehicle		Total (n = 801)
IGA-CHE at DELTA 3 baseline	IGA-CHE 0/1 (n = 138)	IGA-CHE ≥ 2 (n = 422)	IGA-CHE 0/1 (n = 22)	IGA-CHE ≥ 2 (n = 219)	
Number of on-treatment days					
n [a]	138	422	22	219	801
Mean (SD)	132.8 (74.7)	203.5 (68.0)	104.3 (85.4)	193.4 (69.5)	185.8 (75.8)
Median (Q1–Q3)	140.5 (86–197)	242.5 (159–253)	118.5 (0–169)	222 (148–253)	220 (134–253)
Min–max	0–249	27–275	0–226	1–265	0–275
Number of on-treatment periods					
n [a]	138	422	22	219	801
Mean (SD)	1.7 (1.1)	1.5 (0.8)	1.4 (1.2)	1.6 (0.9)	1.5 (0.9)
Median (Q1–Q3)	2 (1–2)	1 (1–2)	1 (0–2)	1 (1–2)	1 (1–2)
Min–max	0–6	1–6	0–4	1–4	0–6
Rate per 100 PYO	125.4	150.3	104.5	153.9	145.4
Duration of on-treatment periods (days)					
n [b]	238	612	31	344	1225
Mean (SD)	77.0 (64.0)	140.3 (92.0)	74.0 (62.1)	123.1 (88.4)	121.5 (89.0)
Median (Q1–Q3)	57 (29–97)	114 (57–253)	56 (29–88)	92 (41–229.5)	86 (36–226)
Min–max	3–249	7–275	20–226	1–265	1–275

An on-treatment day is defined as a day in an on-treatment period. An on-treatment period is defined from the day treatment is (re-)initiated (IGA-CHE score ≥ 2) to the day treatment is stopped (IGA-CHE score of 0 or 1). For patients continuing treatment from the parent trial, the start of the on-treatment period is the day of baseline.

[a] Number of patients with observations.

[b] Number of on-treatment periods.

IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PYO, patient years of observation; Q, quartile; SD, standard deviation. Source: DELTA 3 CSR [89].

2.6.9 DELTA FORCE clinical endpoints

2.6.9.1 Mean change in HECSI

Delgocitinib cream was statistically superior to oral alitretinoin capsules for the primary endpoint, change in HECSI score from baseline to week 12

The mean change in HECSI from baseline to week 12 was the primary endpoint of DELTA FORCE [90]. Patients treated with delgocitinib cream had statistically significantly larger mean reductions (improvements) in HECSI, compared with the oral alitretinoin group (−67.6

vs −51.5; $p < 0.001$; Table 26) [90, 95]. Statistically significant results were also seen at week 24 (−69.6 vs −45.1; $p < 0.001$) [90, 95].

Table 26 Mean improvement in HECSI from baseline to week 12 and week 24 in DELTA FORCE

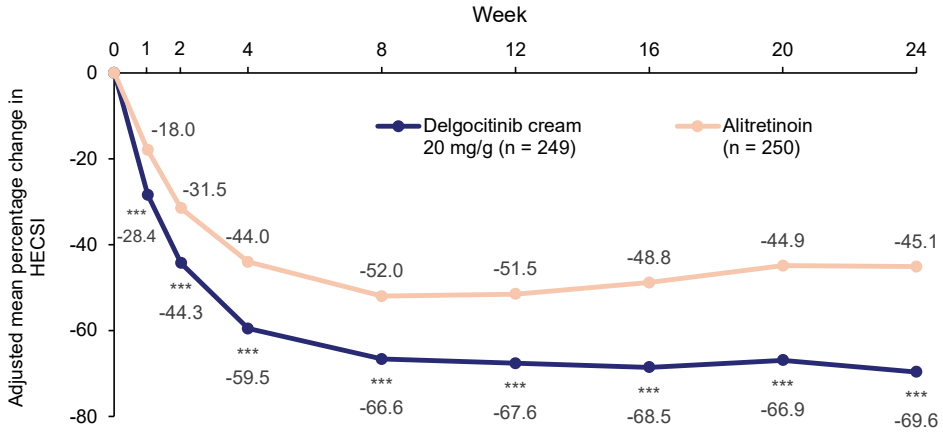
	Delgocitinib cream 20 mg/g (n = 249)	Alitretinoin (n = 250)
Week 12		
Adjusted mean change in HECSI (SE)	−67.6 (3.37)	−51.5 (3.36)
Mean difference (95% CI)	−16.1 (−23.28, −8.86)	
p value	< 0.001	
Week 24		
Adjusted mean change in HECSI (SE)	−69.6 (3.78)	−45.1 (3.77)
Mean difference (95% CI)	−24.5 (−32.55, −16.36)	
p value	< 0.001	

Mean differences: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline HECSI. ANCOVA, analysis of covariance; CI, confidence interval; HECSI, *Hand Eczema Severity Index*; SE, standard error. Source: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

Improvements in HECSI were statistically significantly larger with delgocitinib cream than with oral alitretinoin capsules already from week 1, with the difference between groups increasing during the study

As shown in Figure 22, the percentage reduction (improvement) in mean HECSI was statistically significantly larger among patients treated with delgocitinib cream, compared with the oral alitretinoin group, at week 1 (−28.4 vs −18.0; $p < 0.001$). A statistically significant difference between treatment groups was maintained up to week 24, with the magnitude of the difference generally increasing during the study period [90].

Figure 22 Mean change in HECSI from baseline to week 24 in DELTA FORCE



*** $p < 0.001$. HECSI, Hand Eczema Severity Index. Source: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

2.6.9.2 HECSI-90

Patients treated with delgocitinib cream were statistically significantly more likely than those receiving alitretinoin to achieve HECSI-90 at week 12

Statistically significantly more patients achieved HECSI-90 at week 12 in the delgocitinib cream group than in the alitretinoin group (38.6% vs 26.0%; $p = 0.003$; Table 27); in addition,

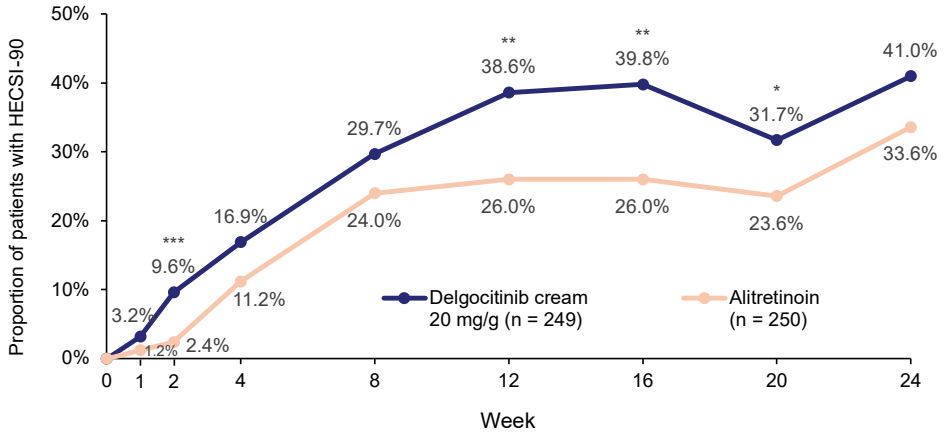
HECSI-90 responder rates were higher with delgocitinib cream than with alitretinoin at all study visits (Figure 23) [90, 95].

Table 27 Proportion of patients with HECSI-90 at week 12 in DELTA FORCE

	Delgocitinib cream 20 mg/g (n = 249)	Alitretinoin (n = 250)
HECSI-90		
Proportion of patients with response, n (%)	96 (38.6)	65 (26.0)
Mean difference in % (95% CI)	12.6 (4.34–20.78)	
p value	0.0027	

CI, confidence interval; HECSI, Hand Eczema Severity Index.
Sources: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

Figure 23 Proportion of patients with HECSI-90 to week 24 in DELTA FORCE



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. HECSI, *Hand Eczema Severity Index*. Sources: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

The HECSI-90 AUC analysis statistically significantly favoured delgocitinib cream over alitretinoin

As shown in Table 28, the mean AUC of HECSI-90 from baseline to week 24 was statistically significantly higher with delgocitinib cream than with alitretinoin [90, 95].

Table 28 HECSI-90 AUC to week 24 in DELTA FORCE

HECSI-90 AUC	Delgocitinib cream 20 mg/g (n = 249)	Alitretinoin (n = 250)
Adjusted mean AUC (SE)	49.2 (4.04)	34.9 (4.03)
Mean difference (95% CI)	14.3 (5.81–22.86)	
p value	< 0.001	

Mean difference: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline HECSI.
ANCOVA, analysis of covariance; AUC, area under the curve; CI, confidence interval; HECSI, Hand Eczema Severity Index; SE, standard error. Sources: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

The results of a *post hoc* analysis of HECSI-50 and HECSI-75 responses are shown in Appendix B.7.1, Table 158.

2.6.9.3 IGA-CHE TS

Statistically significantly more patients achieved IGA-CHE TS at week 12 with delgocitinib cream than with alitretinoin

In DELTA 1 and DELTA 2, achieving IGA-CHE TS required an improvement from baseline of ≥ 2 points (see section 2.6.2.1). However, because all participants in DELTA FORCE were required to have an IGA-CHE score of 4 at baseline, IGA-CHE TS in DELTA FORCE represents an improvement from baseline of ≥ 3 points. The IGA-CHE validation study (see Company evidence submission: Delgocitinib for the treatment of moderate to severe chronic hand eczema in adults

Appendix B.6.1) found that a 1-level change can reflect a clinically meaningful improvement for patients [94]. Therefore, the ≥ 3-level change required for IGA-CHE TS in DELTA FORCE represents a substantial improvement in patients' disease.

In DELTA FORCE, statistically significantly more patients treated with delgocitinib cream achieved IGA-CHE TS at week 12, compared with those receiving oral alitretinoin (27.2% vs 16.6%; *p* = 0.004; Table 29) [90, 95]. A similar difference between groups was seen at week 24.

Table 29 Proportion of patients with IGA-CHE TS at week 12 and week 24 in DELTA FORCE

IGA-CHE TS	Delgocitinib cream 20 mg/g (n = 250)	Alitretinoin (n = 253)
Week 12		
Number of patients with response	68	42
% (95% CI) of patients with response	27.2 (22.1–33.0)	16.6 (12.5–21.7)
Difference in % (95% CI)	10.6 (3.31–17.87)	
p value	0.004	
Week 24		
Number of patients with response	77	54
% (95% CI) of patients with response	30.8 (25.4–36.8)	21.3 (16.7–26.8)
Difference in % (95% CI)	9.4 (1.8–17.1)	
p value	0.016	

CI, confidence interval; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success. Sources: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95].

2.6.9.4 Time to IGA-CHE TS response

The cumulative incidence of IGA-CHE TS was higher among patients treated with delgocitinib cream than in the oral alitretinoin group

The median time to IGA-CHE TS was [redacted] in the delgocitinib cream 20 mg/g group and [redacted] (Table 30) [90]. The 25th percentile time to IGA-CHE TS was [redacted] in the delgocitinib cream group and [redacted] in the oral alitretinoin group [90].

The cumulative incidence of IGA-CHE TS was [redacted] (Table 30) [90].

Table 30 Cumulative incidence of IGA-CHE TS to week 12 and week 24 in DELTA FORCE

IGA-CHE TS	Delgocitinib cream 20 mg/g (n = 250)	Alitretinoin (n = 253)
Week 12		
Cumulative number of events	[redacted]	[redacted]
Number of patients at risk	[redacted]	[redacted]
Estimated cumulative incidence, % (95% CI)	[redacted]	[redacted]
Week 24		
Cumulative number of events	[redacted]	[redacted]
Number of patients at risk	[redacted]	[redacted]
Estimated cumulative incidence, % (95% CI)	[redacted]	[redacted]
Time to event		
25th percentile, weeks (95% CI)	[redacted]	[redacted]
Median, weeks (95% CI)	[redacted]	[redacted]

CI, confidence interval; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; NA, not applicable; TS, treatment success.
Sources: DELTA FORCE CSR [90].

2.6.9.5 Loss of IGA-CHE TS response while off-treatment

Among DELTA FORCE patients who discontinued treatment after achieving IGA-CHE TS, approximately [redacted] had lost their IGA-CHE TS response at week 24

Patients in DELTA FORCE discontinued if they had an IGA-CHE TS response at or after week 16 (delgocitinib cream) or week 12 (oral alitretinoin) [90]. A total of [redacted] patients using delgocitinib cream and [redacted] of those treated with oral alitretinoin discontinued their treatment due to an IGA-CHE TS response. Of these, [redacted] of those in the delgocitinib cream and oral alitretinoin arms, respectively, had restarted their treatment by week 24 due to a loss of response (Appendix B.3, Table 148) [90].

2.6.10 DELTA FORCE daily diary endpoints

2.6.10.1 HESD itch score

Patients treated with delgocitinib cream had statistically significantly larger mean improvements in itch than those receiving alitretinoin

Mean reductions (improvements) from baseline in HESD itch score in DELTA FORCE are shown in Table 31. Patients in the delgocitinib cream group had statistically significantly larger reductions in mean itch score at week 12 and week 24, compared with the alitretinoin group [90, 95]. The mean difference between treatment groups was similar at both time points [90].

Table 31 Mean change in HESD itch score from baseline to week 12 in DELTA FORCE

	Delgocitinib cream 20 mg/g (n = 238)	Alitretinoin (n = 238)
Week 12		
Adjusted mean change in weekly average HESD itch score (SE)	−3.0 (0.22)	−2.4 (0.21)
Mean difference (95% CI)	−0.7 (−1.12, −0.20)	
p value	0.005	
Week 24		
Adjusted mean change in weekly average HESD itch score (SE)	−2.7 (0.24)	−1.8 (0.24)
Mean difference (95% CI)	−0.9 (−1.42, −0.39)	
p value	< 0.001	

Mean difference: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline HESD itch score. ANCOVA, analysis of covariance; CI, confidence interval; HESD, Hand Eczema Symptom Diary; SE, standard error. Sources: DELTA FORCE CSR [90]; Giménez-Arnau et al. 2024 [95].

2.6.10.2 HESD pain score

Patients treated with delgocitinib cream had statistically significantly larger mean improvements in pain than those receiving alitretinoin

Mean reductions (improvements) from baseline in HESD pain score in DELTA FORCE are shown in Table 32. Patients in the delgocitinib cream group had statistically significantly larger reductions in mean pain score at week 12 and week 24, compared with the alitretinoin group [90, 95]. The mean difference between treatment groups was similar at both time points [90].

Table 32 Mean change in HESD pain score from baseline to week 12 and week 24 in DELTA FORCE

	Delgocitinib cream 20 mg/g (n = 238)	Alitretinoin (n = 238)
Week 12		
Adjusted mean change in weekly average HESD pain score (SE)	−2.9 (0.23)	−2.3 (0.23)
Mean difference (95% CI)	−0.6 (−1.08, −0.10)	
p value	0.018	
Week 24		
Adjusted mean change in weekly average HESD pain score (SE)	−2.5 (0.26)	−1.6 (0.26)
Mean difference (95% CI)	−0.9 (−1.49, −0.39)	
p value	< 0.001	

Mean difference: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline HESD pain score. ANCOVA, analysis of covariance; CI, confidence interval; HESD, Hand Eczema Symptom Diary; SE, standard error. Sources: DELTA FORCE CSR [90]; Giménez-Arnau et al. 2024 [95].

2.6.11 DELTA FORCE patient-reported endpoints

2.6.11.1 DLQI

Treatment with delgocitinib cream was associated with statistically significantly larger improvements in DLQI, compared with alitretinoin

Mean reductions (improvements) from baseline in DLQI in DELTA FORCE are shown in Table 33. Patients in the delgocitinib cream group had statistically significantly larger reductions in DLQI at week 12 and week 24, compared with the alitretinoin group (both $p < 0.001$) [90]. A larger difference between treatment groups was seen at week 24 than at week 12 (week 12, −1.8; week 24, −2.5) [90].

Table 33 Mean change in DLQI from baseline to week 12 and week 24 in DELTA FORCE

	Delgocitinib cream 20 mg/g (n = 230)	Alitretinoin (n = 236)
Week 12		
Adjusted mean change in DLQI (SE)	−7.5 (0.48)	−5.8 (0.48)
Mean difference (95% CI)	−1.8 (−2.80, −0.74)	
p value	< 0.001	
Week 24		
Adjusted mean change in DLQI (SE)	−7.1 (0.54)	−4.6 (0.54)
Mean difference (95% CI)	−2.5 (−3.69, −1.38)	
p value	< 0.001	

Mean difference: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline DLQI. ANCOVA, analysis of covariance; CI, confidence interval; DLQI, Dermatology Life Quality Index; SE, standard error. Sources: DELTA FORCE CSR [90].

The DLQI AUC analysis statistically significantly favoured delgocitinib cream over alitretinoin

As shown in Table 34, the mean AUC of the change from baseline in DLQI up to week 24 was statistically significantly higher with delgocitinib cream than with alitretinoin [90, 95].

Table 34 AUC of DLQI change from baseline up to week 24 in DELTA FORCE

AUC of DLQI change from baseline	Delgocitinib cream 20 mg/g (n = 230)	Alitretinoin (n = 236)
Adjusted mean AUC (SE)	1124.7 (61.37)	790.7 (62.67)
Mean difference (95% CI)	334.0 (195.69–472.26)	
p value	< 0.001	

Mean difference: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline DLQI.
ANCOVA, analysis of covariance; AUC, area under the curve; CI, confidence interval; DLQI, *Dermatology Life Quality Index*; SE, standard error. Sources: DELTA FORCE CSR [90]; Giménez-Arnau *et al*. 2024 [95] .

2.6.11.2 EQ-5D-3L and EQ VAS

Patients treated with delgocitinib cream had [redacted] in EQ-5D-3L index and EQ VAS than those receiving alitretinoin

The mean (SD) EQ-5D-3L index at baseline was [redacted] in the DELTA FORCE delgocitinib cream group and [redacted] in the alitretinoin group (EQ-5D-5L data were cross-walked to the EQ-5D-3L, as described in section 2.3.1.7, Table 6) [90].

Compared with alitretinoin, treatment with delgocitinib cream resulted in [redacted] in EQ-5D-3L index from baseline to week 12, and a [redacted] from baseline to week 24 (Table 35) [90].

Similarly, the [redacted] in mean EQ VAS score was [redacted] with delgocitinib cream than with alitretinoin at week 12, with [redacted] seen at week 24 (Table 35) [90].

Table 35 LSM improvement in EQ-5D-3L index and EQ VAS from baseline to weeks 12 and 24 in DELTA FORCE

	Delgocitinib cream 20 mg/g (n = 230)	Alitretinoin (n = 236)
EQ-5D-3L index		
Baseline, mean (SD)	[redacted]	[redacted]
Adjusted mean change to week 12 (SE)	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p value	[redacted]	
Adjusted mean change to week 24 (SE)	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p value	[redacted]	
EQ VAS		
Baseline, mean (SD)	[redacted]	[redacted]
Adjusted mean change to week 12 (SE)	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p value	[redacted]	
Adjusted mean change to week 24 (SE)	[redacted]	[redacted]
Mean difference (95% CI)	[redacted]	
p value	[redacted]	

[a] Nominal *p* values; EQ-5D-3L index and EQ VAS are not included in the DELTA FORCE statistical testing hierarchy (see section 2.4.1.3).
EQ-5D-5L data were cross-walked to the EQ-5D-3L, as described in section 2.3.1.7, Table 6. Missing data were imputed with WOCF. Mean differences: ANCOVA adjusting for hyperkeratotic/non-hyperkeratotic subtype and baseline EQ-5D-5L index/EQ VAS score.
ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; LSM, least squares mean; SE, standard error; VAS, visual analogue scale; WOCF, worst observation carried forward. Source: DELTA FORCE CSR [90].

2.6.12 Additional clinical trial evidence

2.6.12.1 Phase 2b trial

Delgocitinib for the treatment of CHE was investigated in a phase 2b, vehicle-controlled, dose-ranging, RCT. Full results for the phase 2b trial have been published [105]. Participants were adults with at least mild CHE and a recent history of inadequate response or contraindication to TCS. Patients were randomised to delgocitinib cream 1 mg/g, 3 mg/g, 8 mg/g or 20 mg/g BD, or to cream vehicle treatment BD, for 16 weeks [105].

The primary endpoint was IGA-CHE TS, defined as an IGA-CHE score of 0 or 1 with at least a 2-point improvement from baseline (note that the IGA-CHE instrument used in the phase 2b trial is not identical to that used in the DELTA clinical trial programme). Across all randomised groups, 23.6% of patients had mild CHE (IGA-CHE 2). For these patients, achieving IGA-CHE TS required an IGA-CHE score of 0 at week 16 [105].

Key efficacy results for the delgocitinib 20 mg/g group are summarised in Table 36. Patients were significantly more likely to achieve IGA-CHE TS with delgocitinib cream 20 mg/g than with cream vehicle. Delgocitinib-treated patients also had larger decreases (improvements) in HECSI, itch and pain than those receiving cream vehicle [105].

Table 36 Key efficacy results at week 16 in phase 2b trial

Outcome	Delgocitinib 20 mg/g	Cream vehicle
IGA-CHE, n	53	50
Proportion with IGA-CHE TS, %	20 (37.7)	4 (8.0)
Difference, % (95% CI)	29.6 (14.6, 44.7)	
p value	0.0004	
HECSI	47	37
LSM change in HECSI from baseline to week 16 (SE)	−42.0 (3.6)	–26.4 (3.8)
LSM difference (95% CI)	−15.6 (−24.8, −6.4)	
LSM percentage change in HECSI (SE)	−70.5 (10.5)	–41.6 (11.1)
LSM difference in percentage change (95% CI)	−28.9 (−55.4, −2.4)	
Itch and pain NRS scores	42	33
LSM change in weekly average itch NRS score (SE)	−3.2 (0.3)	–1.7 (0.4)
LSM difference (95% CI)	−1.5 (−2.4, −0.6)	
LSM change in weekly average pain NRS score (SE)	−3.2 (0.3)	–1.4 (0.3)
LSM difference (95% CI)	−1.8 (−2.7, −0.9)	

CI, confidence interval; HECSI, *Hand Eczema Severity Index*; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LSM, least squares mean; NRS, numerical rating scale; SE, standard error; TS, treatment success. Source: Worm *et al.* 2022 [105].

2.7 Subsequent treatments used in the relevant studies

In the DELTA clinical trials, patients were considered to be non-responders after initiation of rescue medication (most commonly TCS). Use of rescue medication is shown in Appendix B.7.2, Table 159. No data were collected as to subsequent treatments used by patients after the trial period.

2.8 Subgroup analysis

2.8.1 Subgroup analyses conducted

For DELTA 1 and DELTA 2, key trial outcomes were analysed for patients with moderate CHE (IGA-CHE score of 3) or severe CHE (IGA-CHE score of 4) at baseline.

Additional subgroup analyses were conducted for DELTA 1 and DELTA 2, as well as DELTA FORCE, for CHE aetiological subtype (i.e., atopic vs non-atopic and contact vs non-contact) and history of TCI use. All DELTA 1 and DELTA 2 subgroup analyses were conducted using the pooled population of the two trials.

For DELTA 3, subgroup analyses were performed for severity of CHE at baseline of the parent trial (i.e., DELTA 1 and DELTA 2) for loss of IGA-CHE 0/1 response, incidence of IGA-CHE 0/1 following first treatment re-initiation, IGA-CHE TS, and HECSI-90.

Subgroup analysis results are included in this submission for IGA-CHE TS, HECSI-75, and HECSI-90.

2.8.2 Subgroup analysis results

Subgroup analysis results by condition severity at baseline are presented in full below for DELTA 1 and DELTA 2. For DELTA 3, results for subgroup analysis by condition severity at baseline of the parent trial are summarised below and presented in full in Appendix C. Subgroup analysis results for aetiological subtypes (atopic vs non-atopic CHE; contact vs non-contact CHE) and by history of TCI use (DELTA 1, DELTA 2, DELTA FORCE) are summarised below and are presented in full in Appendix C.

2.8.2.1 DELTA 1 and DELTA 2

Patients with moderate or severe CHE

Delgocitinib cream was [redacted] (Table 37) and [redacted] (Table 38) [79].

Table 37 Proportion of patients with IGA-CHE TS, HECSI-75 and HECSI-90 at week 12 in DELTA 1 and DELTA 2 (pooled data), by disease severity at baseline

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (n = 456)	Cream vehicle (n = 230)	Delgocitinib cream 20 mg/g (n = 182)	Cream vehicle (n = 91)
IGA-CHE TS				
Proportion of patients with response, n (%)	[redacted]	[redacted]	XXXXXX	XXXXXX
Mean difference in % (95% CI)	[redacted]		XXXXXXXXXXX	
p value	[redacted]		XXXXXX	
HECSI-75				
Proportion of patients with response, n (%)	[redacted]	[redacted]	XXXXXX	XXXXXX
Mean difference in % (95% CI)	[redacted]		XXXXXXXXXXXX	
p value	[redacted]		XXXXXX	
HECSI-90				
Proportion of patients with response, n (%)	[redacted]	[redacted]	XXXXXX	XXXXXX
Mean difference in % (95% CI)	[redacted]		XXXXXXXXXXXX	
p value	[redacted]		XXXXXX	

Mean differences: Cochran-Mantel-Haenszel analysis stratified by region. CI, confidence interval; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success (i.e., an IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline).
Source: Statistical appendix, Tables 1.4.272.4, 1.4.280.4 and 1.4.284.4 [79].

Table 38 Proportion of patients with IGA-CHE TS, HECSI-75 and HECSI-90 at week 16 in DELTA 1 and DELTA 2 (pooled data), by disease severity at baseline

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (n = 456)	Cream vehicle (n = 230)	Delgocitinib cream 20 mg/g (n = 182)	Cream vehicle (n = 91)
IGA-CHE TS				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HECSI-75				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HECSI-90				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	

Mean differences: Cochran-Mantel-Haenszel analysis stratified by region. CI, confidence interval; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success (i.e., an IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline).
Source: Statistical appendix, Tables 1.4.207.4, 1.4.205.4 and 1.4.206.4 [79].

Atopic vs non-atopic CHE

As shown in Appendix C, Table 165 and Table 166, delgocitinib was [redacted] in all efficacy outcomes measured (IGA-CHE, HECSI-75, and HECSI-90) at week 12 and week 16 [79, 81, 106].

Contact vs non-contact CHE

As shown in Appendix C, Table 167, delgocitinib was [redacted] in all efficacy outcomes measured (IGA-CHE, HECSI-75, and HECSI-90) at week 16 [79, 81].

Previous use vs no previous use of TCI

As shown in Appendix C, Table 172 and Table 173, delgocitinib was [redacted] in all efficacy outcomes measured (IGA-CHE, HECSI-75, and HECSI-90) at week 12 and week 16 [79].

2.8.2.2 DELTA 3

DELTA 3 subgroup analyses results for severity of the condition at baseline of the parent trial (i.e., patients with moderate or patients with severe CHE at baseline of DELTA 1 and DELTA 2) and response status at baseline of DELTA 3 (i.e., patients with IGA-CHE 0/1 or patients with IGA-CHE ≥ 2) are shown in Appendix C, Tables 175–178. By the end of treatment in DELTA 3, [redacted] (Table 176) [79]. Likewise, the proportion of patients achieving IGA-CHE TS and HECSI-90 [redacted] (Table 177, Table 178) [79].

2.8.2.3 DELTA FORCE

Atopic vs non-atopic CHE

As shown in Appendix C, Table 168, at week 12 results were [redacted], with a [redacted] (IGA-CHE, HECSI-75, and HECSI-90) [79, 80]. Week 24 data show a similar response (Appendix C, Table 169). This highlights [redacted].

Contact vs non-contact CHE

As shown in Appendix C, Table 170, at week 12 results were [redacted], with a [redacted] (IGA-CHE, HECSI-75, and HECSI-90) [80]. Week 24 data show a similar response (Appendix C, Table 171).

Previous use vs no previous use of TCI

As shown in Appendix C, Table 174, at week 12 results were [redacted], with a [redacted] (IGA-CHE, HECSI-75, and HECSI-90) [79].

2.9 Meta-analysis

An NMA was conducted to assess the relative efficacy of delgocitinib, alitretinoin and PUVA, as described in section 2.10. Further, the relative efficacy of delgocitinib and cream vehicle was assessed to inform the efficacy of BSC in the economic model. In addition, discontinuation due to AEs was investigated in the NMA described in section 2.11.7.

2.10 Indirect and mixed treatment comparisons

2.10.1 Overview of network meta-analysis

Full details of the methodology for the NMA and for the SLR and feasibility assessment that were used to identify studies for inclusion in the evidence network are reported in Appendix B.2.

Efficacy outcomes that were assessed included IGA-CHE/PGA 0/1 endpoint response (i.e., the proportion of patients who had achieved a response at a specific timepoint), IGA-CHE 0/1 cumulative response (i.e., the proportion of patients who had ever achieved a response throughout the assessment period), and HECSI-90 (≥ 90% improvement in HECSI from baseline) endpoint response. Several primary and sensitivity analyses were conducted for each outcome of interest.

2.10.2 Evidence included in network meta-analysis

As described in Appendix D.1.2, evidence networks could be constructed using the four delgocitinib clinical trials [87, 88, 90, 105], the ALPHA trial [54] of oral alitretinoin versus immersion PUVA and the BACH [107] and HANDEL [108] trials of oral alitretinoin vs placebo pill (Table 39). Most trials compared an active treatment with cream vehicle or placebo pill; those two inactive comparators were combined into a single node and used to inform the efficacy of the best supportive care (BSC) health state in the economic model (section 3.2.2).

Table 39 Trials included in network meta-analysis

Trial	Comparators
DELTA 1 [87]	Delgocitinib cream vs cream vehicle
DELTA 2 [88]	
Worm 2022 [105]	
DELTA FORCE [90]	Delgocitinib cream vs oral alitretinoin
ALPHA [54]	Oral alitretinoin vs immersion PUVA
BACH [107]	Oral alitretinoin vs placebo pill
HANDEL [108]	

PUVA, psoralen–UV A phototherapy.

2.10.3 Network meta-analyses conducted

Some heterogeneity was observed across the included trials, as described in section 2.10.5 and in Appendix B.2. To explore the impact of heterogeneity across trials in terms of disease severity and timepoint, sensitivity analyses were conducted (Table 40).

Table 40 Overview of network meta-analyses conducted for efficacy outcomes

Analysis	Description
Primary endpoint analysis (week 16 in DELTA 1, DELTA 2 and Worm 2022 trials, week 12 in other studies)	
Primary endpoint analysis	All patients at primary endpoint regardless of moderate or severe disease at baseline, including results reported at weeks 12 and 16
Sensitivity analysis 1 (severe CHE) [a]	Patients with severe CHE at baseline, including results reported at weeks 12 and 16
Sensitivity analysis 2 (moderate CHE) [a,b]	Patients with moderate CHE at baseline, including results reported at weeks 12 and 16
Week 12 analysis (week 12 in delgocitinib trials, week 12 in other studies)	
Week 12 analysis	All patients regardless of moderate or severe disease at baseline, results reported at week 12
Sensitivity analysis 1 (severe CHE) [a]	Patients with severe CHE at baseline, results reported at week 12
Sensitivity analysis 2 (moderate CHE) [a,b]	Patients with moderate CHE at baseline, results reported at week 12

[a] Although subgroup data from Worm *et al.* 2022 could have been generated to feed into these analysis, patient numbers were very small so use of the overall moderate to severe CHE population is likely to be considered to be more reliable.

[b] When moderate-only and severe-only subgroups were reported, the moderate-only patient subgroups were prioritised in sensitivity analysis 2. However, the trials that only included data on severe CHE were still included in this sensitivity analysis, even if no moderate CHE data were reported.

Analysis timepoints

Efficacy analyses focused on two groups of endpoints. In the first analysis, efficacy outcomes evaluated at the primary endpoint from all studies were compared – this was week 16 in DELTA 1, DELTA 2 and the phase 2 delgocitinib trial (Worm *et al.* 2022), and week 12 in all other studies. In the second analysis, efficacy outcomes reported at week 12 from DELTA 1, DELTA 2 and Worm *et al.* 2022 were compared with efficacy outcomes at the primary endpoint (week 12) from all other studies (Table 40).

An additional analysis was performed for IGA-CHE/PGA 0/1 cumulative response which included studies reporting data at the week 24 endpoint only. This analysis included all patients for whom outcome data were reported at week 24, regardless of disease severity.

CHE severity

The primary endpoint analysis included all patients for whom outcome data were reported, including both patients with moderate CHE and those with severe CHE. However, the majority of studies included only patients with severe CHE according to the IGA-CHE or PGA scale. For delgocitinib, trial evidence was available for patients with moderate or severe CHE. Multiple analyses based on the same network of evidence for each outcome were conducted to explore the impact of CHE severity on comparative effects. In two sensitivity analyses, moderate or severe CHE subgroup data from DELTA 1 and DELTA 2 were combined with the evidence from other studies (Table 40).

Comparisons of IGA-CHE and PGA

Three different scales were used across the studies included in the NMAs to assess the proportion of patients achieving clear or almost clear skin. IGA-CHE was used in the DELTA trials, an earlier version of IGA-CHE was used in the phase 2 delgocitinib trial and PGA was used in the phase 3 alitretinoin trials and ALPHA. Differences between these scales are described in section 1.3.1.5 and are considered a potential source of heterogeneity in the

comparison. While there are inherent differences between the PGA and IGA-CHE scales, such as PGA considering patient-reported itch and pain and the IGA-CHE score of 1 being stricter than a PGA score of 1 (barely perceptible erythema), for the purpose of estimating the relative efficacy of PUVA and delgocitinib in an NMA involving DELTA FORCE and ALPHA, it was assumed that the achievement of a 0 or 1 on any of these scales could be considered broadly comparable. As a result of this assumption, the comparison is conducted with a disadvantage to delgocitinib.

Endpoint response and cumulative response

Another key source of outcome heterogeneity is related to the way the IGA-CHE/PGA outcomes were reported across the studies. The majority of studies reported the proportion of patients with a score of 0 or 1 at the trial endpoint (hereafter referred to as endpoint response). However, a subset of studies reported the outcome in terms of time to first response or the proportion of patients with a score of 0 or 1 by the trial endpoint (hereafter referred to as cumulative response). These two methods of estimating response were considered too dissimilar to combine in a single analysis; therefore, for the IGA-CHE/PGA 0/1 outcome, both the endpoint response and cumulative response datasets were analysed separately. The endpoint response included IGA-CHE/PGA data collected at the specific endpoint being assessed, whereas the cumulative response included all IGA-CHE/PGA data collected up to the specific endpoint being assessed (for the delgocitinib trials, cumulative response data were calculated post hoc in order to conduct this NMA).

2.10.4 Network meta-analysis results

2.10.4.1 Model selection

The model selection process is described in detail in Appendix B.2.7. For all analyses, the fixed-effects models were selected due to the imprecise treatment effect estimates generated by the random-effects models. NMA results using random-effects models are shown in Appendix B.2.9.2, Tables 141–144.

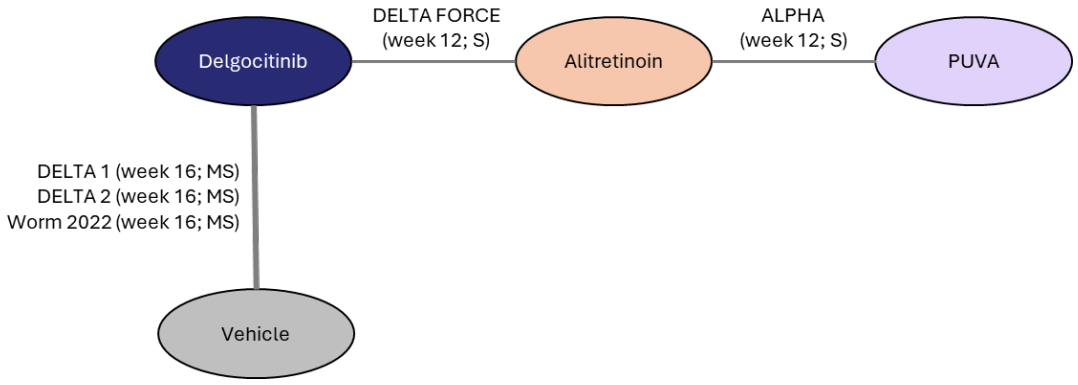
2.10.4.2 IGA-CHE/PGA 0/1 endpoint response

Evidence network

The evidence network for the IGA-CHE/PGA 0/1 primary endpoint response analysis (week 16 or week 12) is shown in Figure 24, and includes the delgocitinib clinical trials and the ALPHA trial. HANDEL could not be included in the network as data were reported only at week 24.

Week 16 data for patients with moderate to severe CHE in DELTA 1, DELTA 2 and Worm et al. 2022 were compared with week 12 data for patients with severe CHE in the other trials. The week 12 analyses used week 12 data from DELTA 1, DELTA 2 and Worm et al. 2022. CHE severity sensitivity analyses used data from the corresponding moderate or severe CHE subgroups in DELTA 1 and DELTA 2, compared with the overall trial populations in the other trials. Sensitivity analysis networks are shown in Appendix B.2.8, Figure 33.

Figure 24 Evidence network for IGA-CHE/PGA 0/1 primary endpoint response analysis



MS, moderate to severe; PUVA, psoralen–UV A phototherapy; S, severe.

Network meta-analysis results

The results of the IGA-CHE/PGA 0/1 primary endpoint response NMAs are shown in Table 41. The odds ratios are used in the economic model to inform the the efficacy of delgocitinib and alitretinoin in severe CHE and of delgocitinib and PUVA in moderate CHE and severe CHE, respectively. Further, the treatment effects of delgocitinib versus vehicle cream are used to inform the efficacy of BSC in moderate and severe CHE.

Table 41 IGA-CHE/PGA 0/1 endpoint response – delgocitinib vs all treatments (fixed effects model)

Delgocitinib vs treatment	Primary endpoint analysis [a]			Week 12 analysis [b]		
	All patients	Severe CHE	Moderate CHE	All patients	Severe CHE	Moderate CHE
Median odds ratio (95% CrI)						
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median risk ratio (95% CrI)						
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Primary endpoint analysis includes primary endpoint for all relevant studies.

[b] Week 12 analysis includes week 12 endpoint for all relevant studies.

Statistically significant odds ratios or risk ratios are shown in **bold**.

CHE, chronic hand eczema; CrI, credible interval; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PGA: Physician Global Assessment; PUVA, psoralen–UV A phototherapy.

Table 42 IGA-CHE/PGA 0/1 cumulative response – delgocitinib vs all treatments (fixed effects model)

Delgocitinib vs treatment	Primary endpoint analysis [a]			Week 12 analysis [b]			Week 24 analysis [c]
	All patients	Severe CHE	Moderate CHE	All patients	Severe CHE	Moderate CHE	All patients
Median odds ratio (95% CrI)							
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median risk ratio (95% CrI)							
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Primary endpoint analysis includes primary endpoint for all relevant studies.

[b] Week 12 analysis includes week 12 endpoint for all relevant studies.

[c] Week 24 analysis includes week 24 endpoint for all relevant studies. Vehicle cream was included in the primary endpoint and week 12 analyses. Placebo pill was included in the week 24 analysis.

CHE, chronic hand eczema; CrI, credible interval; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PGA: Physician Global Assessment.

Compared with PUVA, alitretinoin or cream vehicle, patients treated with delgocitinib cream [redacted] in their respective studies. Similar results were seen in the analysis using week 12 data from DELTA 1, DELTA 2 and Worm et al 2022. In the sensitivity analyses, across moderate CHE and severe CHE, [redacted], where the point estimates for both odds ratios and risk ratios were [redacted].

SUCRA values, shown in Appendix 1.2.9.1, Table 137, indicated that delgocitinib cream was [redacted].

2.10.4.3 IGA-CHE/PGA 0/1 cumulative response

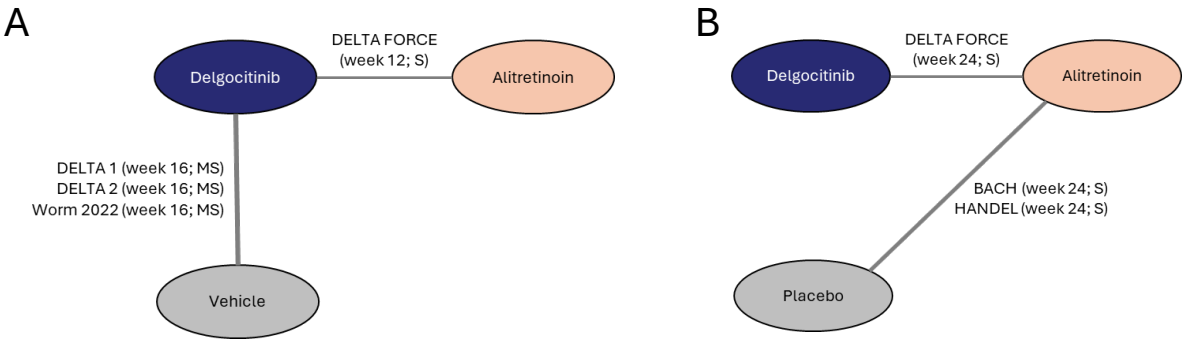
Evidence network

The evidence network for the IGA-CHE/PGA 0/1 primary endpoint analysis of cumulative response (week 16 or week 12) is shown in Figure 25A, and includes the delgocitinib clinical trials. HANDEL and ALPHA could not be included in the primary endpoint network as data were reported only at week 24 and week 52, respectively. BACH reported week 12 cumulative response data but could not be included due to inconsistency (see Appendix B.2.5.3).

Week 16 data for patients with moderate to severe CHE in DELTA 1, DELTA 2 and Worm et al. 2022 were combined with week 12 data for patients with severe CHE in DELTA FORCE. The week 12 analyses used week 12 data from DELTA 1, DELTA 2 and Worm et al. 2022. CHE severity sensitivity analyses used data from the corresponding moderate or severe CHE subgroups in DELTA 1 and DELTA 2, combined with the overall trial populations in DELTA FORCE. Sensitivity analysis networks are shown in Appendix B.2.8, Figure 34.

A week 24 analysis was conducted using data for patients with severe CHE from BACH and HANDEL, combined with the week 24 results from DELTA FORCE (Figure 25B).

Figure 25 Evidence network for IGA-CHE/PGA 0/1 primary endpoint analysis (A) and week 24 analysis (B) of cumulative response



MS, moderate to severe; S, severe.

Network meta-analysis results

The results of the IGA-CHE/PGA 0/1 primary endpoint analysis of cumulative response are shown in Table 42. Compared with alitretinoin or cream vehicle, patients treated with delgocitinib cream [redacted] in their respective studies. Similar results were seen in the analysis using week 12 data from DELTA 1, DELTA 2 and Worm et al 2022. In addition, both odds ratios and risk ratios [redacted].

In the week 24 analysis, which used data from BACH and HANDEL, patients treated with [redacted].

SUCRA values, shown in Appendix B.2.9.1, Table 138, indicated that delgocitinib cream was [redacted].

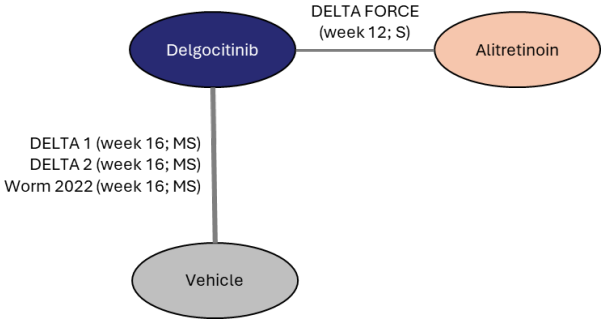
2.10.4.4 HECSI-90 endpoint response

Evidence network

The evidence network for the HECSI-90 primary endpoint response analysis (week 16 or week 12) is shown in Figure 26, and includes the delgocitinib clinical trials.

Week 16 data for patients with moderate to severe CHE in DELTA 1, DELTA 2 and Worm et al. 2022 were compared with week 12 data for patients with severe CHE in the other trials. The week 12 analyses used week 12 data from DELTA 1, DELTA 2 and Worm et al. 2022. CHE severity sensitivity analyses used data from the corresponding moderate or severe CHE subgroups in DELTA 1 and DELTA 2, combined with the overall trial populations in DELTA FORCE. Sensitivity analysis networks are shown in Appendix B.2.8, Figure 34.

Figure 26 Evidence network for HECSI-90 primary endpoint response analysis



MS, moderate to severe; S, severe.

Network meta-analysis results

The results of the HECSI-90 primary endpoint response NMAs are shown in Table 43. Compared with alitretinoin or cream vehicle, patients treated with delgocitinib cream had [redacted] in their respective studies. Similar results were seen in the analysis using week 12 data from DELTA 1, DELTA

2 and Worm et al 2022. In addition, both odds ratios and risk ratios for delgocitinib cream versus alitretinoin were [redacted].

SUCRA values, shown in Appendix 1.2.9.1, Table 139, indicated that delgocitinib cream was [redacted].

Table 43 HECSI-90 endpoint response – delgocitinib vs all treatments (fixed effects model)

Delgocitinib vs treatment	Primary endpoint analysis [a]			Week 12 analysis [b]		
	All patients	Severe CHE	Moderate CHE	All patients	Severe CHE	Moderate CHE
Median odds ratio (95% CrI)						
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median risk ratio (95% CrI)						
Vehicle cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Primary endpoint analysis includes primary endpoint for all relevant studies.

[b] Week 12 analysis includes week 12 endpoint for all relevant studies.

CHE, chronic hand eczema; CrI, credible interval; HECSI, Hand Eczema Severity Index; HECSI-90, ≥ 90% improvement in HECSI from baseline.

2.10.5 Uncertainties in the indirect and mixed treatment comparisons

Several assumptions and sources of heterogeneity should be considered when interpreting the NMA results, as described in detail in section 2.10.3 and Appendix B.2.5 .

In particular, it was necessary to assume that the IGA-CHE and PGA scoring systems were comparable, despite the inherent differences between these scales as set out in section 1.3.1.5. Because the IGA-CHE scoring system is stricter than that of the PGA, the efficacy of delgocitinib cream may be underestimated in the NMAs of IGA-CHE/PGA 0/1 outcomes, with the comparison thus being done with a disadvantage to delgocitinib.

Because BACH and HANDEL reported only cumulative PGA response at 24 weeks, it was necessary to use results of an exploratory endpoint from DELTA FORCE to perform this NMA.

A further source of heterogeneity is the severity of CHE at baseline in the included studies. Only the three studies comparing delgocitinib cream with cream vehicle – DELTA 1, DELTA 2 and Worm *et al.* 2022 – enrolled patients with moderate CHE. Accordingly, the primary endpoint analyses compare data from patients with moderate to severe CHE with results from patients with severe CHE in other studies. Subgroup analyses were also conducted using data from patients with severe CHE in DELTA 1 and DELTA 2 as well as all the patients randomised for the remaining trials, which predominantly recruited patients with severe CHE, and gave similar results to the primary endpoint analysis.

The sensitivity analysis of moderate CHE synthesises evidence from the moderate CHE subgroup of DELTA 1 and DELTA 2 with severe CHE evidence from DELTA FORCE and ALPHA. This is based on the assumption that the relative treatment effects of delgocitinib and alitretinoin in DELTA FORCE and of alitretinoin and PUVA in ALPHA would be similar if evaluated among patients with moderate CHE. The assumption is key to the economic model to allow for a comparison in moderate CHE to be modelled between delgocitinib and PUVA using the best available RCT data, though it relies on the indirect application of the evidence to a moderate CHE population.

A potential source of bias is that in the ALPHA trial of alitretinoin versus PUVA, only observed-case data were reported. As described in Appendix B.2.5.2, patients with missing data were included in the NMA as non-responders. However, the differential proportion of dropouts and differential compliance in ALPHA (more patients discontinued and /or did not meet the criteria of compliance with PUVA than alitretinoin) may favour alitretinoin, though it may represent the clinical reality in the UK.

The ALPHA trial also differed from the DELTA trials in the sense that in the former trial all patients, regardless of their allocated treatment, could use concomitant TCS as-needed, and by week 12 approximately half of the patients had used TCS at least three times per week. This may be a potential source of bias and introduce a disadvantage to the DELTA trials, where patients were not allowed to use concomitant TCS during the treatment period.

It was assumed in constructing the NMA network for discontinuation due to AEs (described in section 2.11.7) that cream vehicle and placebo were clinically equivalent. This could be a potential source of heterogeneity.

2.11 Adverse reactions

2.11.1 Summary of safety data for delgocitinib in CHE

The main sources of safety data in this submission are the DELTA 1 and DELTA 2 vehicle-controlled phase 3 trials, the DELTA 3 extension study and the DELTA FORCE active-controlled phase 3 trial [87-90].

2.11.2 Treatment exposure

Safety data are available for 638 patients receiving delgocitinib cream and 321 patients receiving vehicle cream in the 16-week DELTA 1 and DELTA 2 trials (corresponding to 196.7 and 93.9 patient years of observation [PYO] for delgocitinib and vehicle, respectively) [87, 88, 109], and 802 patients receiving delgocitinib cream in the DELTA 3 extension study (corresponding to 407.5 PYO) [89].

Safety data are available for 253 patients receiving delgocitinib cream and 247 patients receiving alitretinoin capsules in the 24-week DELTA FORCE trial (120.9 and 104.0 PYO, respectively) [90].

2.11.3 Safety results in DELTA 1 and DELTA 2

2.11.3.1 Summary of adverse events

TEAEs during the DELTA 1 and 2 trials are summarised in Table 44, with the most common TEAEs shown in Table 45. Delgocitinib treatment in adults with moderate to severe CHE was well tolerated across the 16-week treatment period [82, 87, 88].

Table 44 Overall summary of TEAEs in DELTA 1 and DELTA 2 (SAS)

Adverse events, n (%) [R]	DELTA 1		DELTA 2	
	Delgocitinib cream (n = 325; PYO = 100.85)	Cream vehicle (n = 162; PYO = 48.55)	Delgocitinib cream (n = 313; PYO = 95.87)	Cream vehicle (n = 159; PYO = 45.36)
All TEAEs	147 (45.2) [305.4]	82 (50.6) [331.6]	143 (45.7) [280.6]	71 (44.7) [319.7]
SAEs	6 (1.8) [6.9]	3 (1.9) [8.2]	5 (1.6) [5.2]	3 (1.9) [8.8]
Deaths	0	0	0	0
Severity				
Mild	106 (32.6) [191.4]	57 (35.2) [197.7]	116 (37.1) [204.4]	63 (39.6) [224.9]
Moderate	68 (20.9) [98.2]	38 (23.5) [113.3]	50 (16.0) [70.9]	22 (13.8) [81.6]
Severe	12 (3.7) [15.9]	5 (3.1) [20.6]	3 (1.0) [5.2]	4 (2.5) [13.2]
TEAEs possibly or probably related to study drug	12 (3.7) [16.9]	13 (8.0) [37.1]	22 (7.0) [31.3]	11 (6.9) [30.9]
TEAEs leading to permanent discontinuation of study drug	2 (0.6) [2.0]	6 (3.7) [14.4]	1 (0.3) [1.0]	5 (3.1) [11.0]

n, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO.
PYO, patient years of observation; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Bissonette *et al*. 2024 [82].

Table 45 Most frequent TEAEs (≥ 2% in any treatment group) in DELTA 1 and DELTA 2 (SAS)

Adverse events, n (%) [R] System organ class Preferred term	DELTA 1		DELTA 2	
	Delgocitinib cream (n = 325; PYO = 100.85)	Cream vehicle (n = 162; PYO = 48.55)	Delgocitinib cream (n = 313; PYO = 95.87)	Cream vehicle (n = 159; PYO = 45.36)
Infections and infestations				
Covid-19	35 (10.8) [34.7]	14 (8.6) [28.8]	36 (11.5) [37.6]	20 (12.6) [44.1]
Nasopharyngitis	23 (7.1) [24.8]	14 (8.6) [33.0]	21 (6.7) [25.0]	10 (6.3) [22.0]
Pharyngitis	2 (0.6) [2.0]	0	3 (1.0) [3.1]	5 (3.1) [13.2]
Herpes simplex	0	0	1 (0.3) [1.0]	4 (2.5) [8.8]
Nervous system disorders				
Headache	9 (2.8) [12.9]	4 (2.5) [12.4]	19 (6.1) [26.1]	9 (5.7) [24.3]
Immune system disorders				
Allergy to metals	7 (2.2) [6.9]	3 (1.9) [6.2]	0	0
Skin and subcutaneous tissue disorders				
Contact dermatitis	4 (1.2) [4.0]	4 (2.5) [8.2]	3 (1.0) [3.1]	2 (1.3) [4.4]
Hand dermatitis	1 (0.3)	7 (4.3) [20.6]	3 (1.0) [3.1]	6 (3.8) [13.2]

n, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO.
Covid-19, coronavirus disease 2019; PYO, patient years of observation; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: Bissonette *et al*. 2024 [82].

The overall frequency of TEAEs (DELTA 1, 45.2% vs 50.6%; DELTA 2, 45.7% vs 44.7%) and SAEs (DELTA 1, 1.8% vs 1.9%; DELTA 2, 1.6% vs 1.9%) was comparable between delgocitinib-treated patients and cream vehicle-treated patients. The majority of TEAEs were mild or moderate in severity, and few were considered to be related to the study drug.

There were no clinically relevant findings from baseline to the end of treatment regarding changes in laboratory parameters (including haematology, biochemistry and lipid profile) and differences in vital signs, physical examination or investigator-assessed electrocardiogram (ECG) [82].

The safety results in DELTA 1 and DELTA 2 are described in more detail in the following sections.

2.11.3.2 Adverse events leading to discontinuation

Few TEAEs led to permanent discontinuation of the study drug, with the number of discontinuations due to TEAEs numerically higher among patients treated with cream vehicle than patients treated with delgocitinib cream (DELTA 1, 0.6% vs 3.7%; DELTA 2, 0.3% vs 3.1%; Table 44) [82].

2.11.3.3 Common adverse events

The most frequently reported TEAEs across the treatment groups in both trials were infections and infestations (Covid-19 [DELTA 1, 10.8% vs 8.6%; DELTA 2, 11.5% vs 12.6%] or nasopharyngitis [DELTA 1, 7.1% vs 8.6%; DELTA 2, 6.7% vs 6.3%]) and were not related to the study drug, with the number of TEAEs overall low and comparable between the delgocitinib cream arm and the cream vehicle arm (DELTA 1, 45.2% vs 50.6%; DELTA 2, 45.7% vs 44.7%; Table 45) [82].

In both trials, contact dermatitis (DELTA 1, 1.2% vs 2.5%; DELTA 2, 1.0% vs 1.3%) and hand dermatitis (DELTA 1, 0.3% vs 4.3%; DELTA 2, 1.0% vs 3.8%) were reported less frequently in the delgocitinib cream group than in the cream vehicle group [82]; all TEAEs of hand dermatitis were reported as worsening CHE [87, 88].

2.11.3.4 Adverse events possibly or probably related to study drug

TEAEs possibly or probably related to the study drug are shown in full in Appendix D1, Tables 179 and 180 [87, 88].

In DELTA 1, TEAEs possibly or probably related to the study drug were infrequent, and were less common in the delgocitinib cream group than in the cream vehicle group (3.7% vs 8.0%; Table 44) [82]. All preferred terms in the delgocitinib cream group were single events, except for streptococcal infection which was reported twice for the same patient, with two different body locations [87]. One of the streptococcal infection events was considered severe; all other TEAEs possibly or probably related to delgocitinib were mild or moderate [87]. Most TEAEs possibly or probably related to cream vehicle were skin and subcutaneous disorders (mainly hand dermatitis and application site reactions) [87].

In DELTA 2, TEAEs possibly or probably related to the study drug occurred with similar frequency in the delgocitinib cream group and the cream vehicle group (7.0% vs 6.9%; Table 44) [82]. Most preferred terms in the delgocitinib cream group were single events, and all were mild or moderate. The most frequently reported TEAE possibly or probably related to delgocitinib cream was headache (5 events in 5 patients; 4 from the same trial site) [88].

2.11.3.5 Serious adverse events

Few serious TEAEs were reported, and none were assessed to be related to delgocitinib cream [82, 91, 93]. Additionally, no pattern was observed in the serious TEAEs reported and no serious TEAE led to a safety concern [87, 88].

2.11.3.6 Adverse events of special interest

No TEAEs of special interest – eczema herpeticum, deep vein thrombosis or pulmonary embolism – were reported [82].

2.11.3.7 Deaths

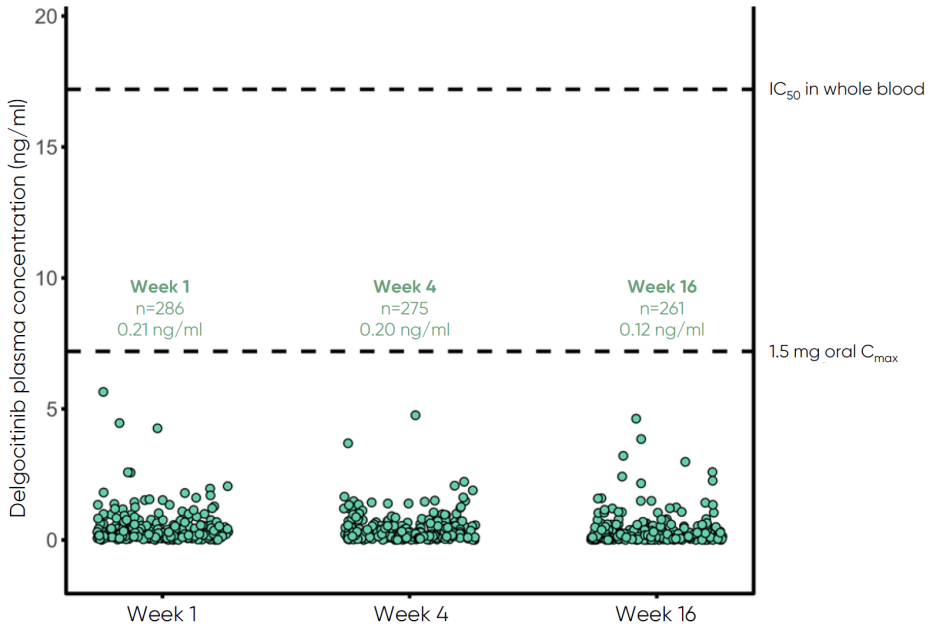
No deaths were reported [82].

2.11.3.8 Systemic exposure

In an analysis of 313 patients on active treatment in DELTA 2, twice-daily application of delgocitinib cream resulted in minimal systemic exposure over 16 weeks (0.12–0.21 ng/mL), at least 80-fold below the whole-blood 50% inhibitory concentration (IC_{50}; 17.2 ng/ml), and at least 30-fold below the systemic exposure resulting from a single oral 1.5 mg delgocitinib sub-therapeutic dose in a phase 1 trial (7.2 ng/mL; Figure 27) [16].

There was no overlap in plasma exposure between oral and topical administration. These data suggest that minimal systemic pharmacological effect is expected with delgocitinib cream 20 mg/g dosing in patients with moderate to severe CHE [16].

Figure 27 Delgocitinib concentration by visit at Weeks 1, 4 and 16 in DELTA 2



Horizontal dashed lines represent geometric mean values. One patient was excluded from this analysis due to an outlier value at week 4. C_{max}, maximum concentration; IC50, 50% inhibitory concentration.
Source: Thaçi *et al.*, EADV 2023 [16].

2.11.4 Safety results in DELTA 3

2.11.4.1 Summary of adverse events

TEAEs during the 36-week plus two weeks safety follow-up extension study, DELTA 3, are summarised in Table 46, with the most common TEAEs shown in Table 47.

Table 46 Overall summary of TEAEs from baseline up to week 52 plus two weeks safety follow-up in DELTA 3 (SAS)

Adverse event, n (%) [R]	On-treatment (n = 779; PYO = 407.52)	Off-treatment (n = 770; PYO = 128.14)	Total (n = 801; PYO = 535.65)
All TEAEs	443 (56.9) [240.2]	155 (20.1) [202.1]	495 (61.8) [231.1]
SAEs	22 (2.8) [6.6]	7 (0.9) [7.0]	27 (3.4) [6.7]
Deaths	1 (0.1) [0.3]	2 (0.3) [1.6]	3 (0.4) [0.6]
Severity			
Mild	339 (43.5) [150.4]	108 (14.0) [123.3]	390 (48.7) [143.9]
Moderate	206 (26.4) [82.4]	66 (8.6) [72.6]	242 (30.2) [80.1]
Severe	23 (3.0) [7.4]	7 (0.9) [6.2]	28 (3.5) [7.1]
TEAEs possibly or probably related to study drug	24 (3.1) [6.6]	4 (0.5) [3.1]	27 (3.4) [5.8]
TEAEs leading to permanent discontinuation of study drug	7 (0.9) [1.7]	2 (0.3) [2.3]	9 (1.1) [1.9]
TEAEs of special interest (eczema herpeticum)	1 (0.1) [0.3]	0	1 (0.1) [0.2]

n, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO.
PYO, patient years of observation; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: DELTA 3 CSR [89].

The safety profile of delgocitinib in DELTA 3 was consistent with the 16-week parent studies (section 2.11.3). Rates of TEAEs and SAEs were similar on and off-treatment, and no important differences in the TEAE rates between patients previously treated with delgocitinib and those previously treated with cream vehicle were observed [89]. There were no new safety signals during long-term use of delgocitinib [89].

2.11.4.2 Adverse events leading to discontinuation

Few TEAEs led to permanent discontinuation of the study drug (0.9% of patients discontinued delgocitinib cream while on-treatment; Table 46) [89].

2.11.4.3 Common adverse events

As in the DELTA 1 and DELTA 2 trials, the most frequently reported TEAEs in DELTA 3 were infections and infestations (Covid-19 or nasopharyngitis) and were not related to the study drug (Table 47) [89].

Table 47 Most frequent TEAEs (≥ 1% of patients in total) from baseline up to Week 52 in DELTA 3 (SAS)

Adverse events, n (%) [R] System organ class/Preferred term	On-treatment (n = 779; PYO = 407.52)	Off-treatment (n = 770; PYO = 128.14)	Total (n = 801; PYO = 535.65)
Infections and infestations			
Covid-19	110 (14.1) [28]	24 (3.1) [18.7]	134 (16.7) [25.8]
Nasopharyngitis	101 (13.0) [29.2]	37 (4.8) [32.8]	128 (16.0) [30.1]
Upper respiratory tract infection	24 (3.1) [5.9]	11 (1.4) [9.4]	32 (4.0) [6.7]

Adverse events, n (%) [R] System organ class/Preferred term	On-treatment (n = 779; PYO = 407.52)	Off-treatment (n = 770; PYO = 128.14)	Total (n = 801; PYO = 535.65)
Influenza	22 (2.8) [5.4]	6 (0.8) [4.7]	28 (3.5) [5.2]
Sinusitis	13 (1.7) [3.7]	1 (0.1) [0.8]	14 (1.7) [3.0]
Bronchitis	10 (1.3) [2.5]	3 (0.4) [2.3]	13 (1.6) [2.4]
Urinary tract infection	10 (1.3) [2.5]	2 (0.3) [1.6]	12 (1.5) [2.2]
Gastroenteritis	10 (1.3) [2.5]	0	10 (1.2) [1.9]
Rhinitis	8 (1) [2.2]	2 (0.3) [1.6]	10 (1.2) [2.1]
Oral herpes	6 (0.8) [1.5]	3 (0.4) [3.1]	9 (1.1) [1.9]
Pharyngitis	4 (0.5) [1]	5 (0.6) [3.9]	9 (1.1) [1.7]
Skin and subcutaneous tissue disorder			
Hand dermatitis	20 (2.6) [5.9]	12 (1.6) [9.4]	31 (3.9) [6.7]
Eczema	16 (2.1) [4.4]	2 (0.3) [2.3]	17 (2.1) [3.9]
Musculoskeletal and connective tissue disorder			
Back pain	17 (2.2) [4.2]	4 (0.5) [3.1]	20 (2.5) [3.9]
Pain in extremity	9 (1.2) [2.2]	1 (0.1) [0.8]	10 (1.2) [1.9]
Arthralgia	9 (1.2) [2.5]	0	9 (1.1) [1.9]
Gastrointestinal disorder			
Diarrhoea	10 (1.3) [2.5]	3 (0.4) [2.3]	13 (1.6) [2.4]
Nervous system disorder			
Headache	19 (2.4) [5.4]	4 (0.5) [3.9]	22 (2.7) [5.0]
Respiratory, thoracic and mediastinal disorders			
Cough	8 (1.0) [2.0]	2 (0.3) [1.6]	10 (1.2) [1.9]
Vascular disorders			
Hypertension	11 (1.4) [2.7]	2 (0.3) [1.6]	13 (1.6) [2.4]

n, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO.
PYO, patient years of observation; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Source: DELTA 3 CSR [89].

2.11.4.4 Adverse events possibly or probably related to study drug

TEAEs possibly or probably related to delgocitinib are shown in full in Appendix D1, Table 181 [89]. Very few TEAEs were assessed as possibly or probably related to delgocitinib (5.8 related TEAEs per 100 PYO). All related TEAEs were considered non-serious and of mild or moderate severity, except for one event of severe lesional/perilesional dermatitis which resolved after 36 days without change to treatment. Most of the TEAEs assessed as possibly or probably related to delgocitinib occurred as single events with no pattern [89].

2.11.4.5 Adverse events of special interest

One event of eczema herpeticum was reported during an on-treatment period. The TEAE was non-serious, moderate and considered possibly related to the IMP by the investigator. No events of deep vein thrombosis or pulmonary embolism were reported [89].

2.11.4.6 Deaths

A total of three deaths were reported during DELTA 3, one during an on-treatment period and two during off-treatment periods [89]:

- Death due to metastatic oesophageal cancer was reported for a patient previously treated with cream vehicle in the parent trial. The 63-year-old male applied one dose of delgocitinib cream in DELTA 3 before the first signs of cancer were reported; the event was considered not related to delgocitinib.

- Death due to myocardial infarction was reported for a patient 206 days after the last dose of delgocitinib cream. The 72-year-old male had a medical history of hypertension; the event was considered not related to delgocitinib.
- Death due to unknown causes was reported for a patient treated with delgocitinib cream in the parent trial and in DELTA 3, 17 days after treatment was discontinued due to an IGA-CHE score of 0. The 72-year-old male had previously had an SAE of peripheral facial nerve palsy considered related to suspected metastasis. The event was considered not related to delgocitinib [89].

2.11.5 Safety results in DELTA FORCE

2.11.5.1 Summary of adverse events

AEs during the DELTA FORCE are summarised in Table 48, with the most common AEs shown in Table 49 [90]. Delgocitinib treatment in adults with moderate to severe CHE was well tolerated across the 24-week treatment period [90].

The overall frequency of AEs and SAEs was lower among patients treated with delgocitinib cream, compared with those receiving alitretinoin [90, 95]. In both groups, the majority of AEs were mild or moderate in severity. Among patients treated with delgocitinib cream, AEs possibly or probably related to the study drug were infrequent; by contrast, 54.3% of patients in the alitretinoin group had one or more AEs possibly or probably related to their treatment, compared with 9.5% in the delgocitinib cream group [90, 95].

No changes in haematology, chemistry or urinalysis parameters were assessed to be of clinical relevance in the delgocitinib cream group. In the alitretinoin group, multiple patients had post-baseline changes in cholesterol and triglycerides which were reported as AEs, consistent with the alitretinoin label [90].

Table 48 Overall summary of TEAEs in DELTA FORCE (SAS)

Adverse events, n (%) [R]	Delgocitinib cream (n = 253; PYO = 120.9)	Alitretinoin (n = 247; PYO = 104.0)
All TEAEs	125 (49.4) [231.5]	188 (76.1) [596.1]
SAE	5 (2.0) [4.1]	12 (4.9) [11.5]
Deaths	0	0
Severity		
Mild	92 (36.4) [138.9]	151 (61.1) [381.7]
Moderate	68 (26.9) [89.3]	104 (42.1) [190.4]
Severe	4 (1.6) [3.3]	14 (5.7) [24.0]
TEAEs possibly or probably related to study drug	24 (9.5) [24.8]	134 (54.3) [299.0]
TEAEs leading to permanent discontinuation of study drug	3 (1.2) [3.3]	25 (10.1) [43.3]

n, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO.
AE, adverse event; PYO, patient years of observation; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: DELTA FORCE CSR [90] Giménez-Arnau *et al*. 2024 [95].

2.11.5.2 Adverse events leading to discontinuation

Few TEAEs led to permanent discontinuation of delgocitinib cream (1.2% of patients), with a higher frequency of discontinuation due to TEAEs seen in the alitretinoin arm (10.1%; Table 48) [90].

2.11.5.3 Common adverse events

The most frequently reported TEAEs in the delgocitinib cream treatment group in DELTA FORCE were infections and infestations (mainly nasopharyngitis, affecting a similar proportion of patients in both arms) (Table 49) [90]. In the alitretinoin group, the most frequently reported TEAE was headache, affecting 32.4% of patients (vs 4.0% in the delgocitinib cream arm; Table 49) [90]. All other TEAEs affecting more than 2% of patients in either group were more common in the alitretinoin arm than in the delgocitinib cream arm (Table 49) [90].

Table 49 Most frequent TEAEs (≥ 2% in any treatment group) in DELTA FORCE (SAS)

Adverse events, n (%) [R] System organ class Preferred term	**Delgocitinib cream (n = 253; PYO = 120.9)**	**Alitretinoin (n = 247; PYO = 104.0)**
Infections and infestations		
Nasopharyngitis	30 (11.9) [31.4]	34 (13.8) [44.2]
Upper respiratory tract infection	6 (2.4) [6.6]	8 (3.2) [7.7]
Covid-19	5 (2.0) [4.1]	9 (3.6) [8.7]
Urinary tract infection	1 (0.4) [0.8]	10 (4.0) [10.6]
Skin and subcutaneous tissue disorders		
Dry skin	3 (1.2) [2.5]	9 (3.6) [8.7]
Eczema	2 (0.8) [1.7]	5 (2.0) [5.8]
Hand dermatitis	2 (0.8) [2.5]	5 (2.0) [4.8]
Dermatitis atopic	1 (0.4) [0.8]	5 (2.0) [4.8]
Erythema	1 (0.4) [0.8]	9 (3.6) [9.6]
Musculoskeletal and connective tissue disorders		
Back pain	2 (0.8) [1.7]	6 (2.4) [5.8]
Investigations		
Blood triglycerides increased	2 (0.8) [1.7]	7 (2.8) [7.7]
Nervous system disorders		
Headache	10 (4.0) [15.7]	80 (32.4) [109.6]
Migraine	2 (0.8) [1.7]	6 (2.4) [6.7]
Dizziness	1 (0.4) [0.8]	6 (2.4) [5.8]
Gastrointestinal disorders		
Nausea	1 (0.4) [0.8]	14 (5.7) [14.4]
Diarrhoea	0	5 (2.0) [4.8]
Lip dry	0	8 (3.2) [7.7]
Respiratory, thoracic and mediastinal disorders		
Epistaxis	1 (0.4) [0.8]	5 (2.0) [5.8]
Metabolism and nutrition disorders		
Hypertriglyceridaemia	3 (1.2) [2.5]	6 (2.4) [6.7]
Hypercholesterolaemia	0	9 (3.6) [9.6]
Vascular disorders		
Flushing	0	5 (2.0) [5.8]
Eye disorders		
Dry eye	0	7 (2.8) [6.7]

N, number of patients with events; %, percentage of patients with events; R, event rate per 100 PYO. Covid19, coronavirus disease 2019; PYO, patient years of observation; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: DELTA FORCE CSR [90].

2.11.5.4 Adverse events possibly or probably related to study drug

TEAEs possibly or probably related to the study drugs are shown in full in Appendix D1, Table 182.

TEAEs considered possibly or probably related to the study drug were less common in the delgocitinib group than in the alitretinoin group (9.5% vs 54.3% of participants) [90].

In the delgocitinib cream group, most Medical Dictionary for Regulatory Activities (MedDRA) preferred terms possibly or probably related to the study drug were reported as single cases, except for dry skin (3 [1.2%] participants, 3 events), hand dermatitis (2 [0.8%] participants, 3 events), pruritus (2 [0.8%] participants, 2 events), and product intolerance (1 [0.4%] participant, 2 events). Of note, the three events of hand dermatitis that were reported by two participants were not new lesions (1 event was reported as worsening of HE; and the other 2 events were reported in the same participant as pain and burning on CHE lesions and were most likely application site reactions) [90].

In the alitretinoin group, the most frequently reported (≥ 3% of participants) TEAEs possibly or probably related to the study drug were headache (72 [29.1%] participants, 97 events), nausea (12 [4.9%] participants, 13 events), erythema (9 [3.6%] participants, 10 events), dry skin (9 [3.6%] participants, 9 events), lip dry (8 [3.2%] participants, 8 events), and hypercholesterolaemia (8 [3.2%] participants, 9 events); all of which were considered expected from the known safety profile of alitretinoin [90].

2.11.5.5 Serious adverse events

Few SAEs were reported, and none were assessed to be related to delgocitinib cream [90]. Additionally, no pattern was observed in the SAEs reported and no SAE led to a safety concern [90].

2.11.5.6 Adverse events of special interest

One TEAE of special interest, deep vein thrombosis, was reported for a patient in the alitretinoin group. No eczema herpeticum or pulmonary embolism events were reported [90].

2.11.5.7 Exploratory adverse event endpoints

The number of TEAEs of hypertriglyceridaemia, hypercholesterolaemia, headache and liver toxicity were exploratory endpoints of the trial [90]. All four were less common in the delgocitinib cream than in the alitretinoin group group, although liver toxicity events were infrequent in both groups (hypertriglyceridaemia, 2.0% vs 5.3% of patients; hypercholesterolaemia, 1.2% vs 5.3% of patients; headache, 4.0% vs 32.8% of patients; liver toxicity, 0.8% vs 1.6% of patients). None of the events were serious except for one episode of severe headache in the alitretinoin group; however, 12 patients treated with alitretinoin discontinued treatment due to headache [90].

2.11.5.8 Deaths

No deaths were reported (Table 48) [90].

2.11.6 Summary of safety data in delgocitinib phase 2b trial

Safety results from the delgocitinib phase 2b trial are summarised in Table 50. Delgocitinib cream was well tolerated in the phase 2b trial, with the most frequently reported TEAEs being nasopharyngitis, eczema and headache [105]. No dose–response relationships were seen in the safety profile, and no safety concerns were identified [105].

Table 50 Summary of TEAEs in delgocitinib phase 2b trial

	Delgocitinib (N)												Vehicle		
	1 mg/g (N = 52)			3 mg/g (N = 51)			8 mg/g (N = 52)			20 mg/g (N = 53)			(N = 50)		
	n (%)	E	R	n (%)	E	R	n (%)	E	R	n (%)	E	R	n (%)	E	R
Overview of TEAEs															
All TEAEs	33 (63.5)	62	451.8	39 (76.5)	86	636.1	32 (61.5)	70	484.7	38 (71.7)	88	577.8	30 (60.0)	64	498.1
Severe TEAEs	1 (1.9)	1	7.3	2 (3.9)	4	29.6	1 (1.9)	1	6.9	0			1 (2.0)	1	7.8
TEAEs related to study treatment	11 (21.2)	16	116.6	2 (3.9)	2	14.8	6 (11.5)	7	48.5	7 (13.2)	7	46.0	7 (14.0)	9	70.0
Serious AEs	0	-	-	2 (3.9)	2	14.8	1 (1.9)	1	6.9	0	-	-	0	-	-
TEAEs leading to withdrawal from trial	6 (11.5)	7	51.0	6 (11.8)	6	44.4	0	-	-	1 (1.9)	1	6.6	3 (6.0)	3	23.3
TEAEs leading to discontinuation of treatment	6 (11.5)	7	51.0	6 (11.8)	6	44.4	1 (1.9)	1	6.9	2 (3.8)	2	13.1	3 (6.0)	3	23.3
Lesional/perilesional TEAEs	10 (19.2)	13	94.7	9 (17.6)	11	81.4	7 (13.5)	9	62.3	10 (18.9)	12	78.8	8 (16.0)	8	62.3
Frequent TEAEs (≥ 5% in any treatment group) by system organ class and preferred term															
Infections and infestations	9 (17.3)	12	87.5	16 (31.4)	23	170.1	15 (28.8)	16	110.8	18 (34.0)	24	157.6	20 (40.0)	20	155.7
Nasopharyngitis	9 (17.3)	11	80.2	15 (29.4)	22	162.7	15 (28.8)	16	110.8	14 (26.4)	20	131.3	20 (40.0)	20	155.7
Influenza	1 (1.9)	1	7.3	1 (2.0)	1	7.4	0			4 (7.5)	4	26.3	0	-	-
Skin and subcutaneous tissue disorders	9 (17.3)	9	65.6	8 (15.7)	10	74.0	4 (7.7)	8	55.4	9 (17.0)	10	65.7	9 (18.0)	10	77.8
Eczema	5 (9.6)	5	36.4	4 (7.8)	5	37.0	3 (5.8)	7	48.5	6 (11.3)	7	46.0	8 (16.0)	9	70.0
Pruritus	3 (5.8)	3	21.9	2 (3.9)	2	14.8	1 (1.9)	1	6.9	3 (5.7)	3	19.7	1 (2.0)	1	7.8
Dermatitis atopic	1 (1.9)	1	7.3	3 (5.9)	3	22.2	0			0			0		
Nervous system disorders	2 (3.8)	2	14.6	2 (3.9)	4	29.6	6 (11.5)	7	48.5	4 (7.5)	5	32.8	2 (4.0)	2	15.6
Headache	2 (3.8)	2	14.6	2 (3.9)	4	29.6	6 (11.5)	7	48.5	4 (7.5)	5	32.8	2 (4.0)	2	15.6
Musculoskeletal and connective tissue disorders	1 (1.9)	1	7.3	0	-	-	2 (3.8)	2	13.8	3 (5.7)	3	19.7	1 (2.0)	1	7.8
Back pain	1 (1.9)	1	7.3	0	-	-	2 (3.8)	2	13.8	3 (5.7)	3	19.7	1 (2.0)	1	7.8
Gastrointestinal disorders	3 (5.8)	3	21.9	1 (2.0)	1	7.4	0	-	-	0	-	-	0	-	-
Toothache	3 (5.8)	3	21.9	1 (2.0)	1	7.4	0	-	-	0	-	-	0	-	-

TEAEs presented are treatment-emergent with onset after the first application of study treatment. Related TEAEs are events considered by the investigator to be possibly or probably related to study treatment. Classification is according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

%, percentage of patients with one or more TEAE; E, number of AEs; N, number of patients within a treatment group, n, number of patients with one or more AE; R, rate number of AEs divided by person years of exposure multiplied by 100 [person years of exposure is calculated as days from first application of study treatment to last application of study treatment (both days included) divided by 365.25]; TEAE, treatment-emergent adverse event.. Source: phase 2b trial publication [105].

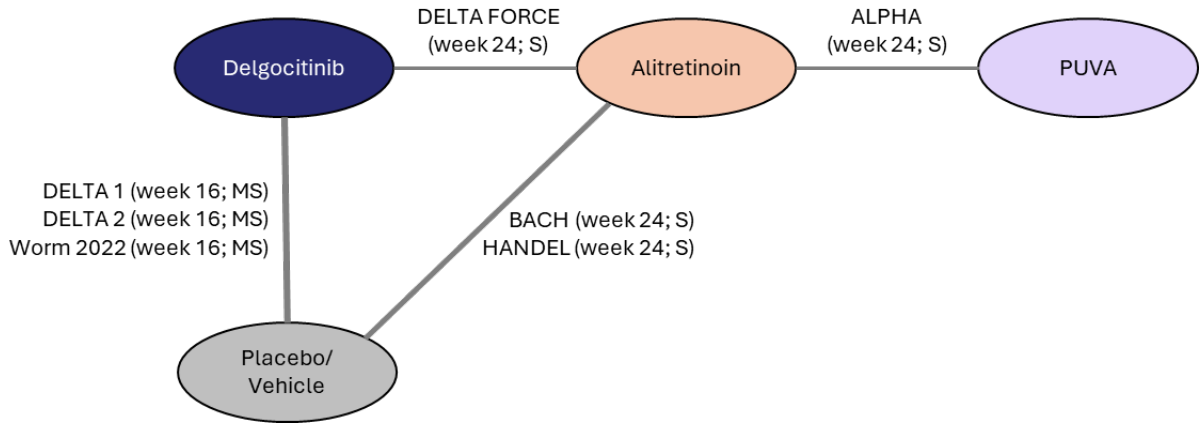
2.11.7 Discontinuation due to AEs – indirect evidence

An NMA was conducted to compare discontinuation due to AEs, as described in detail in section 2.10 and Appendix B.2.

Evidence network

The evidence network for the analysis of discontinuation due to AEs is shown in Figure 28, and includes the delgocitinib clinical trials, ALPHA, BACH and HANDEL. Week 16 data for patients with moderate to severe CHE in DELTA 1, DELTA 2 and Worm *et al.* 2022 were compared with week 24 data for patients with severe CHE in the other trials. A sensitivity analysis using data for severe CHE only patients exposed to treatment for 24 weeks excluded the 16-week DELTA 1, DELTA 2 and Worm *et al.* 2022 trials (the sensitivity analysis network is shown in Appendix B.2.8, Figure 35).

Figure 28 Evidence network for analysis of discontinuation due to AEs



MS, moderate to severe; PUVA, psoralen–UV A phototherapy; S, severe.

Network meta-analysis results

The results of the NMA of discontinuation due to AEs are shown in Table 51. Compared with PUVA, alitretinoin or placebo/cream vehicle, patients treated with delgocitinib cream were [redacted].

Table 51 Discontinuation due to AEs – delgocitinib vs all treatments (fixed-effects model)

Delgocitinib vs treatment	End of treatment					
	All patients [a]			Severe CHE [b]		
Median odds ratio (95% CrI)						
Vehicle cream		[redacted]			[redacted]	
PUVA						
Alitretinoin						
Median risk ratio (95% CrI)						
Vehicle cream		[redacted]			[redacted]	
PUVA						
Alitretinoin						

[a] Includes all trials reporting discontinuation due to adverse events outcome at end of treatment.

[b] Includes patients with severe CHE at baseline for trials reporting data at week 24 endpoint.

CHE, chronic hand eczema; CrI, credible interval; PUVA, psoralen–UV A phototherapy.

SUCRA values, shown in Appendix 1.2.9.1, Table 140, indicated that delgocitinib was [redacted].

2.11.8 Overview of safety in relation to the decision problem

In total, the safety analyses in the delgocitinib phase 3 trial programme include 725 PYO for delgocitinib cream. In DELTA 1 and DELTA 2, delgocitinib cream was well tolerated, demonstrating a safety profile comparable to that of cream vehicle. The results of the DELTA 3 study suggest that use of delgocitinib cream in long-term control of CHE has a safety profile consistent with its use in short-term studies.

In DELTA FORCE, delgocitinib cream had a more favourable safety profile than alitretinoin, with fewer TEAEs overall, lower rates of discontinuation due to TEAEs and substantially fewer TEAEs considered possibly or probably related to the study drug than the alitretinoin group.

Pharmacokinetic data from DELTA 2 suggest that minimal systemic pharmacological effect is expected with delgocitinib cream 20 mg/g dosing in patients with moderate to severe CHE. In addition, the safety issues associated with use of oral JAK inhibitors (see section 1.3.3.5) were not identified as safety concerns for delgocitinib.

Consistent with the safety profile demonstrated in the DELTA clinical trials, the NMA described above found a statistically significantly lower rate of discontinuation due to AEs with delgocitinib than with PUVA or alitretinoin.

2.12 Ongoing studies

There are no ongoing studies that will provide additional relevant evidence in the next 12 months.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the DELTA clinical studies

Delgocitinib cream demonstrated statistically significantly higher efficacy than cream vehicle

The efficacy of delgocitinib cream for the treatment of moderate to severe CHE in adults was demonstrated in three phase 3 trials: DELTA 1, DELTA 2 and DELTA 3. The vehicle-controlled trials DELTA 1 and DELTA 2 met their primary endpoints of IGA-CHE TS at week 16, with statistically significantly more patients achieving IGA-CHE TS at week 16 with delgocitinib cream than with cream vehicle (section 2.6.2.1).

Delgocitinib cream was also statistically significantly more efficacious than cream vehicle in all key secondary endpoints (section 2.6.1). Approximately half of patients treated with delgocitinib cream had a 75% improvement in their symptoms (HECSI-75) at week 8 and week 16 (section 2.6.2.3), and approximately 30% of patients had a 90% improvement in their symptoms (HECSI-90) at week 16 (section 2.6.2.3).

Delgocitinib demonstrated improvements in CHE from early in the treatment period

Although the primary endpoint of DELTA 1 and DELTA 2 was measured at week 16, patients treated with delgocitinib cream had improvements in the signs and symptoms of CHE that were statistically significant versus cream vehicle at earlier study visits. In particular, statistically significant differences between the delgocitinib cream and cream vehicle arms were seen in both trials for IGA-CHE TS from week 4 (section 2.6.2.2) and for HECSI-90 from week 2 (section 2.6.2.4).

As-needed use of delgocitinib is an effective strategy for long-term disease control

At the end of DELTA 1 and DELTA 2, most patients transferred to the DELTA 3 open-label extension study, in which delgocitinib cream was used on an as-needed basis. The results of DELTA 3 demonstrated long-term efficacy of as-needed treatment with delgocitinib cream (section 2.6.5). The maintenance of IGA-CHE TS, HECSI-75, HECSI-90 and HESD responses in DELTA 3 indicates that long-term use of delgocitinib cream results in effective disease control. In addition, approximately 50% of patients who started the extension trial without IGA-CHE TS achieved this response within 36 weeks of as-needed treatment (2.6.5.1).

The results of DELTA 3 demonstrate that using delgocitinib cream until clear or almost clear skin is achieved, and then stopping treatment until signs of CHE return, is an effective strategy for long-term disease management.

Delgocitinib cream demonstrated statistically significant reductions in HESD itch and pain, compared with cream vehicle

As described in section 1.3.1.8, rapid relief of these symptoms of itch and pain is an important goal for patients with CHE. As reported in DELTA 1 and DELTA 2 daily diaries, statistically significantly more patients had already achieved a ≥ 4-point improvement in HESD itch score with delgocitinib cream than with cream vehicle after 2 weeks of use (section 2.6.3). Similarly, statistically significant improvements in HESD pain score versus cream vehicle were seen at week 2 in the delgocitinib cream groups in both trials; statistically significant differences in itch and pain between groups were then maintained up to week 16.

Delgocitinib cream statistically significantly improved patients' HRQoL, compared with cream vehicle

Use of delgocitinib cream was associated with statistically significant, clinically meaningful improvements in patients' HRQoL. In DELTA 1 and DELTA 2, more than 70% of patients with DLQI ≥ 4 at baseline had a clinically important ≥ 4-point improvement by week 4 (section 2.6.4.1). In addition, patients treated with delgocitinib cream had statistically significant improvements in EQ-5D-3L index and EQ VAS, compared with the cream vehicle group (section 2.6.4.2). The HRQoL improvements achieved in DELTA 1 and DELTA 2 were generally maintained during 36 weeks of as-needed treatment in DELTA 3 (section 2.6.7).

Delgocitinib cream has a favourable safety profile

Use of delgocitinib cream was well tolerated in the DELTA clinical trial programme (section 2.10). In DELTA 1 and DELTA 2, delgocitinib cream had a favourable safety profile which was comparable to that of cream vehicle, while DELTA 3 identified no new safety concerns over a further 36 weeks of treatment.

Systemic exposure of delgocitinib was minimal

The use of oral JAK inhibitors is associated with safety concerns, and the US Food and Drug Administration (FDA) requires these treatments to carry black box warnings [68]. Potential systemic exposure after topical use of delgocitinib cream was investigated in DELTA 2 (see section 2.11.3.8). The results of this analysis showed that 16 weeks of delgocitinib cream use BD resulted in minimal systemic exposure, suggesting that no systemic pharmacological effect should be expected. This absence of systemic exposure is a key advantage of the delgocitinib cream formulation.

Subgroup analyses

The results of subgroup analyses of IGA-CHE TS, HECSI-75 and HECSI-90 endpoints showed that at week 12 and week 16 delgocitinib cream [redacted] (section 2.8.2) [79].

Additional subgroup analyses showed that at week 12 and at week 16 delgocitinib was [redacted] (i.e. atopic/non-atopic and contact/non-contact), and [redacted]. In DELTA FORCE, results were [redacted] (at week 12).

Delgocitinib demonstrated statistically significantly greater efficacy than oral alitretinoin at week 12 and week 24

For patients with severe CHE for whom TCS is ineffective or unsuitable, the ESCD guidelines recommend the retinoid alitretinoin as second-line treatment [5]. Oral alitretinoin and delgocitinib cream were compared head-to-head in the DELTA FORCE trial, which showed delgocitinib cream to have statistically significantly greater efficacy than oral alitretinoin for the treatment of severe CHE (section 2.6.8). In addition to the primary endpoint of mean change in HECSI from baseline to week 12, use of delgocitinib cream for 12 weeks led to statistically significantly higher HECSI-90 and IGA-CHE TS response rates, and to statistically significantly larger improvements in HESD itch and pain scores, compared with oral alitretinoin. After week 16 (delgocitinib cream) or week 12 (oral alitretinoin), treatment was used on an as-needed basis. At week 24, the mean change in HECSI and in HESD itch and pain scores, as well as the proportion of patients with IGA-CHE TS, were all statistically significantly superior in the delgocitinib cream arm than in the oral alitretinoin arm.

DELTA FORCE also showed delgocitinib cream to be associated with statistically significantly larger improvements than oral alitretinoin in DLQI at week 12 and week 24.

Improvements in EQ-5D-3L index and EQ VAS [redacted] (EQ-5D-3L index and EQ VAS are not included in the DELTA FORCE statistical testing hierarchy; section 2.6.11).

Delgocitinib cream has a more favourable safety profile than oral alitretinoin

Analysis of comparative safety in DELTA FORCE showed that delgocitinib was associated with fewer TEAEs possibly or probably related to the study drug than oral alitretinoin (9.5% vs 54.3% of patients). The most frequently reported TEAE with oral alitretinoin was headache, affecting 32.4% of patients (vs 4.0% in the delgocitinib cream arm; section 2.11.5).

Indirect evidence shows that delgocitinib has a [redacted]

The efficacy of delgocitinib cream was compared with PUVA and alitretinoin using an NMA (see section 2.10). Analyses were conducted using data from the 16-week primary endpoint in DELTA 1, DELTA 2 and Worm *et al.* 2022, compared with 12-week data from other trials. A further analysis used 12-week data from all studies. The results showed that patients [redacted]. Sensitivity analyses using data for the subgroups of patients with moderate or severe CHE in DELTA 1 and DELTA 2 [redacted].

An NMA of discontinuation due to AEs (section 2.11.7) found that patients treated with delgocitinib cream were [redacted].

Conclusion

Delgocitinib cream is the first topical therapy specifically targeting all four JAK proteins involved in the JAK-STAT pathway, which mediates the activity of multiple inflammatory cytokine pathways involved in the inflammation underlying all of the different CHE subtypes. Consequently, delgocitinib is expected to be efficacious across CHE aetiologies.

The results of the DELTA trial programme demonstrate that the use of delgocitinib cream in adults with CHE is efficacious, with a favourable safety profile. DELTA 3 demonstrated that as-needed use of delgocitinib cream is an effective strategy for long-term disease management, with no new safety concerns during long-term treatment.

DELTA FORCE showed delgocitinib cream to have superior efficacy than oral alitretinoin, the only treatment specifically licensed for CHE (alitretinoin is recommended in the UK for severe CHE only [17]), with a more favourable safety profile. In addition, the NMA of IGA-CHE/PGA 0/1 responses found [redacted].

For adults with moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate, delgocitinib cream has greater efficacy and a

more favourable safety profile than PUVA (for moderate or severe CHE) or alitretinoin (for severe CHE). Delgocitinib cream therefore represents a step-change in the treatment of patients in its proposed position as a second line treatment in moderate to severe CHE, without putting further strain on stretched NHS resources.

2.13.2 Strengths and limitations of the clinical evidence base for delgocitinib

Study design

A strength of the DELTA clinical trial programme is that two identical double-blinded, vehicle-controlled trials were used to confirm the efficacy of delgocitinib cream. For all key secondary endpoints, the treatment effect of delgocitinib cream versus cream vehicle was similar in the two trials. For the primary outcome of IGA-CHE TS, a greater treatment effect was seen in DELTA 2 than in DELTA 1 [82]. This difference is within the range of what can be observed due to random variation relating to factors such as different countries, centres, and seasons, no bias was introduced due to missing data, and the 95% CIs for the two trials overlapped at all time points [82].

One limitation of the DELTA 1 and DELTA 2 study design is that delgocitinib cream was compared with cream vehicle only for 16 weeks. As there are no approved treatments indicated for moderate to severe CHE, designing a long-term controlled trial would have meant some patients being treated with cream vehicle without active ingredients for an extended period. This could not be ethically justified because of the significant disease burden. Accordingly, the DELTA 3 extension trial was designed to represent expected clinical practice, with a further 36 weeks of treatment as-needed in response to disease flares. The results of DELTA 3 demonstrated that as-needed use of delgocitinib cream is an effective strategy for long-term disease management, with no new safety concerns during long-term treatment.

A limitation of DELTA FORCE is that, as described in section 2.3.1.2, a double-dummy design was not feasible and so participants and investigators were not blinded to treatment assignment. However, the evaluation of efficacy was performed by a blinded assessor.

Appropriateness of comparators

The are no licensed drug therapies for adults with moderate CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate. Accordingly, cream vehicle was the most appropriate comparator for the DELTA 1 and DELTA 2 moderate to severe CHE trials.

Alitretinoin, the only treatment approved for CHE by NICE (for severe CHE only), was compared head-to-head with delgocitinib cream in the active-controlled DELTA FORCE trial.

Phototherapy was compared with delgocitinib cream indirectly, as described in section 2.10, and was identified as the most relevant comparator for alitretinoin based on published clinical trials and on feedback from 194 UK dermatologists and the UK Dermatology Clinical Trials Network [54].

Relevance of outcomes

The primary outcome measure in the DELTA 1 and DELTA 2 trials, IGA-CHE, was developed specifically for the DELTA clinical trial programme by clinical experts in accordance with regulatory guidance. The instrument has been psychometrically validated using data for the first 280 patients completing 16 weeks of the DELTA 1 trial, and was shown to have moderate to strong test–retest reliability and strong convergent validity, known-groups validity and ability to detect change [94]. The five-level IGA-CHE scale was shown to discriminate well between clear, almost clear, mild, moderate and severe CHE [94]; these categories are expected to be relevant to decisions to start or stop treatment in clinical practice.

The IGA-CHE categories do not correspond directly to the PGA (which was used, for example, in the alitretinoin phase 3 trial [107] and in ALPHA [54]). For the purposes of the NMA described in section 2.10, the scales were assumed to be comparable. However, there are inherent differences between the scales, such as PGA considering patient-reported itch and pain and the IGA-CHE score of 1 being more strict (only barely perceptible erythema permissible). The assumption that the two scales are comparable may underestimate the efficacy of delgocitinib estimated in the NMA.

In DELTA FORCE, achieving IGA-CHE TS required an improvement from baseline of ≥ 3 points (all participants had an IGA-CHE score of 4 at baseline; see section 2.6.9.3). The IGA-CHE validation study (see Appendix B.6.1) found that a 1-level change can reflect a clinically meaningful improvement for patients [94]. Therefore, in DELTA FORCE IGA-CHE TS, which was achieved by statistically significantly more patients treated with delgocitinib cream than with oral alitretinoin, represents a substantial improvement in patients' disease.

Loss of response/relapse was defined differently in DELTA 3 and DELTA FORCE than in some trial of other therapies. In the DELTA trials, loss of response was defined as an IGA-CHE score ≥ 2 after having achieving response (IGA-CHE 0/1) [89, 90]. By contrast, in the BACH trial of alitretinoin versus placebo, relapse was defined as a modified total lesion symptom score (mTLSS) score ≥ 75% of the baseline score (during TA177 this was considered to be a high threshold) [17, 107]. A second trial of alitretinoin versus placebo, HANDEL, defined relapse as a PGA rating of 'severe' [108]. The ALPHA trial of alitretinoin versus PUVA report on end of remission, defined as no longer having clear/almost clear PGA, and on relapse, defined as ≥ 50% and ≥ 75% of baseline HECSI [54]. Accordingly, the DELTA trial definition of loss of response/relapse includes a return to a mild CHE state, while other trials only consider patients to have relapsed when they have moderate or severe disease (see Appendix B.1.2.5.2). This may limit the comparability of loss of response/relapse data between trials.

A key strength of the DELTA trial programme is the use of HECSI-90 – a 90% reduction in HECSI from baseline – as a key secondary endpoint. HECSI-90 is a stringent endpoint which demonstrates a high degree of improvement in patients' CHE. As a contemporary measure of response, the HECSI scale has not been used in older trials, namely BACH and HANDEL.

In addition, the symptoms of itch and pain, which are of particular importance to patients (see section 1.3.1.8), were assessed using a daily symptom diary, the HESD, which was designed and psychometrically validated as part of the trial programme [32, 92].

CHE has a substantial impact on patients' HRQoL [13]. In the DELTA clinical trial programme, delgocitinib cream was associated with statistically significant improvements in HRQoL, compared with cream vehicle/oral alitretinoin. HRQoL was assessed with the DLQI, which is the most frequently used patient-reported outcome measure in CHE trials [111], and the EQ-5D-3L (cross-walked from the EQ-5D-5L), which is the HRQoL measure preferred by NICE.

Trial population

The DELTA 1 and DELTA 2 trial population included patients with both moderate and severe CHE, and all patients had a recent history of inadequate response to TCS or a contraindication to TCS. This matches the licensed indication for delgocitinib cream. The demographics of the DELTA 1 and DELTA 2 trials, which were conducted in Canada and Europe (including the UK) are similar to those of England and Wales (the trial population was 87% White, compared with 82% in England and Wales) [82, 112]. The results of the DELTA clinical studies are expected to be generalisable across different demographics within the population.

Relevance to UK clinical practice

The results of the DELTA clinical trial programme are expected to be applicable to UK clinical practice. The enrolled population matches the approved indication: adults with moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate. In addition, the subgroup analysis results show that delgocitinib cream is [redacted].

As might be expected in UK clinical practice, many patients in the DELTA trials had also previously received CHE treatments other than TCS, including phototherapy and retinoids (in DELTA 1 and DELTA 2). The only licensed treatment for severe CHE in the UK is the retinoid alitretinoin. In the DELTA FORCE trial, delgocitinib cream was shown to be statistically significantly more efficacious than oral alitretinoin for patients with severe CHE, with a more favourable safety profile.

The results of the DELTA trials showed that delgocitinib cream was an efficacious therapy after 12 weeks, which is the recommended timepoint after which treatment should be stopped if no improvement is seen. Beyond 12 weeks, patients are expected to stop using delgocitinib cream when they achieve clear or almost clear skin, and to reinitiate treatment in the event of recurrence of the signs and symptoms of CHE [70, 113]. This pattern of treatment use was assessed in DELTA 3, which showed that patients were able to recapture a treatment response following a loss of response.

3 Cost effectiveness

Summary

Model framework

- A *de novo* cost–utility model was developed to compare delgocitinib with alitretinoin and PUVA, in adults with moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate. PUVA was considered a relevant comparator in the moderate and severe CHE populations. Based on its marketing authorization and current NICE recommendation, alitretinoin was considered a relevant comparator in the severe CHE population only.
- Given the fluctuating nature of CHE, relapses are a key component of the condition and are reflected in the economic model – health states are defined by whether patients are on-treatment or off-treatment following a full response and by their level of response; IGA-CHE scores were used to determine response levels.
- The model's perspective adheres to the NICE reference case.

Model inputs

- Clinical evidence from the DELTA trial programme and the NMA (section 2.10) was used to inform the efficacy and safety of delgocitinib, alitretinoin and PUVA.
- The probabilities of achieving a treatment response during an initial 12-week treatment period were derived from the NMA results.
- For patients who discontinued treatment following a full response, the probability of experiencing a loss of response was based on data from DELTA FORCE and ALPHA, and differentiated by treatment. The probability of experiencing a relapse to moderate or severe CHE was based on data from ALPHA and assumed to be the same for all comparators.
- For patients with a relapse who resumed treatment, the probability of regaining a full response was based on data from DELTA 3 and was assumed to be the same for all comparators.
- Health state utility values were based on EQ-5D-3L data from DELTA 1 and DELTA 2.
- The only AEs included in the model were headache and nasopharyngitis, for which UK disutility values were used.
- Costs included treatment acquisition and monitoring, as well as health state-specific resource use, all of which were derived from UK sources.

Model results

- The base-case model results found delgocitinib to be dominant to PUVA (less costly and more effective) for both moderate CHE and severe CHE.
- Delgocitinib was cost effective compared with alitretinoin in the treatment of severe CHE, with an incremental cost-effectiveness ratio (ICER) of £8,221 per QALY gained.

Sensitivity analyses

- Sensitivity analyses (probabilistic and deterministic) and scenario analyses suggest that the model results are robust to input changes and uncertainty.

3.1 Published cost-effectiveness studies

Identification and selection of relevant cost-effectiveness studies is described in Appendix E. In brief, searches of relevant publication databases and grey literature sites were conducted on 23 July 2024. The SLR identified five published economic evaluations (Table 52) [54, 106, 114-116].Two studies describing the economic model in TA177 [115, 117] and a

comparative cost-effectiveness of oral alitretinoin and immersion PUVA in ALPHA [54] were conducted from a UK perspective. These published studies were used to inform the development of the delgocitinib economic model.

3.2 Economic analysis

The objective of the economic analysis was to evaluate the cost-effectiveness of delgocitinib, compared with alitretinoin and PUVA in the treatment of adult patients with moderate to severe CHE who have not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate (see section 1.3.3).

None of the studies identified in the SLR of economic evaluations included delgocitinib as a comparator. Accordingly, a de novo cost–utility analysis (CUA) model was developed. The analysis used a Markov state-transition model developed in Microsoft Excel for 365® with health states based on levels of response achieved, defined by IGA-CHE score in the base case and HECSI response in a sensitivity analysis (see section 2.3.1.5).

The steps undertaken to develop the model concept plan followed best practice guidance on conceptualising models, as recommended by Tappenden *et al.* 2012 [34] and Roberts *et al.* 2012 [118]. Expert advice was sought on the appropriateness of the CHE treatment pathway in the UK and the model structure.

The NICE reference case was followed in all aspects of the CUA design and perspective; including costs reflecting the NHS and personal social services (PSS) and outcomes reported as quality-adjusted life years (QALYs) gained.

3.2.1 Patient population

In the base-case analysis, the model cohort reflected the patient characteristics of the DELTA 1 and DELTA 2 trial populations, which comprised adult patients with moderate to severe CHE. As outlined in section 2.13.2, this population is well aligned with the licensed indication for delgocitinib, and results are expected to be generalisable across different demographics within the population of England and Wales.

The target population is adult patients with moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate. Not all relevant comparators are recommended for the treatment of both patients with moderate and severe CHE (see section 3.2.3); therefore, the model considers moderate CHE patients and severe CHE patients separately.

Table 52 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)
Blank [106]	2010	Markov model with three PGA health states Swiss third-party payer perspective	CHE not responding to standard therapy	Alitretinoin: 11.21 Supportive care: 10.98	Alitretinoin: €42,208 Conventional treatment: €38,795 No indirect costs included	Alitretinoin vs supportive care: €14,816
Nam [114]	2017	Markov model South Korean societal perspective	Patients with severe CHE refractory to steroids	NR	NR	Alitretinoin vs control: • 1 year: $31,350 • 3 years: $15,854 • 20 years: $8,917
Paulden [115] Rodgers [117] (Model used in TA177)	2010	Markov based discrete event simulation with remission, mild, moderate, severe and refractory health states England and Wales NHS/PSS perspective	Adults with severe chronic eczema of the hand that is unresponsive to TCS	Alitretinoin: 2.00 Ciclosporin: 1.79 PUVA: 1.80 Azathioprine: 1.75	Alitretinoin: £3,388.33 Ciclosporin: £1,580.72 PUVA: £3,481.28 Azathioprine: £805.25	*Original submission*: • alitretinoin vs ciclosporin: £8,614 • alitretinoin vs PUVA: £−469 (alitretinoin dominant) • alitretinoin vs azathioprine: £10,612 *Revised model with alternative HRQoL data*: • alitretinoin vs ciclosporin: £16,756 • alitretinoin vs PUVA: £-884 • alitretinoin vs azathioprine: £22,312 • alitretinoin vs supportive care: £12,931.
Vicente [116]	2012	Markov model with three PGA health states Canadian public healthcare and societal perspectives	Adults with severe CHE unresponsive to potent TCS	NR	NR	*Original model* Alitretinoin versus ciclosporin: • Public healthcare perspective: $15,452 • Societal perspective: alitretinoin dominates ciclosporin *Revised model with conservative HRQoL estimates*: • alitretinoin vs ciclosporin: over $25,000 • alitretinoin vs supportive care: over $89,000
ALPHA [54]	2024	Within-trial analysis over 12 and 52 weeks and long-term (10 year) analysis using Markov model with three PGA health states NHS and PSS perspective	Patients with severe CHE unresponsive to at least 4 weeks of treatment with potent topical corticosteroids	Week 12: Alitretinoin: 0.1589 PUVA: 0.1651 Week 52: Alitretinoin: 0.7618 PUVA: 0.7984 10 years: Alitretinoin: 6.530 PUVA: 6.536	Week 12[a]: Alitretinoin: £1,907 PUVA: £3,235 Week 52[a]: Alitretinoin: £3,353 PUVA: £4,389 10 years: Alitretinoin: £5,433 Immersion PUVA: £5,362	Immersion PUVA vs alitretinoin: • Week 12: £699,682 • Week 52: £39,787 • 10 years: PUVA dominates (probabilistic analysis shows probability of being most cost-effective is 50% for both alitretinoin and PUVA)

[a] Totals without out-of-pocket costs; CHE, chronic hand eczema; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NR, not reported PGA, Physician's Global Assessment; PSS, Personal Social Services; PUVA, psoralen–UV A phototherapy; QALY, quality-adjusted life year; TCS, topical corticosteroids.

Baseline characteristics from DELTA 1 and DELTA 2 were used to inform key population characteristics in the model (Table 53) [82]. Subgroup analyses were performed among patients with moderate CHE and severe CHE.

Table 53 Population baseline characteristics from pooled DELTA 1 and 2 trials (N = 960)

Parameter	Moderate [IGA-CHE 3]	Severe [IGA-CHE 4]
Mean age [a]	43.7 years	45.2 years
Sex (% male) [a]	34.6%	38.2%

[a] The mean age and gender percentage split of patients were included as parameters in the model to calculate all-cause mortality rates and HRQoL adjustments (see sections 3.3.6, 3.4.4 and 3.4.6).
CHE, chronic hand eczema; IGA-CHE, investigator global assessment for chronic hand eczema.

3.2.2 Model structure

Model structure

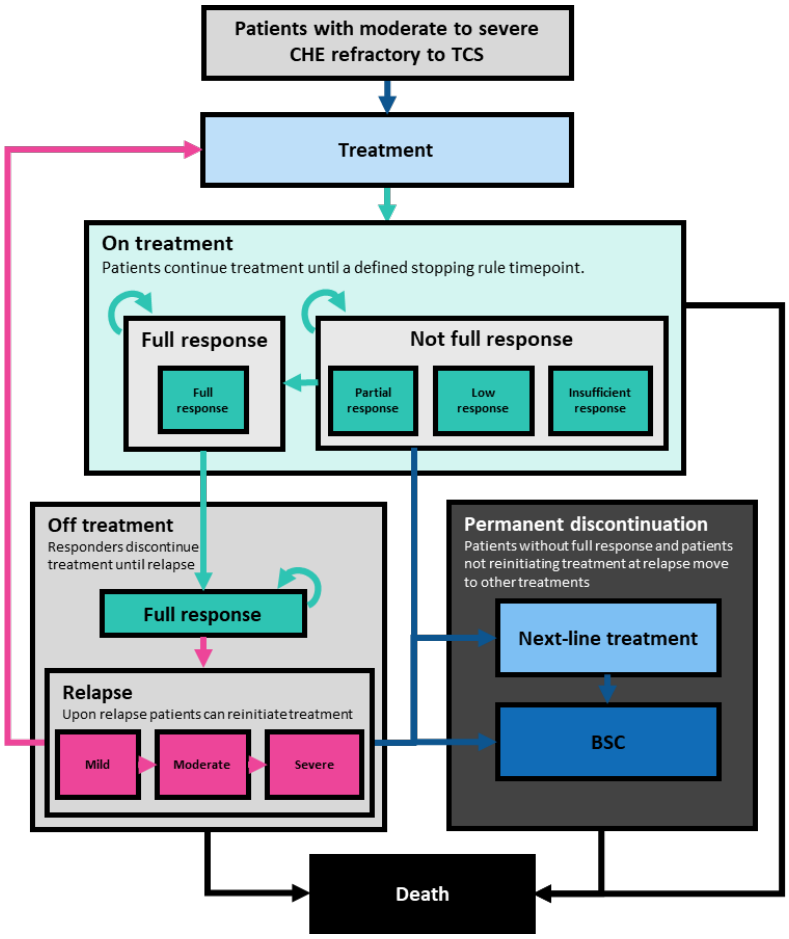
The model structure is shown in Figure 29. Patients receive treatment for at least 12 weeks; treatment beyond 12 weeks is dependent on responses and treatment-specific stopping rules (see section 3.2.4).

At week 12 and beyond, patients are assumed to discontinue their treatment after achieving full response. Given the fluctuating nature of CHE, relapses are a key component of the condition and are reflected in the economic model: having discontinued their treatment, patients may then reinitiate treatment following a relapse. This is consistent with the as-needed use of delgocitinib and with the retreatment recommendations of alitretinoin specified in their respective labels.

The model health states are defined by whether patients are on-treatment or off-treatment (following a full response), and by their level of response (measured with the IGA-CHE in the base-case analysis, or with HECSI in a scenario analysis). The response definitions used in the model are summarised in Table 54; note that all parameters associated with HECSI response scenario are presented in Appendix J. Patients can also discontinue their initial treatment and move to next-line treatment, or to BSC, a strategy comprising topical therapies only.

Though neither CHE nor its treatment affect overall mortality, patients face the same background risk of death as the general population.

Figure 29 Model schematic



BSC, best supportive care; CHE, chronic hand eczema; TCS, topical corticosteroids.

Table 54 Response definitions

Health state	IGA-CHE (base case)	HECSI (scenario analysis)
Full response	IGA-CHE 0 (clear) or 1 (almost clear)	HECSI 90
Partial response	IGA-CHE 2 (mild)	HECSI 75 to 89
Low response	IGA-CHE 3 with 1-point improvement from baseline (moderate)	HECSI 50 to 74
Insufficient response	IGA-CHE 3 without improvement from baseline or IGA-CHE 4 (severe)	< HECSI 50

HECSI response categories are defined based on the achievement of a certain percentage improvement in HECSI from baseline, e.g., at least a 90% improvement or between a 50% and 75% improvement.
HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

Initial treatment

All patients are treated for an initial 12 weeks and can achieve a full response in any 4-week cycle during this period. At week 12, patients who have not yet achieved full response are assessed and allocated across the partial, low and insufficient response states based on their level of improvement from baseline. The approach to treatment during the first 12 weeks is hereafter referred to as a *fixed course*, meaning that all patients receive continuous treatment for the duration regardless of their response.

After week 12, each comparator has a specific set of stopping rules based on their marketing authorisation, reimbursement criteria and/or recommended use in clinical practice (see section 3.2.4). Depending on the treatment received and the level of response achieved at

week 12, patients will either discontinue treatment or they will continue for a further period, the duration of which is treatment and response dependent. During each 4-week cycle of continued treatment, patients can achieve full response (and stop treatment), maintain their response or discontinue. The approach to treatment during this continued treatment phase is hereafter referred to as *as-needed*, meaning that patients receive continuous treatment until they achieve full response or discontinue treatment, or up to the maximum duration of the stopping rule, whichever comes first.

Relapse and retreatment

Patients who achieve a full response at week 12 or later discontinue their treatment. During the off-treatment period, patients have a risk of their CHE relapsing. Depending on the severity of a relapse, treatment may be reinitiated on an as-needed basis. During each 4-week cycle of re-treatment, patients can achieve full response (and stop treatment), maintain their current level of CHE severity or discontinue. The maximum duration of retreatment is 24 weeks and there is no limit to the number of rounds of retreatment a patient can receive following response and relapse.

Next-line treatment and best supportive care

Patients who discontinue treatment for any reason other than the achievement of full response proceed to next-line treatment or BSC. There is substantial variation in clinical practice as to which next-line treatments are used and in what order. Accordingly, each subsequent line of care was represented by a 'basket' of relevant treatments. Patients who do not respond to one of the comparator treatments may go on to receive multiple treatment options including PUVA, systemics, biologics and TCS. The costs and effects of this basket were defined by a distribution of each treatment's use, an expected duration of use as a proportion of time, and an estimate of efficacy.

Patients receiving next-line treatment can either continue in this state or discontinue to BSC, which comprises emollients, TCS and TCI.

Death

Death is an absorbing state to which patients can transition from any model state at any time. Mortality was not conditioned on treatment or level of response.

Features of the economic analysis

Key features of the analysis are summarised in Table 55.

Table 55 Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	TA177 [17, 115, 117]	Chosen values	Justification
Time horizon	3 years	10 years	To capture all relevant differences in costs and benefits
Source of utilities	Derived from DLQI data in the alitretinoin phase 2 trial BAP0003	Derived based on EQ-5D-5L data collected in the DELTA trials and cross-walked to EQ-5D-3L values [79]	As per NICE reference case
Source of costs	Published sources; BNF, PSSRU and NHS reference costs	BNF [119], PSSRU [120], NHS tariffs and NHS reference costs [121]	As per NICE reference case

Discount rate	3.5%	3.5%	As per NICE reference case
Health effects measure	QALYs	QALYs	As per NICE reference case
Cycle length	Discrete event simulation Markov model with monthly intervals	4 weeks	To account for differences in treatment response at 4-week intervals
Half cycle correction	No	Yes	ISPOR Good Research Practices in Modelling recommendation [122]

BNF, British National Formulary; DLQI, Dermatology Life Quality Index; EQ-5D-5L, 5-dimension, 5-level EuroQol questionnaire; ISPOR, The Professional Society for Health Economics and Outcomes Research; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

3.2.3 Intervention technology and comparators

For patients with moderate to severe CHE, the pathway of care after inadequate response to TCS, with or without TCIs, is not well documented, and may be based on individual prescriber preference (see section 1.3.3) [123]. Only alitretinoin is specifically recommended by NICE for severe CHE. Alitretinoin was compared with PUVA in the recent ALPHA trial, an NIHR-funded study conducted among patients with severe CHE which was unresponsive to treatment with first-line therapy with TCS (see section 1.3.3.4) [54]. There are no medications currently licensed for moderate CHE following an inadequate response to TCS and established practice may vary more than for severe CHE. As outlined in section 1.3.3.2, ESCD guidance suggests that phototherapy (PUVA or UVB) may be used for moderate to severe CHE refractory to TCS.

Delgocitinib is indicated for the treatment of moderate to severe CHE in adults who have not responded to treatment with TCS, or for whom TCS are inadequate or inappropriate. The expected position of delgocitinib in the treatment pathway (Section 1.3.3, Figure 2), is as a second-line therapy for patients with moderate to severe CHE requiring long-term management, after TCS/TCI and before systemic therapy and biologics. It is expected that delgocitinib will be prescribed in secondary care, with routine follow-up in primary care, although it is possible that in clinical practice some patients may have follow-up in secondary care.

Therefore, the comparators included in the model were alitretinoin and PUVA. The relevance of each comparator is discussed further in section 1.3.3.7. The comparators were modelled as per their marketing authorisation, where available. PUVA was considered a relevant comparator in the moderate and severe CHE populations. Alitretinoin was considered a relevant comparator in the severe CHE population only.

The clinical evidence for narrow-band UVB did not allow for synthesis with the other comparators (Appendix B.2.1), and PUVA was assumed to serve as a proxy for narrow-band UVB. This assumption may be conservative given that the limited available evidence suggests that narrow-band UVB may be less effective than PUVA [124], though the unit cost of both strategies is the same according to the NHS tariffs and NHS reference costs, as they fall under the same Health Related Group (HRG) code (JC47Z).

The key characteristics of the comparators including the route of administration, dosing assumptions and stopping rules are summarised in section 3.2.4.

3.2.4 Stopping rules

Initial treatment (first 12 weeks)

Stopping rules for each treatment are shown in Table 56. In the base case, all patients continue treatment to week 12 regardless of response (fixed course). This is consistent with the way that treatments were used and evaluated in the clinical trials. In a scenario analysis, full responders to delgocitinib are assumed to stop treatment during any 4-week cycle up to week 12, which is consistent with its label. For all treatments, patients who are off treatment following a full response have a risk of relapse, at which point they can reinitiate treatment with the same therapy on an as-needed basis.

Initial treatment (beyond 12 weeks)

Patients with an insufficient response at week 12 (i.e., no improvement from baseline) discontinue the initial treatment. For the therapies being evaluated, 12 weeks is considered sufficient to have observed some improvement and consistent with the label for both delgocitinib and alitretinoin and with the trial evidence for PUVA. Patients with a low or partial response at week 12 continue their treatment (as-needed) up to week 24. During any 4-week cycle between week 12 and week 24, patients can achieve a full response and stop treatment. The 24-week stopping rule is consistent with the alitretinoin label and the clinical trials for PUVA. The rule is applied to delgocitinib as well on the basis that patients who have not achieved a full response after 6 months of ongoing treatment are likely to seek alternative effective treatment options.

Retreatment

Retreatment following relapse follows a slight variation on the stopping rules, with the maximum duration of treatment for all comparators being 24 weeks but without an interim assessment at week 12. Given that patients have previously received and responded to the treatment, the evidence suggests that patients may need less time to respond to treatment. Treatments are used in an as-needed fashion, so during any 4-week cycle of re-treatment, patients can achieve full response and stop treatment. Patients who have not achieved a full response by week 24 discontinue and move to next-line therapy or BSC. As in the case of initial treatment, the 24-week stopping rule for retreatment is based on the expectation that patients who have not achieved a full response after 6 months of ongoing treatment are likely to seek alternative effective treatment options.

Table 56 Key characteristics of comparators included in the model

Treatment	Treatment Type	Indication	Administration and dosing instruction	Modelled stopping rules
Delgocitinib	JAKi	• MHRA licence: delgocitinib is indicated for the treatment of moderate to severe CHE in adults for whom TCS are inadequate or inappropriate [70]	• Topical • Each affected area should be treated twice daily until the skin is clear or almost clear. In the event of recurrence of the signs and symptoms of CHE (flares), twice daily treatment of the affected areas should be re-initiated as-needed • Consumption informed by DELTA 1, DELTA 2 and DELTA FORCE [82, 90]	• All patients continue treatment to week 12 regardless of response (fixed course base case consistent with the clinical trials) [a] • Patients with full response by week 12 stop treatment at week 12 (first stopping rule) • Patients with insufficient response at week 12 stop treatment • Patients with partial or low response at week 12 continue treatment as-needed up to week 24 (second stopping rule), stopping treatment in the next cycle if they achieve full response or if they are still not full responders by the defined second stopping rule • During retreatment following relapse, patients are treated as-needed up to week 24, stopping treatment in the next cycle if they achieve full response or if they are still not full responders by week 24
Alitretinoin	Retinoid	• MHRA licence: alitretinoin is indicated for use in adults who have severe chronic hand eczema that is unresponsive to treatment with potent TCS [125] • Only treatment currently recommended by NICE for use in adults with severe CHE who are unresponsive to treatment with TCS [17] • May be used off label among patients with moderate CHE though this is unsupported by RCT evidence	• Oral • 30 mg capsule once daily for 12-24 weeks (with an option to reduce to 10 mg if there are unacceptable AEs) • Treatment should be stopped as soon as an adequate response has been achieved or if the eczema remains severe (as defined by the PGA) at 12 weeks or if an adequate response (hands clear or almost clear) has not been achieved by 24 weeks [17]	• All patients continue treatment to week 12 regardless of response (fixed course) • Patients with full response by week 12 stop treatment at week 12 (first stopping rule) • Patients with insufficient response at the defined first stopping rule stop treatment • Patients with partial or low response at week 12 continue treatment as-needed up to week 24 (second stopping rule), stopping treatment in the next cycle if they achieve full response or if they are still not full responders by the defined second stopping rule • During retreatment following relapse, patients are treated as-needed up to week 24, stopping treatment in the next cycle if they achieve full response or if they are still not full responders by week 24
PUVA	Phototherapy	• Phototherapy may be used to treat moderate to severe CHE refractory to TCS [5]	• Oral or topical psoralen and ultraviolet A delivered in a hospital setting under dermatologist supervision	• All patients continue treatment to week 12 regardless of response (fixed course) • Patients with full response by week 12 stop treatment at week 12 (first stopping rule)

Treatment	Treatment Type	Indication	Administration and dosing instruction	Modelled stopping rules
			• 2 session per week for 12 weeks [54]	• Patients with insufficient response at week 12 stop treatment • Patients with partial or low response at week 12 continue treatment as-needed up to week 24 (second stopping rule), stopping treatment in the next cycle if they achieve full response or if they are still not full responders by the defined second stopping rule • During retreatment following relapse, patients are treated as-needed up to week 24, stopping treatment in the next cycle if they achieve full response or if they are still not full responders by week 24

[a] In a scenario analysis, patients treated with delgocitinib can achieve full response and stop treatment during any 4-week cycle up to week 12 (as-needed usage, which is consistent with the delgocitinib label).

AD, atopic dermatitis; AE, adverse event; CHE, chronic hand eczema; JAKi, Janus kinase inhibitor; kg, kilogram; mg, milligram; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute of Health and Care Excellence, PGA, physician global assessment; PUVA, psoralen–UV A phototherapy; RCT, randomised controlled trial; TCS, topical corticosteroids.

3.2.1 Re-initiation following loss of response

Responders who have stopped treatment due to a complete response may lose their response and may then re-initiate treatment. In the model, the threshold severity at which patients are eligible to re-initiate treatment varies by comparator. Delgocitinib may be restarted at the point of a loss of response (IGA-CHE ≥ 2), reflecting the clinical trial data as well as its expected as-needed use in clinical practice. Alitretinoin and PUVA are only restarted at the point of a moderate or severe relapse (IGA-CHE ≥ 3 or IGA-CHE 4), reflecting their use in clinical practice and, in the case of alitretinoin, their label.

To test the impact of these assumptions, scenario analyses were run in which all treatments were resumed at the same point: loss of response or mild relapse (IGA-CHE ≥ 2); moderate relapse (IGA-CHE ≥ 3); or severe relapse (IGA-CHE = 4) (see section 3.10.2).

3.3 Clinical parameters and variables

3.3.1 Response to initial treatment

3.3.1.1 Response to treatment up to week 12

In the DELTA trials, response to delgocitinib was evaluated at 16 weeks, but the licence for delgocitinib recommends that response should be evaluated after 12 weeks.

The probabilities of response for all treatments were derived from the results of the NMAs (see section 2.10.4). Results from the moderate CHE and severe CHE NMAs were used to enable appropriate subgroup analyses. In the base case economic analysis, the week 12 NMAs were used (see section 2.10.4.2). Data from the primary endpoint analyses, corresponding to the week 16 outcomes for delgocitinib, as well as the cumulative response analyses at week 12 (see section 2.10.4.3), were tested in scenario analyses (see section 3.10.2).

It is worth remembering that the only available clinical data for alitretinoin and PUVA are for patients with severe CHE, but PUVA is also the only treatment that European guidance suggests for the treatment of moderate CHE that has not responded to TCS. The NMA of moderate CHE synthesises evidence from the moderate CHE subgroup of DELTA 1 and DELTA 2 with severe CHE evidence from DELTA FORCE and ALPHA. This is based on the assumption that the relative treatment effects of delgocitinib and alitretinoin in DELTA FORCE and of alitretinoin and PUVA in ALPHA would be similar if evaluated among patients with moderate CHE. The assumption enables a comparison to be modelled between delgocitinib and PUVA using the best available RCT data, though it relies on the indirect application of the evidence to a moderate CHE population.

The probabilities of response for delgocitinib from the NMAs formed the baseline risk of response in the model. To estimate the efficacy of other comparators, relative effects versus delgocitinib from the NMAs were applied to the baseline risks to derive response rates at week 12.

To estimate the per-cycle probability of achieving full response, the probability of full response at week 12 from the NMAs was cycle-adjusted based on the formula below, assuming that the underlying rate of response was constant up to week 12. This four-weekly probability was applied at each cycle up to week 12.

$$p_{4wk} = 1 - (1 - p_{12wk})^{\frac{4}{12}}$$

In a scenario analysis, the probability of response at week 16 was used to derive the four-weekly probability and applied up to the week 12 timepoint.

Table 57 presents the 12-week probabilities of full response for each comparator along with the odds ratio used to estimate the probabilities from the baseline risk of delgocitinib. To note, the model used NMA outputs on the log scale (see Table 72). Table 57 also presents the cycle-adjusted probabilities of full response used in the model for each treatment up to week 12. Values are presented for the base case using the week 12 NMA results and the scenario using the primary endpoint NMA results. Equivalent values using HECSI 90 as the definition of full response are shown in Appendix J.3, Table 251.

In the absence of comparative efficacy for PUVA on the outcome of HECSI 90 (see section 2.10.4.4), the relative effect between PUVA and alitretinoin on IGA-CHE 0/1 was assumed to apply.

Table 57 Probabilities of and treatment effects for full response (IGA-CHE 0/1) in first 12 weeks of treatment

Treatment	12-week risk [a]	Odds ratio [b]	4-week risk [c]	Source
Week 12 analysis (base case)				
Severe CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
Alitretinoin	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC [d]	[redacted]	[redacted]	[redacted]	NMA
Moderate CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC [d]	[redacted]	[redacted]	[redacted]	NMA
Primary endpoint analysis (scenario analysis)				
Severe CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
Alitretinoin	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC [d]	[redacted]	[redacted]	[redacted]	NMA
Moderate CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC [d]	[redacted]	[redacted]	[redacted]	NMA

[a] The probability of response for comparators other than delgocitinib is calculated by applying the odds ratio versus delgocitinib to the odds of delgocitinib, which is derived from the probability using the formula odds = probability/(1-probability). The odds are then transformed back into a probability using the formula: probability = odds/(1+odds).

[b] Delgocitinib versus comparator.

[c] The 4-week probability is derived from the 12-week probability by the formula $1-(1-p)^t$ and assuming a constant underlying rate.

[d] Values are based on the vehicle / placebo comparator in the NMA and define the probability of full response in the BSC health state.
HECSI, Hand Eczema Severity Index; IGA-CHE, investigator global assessment for chronic hand eczema; NA, not applicable; PUVA, psoralen–UV A phototherapy.

3.3.1.2 Health state allocation at week 12

At week 12, patients not yet in full response were distributed across three non-response health states based on clinical trial data from the DELTA trials. Table 58 presents the values used to allocate patients who have not yet fully responded at the end of week 12 using IGA-CHE (base case). Distributions across HECSI states (scenario analysis) are presented in Appendix J.3, Table 252.

For IGA-CHE, data regarding the distribution of patients across non-responder IGA-CHE severity states (mild, moderate and severe) at week 12 were taken from subgroup analyses of the DELTA trials for delgocitinib (DELTA 1, DELTA 2 and DELTA FORCE) and alitretinoin (DELTA FORCE). Here, missing data were imputed to worst observation carried forward. These were then mapped to the IGA-CHE response states based on improvement from baseline. For patients with severe CHE at baseline, the distribution across the non-responder IGA-CHE severity states (scores of 2, 3 and 4) was the same as the distribution across the IGA-CHE response states (partial, low and insufficient response). For patients with moderate CHE at baseline, patients in the IGA-CHE 3 severity state at week 12 were classified as insufficient responders in the IGA-CHE response state because they had not achieved ≥ 1-point improvement from baseline.

The ALPHA trial also reported data to inform distributions across non-response PGA states at week 12 for alitretinoin and PUVA. These showed a high degree of missing data. If missing data were counted as insufficient response (consistent with a worst observation carried forward approach), then the distribution across non-responder states for alitretinoin was skewed more towards insufficient response than seen in DELTA FORCE. If only observed cases were used, then the distribution was more centred around low response than seen in DELTA FORCE. Under both approaches to handling the missing data, the distribution among PUVA non-responders tended to be more skewed towards insufficient response than alitretinoin.

As stated above, non-responder distributions for delgocitinib and alitretinoin in the severe CHE subgroup were taken from DELTA FORCE as this was considered the best available data for these comparators. The distribution applied to PUVA non-responders was assumed to be the same as that for alitretinoin from DELTA FORCE, which may underestimate the number of insufficient responders relative to observations in ALPHA. In a set of scenario analyses, the ALPHA distributions were tested, one in which missing data was counted as insufficient response the other which relied on observed cases only.

In the absence of health state allocation data for PUVA in the moderate CHE subgroup, the distribution of patients across non-response health states was assumed to be the same as for delgocitinib. Based on trends observed in the severe CHE subgroup, this may underestimate insufficient response to PUVA.

Table 58 Proportion of patients in each non-full response state at week 12

Comparator	IGA-CHE severity states			IGA-CHE response states			Source/notes
				PR	LR	InR	
	IGA-CHE 2	IGA-CHE 3	IGA-CHE 4	IGA-CHE 2	IGA-CHE 3 with 1-pt Δ	No Δ	
Moderate CHE							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate subgroup analysis of DELTA 1 and DELTA 2 [79]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to delgocitinib.
BSC [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate subgroup analysis of DELTA 1 and DELTA 2 vehicle arm [79]
Severe CHE (base case)							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Severe subgroup analysis of DELTA 1 and DELTA 2 and DELTA FORCE, pooled [79]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DELTA FORCE [79]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to alitretinoin
BSC [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Severe subgroup analysis of DELTA 1 and DELTA 2 vehicle arm [79]
Severe CHE (sensitivity analysis using ALPHA data for alitretinoin and PUVA, assuming NRI for missing data)							
Alitretinoin	21.4%	35.8%	42.8%	21.4%	35.8%	42.8%	ALPHA [54]
PUVA	15.6%	28.0%	56.5%	15.6%	28.0%	56.5%	
Severe CHE (sensitivity analysis using ALPHA data for alitretinoin and PUVA, observed cases)							
Alitretinoin	30.1%	50.4%	19.5%	30.1%	50.4%	19.5%	ALPHA [54]
PUVA	25.7%	46.0%	28.3%	25.7%	46.0%	28.3%	

[a] Values are based on the vehicle arms of DELTA 1 and DELTA 2 and define the distribution of non-responders in the BSC health state.

IGA-CHE, investigator global assessment for chronic hand eczema; InR, insufficient response; LR, low response; NRI, non-responder imputation; PR, partial response; PUVA, psoralen–UV A phototherapy; Δ, change/improvement

3.3.1.3 Response to initial treatment beyond week 12

Evidence from a *post hoc* analysis of the DELTA 3 trial indicates that partial responders may achieve full response with further delgocitinib therapy. The relative cumulative incidence curves for time to first IGA-CHE 0/1 response among patients who achieved a partial response (IGA-CHE 2) or low response (IGA-CHE 3 with a 1-point improvement) at the end of DELTA 1 and DELTA 2 and continued delgocitinib in DELTA 3 are shown in Appendix B.7.1, Figure 41 [79].

A *post hoc* analysis of DELTA FORCE indicated that for patients with IGA-CHE 2 or 3 at week 12, the probability of achieving IGA-CHE 0/1 at week 24 was [redacted] [79]. Therefore, the [redacted]. Though the ALPHA trial protocol allowed for partial responders to continue with alitretinoin and PUVA between week 12 and week 24, no data were reported that could be used to derive probabilities of response during this period. In the absence of evidence for PUVA, the response probabilities for delgocitinib and alitretinoin were assumed to apply. Based on the comparative efficacy of PUVA relative to alitretinoin in the first 12 weeks, this assumption of equivalence with further treatment could overestimate the response probabilities for PUVA.

A similar analysis could not be conducted for health states defined by HECSI responses due to the design of the DELTA trials (since patients discontinued their treatment based on IGA-CHE responses). Accordingly, for the scenario using HECSI health states, the probability of achieving a full response after week 12 was assumed to be the same as for the IGA-CHE analysis.

The cumulative probabilities of achieving a full response at week 36 in DELTA 3 were used to calculate per-cycle probabilities of achieving a full response beyond week 12 from the partial response and low response health states (Table 59).

Table 59 Per-cycle probability of full response with continued treatment by non-responder health state

Strategy	Per-cycle probability of achieving full response [a]			Source/notes
	From partial response		From low response	
	Moderate at baseline	Severe at baseline		
Delgocitinib	[redacted]	[redacted]	[redacted]	*Post hoc* analysis of DELTA 3.
Alitretinoin	[redacted]	[redacted]	[redacted]	Assumed to be the same as delgocitinib based on *post hoc* analysis of DELTA FORCE.
PUVA	[redacted]	[redacted]	[redacted]	Assumed equivalent to alitretinoin in absence of evidence.

[a] Values are based on IGA-CHE 0/1 and, in the absence of evidence, assumed to apply to HECSI-90 in scenario analysis as well.

[b] Cycle-adjusted from cumulative incidence of [redacted] at week 36 from DELTA 3 among moderate patients treated with delgocitinib in DELTA 1 and DELTA 2 who attained an IGA-CHE of 2 but not IGA-CHE of 0/1.

[c] Cycle-adjusted from cumulative incidence of [redacted] at week 36 from DELTA 3 among severe patients treated with delgocitinib in DELTA 1 and DELTA 2 who attained an IGA-CHE of 2 but not IGA-CHE of 0/1.

[d] Cycle-adjusted from cumulative incidence of [redacted] at week 36 from DELTA 3 among patients treated with delgocitinib in DELTA 1 and DELTA 2 who attained an IGA-CHE of 3 with 1-point improvement but not IGA-CHE of 0/1.
IGA-CHE, investigator global assessment for chronic hand eczema; NA, not applicable; PUVA, psoralen–UV A phototherapy. Source: Statistical appendix, Tables HTA21.1, HTA21.2 [79].

3.3.2 Loss of IGA-CHE response and relapse

In DELTA 3, patients with IGA-CHE 0/1 at the end of DELTA 1 and DELTA 2 started the extension study off-treatment, and reinitiated treatment with delgocitinib when their IGA-CHE score reached ≥ 2. However, this does not necessarily mean that patients have returned to their baseline severity score of moderate or severe (IGA-CHE 3 or 4). Similarly, in DELTA FORCE, patients with IGA-CHE 0/1 stopped treatment with delgocitinib or alitretinoin after week 16 or week 12, respectively, and reinitiated treatment when their IGA-CHE score reached ≥ 2. During the off-treatment periods, patients were prohibited from using treatments other than emollients to manage their condition. The maximum follow-up in DELTA 3 during which a loss of response could be observed was 36 weeks. In DELTA FORCE, only patients who had achieved a response to delgocitinib or alitretinoin at week 16 or week 12, respectively, could be assessed for a subsequent loss of response up to week 24.

In DELTA 3, patients could experience a loss of response having previously:

1. achieved IGA-CHE 0/1 during DELTA 1 or DELTA 2 and started DELTA 3 off-treatment;
2. achieved IGA-CHE 0/1 for the first time during DELTA 3 and discontinued treatment; or
3. had a loss of response during DELTA 3, then achieved IGA-CHE 0/1 again during re-treatment, and discontinued treatment for a second time.

A *post hoc* analysis showed that the time to loss of IGA-CHE response was similar for these groups, so a pooled analysis was conducted (Appendix B.7, Figure 42). The median time to loss of response (IGA-CHE ≥ 2) [redacted]. The median time to moderate (IGA-CHE 3) or severe (IGA-CHE 4) relapse could not be estimated, because patients reinitiated treatment as soon as they experienced an IGA-CHE ≥ 2 (mild CHE).

In DELTA FORCE, the median time to IGA-CHE ≥ 2 among responders was [redacted]), though the sample is small (n = [redacted] for delgocitinib and n = [redacted] for alitretinoin) and follow-up limited (maximum of 8 weeks for delgocitinib and 12 weeks for alitretinoin). The results for alitretinoin are not dissimilar from those from the BACH and HANDEL studies, which reported a median time to PGA ≥ 2 of 8 weeks (IQR: 4.1 weeks, not estimable) and 8.3 weeks (95% CI: 8.1 to 8.9 weeks), respectively [107, 108].

The ALPHA trial reported the proportion of patients who experienced a loss of remission, defined as no longer having a clear/almost clear PGA (PGA ≥ 2), during the 52-week trial period as 90.7% among alitretinoin-treated patients and 70.2% among PUVA-treated

patients. The authors did not report on the median time to loss of remission though they did present KM curves and concluded that there was no evidence of a difference in the rate of loss of remission between treatment groups [54].

Due to protocol-driven re-initiation of treatment in DELTA 3 and DELTA FORCE at IGA-CHE ≥ 2, it is not possible to determine the likelihood or rate of relapse to moderate or severe CHE for delgocitinib. Such data are partially available for alitretinoin from the BACH and HANDEL studies, though there were differences between these studies in terms of the definition of relapse and the use of other treatments after the discontinuation of alitretinoin following response which might affect the rate of relapse and introduce potential bias (see Appendix B.1.2.5.2). Similarly, the ALPHA trial reported time to relapse, defined as achieving 50% and 75% of baseline HECSI score, but the design of the study allowed for the attending clinical team to continue with "standard clinical practice" in the event of any relapse, which could include a PGA ≥ 2. These issues make it difficult to differentiate between treatments in terms of the likelihood of relapse to moderate or severe CHE.

In a simplifying assumption, the model uses available evidence from the DELTA trials and ALPHA to inform treatment-specific probabilities of transitioning from full response to mild CHE and then assumes a common set of probabilities across all treatments, informed by the ALPHA trial, for transitioning to states of moderate and severe CHE [54]. These probabilities were derived from the transition matrices reported by Wittmann *et al*. which defined movement between response, moderate and severe health states between week 24 and 36 and week 36 and week 52 of trial follow-up. Note that the ALPHA trialists state "that patient status at week 52 was" assumed to be "equivalent to that observed at week 48" [54]. The rates over these two 12-week periods and across both alitretinoin and PUVA arms were averaged to arrive at a single set of probabilities used in the model for all treatments.

Published study data reporting on relapses for delgocitinib, alitretinoin and PUVA are described in Appendix J.1 (including Table 246).

The probability of relapse to each CHE severity level in each cycle was calculated as shown in Appendix J.1, Table 247), and is presented in Table 60.

Table 60 Probability of relapse (all patients regardless of starting severity)

Strategy	Mild relapse (pMild)	Moderate relapse (pMod)	Severe relapse (pSev)	Source
Delgocitinib	[redacted][a]	20.9%	2.2%	Probability of mild relapse calculated from DELTA FORCE [79]; probability of moderate and severe relapse based on data from ALPHA [54].
Alitretinoin	[redacted][b]	20.9%	2.2%	
PUVA	[redacted]	20.9%	2.2%	Assumed equal to alitretinoin based on conclusions of no difference from ALPHA [54].

[a] Cycle-adjusted probability based on assumption of 50% loss of response within [redacted] weeks (median) from DELTA FORCE. Scenario analysis assumed 50% loss of response within [redacted] weeks (median) from DELTA 3 (= [redacted]).
[b] Cycle-adjusted probability based on assumption of 50% loss of response within [redacted] weeks (median) from DELTA FORCE.
PGA, Physician Global Assessment; PUVA, psoralen–UV A phototherapy; TA, technology appraisal.

The rate and severity of relapse was assumed to be constant over time and independent of the time on-treatment prior to full response, time in full response on or off-treatment, severity of CHE prior to starting treatment and previous relapse.

3.3.3 Response to re-treatment

Probabilities of response following reinitiation of treatment differ from initial treatment because the patients reinitiating have previously responded, and because the severity at which patients reinitiate treatment may be different than when they initially received treatment. For example, patients reinitiate treatment with delgocitinib when their condition is mild rather than when it is moderate or severe. This reflects the clinical trial data as well as the expected use of delgocitinib in clinical practice.

Data from DELTA 3, the open-label extension study of patients who completed DELTA 1 and DELTA 2, showed that median time to IGA-CHE 0/1 following the first treatment re-initiation with delgocitinib was 12 weeks (IQR, 4 to 28). This included patients who entered DELTA 3 with an IGA-CHE 0/1, who lost response and resumed delgocitinib as well as patients who entered DELTA 3 with an IGA-CHE ≥2, achieved an IGA-CHE 0/1, lost response and resumed delgocitinib. After up to 32 weeks of follow-up in DELTA 3, 83.6% (95% CI, 77.2% to 89.1%) of patients who had experienced an IGA-CHE ≥ 2 and reinitiated delgocitinib had regained IGA-CHE 0/1. The data suggest that IGA-CHE 0/1 may be regained more quickly among the delgocitinib-treated patients who entered DELTA 3 with an IGA-CHE 0/1 (median 8 weeks [IQR, 4 to 32]) [79].

In DELTA FORCE, the median time to regain IGA-CHE 0/1 with re-treatment was [redacted] among delgocitinib-treated patients (n = [redacted]) with [redacted]% (95% CI, [redacted]% to [redacted]%) having responded within [redacted] weeks [79].

In the economic model submitted during TA177 [17], the company used data from the alitretinoin clinical trials to justify higher response rates in subsequent cycles of alitretinoin. Data from a phase 3 randomised retreatment trial among patients who had previously responded to alitretinoin but experienced a relapse showed that 80% of patients regained PGA 0/1 response by week 24, with a median time to response of 12.1 weeks [126]. Patients in this trial re-initiated treatment from a state of moderate or severe CHE (PGA 3 or 4). In DELTA FORCE, in which patients re-initiated treatment from a state of mild CHE (IGA-CHE 2), the median time to regain IGA-CHE 0/1 with alitretinoin was [redacted] weeks (n = [redacted]) with [redacted]% (95% CI, [redacted]% to [redacted]%) having responded within 12 weeks of retreatment [79].

In the absence of reliable comparative data for delgocitinib and alitretinoin to inform this parameter, the probability of achieving a full response with retreatment following a relapse of any severity was assumed to be the same for both treatments. Based on the data from DELTA FORCE, this may underestimate potential advantages of delgocitinib over alitretinoin in terms of the rate of response to retreatment; however, this is mitigated to some degree by the different thresholds in the model at which point patients re-initiate treatments following a loss of response. In the absence of evidence for PUVA, this treatment was also assumed to

have an equivalent efficacy when used among relapsed responders. These assumptions were tested in sensitivity analysis.

A constant, per-cycle probability of regaining full response was calculated to be 20.2%, based on the probability of 83.6% of delgocitinib patients regaining IGA-CHE 0/1 within 32 weeks of follow-up in DELTA 3. This was assumed to be equal for all the comparators and applied regardless of CHE severity at baseline or at treatment re-initiation. The assumption of similarity across comparators was tested in sensitivity analysis.

3.3.4 Discontinuation not due to response

Patients might choose to permanently discontinue treatment or refuse re-treatment regardless of their prior response.

3.3.4.1 Discontinuation during initial treatment

Discontinuation during the first 12 weeks of treatment (section 3.3.1.1) is accounted for through the use of non-responder imputation in the trial data, with patients who discontinue prematurely counted as having an insufficient response. This assumption applies to all comparators.

3.3.4.2 Discontinuation during continued treatment and re-treatment

The percentage of patients who discontinue treatment after the first 12 weeks was estimated from different sources.

Discontinuation during the continued treatment phase (section 3.3.1.3) among patients without a full response is accounted for using data from the open-label extension studies for delgocitinib. A *post hoc* analysis was undertaken on the DELTA 3 study data which showed that by week 36 of follow-up, among 301 patients who had not achieved an IGA-CHE 0/1 response in DELTA 1 or DELTA 2, 12.3% (95% CI, 8.6% to 16.0%) had discontinued [79]. When adjusted for cycle length, the probability of discontinuation from delgocitinib was estimated to be 1.4%.

A *post hoc* analysis of DELTA FORCE showed [redacted]% ([redacted]) of delgocitinib treated patients who continued treatment after week 12 as a non-responder discontinued before week 24. The same analysis showed [redacted]% ([redacted]) of alitretinoin-treated patients discontinued before week 24. This indicates that the odds of discontinuing after week 12 as a non-responder were [redacted] times higher with alitretinoin than delgocitinib (95% CI, [redacted]) [79]. This odds ratio was applied in the model to derive a probability of discontinuation for alitretinoin, which was applied to the cycle-adjusted probability of discontinuation for delgocitinib of [redacted]%.

In the ALPHA trial, 21.6% (19/88) of patients who continued alitretinoin beyond week 12 discontinued or had missing data by week 24. For patients continuing PUVA, 47.8% (33/69) discontinued or had missing data between week 12 and week 24 [54]. Assuming that missing data also represented discontinuation, then the odds of discontinuation with PUVA were 3.33 times higher than the odds of discontinuation with alitretinoin. A simple indirect

comparison with the effect of alitretinoin versus delgocitinib in DELTA FORCE ([redacted]) suggests that the odds of discontinuation with PUVA is [redacted] times higher than with delgocitinib. This odds ratio was applied in the model to derive a probability of discontinuation for PUVA.

No discontinuation data for patients undergoing retreatment are available. Therefore, the same discontinuation rates as used in the Initial treatment period were applied and tested in sensitivity analysis. Finally, among patients who have moved on to next-line treatment, an assumption was made that 5% will discontinue in any given cycle and move on to BSC.

Table 61 reports the estimates used in the model base case.

3.3.4.3 Uptake of re-treatment following loss of response

The percentage of patients who relapse following a response to a given treatment and who would choose not to reinitiate the same treatment was estimated from different sources.

For delgocitinib, an analysis was undertaken on data from DELTA 3 to estimate the time to regain response following first treatment re-initiation. This analysis showed that [redacted] out of [redacted] delgocitinib patients who re-initiated treatment were censored, thus it was assumed that [redacted]% delgocitinib patients did not elect to re-initiate treatment [89]. For alitretinoin, a similar *post hoc* analysis was undertaken on the DELTA FORCE study data and this showed that [redacted] out of [redacted] alitretinoin patients eligible to re-initiate were censored [79]; it was therefore assumed from these data that [redacted]% of alitretinoin patients did not elect to re-initiate treatment. As the re-initiation of treatment was protocol driven in the DELTA 3 and DELTA FORCE studies, these values are likely to represent the most optimistic scenarios of re-treatment uptake.

ALPHA reported the number of patients who were confirmed to receive other treatments for their CHE over 52 weeks and the number who were confirmed to receive further treatment with the same treatment to which they were originally randomised [54]. Of the patients originally allocated to receive alitretinoin, 47.9% (58/121), received further treatment with alitretinoin for their CHE, while 4.4% (4/90) patients who originally received PUVA went on to receive further phototherapy (type not specified). These data were considered the most relevant to inform rates of re-initiation with alitretinoin and PUVA following a relapse of any severity.

Table 61 reports the estimates used in the model base case.

Table 61 Per-cycle probability of discontinuation

Strategy	Odds ratio vs delgocitinib	Probability	Source
Discontinuation from continued initial treatment and re-treatment			
Delgocitinib	NA	[redacted]	DELTA FORCE *post hoc* analysis [79]
Alitretinoin	[redacted]	[redacted]	DELTA FORCE *post hoc* analysis [79]
PUVA	[redacted]	[redacted]	Simple ITC comparing PUVA vs delgocitinib using odds ratio of PUVA vs alitretinoin from ALPHA (3.329) and odds ratio of alitretinoin vs delgocitinib from DELTA FORCE (2.509).
Proportion of patients electing not to re-initiate initial treatment following loss of response			
Delgocitinib	NA	[redacted]	D3, post-hoc analysis
Alitretinoin	NA	52.1%	ALPHA [54]

Strategy	Odds ratio vs delgocitinib	Probability	Source
PUVA	NA	95.6%	ALPHA [54]
Discontinuation from next-line treatment			
Second line	NA	5.0%	Assumption
Third line	NA	10.0%	Assumption

[a] Cycle-adjusted from a 12-week probability of [redacted] using formula $1-(1-p)^t$.

HECSI, Hand Eczema Severity Index; IGA-CHE, investigator global assessment for chronic hand eczema; NA, not applicable; PUVA, psoralen–UV A phototherapy; TCS, topical corticosteroids.

3.3.5 Adverse events

Delgocitinib was well tolerated in the DELTA trials (see section 2.11.4). In DELTA FORCE, 9.3% (24/253) of patients treated with delgocitinib experienced treatment-related AEs, including [redacted] skin and subcutaneous tissue disorders (see section 2.11.5). By contrast, 54.3% (134/247) of patients receiving alitretinoin in DELTA FORCE experienced treatment-related AEs. The model includes AEs observed in DELTA FORCE if they were associated with an incidence of at least 10% and if the difference between treatments was at least 1.5%. Based on these criteria, headache and nasopharyngitis were the only AEs considered relevant for inclusion in the model.

Neither headache nor nasopharyngitis were reported in the ALPHA trial. Adverse reactions reported for PUVA included PUVA burn, PUVA itch, PUVA pain and other skin-related events such as pruritus, erythema, and eczema exacerbation. These were conservatively not included in the economic model as they were not expected to be associated with additional costs or disutility.

Table 62 reports the common AEs included in the model. Given that the target population consists of patients who are refractory to TCS, it was assumed that patients in the BSC arm are on a stable, well-tolerated treatment regimen, and therefore do not experience AEs.

Table 62 AEs frequency reported by cycle

Comparator	Adverse event	Frequency	Source
Delgocitinib	Headache	0.67%	DELTA FORCE
Alitretinoin	Headache	6.41%	DELTA FORCE
Delgocitinib	Nasopharyngitis	2.08%	DELTA FORCE
Alitretinoin	Nasopharyngitis	2.44%	DELTA FORCE
PUVA	None	NA	Assumed
BSC	None	NA	Assumed

NA, not applicable; PUVA, psoralen–UV A phototherapy.

3.3.6 Mortality

Age-dependent all-cause mortality rates were obtained from UK life tables and applied to the model as a background risk of death to all patients [127]. It was assumed that neither CHE nor its treatment affect overall mortality.

3.3.7 Next-line treatment and BSC

Patients who discontinue, after not responding to treatment or for any other reason, move on to next-line therapy or BSC. Based on data from the RWEAL study [8], 76.8% of patients with moderate CHE and 59.1% of patients with severe CHE, who had an inadequate

response to TCS or for whom the TCS are not medically advisable, reported TCS use without the use of oral, biological or phototherapy. These figures were used to define the probability of patients moving straight from the initial treatment strategy to BSC. The remaining patients were assumed to move to the next-line therapy basket before ultimately moving to BSC.

In a sensitivity analysis, data on the use of other treatments for CHE from ALPHA were used to inform the rate of next-line treatment uptake [54]. Across both treatment arms in ALPHA, 52 of 264 patients (19.7%) for whom data were not missing did not receive other treatments for their CHE and 80.3% of patients did.

3.3.7.1 Next-line treatment composition

Next-line treatment was modelled as a 'basket' of available treatments with a weighted distribution of utilisation. The utilisation of different treatments was derived from the UK cohort of the RWEAL study [8] and is tailored to whether patients have moderate or severe CHE.

Table 71 reports the treatment utilisation basket for next-line treatment, which 23.2% of moderate CHE patients and 40.9% of severe CHE patients receive upon discontinuation of initial treatment. Each treatment in the basket is assumed to be used intermittently or in courses rather than continuously throughout any given year; the duration of therapy for each treatment family was based on the RWEAL study [8].

In a sensitivity analysis, data on the other treatments used after alitretinoin and PUVA from the ALPHA trial were used to inform the utilisation [54]. In this scenario, the usage of alitretinoin and phototherapy is higher than RWEAL and of other systemic treatments is lower. The type of other treatments received by around 20% of patients in ALPHA is reported only as "other". In the sensitivity analysis relying on the ALPHA data for the next-line basket utilisation, dupilumab was assumed to be a proxy for these "other" treatments.

3.3.7.2 Next-line treatment efficacy

The efficacy of next-line treatments relies on a simplifying assumption. In the RWEAL study, physicians were asked to judge the treatment outcomes for patients receiving ongoing treatment with alitretinoin and patients who stopped taking alitretinoin [8]. In total, 40.6% of alitretinoin patients were judged to be in a low disease activity state. Low disease activity was not specifically defined, but for the model, it has been assumed to correspond to an average across full and partial response, or an IGA-CHE ≤2. The alitretinoin response rate was considered a reasonable proxy for all the therapies in the next-line treatment basket. Therefore, the model assumes that 40.6% of patients receiving a basket of next-line treatments, including oral systemics, biologics and phototherapy, will have low disease activity at any given time. The other 59.4% of patients are assumed to have an IGA-CHE of 3 or 4 despite treatment.

In a sensitivity analysis, low disease activity was defined as an IGA-CHE 0/1 and patients not in low disease activity were those who had an IGA-CHE of 2, 3 or 4.

3.3.7.3 BSC treatment composition

BSC is a health state to which patients transition after they have discontinued their initial treatment or next-line treatment. From BSC, the only further transition patients can make is to death. In this health state, patients are assumed to receive TCS, TCIs and emollients only. Utilisation for TCS and TCI was informed by the RWEAL study [8], but emollients were assumed to be used by all patients. Table 71 reports the composition and duration of treatments for the BSC basket.

3.3.7.4 BSC treatment efficacy

In the base case, efficacy of BSC was assumed to be equivalent to the efficacy of the vehicle arm in the NMA. In a scenario analysis (see section 3.10.2), BSC was modelled to reflect disease management with topical therapies that had been previously tried and found to be ineffective or inadequate. In this scenario, BSC had no independent effect and patients in this state revert to baseline severity. In practical terms, this means that, in addition to receiving topical therapies in the BSC basket, patients will return to their baseline utility value and accrue health state costs associated with moderate CHE (i.e. low response) or severe CHE (i.e. insufficient response), based on their severity at entry to the model.

3.4 Measurement and valuation of health effects

Health effects in the analysis were expressed in QALYs, in accordance with the NICE reference case [102].

3.4.1 Utility measures

The selection of utility values for the economic model was based on a preference for UK-applicable and EQ-5D-derived utilities (vs utilities derived by alternative quality of life questionnaires [i.e., SF-36, HUI] or mapped from clinical outcomes), in line with NICE methodology [102]. Utilities values included in the model were EQ-5D-3L, reported in *post hoc* analyses undertaken explicitly for the model [79].

3.4.2 Mapping

EQ-5D-5L data collected in the DELTA clinical trial programme were mapped from the 5-level system to the 3-level system using the EQ-5D-5L crosswalk value set [101]. Index scores are based on the UK-specific value set (see section 2.3.1.5).

3.4.3 Estimation of utility values

To follow best practice, the model used a mixed model with repeated measures (MMRM) on EQ-5D-3L data from DELTA 1 and DELTA 2 to determine the extent to which response to treatment affects change in EQ-5D from baseline.

Utility values associated with different levels of response were generated from pooled DELTA 1 and DELTA 2 results [79]. Mixed models were fitted for DELTA 1 and DELTA 2 (pooled) using a backward selection process, to estimate improvement in EQ-5D as a

function of age, baseline EQ-5D, HECSI score, HESD pain score and treatment received (active treatment represented by delgocitinib was the reference category versus vehicle) and category of response. β_n can be interpreted as the improvement from baseline EQ-5D-3L for each variable. This is shown in the equation below. Only significant variables were kept in the regression.

The change in EQ-5D-3L from baseline to week 16 was modelled as a function of age, baseline EQ-5D-3L, HECSI, HESD pain score and treatment received (active treatment represented by delgocitinib was the reference category versus vehicle) for each health state.

$$\text{EQ-5D}=\alpha+\beta_1\text{Age}+\beta_2\text{EQ5D baseline}+\beta_3(\text{HECSI})+\beta_4(\text{HESDpain})+\beta_5\text{Treatment}$$

HECSI and HESD pain scores were measured over the duration of the trial, and the other variables were measured at baseline. The model accounts for the fact that HECSI and HESD pain score may vary with disease severity over time. It was assumed that the entire treatment effect of HECSI and HESD pain on EQ-5D-3L would be expressed via the health states and that any differences between the treatments would be addressed through inclusion of the treatment parameter, which was statistically significant.

The parameter estimates used in the MMRM regression for the IGA-CHE and HECSI response definitions and the mean value estimates for HECSI and HESD pain scores used in the regression are presented in Appendix J.2, Tables 248 and 250, respectively. The resulting health state utility values are shown in Table 63. Active treatment values are applied to all of the comparator therapies in the model and used to calculate the utility associated with next-line treatment. This assumes that the differential effect of delgocitinib over vehicle is similarly applicable to any active treatment. Vehicle treatment values are used to calculate the utility for patients receiving BSC, consistent with the approach of assuming the efficacy of BSC is informed by the vehicle effects from the NMA.

For a scenario analysis, the same regression analysis was performed on pooled data from DELTA 1, DELTA 2 and DELTA FORCE, excluding the treatment effect covariate (see Appendix J.2, Table 249). Utility values generated from this analysis were applied according to the response achieved regardless of treatment, thereby ignoring any potential differences in health state utilities between active arms and BSC (see section 3.10.2).

For patients receiving next-line treatment, the active treatment health state values were weighted by the proportion of patients achieving low disease activity (see section 3.3.7.2). For the BSC health state, the vehicle treatment health state values were weighted according to the week 12 health state allocation in the vehicle arm (see section 3.3.7.4).

Table 63 Health state utility values used in the model

Health state	Active treatment	Vehicle treatment	Common effect [a]
Severe CHE			
Baseline	0.577	0.577	0.577
Full response	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states			
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]
Moderate CHE			
Baseline	0.670	0.670	0.670
Full response	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states			
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]

[a] Used in a scenario analysis and applied to response states independent of treatment received.

CHE, chronic hand eczema; IGA-CHE, investigator global assessment for chronic hand eczema.

3.4.4 Utility baseline adjustment

Utilities were adjusted over time to account for the natural decline of health due to age and other comorbidities using the method described by Ara and Brazier [128, 129]. A multiplier was estimated and applied to each health state to adjust utility estimates. A baseline EQ-5D score was estimated specifically for the CHE patient population (see section 3.2.1, Table 53), rather than for general population with and without CHE, as follows:

$$u = multiplier * \sum_{i=1}^{j} response_i * u_{response_i} + 0.0212126 * male - 0.0002587 * age - 0.0000332 * \text{age}^2$$

3.4.5 Health-related quality-of-life studies

Identification of relevant HRQoL studies was conducted via an SLR, which is described in detail in Appendix F. Searches of relevant publication databases and grey literature sites were conducted on 22 July 2024, which identified fifteen relevant studies. Utility values for patients with CHE (n = 8 studies) are described in Appendix F.3.2, Table 199.

3.4.6 Adverse reactions

As described in section 3.3.5, the only AEs included in the model were headache and nasopharyngitis. The disutility of both events was taken from a catalogue of EQ-5D-3L utility scores derived using the UK value set and reported by Falk Hvidberg *et al.* (2023) [130]. A weighted average of the scores for men and women aged 50 with no chronic conditions was used to match the modelled population (as described in section 3.2.1, Table 53). The resulting disutility applied for headache and nasopharyngitis was −0.038. In a sensitivity analysis, these quality-of-life decrements were not applied.

3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

Utility values used in the economic model are summarised in Table 64.

Table 64 Summary of utility values for base-case cost-effectiveness analysis

State	Mean utility value		95% CI	Section and page number	Justification
	Moderate	Severe			
Baseline	0.670	0.577			
Active comparators					
Full response	[redacted]	[redacted]	NA	3.4.3, p137	Estimated using EQ-5D-3L data from DELTA 1 and DELTA 2 for delgocitinib [79]
Partial response and mild CHE states	[redacted]	[redacted]			
Low response and moderate CHE states	[redacted]	[redacted]			
Insufficient response and severe CHE states	[redacted]	[redacted]			
BSC (used to inform weighted average of BSC health state)					
Full response	[redacted]	[redacted]	NA	3.4.3, p137	Estimated using EQ-5D-3L data from DELTA 1 and DELTA 2 for vehicle [79]
Partial response and mild CHE states	[redacted]	[redacted]			
Low response and moderate CHE states	[redacted]	[redacted]			
Insufficient response and severe CHE states	[redacted]	[redacted]			
Next-line treatment and BSC					
Next-line treatment health state	[redacted]	[redacted]	NA	3.4.3, p137 3.3.7.2, p136	Calculated based assumption of 40.6% of patients are evenly distributed across IGA-CHE 0/1 and 2 states and 59.4% are evenly distributed across IGA-CHE 3 and 4 states [8]
BSC health state	[redacted]	[redacted]	NA	3.4.3, p137 3.3.1.1, p125 3.3.1.2, p127	Based on the BSC health state values weighted according to the week 12 health state allocation in the vehicle arm
Adverse reactions					
Headache	−0.038		NA	3.4.6, p139	Calculated from published UK data [130]
Nasopharyngitis					

BSC, best supportive care; CHE, chronic hand eczema; CI, confidence interval; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; NA, not applicable; QoL, quality of life.

3.5 Cost and healthcare resource use identification, measurement and valuation

A SLR was conducted to identify relevant cost and resource use data, as described in Appendix G.

The model included the costs of treatment acquisition (section 3.5.1), the costs of monitoring patients receiving certain treatments (section 3.5.4), the costs associated with each health state (section 3.5.2), and the costs of treating adverse events (section 3.5.3). Where costs are not reported for the latest cost year the healthcare inflation indices provided by the PSSRU were used to inflate costs as necessary [120].

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Acquisition costs

Unit cost and dosing for each treatment included in the model are summarised in Table 65. Unit costs were sourced from the pricing information published in the British National Formulary (BNF) [119], from NHS National Tariff Payment System [121] or NHS Reference Costs [131]and from the costs used in TA177 [17].

Table 65 Summary of acquisition costs for intervention and comparators

Treatment	Pack type	Unit cost	Source	Dosing/consumption
Model comparators				
Delgocitinib	One tube (60g)	£[redacted]	Pack price	• Patients apply a thin layer covering the affected areas twice daily, as needed. Weekly usage estimated from DELTA 1, DELTA 2 and DELTA FORCE (see Table 66)
Alitretinoin	30 soft capsules (10 mg)	£493.72	Drug tariff price is the same for 10 mg and 30 mg capsules [119, 132]	• Single capsule daily [133] • 21.1% of alitretinoin-treated patients in DELTA FORCE had a reduction in dose [90] • The dose-effects of alitretinoin are not considered and costs do not differ.
	30 soft capsules (30 mg)	£493.72		
PUVA	One session	£94.00	NHS tariff 2023/25 (JC47Z outpatient procedure) [121]	• 2 sessions per week [54]
		£140.12	NHS Reference costs 2022/23 (JC47Z outpatient procedure) , used in scenario analysis (see section 3.10.2) [131]	

g, gram; mg, milligram; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PUVA, psoralen–UV A phototherapy; SmPC, summary of product characteristics.

Given the as-needed application of delgocitinib, the amount used may vary by individual and by their CHE severity at any given time. To best capture this variation, the weekly usage of delgocitinib was derived from a mixed model with repeated measures (MMRM) regression on weekly consumption data from DELTA 1, DELTA 2 and DELTA FORCE to determine the extent to which response to treatment affects usage over time.

Weekly mean usage for the population with moderate CHE at baseline was derived by taking an average over the first 12 weeks of treatment for each IGA-CHE health state from the MMRM regression of DELTA 1 and DELTA 2 only. For the population with severe CHE at baseline, an average over the first 12 weeks was taken from the regression of DELTA 1, DELTA 2 and DELTA FORCE.

In scenario analyses, higher and lower delgocitinib consumption was modelled. In one scenario, a mean across all health states from the regression of the three DELTA trials was applied equally to all health states ([redacted] g/week). In a second and third scenario, the mean usage from the DELTA trials with the lowest and highest reported mean usage were applied ([redacted] g/week from DELTA 2 and [redacted] g/week from DELTA FORCE).

A summary of inputs for delgocitinib consumption per week are presented in Table 66.

Table 66 Summary of delgocitinib usage

Health state	Weekly usage (grams)				
	Base Case		Scenarios		
	Moderate CHE	Severe CHE	Overall average	DELTA 2	DELTA FORCE
Full response [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response / mild CHE					
Low response / moderate CHE					
Insufficient response / severe CHE					

[a] These values apply to patients who achieve full response prior to week 12 and continue treatment to week 12.

Source: DELTA 2 CSR [88]; DELTA FORCE CSR [90]; Statistical appendix [79].

3.5.1.2 Monitoring costs

Patients treated with alitretinoin require monitoring while on-treatment. The required resources and unit costs are shown in Tables 67.

Table 67 Per cycle monitoring resource use associated with alitretinoin

Parameter	Usage	Price	Notes	Source
Proportion of women who are of childbearing potential	15%	NA	NA	NICE TA177 [17]
Contraceptives	0.3	£2.82 per 63-tablet pack	Contraception required for duration of alitretinoin treatment and two additional months (in line with TA177) [17]	Microgynon 30 (one 3-month box) [119]
Pregnancy test kit	1.3	£1.00 per kit	In line with TA177, pregnancy consultation one month prior to and at start of treatment, then every 28 days for duration of alitretinoin treatment and at 5 weeks following end of treatment [17]	ALPHA trial [54]
Ward nurse time	1.3	£8.83 for 10 minutes	Same frequency as pregnancy test kit	Nurse time based on band 5 ward nurse hourly salary of £53 [120] 10 minutes per test [134]
Lipid monitoring	1.0	£6.63 per test	Every four weeks	DAPS08 – Phlebotomy [131]

NHS, National Health Service; NICE, National Institute of Health and Care Excellence; TA, technology appraisal.

3.5.2 Health-state unit costs and resource use

Resource use data were not collected in the DELTA trials, and cost and resource use data were not reported by health state in TA177 [17].

The SLR described in Appendix G identified CHE resource use including hospitalisation, consultations, tests and treatment. However, the included studies typically did not include samples representative of the CHE population, and none reported resource use estimates by disease state. Values from the ALPHA trial were not reported in a way that allowed for use directly in the model [54].

Accordingly, healthcare usage for each health state was informed by assumptions, as shown in Table 68. Patients with partial, low or insufficient response would visit their dermatologist more frequently, compared with patients with full response, as their disease is not well managed (i.e., 4 visits per year instead of 1 visit per year). It was also assumed that all

patients with CHE would visit their primary care physician once a year for follow-up of their disease.

Table 68 Health state resource use

Type of resource use	Unit cost	Source	Annual number of visits by health state			
			FR	PR	LR	InR
Dermatologist visit	£90.00	WF01A-Dermatology follow-up attendance – single professional [135]	1	4	4	4
GP visit (10 minutes)	£49.00	Jones (2023) [120]	1	1	1	1

BSC, best supportive care; FR, full response; GP, general practitioner; InR, insufficient response; LR, low response; NHS, National Health Service; PR, partial response.

A single study was identified that reported inpatient and outpatient costs according to disease severity. Augustin *et al.* (2011) described a cross-sectional study conducted in 25 outpatient practices and clinics across Germany [136]. Although management of eczema in the German healthcare system differs from the UK (e.g., hospitalisations were shown to last 10.6 days in Germany), the study provides evidence that could be adapted to the model.

The data showed that costs increased by average severity, as measured by a CHE photographic guide. Outpatient costs were relatively stable across severities because, the authors assert, all patients are in the continuous care of dermatologists. The major drivers of increase were drug costs, UV therapy costs and inpatient costs. Excluding the former two cost elements, the increases in inpatient costs were used to calculate a multiplier which could adjust the health state costs by response. This was used in a scenario analysis (see Appendix K.3).

Total annual costs for each health state used in the base case and scenario analysis are presented in Table 69.

Table 69 Health state costs

Health state	Total cost		Source/notes
	Base case	Scenario analysis	
Full response	£197	£197	Base case: see Table 68 Scenario analysis: Augustin 2011 [136]
Partial response	£641	£385.10 [a]	
Low response	£641	£949.41 [b]	
Insufficient response	£641	£1,093.03 [c]	
Next-line treatment	£550.89	£724.84	Weighted average by efficacy of next-line basket (see section 3.3.7.1).
BSC (moderate)	£585.52	£772.05	Weighted average based on efficacy of BSC (see sections 3.3.1.1 and 3.3.1.2)
BSC (severe)	£599.95	£822.95	

[a] Estimated by applying ratio of 1.95 to full response costs calculated from relationship reported between moderate and clear/nearly clear annual inpatient costs (= €303/€155) in Augustin 2011.
[b] Estimated by applying ratio of 4.82 to full response costs calculated from relationship reported between severe and clear/nearly clear annual inpatient costs (= €747/€155) in Augustin 2011.
[c] Estimated by applying ratio of 5.55 to full response costs calculated from relationship reported between very severe and clear/nearly clear annual inpatient costs (= €860/€155) in Augustin 2011.

3.5.3 Adverse reaction unit costs and resource use

As described in section 3.3.5, two common adverse events for alitretinoin were identified from DELTA FORCE (headache and nasopharyngitis). Patients experiencing AEs were assumed to visit their general practitioner (GP) once at a cost of £49 for 10 minutes [120]. In one sensitivity analysis, these costs were removed. In another sensitivity analysis, these

costs were increased to reflect consultation with a dermatologist who would be monitoring treatment with alitretinoin.

3.5.4 Miscellaneous unit costs and resource use

As discussed in section 3.3.7, as patients discontinue the initial treatment, they proceeded to next-line treatment baskets or BSC. Unit cost and dosing for additional treatments included in the next-line therapy and BSC baskets are summarised in Table 70. For simplicity, treatment costs included in the next-line and BSC baskets are based on acquisition costs and health state costs only; no administration or monitoring costs are included for the constituent treatments.

Annual treatment costs associated with the next-line treatment basket are based on the proportion receiving each treatment combined with the average amount of time spent on or off the treatment; these are cycle-adjusted and applied for each 4-week cycle. The weighted average cost of next-line treatment and BSC per cycle are reported in Table 71.

Table 70 Summary of acquisition costs for next-line therapy and BSC

Treatment	Pack description	Unit cost	Source	Dosing/consumption
Additional treatments included in next-line therapy basket				
Ciclosporin	30 caps (50 mg)	£35.97	Drug tariff price [119]	200 mg median daily dose according to data from RWEAL (consistent with 2.5-3 mg/kg/day based on SmPC)
Metho-trexate	100 tablets (2.5 mg)	£5.29	Methotrexate 2.5mg tablets Alliance Healthcare (Distribution) Ltd [119]	15 mg per week Based on SPC
Acitretin	60 capsules (25 mg)	£55.24	Drug tariff price [119]	25 mg median daily dose according to data from RWEAL
Azathioprine	56 tablets (50 mg)	£1.31	Drug tariff price [119]	50 mg median daily dose according to data from RWEAL
Oral steroids	56 tablets (25 mg)	£50.00	Prednisolone, Drug tariff price[119]	25 mg median daily dose according to data from RWEAL
UVB	One session	£94.00	Same as PUVA [121]	2 sessions per week
Dupilumab	2 pre-filled disposable injection	£1,264.89	Dupixent 300mg/2mL solution for inject pre-filled pens Sanofi [119]	300 mg every other week based on SmPC for AD
Components of BSC				
Emollients	One tub (500 g)	£4.95	Drug tariff price for E45 cream Karo Pharma UK Ltd [119]	8.6 g per week based on average vehicle consumption from DELTA 1 and 2 [82]
TCIs	One tube (60 g)	£39.74	Tacrolimus 0.1% ointment, Drug tariff price [119]	2 g applied twice daily [137]; 28 g per week
TCS (cost per g calculated as weighted average across different potencies; weights from RWEAL[a])				
Mild potency	One tube (15 g)	£2.48	Drug tariff price for hydrocortisone 1% cream [119]	1 g applied once or twice daily [138]; 11 g per week
Moderate potency	One tube (100 g)	£6.49	Drug tariff price for betamethasone valerate cream [119]	
High potency	One tube (100 g)	£6.12	Drug tariff price for betamethasone dipropionate cream [119]	
Ultra-high potency	One tube (100 g)	£7.90	Drug tariff price for clobetasol propionate cream [119]	

[a] 7.9% mild potency TCS; 30.5% moderate potency TCS; 62.1% split between high and ultra-high potency TCS
AD, atopic dermatitis; BSC, best supportive care; g, gram; mg, milligram; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PUVA, psoralen–UV A phototherapy; SmPC, summary of product characteristics; TCI, Topical calcineurin inhibitors; TCS, Topical corticosteroids; UVB, ultraviolet B.

Table 71 Composition, duration and cost per cycle of next-line treatment basket and best supportive care

Treatment family	Treatment	Cost per cycle	Utilisation			Median duration of treatment (% of year using treatment)	Weighted average cost		
			RWEAL [8]		ALPHA		RWEAL [8]		ALPHA
			Moderate	Severe			Moderate	Severe	
Next-line treatment							***£152.40***	***£170.45***	***£226.67***
Oral systemic drugs	Acitretin	£25.78	4.1%	0.0%	4.5%	31.5 weeks (60.5%)	£6.53	£11.84	£27.88
	Azathioprine	£0.66	6.1%	4.8%	1.3%				
	Methotrexate	£1.27	24.5%	17.5%	9.1%				
	Ciclosporin	£134.29	18.4%	11.1%	8.1%				
	Oral steroids	£25.00	8.2%	14.3%	11.3%				
	Alitretinoin	£207.36	12.2%	23.8%	39.8%				
Photo-therapy	PUVA	£752.00	10.2%	6.3%	12.0%	12.5 weeks (24.1%)	£15.73	£17.01	£21.71
	UVB	£752.00	6.1%	11.1%					
Biologic	Dupilumab	£1,264.89	10.2%	11.1%	13.9% [a]	75.6 weeks (100.0%)	£129.07	£140.54	£176.02
Topical	TCS	£3.21	100%	99.4%	as RWEAL	17.4 weeks (33.4%)	£1.07	£1.07	£1.07
Best supportive care							***£2.39***	***£2.66***	***£2.66***
Best supportive care	Emollients	£0.34	100%	100%	same as RWEAL	21.5 weeks (41.4%)	£0.14	£0.14	£0.14
	TCS	£3.21	100%	99.4%		17.4 weeks (33.4%)	£1.07	£1.07	£1.07
	TCI	£74.18	4.7%	5.8%		17.4 weeks (33.4%)	£1.18	£1.45	£1.45

[a] Described as “other treatments” and assumed to be biologics.

PUVA, psoralen–UV A phototherapy; TCI, Topical calcineurin inhibitors; TCS, Topical corticosteroids; UVB, ultraviolet B.

3.6 Severity

The technology does not meet the criteria for a severity weight.

3.7 Uncertainty

The signs and symptoms of CHE can fluctuate in severity over time and available treatments are used intermittently, vary considerably in their route and ease of access and administration, short- and long-term safety profile and the durability of response. There is notable variation in the scales used to measure disease severity, clinical impact and response. These complexities introduce uncertainty in estimating patients' quality of life and use of NHS resources. The DELTA clinical trial programme provides a robust framework for evaluating the efficacy and safety of delgocitinib among patients with moderate and severe CHE, but the clinical evidence for alitretinoin and PUVA is more limited and uncertain. Clinical data for alitretinoin and PUVA are available for patients with severe CHE, but PUVA is also the only suggested treatment for moderate CHE that has not responded to TCS. To model treatment effects of PUVA in patients with moderate CHE, it was necessary to assume that the relative treatment effects of delgocitinib and alitretinoin and of alitretinoin and PUVA in severe CHE also applied to moderate CHE. Notably, disease severity as well as response were measured using different scales in these studies: PGA was used in ALPHA and IGA-CHE was used in DELTA FORCE. This approach to the data – assuming similarity of head-to-head treatment effects across CHE severity and assuming similarity across 5-point severity scales – was validated by advisors with health economic expertise.

3.8 Summary of base-case analysis inputs and assumptions

3.8.1 Summary of base-case analysis inputs

The variables included in the economic model are summarised in Tables 72 and 73; equivalent variables for the HECSI response state scenario analysis are shown in Appendix J.3, Tables 254 and 255.

Table 72 Summary of variables applied in the economic model

Variable		Value	Confidence interval [SE] (distribution)	Section
Treatment effect: IGA-CHE 0/1 response at week 12				
Severe CHE				
Delgocitinib	Log odds	[redacted]	[redacted] (Coda)	2.10.4.2 and 3.3.1.1
Alitretinoin	Log OR (vs delgocitinib)	[redacted]	[redacted] (Coda)	
PUVA	Log OR (vs delgocitinib)	[redacted]	[redacted] (Coda)	
BSC	Log OR (vehicle vs delgocitinib)	[redacted]	[redacted] (Coda)	
Moderate CHE				
Delgocitinib	Log odds	[redacted]	[redacted] (Coda)	2.10.4.2 and 3.3.1.1
PUVA	Log OR (vs delgocitinib)	[redacted]	[redacted] (Coda)	
BSC	Log OR (vehicle vs delgocitinib)	[redacted]	[redacted] (Coda)	
Alitretinoin (included only to inform other parameters)	Log OR (vs delgocitinib)	[redacted]	[redacted] (Coda)	

Variable		Value	Confidence interval [SE] (distribution)	Section
Response to continued treatment beyond week 12				
Severe CHE				
Delgocitinib	36-week risk from partial response	0.54	0.42–0.65 [0.059] (Beta)	36-week probability adjusted for cycle length, 3.3.1.3
	36-week risk from low response	0.24	0.11–0.39 [0.071] (Beta)	
Alitretinoin and PUVA	Odds ratio vs delgocitinib risks	1.0	0.608–1.392 [0.200 [a]] (Lognormal)	
Moderate CHE				
Delgocitinib	From partial response	0.66	0.59–0.73 [0.036]	36-week probability adjusted for cycle length, 3.3.1.3
PUVA	Odds ratio vs delgocitinib risks	1.0	0.608–1.392 [0.200 [a]] (Lognormal)	
Loss of response and relapse				
Delgocitinib	Weekly rate of loss of response (based on median time to IGA-CHE ≥2 = [redacted] weeks [95% CI: [redacted]])	[redacted]	0.09–0.14 [0.01] (beta)	Cycle-adjusted probabilities calculated from weekly rates 3.3.2
Alitretinoin	Weekly rate of loss of response (based on median time to IGA-CHE ≥2 = [redacted] weeks [95% CI: [redacted]])	[redacted]	0.02–0.14 [0.03] (beta)	
PUVA	Weekly rate of loss of response	Assumed equal to alitretinoin		
All comparators	Probability of moderate relapse (12-week)	0.51	To ensure a logical relationship between relapse probabilities in the PSA, the probability of a mild relapse was randomly sampled according to the above parameters and the probability of a moderate and severe relapse were derived by applying a fixed rate ratio based on the relationship between mean estimates. For example, the rate ratio of a mild relapse with delgocitinib compared to a moderate relapse for all comparators was calculated as [redacted] (=[redacted]/0.059). Similarly, the rate ratio of a mild relapse with delgocitinib compared to a severe relapse for all comparators was calculated as [redacted] (=[redacted]/0.0056). The same figures for alitretinoin were [redacted] (=[redacted]/0.059) and [redacted] (=[redacted]/0.0056), respectively.	12-week probabilities adjusted for cycle length, 3.3.2
	Probability of severe relapse (12-week)	0.07		
Response to retreatment following relapse				
Delgocitinib	Probability of IGA-CHE 0/1 (32 weeks)	0.836	0.772–0.891 [0.03] (Beta)	32-week probability adjusted for cycle length, 3.3.3
Alitretinoin and PUVA	Odds ratio vs delgocitinib	1.0	0.608–1.392 [0.200 [a]] (lognormal)	
Permanent discontinuation (after week 12 and during re-treatment)				
Delgocitinib	Probability of discontinuation (12-week)	0.083	0.038–0.127 [0.023] (Beta)	12-week probability adjusted for
Alitretinoin	Odds ratio vs delgocitinib	2.509	1.771–3.248 [0.377] (Lognormal)	

Variable		Value	Confidence interval [SE] (distribution)	Section
PUVA	Odds ratio vs alitretinoin	3.329	2.635–4.022 [0.354] (lognormal)	cycle length, 3.3.4
PUVA	Odds ratio vs delgocitinib	8.354	Calculated as the product of the OR of alitretinoin vs delgocitinib and OR of PUVA vs alitretinoin	
Non-reinitiation of initial treatment following loss of response and relapse				
Delgocitinib	Probability	0.046	0.021–0.071 [0.013] (beta)	3.3.4
Alitretinoin	Probability	0.521	0.432–0.609 [0.045] (beta)	
PUVA	Probability	0.956	0.914–0.998 [0.021] (beta)	
Permanent discontinuation from next-line treatment				
Second line	Probability per cycle	0.05	0.03–0.07 [0.010 [a]] (Beta)	3.3.4
Third line	Probability per cycle	0.10	0.061–0.139 [0.020 [a]] (Beta)	
Adverse events				
Delgocitinib	24-week probability of headache	0.0395	0.0156–0.0635 [0.012] (Beta)	24-week probability adjusted for cycle length, 3.3.53.3.5
Alitretinoin		0.3279	0.2695–0.3864 [0.030] (Beta)	
Delgocitinib	24-week probability of nasopharyngitis	0.1186	0.1008–0.1364 [0.020] (Beta)	
Alitretinoin		0.1377	0.1170–0.1583 [0.022] (Beta)	
Next lines and BSC				
Proportion moving directly to BSC	Severe	0.591	0.517–0.665 [0.038] (beta)	3.3.7
	Moderate	0.768	0.690–0.846 [0.040] (beta)	
Severe CHE				
Proportion receiving different treatments in the next-line basket	Acitretin	0.0%	Dirichlet distribution	3.3.7.1
	Azathioprine	4.8%		
	Methotrexate	17.5%		
	Ciclosporin	11.1%		
	Oral steroids	14.3%		
	Alitretinoin	23.8%		
	PUVA	6.3%		
	UVB	11.1%		
	Dupilumab	11.1%		
	TCS	99.4%	0.981– 1.000 [0.006] (beta)	
Proportion receiving different treatments in BSC	Emollients	100%	No sampling	3.3.7.3
	TCS	99.4%	0.981– 1.000 [0.006] (beta)	
	TCI	5.8%	0.022–0.095 [0.018] (beta)	
Moderate CHE				
Proportion receiving different treatments in the next-line basket	Acitretin	4.1%	Dirichlet distribution	3.3.7.1
	Azathioprine	6.1%		
	Methotrexate	24.5%		
	Ciclosporin	18.4%		
	Oral steroids	8.2%		
	Alitretinoin	12.2%		
	PUVA	10.2%		
	UVB	6.1%		
	Dupilumab	10.2%		
	TCS	100%	0.993–1.00 [0.003] (beta)	
Proportion receiving different treatments in BSC	Emollients	100%	No sampling	3.3.7.3
	TCS	100%	0.993–1.00 [0.003] (beta)	
	TCI	4.7%	0.019–0.076 [0.015] (beta)	
Treatment duration of therapies in next-line basket and BSC				
Median treatment duration (days)	Oral	221.0	SE = 38.4 (gamma)	3.3.7.1 and 3.3.7.3
	Phototherapy	88.0	SE = 31.9 (gamma)	
	TCS	122.0	SE = 31.5 (gamma)	
	Dupilumab	530.5	SE = 62.7 (gamma)	
	Topicals (not TCS, not emollients)	122.0	SE = 32.1 (gamma)	
	Emollients	151.0	SE = 52.9 (gamma)	
Efficacy of therapies in next-line basket and BSC				
Proportion with Low Disease Activity (assumed	Next-line basket	0.406	0.290–0.522 [0.059] (beta)	3.3.7.2

Variable		Value	Confidence interval [SE] (distribution)	Section
equivalent to IGA-CHE ≤2)				
Distribution across response states	BSC – severe	FR: 0.09 PR: 0.13 LR: 0.20 InR: 0.58	Informed by response parameters for BSC (vehicle)	3.3.7.4
Distribution across response states	BSC - moderate	FR: 0.12 PR: 0.13 LR: 0.19 InR: 0.57	Informed by response parameters for BSC (vehicle)	
Utility regression coefficients				
IGA-CHE health states	Intercept	[redacted]	[redacted] (Cholesky)	3.4.3 Appendix J.2
	Age	[redacted]	[redacted] (Cholesky)	
	EQ-5D baseline	[redacted]	[redacted] (Cholesky)	
	HECSI score	[redacted]	[redacted] (Cholesky)	
	HESD pain score	[redacted]	[redacted] (Cholesky)	
	Delgocitinib	[redacted]	[redacted] (Cholesky)	
	Vehicle	Reference	NA	
	IGA 0/1	[redacted]	[redacted] (Cholesky)	
	IGA 2	[redacted]	[redacted] (Cholesky)	
	IGA 3	[redacted]	[redacted] (Cholesky)	
	IGA 4	Reference	NA	
Utility regression parameters				
Severe CHE				
Baseline utility (EQ-5D-3L)	Severe	0.577	0.560–0.594 [0.008] (Beta)	3.4.3
HECSI	IGA-CHE 0/1	[redacted]	[redacted] (Normal)	Appendix J.2
	IGA-CHE 2	[redacted]	[redacted] (Normal)	
	IGA-CHE, 3	[redacted]	[redacted] (Normal)	
	IGA-CHE 4	[redacted]	[redacted] (Normal)	
HESD pain score	IGA-CHE 0/1	[redacted]	[redacted] (Normal)	
	IGA-CHE 2	[redacted]	[redacted] (Normal)	
	IGA-CHE, 3	[redacted]	[redacted] (Normal)	
	IGA-CHE 4	[redacted]	[redacted] (Normal)	
Moderate CHE				
Baseline utility (EQ-5D-3L)	Moderate	0.670	0.656–0.684 [0.007] (Beta)	3.4.3
HECSI	IGA-CHE 0/1	[redacted]	[redacted] (Normal)	Appendix J.2
	IGA-CHE 2	[redacted]	[redacted] (Normal)	
	IGA-CHE, 3	[redacted]	[redacted] (Normal)	
	IGA-CHE 4	[redacted]	[redacted] (Normal)	
HESD pain score	IGA-CHE 0/1	[redacted]	[redacted] (Normal)	
	IGA-CHE 2	[redacted]	[redacted] (Normal)	
	IGA-CHE, 3	[redacted]	[redacted] (Normal)	
	IGA-CHE 4	[redacted]	[redacted] (Normal)	
Adverse event disutilities				
Disutility	Headache Nasopharyngitis	−0.038	−0.032 to −0.044 [0.0029] (Lognormal)	3.4.6
Delgocitinib consumption				
Severe CHE				
Weekly usage (grams)	IGA-CHE 0/1	[redacted]	See Appendix J	3.5.1.1
	IGA-CHE 2	[redacted]		
	IGA-CHE 3	[redacted]		
	IGA-CHE 4	[redacted]		
Moderate CHE				
Weekly usage (grams)	IGA-CHE 0/1	[redacted]	See Appendix J	3.5.1.1
	IGA-CHE 2	[redacted]		
	IGA-CHE 3	[redacted]		
	IGA-CHE 4	[redacted]		

Variable		Value	Confidence interval [SE] (distribution)	Section
Emollients consumption				
Weekly usage (grams)	BSC	8.68	See Appendix J	3.5.1.1
Treatment acquisition costs				
Delgocitinib	One tube (60g)	[redacted]	No sampling	3.5.1.1
Alitretinoin	30 soft capsules (10 mg)	£493.72		
	30 soft capsules (30 mg)			
PUVA	One session	£94.00		
Acitretin	60 capsules (25 mg)	£55.24	No sampling	3.5.4
Azathioprine	56 tablets (50 mg)	£1.31		
Methotrexate	100 tablets (2.5 mg)	£5.29		
Ciclosporin	30 caps (50 mg)	£35.97		
Oral steroids	56 tablets (25 mg)	£50.00		
UVB	One session	£94.00		
Dupilumab	2 pre-filled disposable injections	£1,264.89		
TCS (mild)	One tube (15g)	£2.48		
TCS (moderate)	One tube (100g)	£6.49		
TCS (high)	One tube (100g)	£6.12		
TCS (ultra-high)	One tube (100g)	£7.90		
TCI	One tube (60g)	£39.74		
Emollients	One tub (500g)	£4.95		
Monitoring resource use associated with alitretinoin				
Percentage of patients using higher dose of alitretinoin		17.0%	14.5–19.6% [3.4% [a]] (Beta)	3.2.3
Proportion of population that is women of childbearing potential		0.15	0.1275–0.1725 [0.030 [a]] (Beta)	3.5.1.2
Frequency per cycle	Contraceptives (3-month pack)	0.33	0.28–0.38 [NA] (Lognormal)	
	Pregnancy test	1.25	1.06–1.44 [NA] (Lognormal)	
	Ward nurse time	1.25	1.06–1.44 [NA] (Lognormal)	
	Lipid monitoring	1.00	0.85–1.15 [NA] (Lognormal)	
Health state resource use				
Dermatologist visits (per year)	Full response	1.0	No sampling	3.5.2
	Partial response	4.0		
	Low response	4.0		
	Insufficient response	4.0		
GP visits (per year)	Full response	1.0	No sampling	
	Partial response	1.0		
	Low response	1.0		
	Insufficient response	1.0		
Adverse event resource use (per event)				
Headache	GP visit	1	No sampling	3.5.3
Nasopharyngitis				3.5.3
Unit costs of health state resources used				
Dermatologist visit		£148	£125.80–170.20 [NA] (Lognormal)	3.5.2
GP visit		£49	£41.65–56.35 [NA] (Lognormal)	

For costs, 95% CIs were calculated by varying the mean ± 10%.

[a] SE was calculated by multiplying the mean value by 0.2.

BSC, supportive care; CHE, chronic hand eczema; CI, confidence interval CTR, clinical trial report; EQ-5D-3L, 5-dimension, 3-level EuroQol questionnaire; HECSI, Hand Eczema Severity Index; GP, general practitioner; HLCI, high limit confidence interval; IGA, investigator global assessment; LDA, low dose alitretinoin; LLCI, low limit confidence interval; NA, not applicable; NR, not reported; OR, odds ratio; PUVA, psoralen–UV A phototherapy; SE, standard error; TCS, topical corticosteroids.

Table 73 Variables describing distribution of patients not in full response at week 12

Treatment	Distribution across non-responder categories			Distribution and section in submission
IGA-CHE states	IGA-CHE 2	IGA-CHE 3	IGA-CHE 4	
Severe CHE				

Delgocitinib	[redacted]								Dirichlet distribution (3.3.1.2)
Alitretinoin									
BSC [a]									
PUVA									Assumed same as alitretinoin
Moderate CHE									
Delgocitinib									Dirichlet distribution (3.3.1.2)
BSC [a]									
PUVA									Assumed same as delgocitinib

[a] informed by outcomes from the vehicle arms of DELTA 1 and DELTA 2.

IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

3.8.2 Assumptions

Assumptions in the base-case analysis are shown in Table 74.

Table 74 List of assumptions for the base-case analysis

Aspect	Assumption	Justification/implication
Model structure	All patients receive treatment for at least 12 weeks; continuation beyond 12 weeks is dependent on response and treatment received	The point at which response to treatment is assessed and decisions are made varies by treatment. Decisions to continue a course of treatment or stop are influenced by the level of response achieved, the drug label, clinical guidelines and/or reimbursement criteria. The SmPC for delgocitinib states that "treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment." Similarly, the SmPC for alitretinoin states a treatment course of alitretinoin may be given for 12 to 24 weeks depending on response and that discontinuation of therapy should be considered for patients who still have severe disease after the initial 12 weeks of continuous treatment.
	Patients who discontinue treatment following a full response face a risk of relapse at which point treatment can be re-initiated. Relapses can be mild, moderate or severe and the point at which patients re-initiate is treatment-dependent	The SmPC for delgocitinib recommends treatment should be re-initiated as needed in the event of recurrence of CHE. Delgocitinib is designed for long-term disease management and as a topical treatment with a 1-year shelf-life, it will be easier to resume as patients can access unused cream from prior courses before seeking further consultation with a clinician. Alitretinoin and PUVA are assumed to require a dermatologist visit for further prescriptions and may therefore only be reinitiated once symptoms have returned to the point of a moderate or severe relapse.
	There is no limit to the maximum number of times a patient can re-initiate the same treatment following response and relapse	Due to the potential for long-term side effects of some treatments, clinicians may limit the number of courses of a given treatment even where it has proven effective. This may be particularly true for PUVA. This assumption could therefore over-estimate the real-world use of such treatments, and because it cannot adequately capture the long-term or cumulative adverse effects, might

Aspect	Assumption	Justification/implication
		overestimate benefits relative to costs. This is likely to reduce the incremental differences with delgocitinib and therefore be conservative. However, the impact of this in the base case of the model is likely to be limited as the data from ALPHA shows a very low likelihood of reinitiating PUVA following a relapse.
Effectiveness of PUVA in moderate CHE	In the absence of data to compare delgocitinib with PUVA in the moderate space, we assume that treatment effects (i.e. the odds ratio) observed in the severe population in DFORCE and ALPHA are generalisable to the moderate population	Clinical trial data for PUVA are available for patients with severe CHE only, though it is the only currently suggested strategy to treat patients with moderate CHE. Though baseline CHE severity may be a prognostic variable it is not expected to be an effect modifier in a head-to-head comparison. Disease severity is expected to affect the likelihood of response similarly for the compared treatments; therefore, in the head-to-head comparison of ALPHA among patients with severe CHE, the treatment effects are expected to be similar if the strategies were compared among patients with moderate CHE. The same is expected for treatment effects observed between delgocitinib and alitretinoin in DELTA FORCE. This assumption allows for an indirect comparison between delgocitinib and PUVA among patients with moderate CHE using the best data available even if they are slightly indirect to the population.
Effectiveness – late response with continued treatment	Probabilities of achieving full response among patients who continue treatment are assumed to be similar across treatments	A *post hoc* analysis of DELTA FORCE showed [redacted]. Due to lack of comparative evidence for PUVA, similarity with delgocitinib was assumed.
Effectiveness - relapse	The rate of relapse is assumed constant over time, regardless of the number of previous treatments consumed, baseline disease severity or time to achieve or time in response	Informed by statistical analyses of the DELTA 3 trial that show similarity across rate of relapse for different groups based on whether response was achieved early or late and following initial or re-initiated treatment. Use of a constant relapse rate over time may underestimate early relapses and overestimate relapses in the longer term, but given the time horizon, this is not expected to have a substantial impact on conclusions.
Effectiveness – next-line treatment	The real-world efficacy of alitretinoin, from the RWEAL study, is a proxy for the expected efficacy of the next-line treatment basket comprising systemic therapy (conventional and biologic), phototherapy and topical therapies	Due to limited evidence available a simplification was deemed appropriate and tested in sensitivity analysis. As most patients in the model end up on next-line treatment, the impact of variation on this parameter is expected to have a minimal impact on the incremental results.

Aspect	Assumption	Justification/implication
Efficacy – BSC	The efficacy of BSC is assumed to equal that of the placebo/vehicle arm in the NMA and DELTA 1 and DELTA 2 trials.	This assumption is consistent with previous technology appraisals in other dermatological conditions (e.g., psoriasis and atopic dermatitis) and is more conservative than a scenario in which patients on BSC were assumed to revert to baseline CHE severity and accrue associated costs and benefits.
HRQoL – treatment effect	It is assumed that delgocitinib treatment effect on the EQ-5D baseline is applied to all the active comparators and the next-line treatments. The impact of the BSC EQ-5D is derived from the vehicle arm in the D1/D2 studies.	Delgocitinib is the only active treatment with available data to estimate treatment effect vs vehicle on EQ-5D (DELTA 1 and DELTA 2 studies). In a scenario analysis, treatment-independent health state utilities were derived from all the DELTA studies and applied to active treatments and BSC.
Costs – treatment and monitoring	No wastage costs are assumed for delgocitinib	The shelf-life of delgocitinib is 1 year. As the time to loss of response observed in the clinical trials falls well within 1 year, it is unlikely that the product would expire between two treatment phases. Therefore a patient who has experienced a loss of response is likely to be able to apply unused cream from a prior course.
	Adverse event costs assume that that all patients experiencing headache or nasopharyngitis visit their GP once	Simplifying assumption, though it may overestimate costs of alitretinoin relative to delgocitinib given the greater incidence of these AEs in the alitretinoin arm. A sensitivity analysis excluding these costs was performed along with one assuming that they were handled by a dermatologist instead of a GP.
	Costs of a baseline assessment visit with a dermatologist are excluded and follow-up costs associated with treatment monitoring by a dermatologist are covered under health state costs	As baseline assessment is performed for all patients at entry to the model, the costs do not contribute to incremental results. Health state costs for patients with mild, moderate or severe CHE assume 1 dermatologist visit per quarter, which should cover the cost of drug monitoring. Further inclusion of dermatologist visits would risk double-counting.
	Emollient costs are reimbursed by the public payer if included in BSC.	This is aligned with NICE TA177 and is not expected to have an impact on the incremental results.
Dosing – alitretinoin	The proportion of patients taking the upper and lower dose of alitretinoin is assumed constant over time; dose adjustments due to AEs are not accounted for	Both doses of alitretinoin have the same unit cost therefore the impact of differential dosing is assumed to be nil. This may be conservative, given that there could be multiple packs prescribed within a given cycle if the dose needs to be adjusted.
Dosing – delgocitinib	The weekly usage of delgocitinib is linked to the current CHE severity or level of response achieved.	This is informed by a MMRM regression analysis which showed that weekly usage varied by level of response over time. In a series of scenario analyses, weekly usage was set to be equal across health states, assuming an average usage from the DELTA trials as well as the lowest mean usage (from DELTA 2) and the highest mean usage (from DELTA FORCE).
HCRU	Health state HCRU was assumed to be equal across mild, moderate and severe CHE states and less for	The 2011 German study identified in HCRU SLR (Augustin et al.) [136] indicated that outpatient costs were relatively stable by average CHE severity, but that drug, phototherapy and

Aspect	Assumption	Justification/implication
	patients in full response (clear/nearly clear).	inpatient costs increased. Hospitalisations were considered unlikely to be as common in the UK setting, therefore costs were likely to be considered fairly stable. In a scenario analysis, health state costs were adjusted to reflect increased resource use with worse severity.
Next-line treatment	An additional line of treatment was modelled as a treatment basket comprising retinoids, immunosuppressants, dupilumab, PUVA and TCS.	Simplifying assumption that allows the user to amend the utilisation, efficacy, duration of therapy and costs of therapies included in the basket to explore alternative scenarios.

AE, adverse event; BSC, best supportive care; EQ-5D, 5-dimension EuroQol questionnaire; GP, general practitioner; HCRU, healthcare resource utilisation; HRQoL, health-related quality of life; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PUVA, psoralen–UV A phototherapy; SLR, systematic literature review.

3.9 Base-case results

Clinical outcomes from the model and disaggregated results of the base-case incremental cost-effectiveness analysis are presented in Appendix H.

3.9.1 Base-case incremental cost-effectiveness analysis results

Base-case cost-effectiveness results for patients with severe CHE and with moderate CHE are shown in Table 75. Delgocitinib was less costly and more effective than PUVA in both populations. The ICER for delgocitinib compared with alitretinoin was £8,221 per QALY. Delgocitinib is ranked first in terms of net health benefit at the £20,000 and £30,000 per QALY thresholds across both moderate and severe CHE populations.

Table 75 Base case results

Treatment		Severe CHE			Moderate CHE	
		Alitretinoin (reference)	Delgocitinib	PUVA	Delgocitinib (reference)	PUVA
Total	Costs (£)	8,896	9,208	9,849	8,297	8,809
	LYs	8.371	8.371	8.371	8.371	8.371
	QALYs	5.645	5.683	5.634	5.885	5.837
Incremental vs reference	Costs (£)	-	312	953	-	512
	LYG	-	0	0	-	0
	QALYs	-	0.038	−0.011	-	−0.047
ICER (£/QALY)	vs reference	-	8,221	Dominated	-	Dominated
	Fully incremental	-	8,221	Dominated	-	Dominated
NHB at	£20,000	5.20	5.22	5.14	5.47	5.40
	£30,000	5.35	5.38	5.31	5.61	5.54
Rank based on NHB		2	1	3	1	2

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.

In addition to total QALYs, life years and costs, the model also provides an estimate of the expected time on treatment and usage of delgocitinib over the modelled time horizon. This accounts for both continuous use during the initial 12 weeks and as-needed use thereafter. These results are presented in Appendix H along with other disaggregated results.

3.10 Exploring uncertainty

3.10.1 Probabilistic sensitivity analysis

A PSA with 1000 model simulations was conducted to explore the uncertainty in model variables. A full list of all parameters included in the PSA, including mean values, standard errors and distributions, is presented in section 3.8.1, Table 72. Probability distributions were based on estimates of uncertainty from data sources, such as confidence intervals. In the absence of data on the variability around the sampling distribution of mean values, the standard error is assumed to be equal to 20% of the mean. Uncertainty around the estimates of effect from the ITC were incorporated using the CODA output of the posterior distribution, ensuring the preservation of correlations [139]. PSA was conducted for both severe CHE and moderate CHE subgroups.

PSA results are shown in Table 76. Graphical representations of the simulations are shown in Appendix K.1, Figures 60–62.

For patients with severe CHE, the mean ICER for delgocitinib compared with alitretinoin was £10,781 per QALY. PUVA was dominated by both delgocitinib and alitretinoin. Cost-effectiveness acceptability curves are shown in Figure 30. At cost-effectiveness thresholds of £20,000 and £30,000 per QALY, delgocitinib has the highest likelihood of the comparators of being cost effective (83.9% and 92.3%), followed by alitretinoin (16.1% and 7.7%). Delgocitinib was dominant (i.e., less costly and more effective) in 12.2% of simulations compared to alitretinoin and in 93.5% of simulations compared to PUVA.

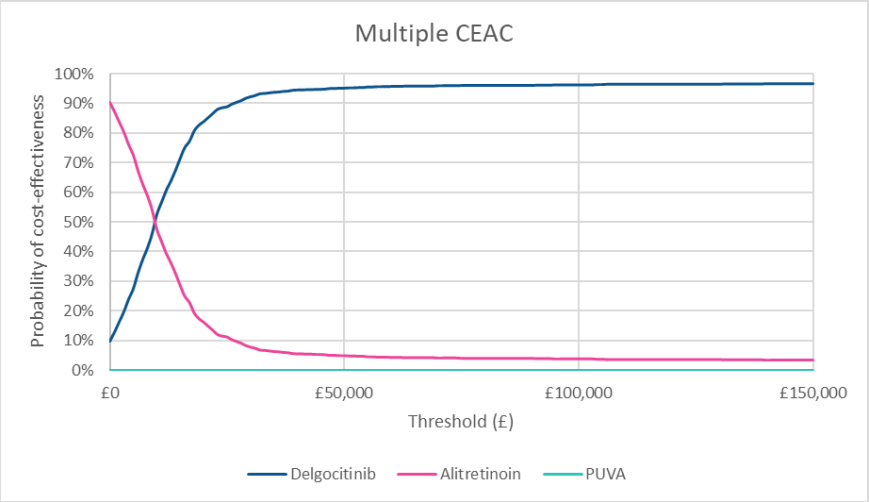
For patients with moderate CHE, delgocitinib dominated PUVA. Cost-effectiveness acceptability curves are shown in Figure 31. Delgocitinib had a 99.5% and 99.7%% likelihood of being more cost effective than PUVA at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, respectively, and dominated PUVA in 89.5% of simulations.

Table 76 PSA results for severe and moderate CHE subgroups

Treatment	Total, mean (95% CrI)		Total NHB, mean (95% CrI)		Incremental vs reference, mean (95% CrI)		iNHB vs reference, mean (95% CrI)	
	Costs (£)	QALYs	£20k	£30k	Costs (£)	QALYs	£20k	£30k
Severe CHE								
Alitretinoin	8869 (7892, 9960)	5.666 (5.483, 5.938)	5.22 (5.03, 5.52)	5.37 (5.18, 5.66)	-	-	-	-
Delgocitinib	9227 (8292, 10358)	5.700 (5.517, 5.977)	5.24 (5.05, 5.52)	5.39 (5.2, 5.67)	358 (−153, 1011)	0.033 (−0.0008, 0.06)	0.015 (−0.034, 0.044)	0.021 (−0.019, 0.047)
PUVA	9812 (8755, 10954)	5.654 (5.475, 5.923)	5.16 (4.97, 5.47)	5.33 (5.14, 5.62)	943 (706, 1097)	−0.013 (−0.032, −0.004)	−0.06 (−0.083, −0.046)	−0.044 (−0.066, −0.033)
Moderate CHE								
Delgocitinib	8284 (7508, 9108)	5.914 (5.697, 6.232)	5.5 (5.28, 5.82)	5.64 (5.42, 5.96)	-	-	-	-
PUVA	8714 (7639, 9663)	5.87 (5.655, 6.185)	5.43 (5.19, 5.79)	5.58 (5.35, 5.93)	−430 (−931, 335)	0.044 (0.0191, 0.069)	−0.066 (−0.092, −0.023)	–0.059 (−0.08, −0.025)

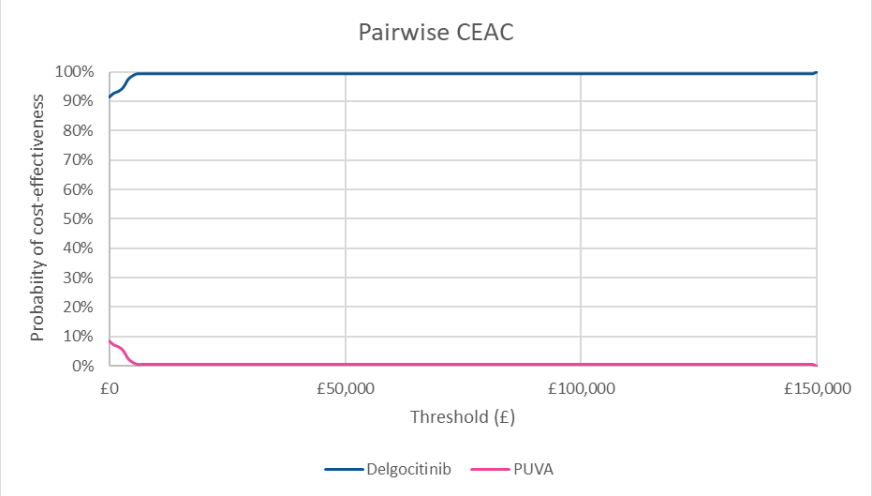
CHE, chronic hand eczema; CrI, credible interval; iNHB, incremental net health benefit; NHB, net health benefit; PSA, probabilistic sensitivity analysis; PUVA, psoralen–UV A phototherapy; QALYs, quality-adjusted life years.

Figure 30 PSA cost-effectiveness acceptability curves of all comparators for severe CHE



CEAC, cost-effectiveness acceptability curve; PUVA, psoralen–UV A phototherapy.

Figure 31 PSA cost-effectiveness acceptability curves for moderate CHE



CEAC, cost-effectiveness acceptability curve; PUVA, psoralen–UV A phototherapy.

3.10.1 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was undertaken to assess the impact of key variables on the outcomes of the model. The parameters that were assessed are noted in section 3.8.1, Table 72; inputs were varied to the limits of their 95% credible intervals/confidence intervals or to values 15% higher and lower than the mean. OWSA was conducted for delgocitinib versus PUVA for both moderate and severe CHE patient and delgocitinib versus alitretinoin for severe CHE patients only. Full OWSA results are reported in Appendix K.2 in terms of incremental net monetary benefit (INMB), calculated at a willingness-to-pay (WTP) of £20,000 per QALY; positive values suggest that delgocitinib is more cost-effective at this threshold than the comparators. .

The results illustrate that the parameters with the greatest impact relate to the risk of relapse, the weekly usage of delgocitinib and the probability of response to delgocitinib relative to PUVA and alitretinoin.

3.10.2 Scenario analysis

As described in the following sections, a series of scenario analyses were performed in order to test particular assumptions and/or data sources. As the results of the deterministic and probabilistic analyses were well aligned, all scenario results are presented based on deterministic analysis unless otherwise specified.

3.10.2.1 Alternative stopping rules for delgocitinib

The base-case analysis assumed that all patients receiving delgocitinib would discontinue treatment either at week 12 or by week 24, depending on their response (see section 3.2.4). This scenario analysis investigated the impact of alternative stopping rules, which would allow for continued use of delgocitinib beyond week 24 by some patients.

Three amendments to the base case stopping rules were explored, each building from the previous.

- Scenario 1: the week 24 stopping rule is extended to week 52 for patients who achieve a partial response at week 12. No change is applied to other stopping rules.
- Scenario 2: the week 24 stopping rule is extended to week 52 for patients who achieve a partial or low response at week 12. No change is applied to other stopping rules.
- Scenario 3: the week 24 stopping rule is extended to week 52 for patients who achieve a partial or low response at week 12 and the week 24 stopping rule during re-treatment following relapse is extended to 52 weeks. No change is applied to other stopping rules.

Results for these three scenarios are presented in Table 77. The ICERs for delgocitinib versus alitretinoin in patients with severe CHE increased as more patients are assumed to continue delgocitinib beyond week 24 to a maximum of £22,669 in scenario 3. Compared with PUVA among patients with moderate CHE, delgocitinib was still likely to be more cost effective in these scenarios, though no longer dominant. The ICER was £2,851 when partial responders continued up to week 52 and £13,309 when partial responders and all retreated patients continued up to week 52. Note that the results for scenario 1 and scenario 2 among patients with moderate CHE are identical given that the low response health state is not relevant for moderate CHE (i.e., it is defined as IGA-CHE 3 with 1-point improvement from baseline).

3.10.2.2 Alternative assumptions around re-initiation following relapse

The base case analysis assumed that patients who experienced a loss of response following treatment with delgocitinib would reinitiate delgocitinib at the point of IGA-CHE ≥ 2 (at least a mild relapse). Patients who experienced a loss of response following treatment with alitretinoin or PUVA would reinitiate the same treatment at the point of IGA-CHE ≥ 3 (at least a moderate relapse; see section 3.3.3). This scenario analysis investigated the impact of alternative re-initiation rules across treatments.

Three amendments to the re-initiation rules were explored.

- Scenario 1: all patients are eligible to re-initiate at IGA-CHE ≥ 2 (mild relapse)
- Scenario 2: all patients are eligible to re-initiate at IGA-CHE ≥ 3 (moderate relapse)

In a separate scenario conducted only for patients with severe CHE, an alternative rate of re-initiation for alitretinoin was also explored. In the base case, the probabilities of re-initiating treatment following a loss of response or relapse were based on DELTA FORCE for delgocitinib and on ALPHA for alitretinoin (see section 3.3.4.3). The DELTA FORCE values may overestimate treatment re-initiation given that re-initiation was driven by the trial protocol. There is also some uncertainty in the values from ALPHA as the context around receipt of further treatment with alitretinoin and PUVA versus other treatments was not well reported.

- Scenario 3: The estimated non-reinitiation rate of 12% for alitretinoin from DELTA FORCE is assumed.

Results for these three scenarios are presented in Table 77. The ICERs for delgocitinib versus alitretinoin in patients with severe CHE were lower in scenarios where all patients were eligible to re-initiate treatment at the same point, whether at the point of a mild or moderate relapse. PUVA remained dominated by both delgocitinib and alitretinoin in these scenarios.

Results of scenario 3 illustrate that the incremental costs and benefits between delgocitinib and alitretinoin are very sensitive to assumptions about the relative proportion of patients who opt to re-initiate at the point of relapse. When more patients who previously responded to alitretinoin opt to re-initiate at relapse, the incremental costs and QALYs of delgocitinib decrease and the ICER decreases. A threshold analysis shows that if more that 80% of alitretinoin patients chose to re-initiate, then delgocitinib goes from cost effective to dominant.

3.10.2.3 Exploration of additional assumptions

A range of additional scenarios were tested for severe and moderate CHE patients, with results presented as the ICER and incremental NHB of delgocitinib versus alitretinoin (severe CHE only) and delgocitinib versus PUVA (moderate and severe CHE; Table 77).

The incremental net health benefit for delgocitinib was positive in all scenarios, versus both alitretinoin (severe CHE only) and PUVA (moderate and severe CHE). Delgocitinib dominated PUVA across all scenarios, consistently generating greater QALYs at lower cost in both moderate CHE and severe CHE populations. Among patients with severe CHE delgocitinib was consistently more cost effective than alitretinoin given a WTP threshold of £20,000 per QALY gained. The scenarios that had the greatest impact on the ICER of delgocitinib versus alitretinoin were those related to the time horizon, weekly delgocitinib usage, the distribution of patients across non-responder states at week 12 and rates of relapse following response.

The base case used a time horizon of 10 years as this was considered sufficient to capture all differences between strategies. The similarity of results at a time horizon of 30 years shows that this was reasonable. At shorter time horizons of 3 and 5 years, the ICER for delgocitinib versus alitretinoin in the treatment of severe CHE was lower than the base case and delgocitinib dominated alitretinoin if only the first year of treatment was considered.

In the base case, the weekly dose of delgocitinib was based on a regression analysis of delgocitinib usage and IGA-CHE severity. Three alternative values were explored to test the sensitivity of the model to predicted consumption, each applied regardless of IGA-CHE severity. In the first, the mean usage from the regression independent of IGA-CHE severity was used: [redacted] grams per week. In the second, the mean usage from DELTA 2 was used, as it was the DELTA trial with the lowest weekly usage: [redacted] grams per week. In the third, the mean usage from the first 12 weeks of DELTA FORCE was used, as it was the DELTA trial with the highest weekly usage: [redacted] grams per week. Results indicate that the ICER versus alitretinoin (in severe CHE) is quite sensitive to variation in delgocitinib consumption, with a threshold analysis showing delgocitinib dominating where usage is less than [redacted] grams per week and cost effective at WTP thresholds of £20,000 and £30,000 per QALY where usage is less than [redacted] grams and [redacted] grams per week, respectively.

Among the severe CHE population, there were multiple sources to inform the distribution of non-responders at week 12 across partial, low and insufficient response (see section 3.3.1.2). In the base case, data from DELTA FORCE were used for delgocitinib and alitretinoin; PUVA was assumed to have the same efficacy as alitretinoin. In one scenario analysis, the distribution was set equal to delgocitinib for alitretinoin and PUVA. This halved the ICER versus alitretinoin and PUVA remained dominated. In a second set of scenarios, the distributions for alitretinoin and PUVA were taken from the ALPHA trial, assuming in one case that missing data counted as being in a severe state (i.e., insufficient response) and in the other that missing data was ignored (i.e., observed cases only). The observed case analysis reduced the ICER of delgocitinib versus alitretinoin by nearly half and in the analysis where missing data was treated as insufficient response the ICER was slightly higher than in the base case.

The rate of relapse was also associated with uncertainty and multiple sources (see section 3.3.2). In the base case, the probability of losing response following treatment with delgocitinib was taken from DELTA FORCE. In a scenario, the rate was taken from DELTA 3, in which the median time to relapse was 4.1 weeks, corresponding to a per-cycle probability of 48.8%. This increased rate of loss of response increased the ICER versus alitretinoin among severe CHE patients. In the absence of high-quality evidence to differentiate the relapse rate for alitretinoin and PUVA from that for delgocitinib, a hypothetical scenario assuming that the rate of relapse was 50% lower than with delgocitinib was run. Delgocitinib still dominated PUVA across both moderate and severe CHE populations and the ICER versus alitretinoin remained under the £20,000 threshold among patients with severe CHE.

In another scenario, a set of utility values that were response-dependent and treatment-independent were used. The ICER for delgocitinib versus alitretinoin among patients with severe CHE increased from the base case, though it was still less than £10,000 per QALY. Delgocitinib remained dominant (less costly and more effective) to PUVA for patients with moderate and with severe CHE.

Finally, assumptions about the composition and uptake of the next-line treatment basket and the efficacy of BSC were tested. The only scenario that had a substantial impact on the results was when patients who reach BSC were assumed to return to their baseline CHE severity and

corresponding HRQoL and expected resource use. Here, the ICER of delgocitinib versus alitretinoin among severe CHE patients reduced by nearly 50% relative to the base case.

Table 77 Scenario analyses for moderate or severe CHE

Scenario	Severe CHE		Moderate CHE
	Delgocitinib vs alitretinoin ICER	Delgocitinib vs PUVA ICER	Delgocitinib vs PUVA ICER
Base case	£8,221	Dominates	Dominates
Time horizon			
1 year	Dominates	Dominates	Dominates
3 years	£4,817	Dominates	Dominates
5 years	£7,430	Dominates	Dominates
30 years	£8,247	Dominates	Dominates
Stopping rules			
Scenario 1	£15,686	£1,519	£2,851
Scenario 2	£20,621	£7,144	£2,851
Scenario 3	£22,669	£14,604	£13,309
Delgocitinib usage (g/week)			
Overall average ([redacted])	£6,801	Dominates	Dominates
DELTA 2 ([redacted])	£135	Dominates	Dominates
DELTA FORCE ([redacted])	£18,134	Dominates	Dominates
As-needed initial treatment	£7,926	Dominates	Dominates
Health state definition			
HECSI responses (< 50, 50, 75, 90)	£9,656	Dominates	Dominates
NMA results			
Primary endpoint NMA	£6,007	Dominates	Dominates
Cumulative response NMA	£9,542 [a]	Dominates [a]	Dominates [b]
Distribution of non-responders at week 12			
Equal for all treatments based on delgocitinib	£4,281	Dominates	NA
ALPHA for alitretinoin and PUVA (severe only) – NRI	£9,917	Dominates	NA
ALPHA for alitretinoin and PUVA (severe only) - OC	£4,630	Dominates	NA
Relapse			
Delgocitinib informed by D3	£10,547	Dominates	Dominates
Risk of relapse with alitretinoin and PUVA assumed to be 50% of risk with delgocitinib	£18,128	Dominates	Dominates
Alternative re-initiation assumptions			
All reinitiate at IGA-CHE ≥ 2	£7,653	Dominates	Dominates
All reinitiate at IGA-CHE ≥ 3	£6,303	Dominates	Dominates
Alitretinoin non-reinitiation: 12%	Dominates	Dominates	Dominates
Response and discontinuation from retreatment			
Differential probabilities of response by treatment [c]	£7,153	Dominates	Dominates
Retreatment discontinuation 50% of initial continued treatment discontinuation	£9,587	Dominates	Dominates
Utilities			
Response-dependent and treatment-independent utilities from DELTA 1, 2 and FORCE	£9,873	Dominates	Dominates
Health state costs			
Health state costs increase with IGA-CHE severity based on data from Augustin 2011	£6,679	Dominates	Dominates
Adverse effects			
No utility decrement	£8,366	Dominates	Dominates
No cost impact	£8,512	Dominates	Dominates
No cost nor utility decrement	£8,662	Dominates	Dominates

Scenario	Severe CHE		Moderate CHE
	Delgocitinib vs alitretinoin ICER	Delgocitinib vs PUVA ICER	Delgocitinib vs PUVA ICER
Dermatologist visit for AEs	£7,633	Dominates	Dominates
Next-line and BSC assumptions			
Next-line progression and basket composition from ALPHA	£7,630	Dominates	Dominates
Next-line efficacy: 75% in LDA	£8,553	Dominates	Dominates
Percent move to next-line treatment: 75%	£7,949	Dominates	Dominates
LDA defined as full response [d]	£8,316	Dominates	Dominates
Patients on BSC revert to baseline CHE severity	£4,337	Dominates	Dominates

[a] In this scenario, [redacted], [redacted], [redacted] and [redacted] of delgocitinib, alitretinoin, PUVA and BSC patients, respectively, achieve full response at week 12.

[b] In this scenario, [redacted], [redacted] and [redacted] of delgocitinib, PUVA and BSC patients, respectively achieve full response at week 12.

[c] In this scenario, probabilities of response to retreatment for alitretinoin and PUVA were adjusted by the odds ratios from the initial period; the resulting per-cycle response rates were 20.2% for delgocitinib, [redacted]% for alitretinoin and [redacted]% for PUVA.

[d] In this scenario, the NL treatment HS costs equals £460.77 and the utility equals 0.776

BSC, best supportive care; CHE, chronic hand eczema, g, gram; HECSI; hand eczema severity index; ICER, incremental cost-effectiveness ratio; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; NMA, network meta-analysis; NRI, non-responder imputation; OC, observed case; PUVA, psoralen–UV A phototherapy.

3.11 Subgroup analysis

Base case results are presented for patients with moderate CHE and patients with severe CHE and no further subgroup analyses were performed. Subgroup analysis results for hand eczema patients by primary cause (atopic or contact) showed a similar trend to the overall trial populations (see section 2.8); therefore, the results of the economic model base case and sensitivity analyses are expected to apply regardless of primary cause.

3.12 Benefits not captured in the QALY calculation

As a topical therapy for CHE, delgocitinib has several benefits that are not captured in the QALY calculation.

Favourable safety profile versus systemic therapies

As described in section 1.3.3.5, the systemic therapies sometimes used in clinical practice (off label, except in the case of alitretinoin for severe CHE) are associated with a risk of SAEs, which were not seen for delgocitinib in the DELTA trial programme. As the economic model only includes the AE of headache and nasopharyngitis, the benefits of avoiding these SAEs will not be included in the QALY calculation.

In contrast to alitretinoin, no pregnancy prevention programme is necessary with delgocitinib

Alitretinoin, which is licensed for severe CHE only, is teratogenic. Accordingly, women of childbearing potential using alitretinoin are required to follow a strict pregnancy prevention programme (see section 1.3.3.5), potentially interfering with their plans to start a family. No such

requirement exists for delgocitinib. The risks may also contribute to a fear of becoming pregnant, due to the known risk of birth defects, which would not be captured by the QALY calculation.

In contrast to phototherapy, which requires specific facilities, equitable access can be readily achieved for delgocitinib

As described in section 1.3.3.5, phototherapy can be inconvenient and costly to access [57]. Patients may live too far away from the hospital or the opening times of a local unit may not fit in with their work and home commitments [56]. As a topical therapy that patients can apply at home, no such issues apply to delgocitinib.

Compared with alitretinoin, delgocitinib has fewer barriers to timely re-initiation of treatment

Patients who experience a relapse after achieving a treatment response on alitretinoin and stopping therapy may need a specialist appointment, and potentially to undergo pregnancy testing and additional monitoring, in order to re-initiate therapy. By contrast, re-initiation of delgocitinib may require only a GP phone call, and patients may still have leftover delgocitinib cream from their previous treatment. In addition to the reduced use of NHS resources seen with delgocitinib, compared with alitretinoin, the benefit of more timely re-initiation of treatment is not captured in the model.

Delgocitinib is expected to have additional benefits to patients and society

As described in section 1.3.1.8, many patients report that their CHE affects their work or education, particularly healthcare professionals and those in the service industry (87% and 77%, reported at least some impact in the CHE Patient Impact Report), while job losses/changes due to CHE are not uncommon [12, 43]. Patients may also need to take substantial time off work due to flare ups of symptoms and to attend appointments. The benefits of avoiding these problems through effective CHE treatment are not captured in the QALY calculation.

3.13 Validation

3.13.1 Validation of cost-effectiveness analysis

Face validity of the model concept was checked during an advisory board made up of clinical and health economic experts. Several quality control measures were undertaken to validate the model findings included in this submission. Internal quality control was undertaken by the developers of the model on behalf of the manufacturer. A second modeler, not involved in the programming, reviewed the model code and formulae, and conducted extreme value analysis to verify the model results. The lead modeler scrutinised the programming and references.

The model outputs were compared against the clinical trial inputs to identify discrepancies. The results were also compared to the alitretinoin NICE appraisal (TA177) and the outcomes of the ALPHA economic evaluation, bearing in mind the structural assumptions and parameter values that could explain differences.

3.14 Interpretation and conclusions of economic evidence

3.14.1.1 Summary of economic model results

This was a cost-effectiveness analysis of delgocitinib for the treatment of moderate and severe CHE. The model considered patients with moderate CHE and those with severe CHE separately, given the differences in the relevant comparators for these populations. Delgocitinib was compared with PUVA for the treatment of patients with moderate or severe CHE and with alitretinoin only for the treatment of patients with severe CHE, as per current NICE guidance. The analysis in these populations and comparisons between these treatments are consistent with the proposed position of delgocitinib in the treatment pathway and its marketing authorisation.

The cost-effectiveness analysis was based on a comprehensive evidence review and a NMA of the available evidence from randomised clinical trials. The structure of the economic model was informed by the 2009 model used in TA177 of alitretinoin, with several updates to reflect clinical practice and address elements of the TA177 model that were critiqued by NICE, a more contemporary evidence-base and the current requirements of the NICE reference case. The final model structure was validated by clinicians and HTA experts.

The results of the base case and sensitivity analyses indicated that delgocitinib is the most cost-effective strategy for both moderate and severe CHE patients, given a WTP threshold of £20,000 per QALY. Compared to PUVA, delgocitinib was consistently dominant (less costly and more effective). Among patients with severe CHE, delgocitinib was found to be cost effective versus alitretinoin, with a base-case ICER of £8,221 per QALY gained. PSA results were similar to the deterministic base case results and showed that, at a £20,000 per QALY threshold, delgocitinib had a probability of 83.9% of being the most cost-effective treatment for severe CHE (comparators, delgocitinib, alitretinoin and PUVA) and a 99.5% probability of being the most cost-effective treatment for moderate CHE (comparators, delgocitinib and PUVA).

In deterministic sensitivity and scenario analyses, the most significant drivers of delgocitinib's cost effectiveness versus comparators were those associated with time on treatment, weekly usage of delgocitinib, rate of loss of response or relapse and re-initiation and the efficacy of BSC. The timing and criteria for stopping and starting treatment affect the duration of delgocitinib treatment relative to comparators. The base-case stopping rules are the same across comparators, with full responders and patients with no improvement from baseline stopping at 12 weeks and those with either a 1- or 2-point improvement in IGA-CHE continuing for up to 24 weeks. In scenario analyses, the week-24 stopping rule is shifted to week 52 for delgocitinib, which means an increase in both total QALYs but also total costs. The ICER increases from the base case according to the proportion of patients continuing beyond week 24, but never exceeds the upper end of the NICE cost-effectiveness threshold of £30,000 per QALY compared with alitretinoin in severe CHE and the lower end of the NICE threshold of £20,000 per QALY compared with PUVA in moderate or severe CHE.

The amount of delgocitinib used during treatment periods was also a key driver of cost effectiveness. In the base case, usage was related to CHE severity based on a regression of

consumption from the DELTA trials. When weekly usage was defined by the mean weekly usage from DELTA 2, the phase 3 RCT that reported the lowest mean weekly usage, delgocitinib was found to be less costly than in the base case, and to dominate both alitretinoin and PUVA. When weekly usage was defined by the mean weekly usage from DELTA FORCE, the phase 3 RCT that reported the highest mean weekly usage, delgocitinib still dominated PUVA and was still cost effective versus alitretinoin given the NICE threshold of £20,000 per QALY.

Another pair of model drivers include the rate of loss of response or relapse and the likelihood of reinitiating treatment. The faster responders lose response once they are off treatment, the sooner they are eligible to re-initiate. Across several scenarios around these parameters, delgocitinib consistently dominated PUVA and remained cost effective versus alitretinoin at a threshold of £20,000 per QALY.

The more patients who re-initiate initial treatment, the higher the costs and benefits of the initial strategy that accrue. Re-uptake of delgocitinib is assumed to be high based on the ease of use and accessibility of unused cream from prior courses and given that the median time to loss of response falls well within the 1-year shelf life of the cream, once opened. The data on re-uptake of delgocitinib is from clinical trials and the protocol likely drove the high re-initiation rates. The rates for alitretinoin and PUVA were sourced from a contemporary, pragmatic UK trial, which showed moderate to low levels of re-initiation. This combination of high re-uptake of delgocitinib and moderate to low re-uptake of alitretinoin and PUVA made for a conservative base case which is reflective of expected clinical practice. Delgocitinib consistently dominated PUVA and the ICER decreased versus alitretinoin. A threshold analysis showed that if more than 80% of alitretinoin patients chose to re-initiate, then delgocitinib goes from cost effective to dominant.

Finally, assumptions about the efficacy of BSC had a substantial impact on the relative cost effectiveness of delgocitinib. The base case took the conservative assumption that patients receiving BSC (a care strategy of emollients, TCS and TCIs only), would experience efficacy similar to the vehicle arm of the clinical trials. In an alternative scenario, these patients are assumed to regress to their baseline CHE severity despite topical therapies on the notion that they had previously tried and failed on these therapies. Under this alternative assumption, the cost effectiveness of delgocitinib relative to alitretinoin improves.

It is also useful to compare the results of this analysis with those reported in the economic evaluation conducted alongside the ALPHA trial. The ALPHA trial, which compared alitretinoin and PUVA as second-line therapies among patients with severe CHE who were unresponsive to TCS, found alitretinoin to be the most cost-effective strategy over a 12 and 52-week time horizon and for both strategies to have an equal probability of being most cost-effective over a 10-year time horizon. The high cost of PUVA during the intervention phase was the main driver of the results in the first year, though the cost differences between strategies evened out over a longer time horizon. The analysis presented here leads to similar conclusions regarding alitretinoin and PUVA but demonstrates that delgocitinib is a more cost-effective second-line treatment than both.

Overall, the model demonstrates the stability of the base-case conclusions over a range of alternative scenarios and suggests that delgocitinib is a cost-effective treatment relative to other second-line treatments in moderate and severe CHE.

3.14.1.2 Strengths and limitations

A key strength of the model is its structure, which is designed to represent the fluctuating nature of CHE and to reflect its long-term impact on quality of life. The model health states are based on response to treatment and whether patients are on- or off-treatment.

Another strength of the model is that all the key inputs for delgocitinib, alitretinoin and PUVA were drawn directly from the DELTA trials or the recent ALPHA trial, a large, pragmatic RCT conducted in UK NHS secondary care dermatology outpatient clinics. The model maximises the use of both short-term data up to week 12 as well as longer-term data to weeks 24 and 52 and makes reasonable and conservative assumptions when there are gaps.

Finally, the model has been designed and built to explore key areas of structural uncertainty, ranging from the timing and definition of stopping rules, definitions of response and severity, approach to initial treatment, eligibility for treatment re-initiation, and subsequent treatments. Exploration of these aspects illustrates how conclusions of delgocitinib's cost effectiveness versus both alitretinoin (in severe CHE) and PUVA (in moderate and severe CHE) are stable across a range of alternative assumptions.

The main limitations of this analysis stem from gaps in the clinical and economic evidence base. Though PUVA is the main comparator for patients with moderate CHE who have had an inadequate response to TCS, the evidence for its efficacy and safety in this population is limited. The ALPHA trial provides estimates of PUVA's clinical and economic value compared with alitretinoin but was conducted only in a population with severe CHE. In order to make a comparison between delgocitinib and PUVA in the moderate CHE population, the model uses an NMA that combines data from the moderate population of DELTA 1 and DELTA 2 with the severe population of DELTA FORCE and ALPHA, assuming that the head-to-head treatment effects are similar across subgroups. There is no way to validate this evidence transfer, though the model results indicate that even if PUVA and delgocitinib were equally effective in the moderate population, delgocitinib would still dominate.

Variation across scales and outcomes to measure disease severity and response to treatment also represent a limitation of the clinical data to the economic modelling. As mentioned in section 1.3.1.5, the IGA-CHE categories do not correspond directly to the PGA, which was used in the alitretinoin phase 3 trials [107, 108] and in ALPHA [54]). The NMA, described in section 2.10.3, assumed these scales were comparable despite inherent differences that could underestimate the efficacy of delgocitinib. Similarly, the scenario defining health states by levels of HECSI response was limited by the availability of data. First, the ALPHA trial did not report HECSI response (e.g., HECSI 75 or 90) despite measuring change in HECSI. Second, long-term fluctuations of disease and re-initiation of treatment could not be informed by HECSI because these were driven by IGA-CHE based on the trial protocols.

Another limitation in the evidence base relates to estimates of loss of response and relapse as well as the context around re-treatment or the introduction of other treatments. Due to the design of DELTA 3 and DELTA FORCE, off-treatment responders resumed treatment when they experience an IGA-CHE ≥ 2. For this reason, there are no data about the probability or rate of relapse to

moderate or severe states for delgocitinib. The ALPHA trial showed that rates of loss of response as well as relapse to moderate and severe states were similar across alitretinoin and PUVA. The model makes use of data to differentiate treatments by the rate of loss of response (IGA-CHE ≥ 2), but uses a common set of probabilities for relapses to moderate and severe CHE due to limitations in available evidence. However, a scenario analysis showed that even if the risk of mild, moderate and severe relapse for alitretinoin and PUVA was half of the risk for delgocitinib, delgocitinib would remain the most cost-effective therapy at a threshold of £20,000 per QALY. Even this scenario may be conservative for delgocitinib, given that to achieve a reduction in rate of relapse compared to delgocitinib, background treatments might be introduced for off-treatment responders to alitretinoin or PUVA. These are not accounted for in the model but would presumably increase costs even as they slow worsening to baseline.

Other gaps in the evidence that were informed by assumptions in the model relate to the efficacy of comparators beyond week 12 and as retreatment. The best available data to inform these parameters came from DELTA 3 and DELTA FORCE. Assumptions of equivalence across treatments for these parameters was informed by crude comparisons across delgocitinib and alitretinoin data sources. With rates appearing similar, a simplifying assumption of equivalence across all treatments was made; sensitivity analyses show that these have a minor impact on results.

Further limitations of the analysis stem from a lack of consensus on the treatment pathways in moderate and severe CHE following an inadequate response to TCS. The model was not built to formally assess the cost effectiveness of a sequence involving delgocitinib, alitretinoin or PUVA because there was no evidence to inform the efficacy of treatments based on their positioning in a sequence. Similarly, there was no good quality evidence to inform the efficacy of potential third-line treatments. For these reasons, a model that evaluated a specific pathway was considered unnecessarily complex to determine the cost-effectiveness of available second-line interventions. Instead, the model takes a simplified approach comparing delgocitinib, PUVA and alitretinoin as second-line treatments followed by a next-line basket and BSC. The basket is informed by real-world data from the UK [8] and by input from UK clinicians and allows the user to easily explore alternative assumptions about the composition of the basket as well as its costs and effects.

A final limitation of the analysis relates to the lack of flexibility to explore some structural elements of the model. For example, the model assumes no limit to the number of rounds of retreatment with a given treatment among patients that have previously achieved a full response even though this might not be consistent with clinical practice. The impact of this is blunted somewhat by the very low re-initiation rates seen in ALPHA for PUVA, which mean that when implemented in the model, there is a very low probability that patients receive multiple rounds of PUVA, except as a strategy included in the next-line treatment basket. Also during retreatment, the model assumes that all treatments are used to the point of full response up to a maximum of 24 weeks. The stopping rules during the initial period are not applied because all patients have previously responded and the data shows that they are more likely to respond again, compared with patients in the initial period. Finally, the model does not allow patients to transition between different levels of response between week 12 and week 24 nor during retreatment. Patients can only move to full response,

remain in the same state or permanently discontinue. In reality, there may be incremental fluctuations between states at the individual patient level. However, this is consistent with modelling in other dermatological conditions (e.g., psoriasis and AD), in which it has been reasonable to assume that the distribution of patients across states is stable with continued treatment. On that basis, the assumption used here is not a major divergence from relevant precedent.

3.14.1.3 Conclusions

The results of the model showed that delgocitinib is dominant (less costly and more effective) to PUVA in both moderate and severe CHE when used as a second-line therapy. The results also showed delgocitinib to be cost effective versus alitretinoin among patients with severe CHE, with an ICER of £8,221 per QALY gained. The most impactful parameters and therefore the key drivers of the model were those associated with delgocitinib consumption (including time on treatment and quantity used), probability of relapse and re-initiation of treatment, and the efficacy of BSC. The conclusion that delgocitinib was the most cost effective second line treatment option for both moderate and severe CHE was robust to exploration of different parameters and structural assumptions in the model. The first treatment specifically licensed for both moderate and severe CHE, delgocitinib is a safe, effective and cost-effective treatment with a simple topical administration which has the potential to reduce strain on NHS resources in managing this condition.

4 References

1. Lee GR, Maarouf M, Hendricks AK, Lee DE, Shi VY. Current and emerging therapies for hand eczema. Dermatol Ther. 2019;32(3):e12840.
2. Lynde C, Guenther L, Diepgen TL, Sasseville D, Poulin Y, Gulliver W*, et al.* Canadian hand dermatitis management guidelines. J Cutan Med Surg. 2010;14(6):267–84.
3. Menne T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis G. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis. 2011;65(1):3–12.
4. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J*, et al.* Guidelines for diagnosis, prevention and treatment of hand eczema--short version. J Dtsch Dermatol Ges. 2015;13(1):77–85.
5. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM*, et al.* Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis. 2022;86(5):357–78.
6. Grant L, Seiding Larsen L, Burrows K, Belsito DV, Weisshaar E, Diepgen T*, et al.* Development of a Conceptual Model of Chronic Hand Eczema (CHE) Based on Qualitative Interviews with Patients and Expert Dermatologists. Adv Ther. 2020;37(2):692–706.
7. LEO Pharma. Data on file, CHECK study results. 2024.
8. LEO Pharma. Data on file, RWEAL study results. 2024.
9. Tauber M, Berard E, Lourari S, Questel E, Redoules D, Paul C*, et al.* Latent class analysis categorizes chronic hand eczema patients according to skin barrier impairment. J Eur Acad Dermatol Venereol. 2020;34(7):1529–35.
10. Agner T, Elsner P. Hand eczema: epidemiology, prognosis and prevention. J Eur Acad Dermatol Venereol. 2020;34 Suppl 1(S1):4–12.
11. Cortesi PA, Scalone L, Belisari A, Bonamonte D, Cannavo SP, Cristaudo A*, et al.* Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. Contact Dermatitis. 2014;70(3):158–68.
12. LEO Pharma, Allergy UK. The Chronic Hand Eczema Patient Impact Report. 2024.
13. Capucci S, Hahn-Pedersen J, Vilsboll 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.
14. Dubin C, Del Duca E, Guttman-Yassky E. Drugs for the Treatment of Chronic Hand Eczema: Successes and Key Challenges. Ther Clin Risk Manag. 2020;16:1319–32.
15. Tanimoto A, Ogawa Y, Oki C, Kimoto Y, Nozawa K, Amano W*, et al.* Pharmacological properties of JTE-052: a novel potent JAK inhibitor that suppresses various inflammatory responses in vitro and in vivo. Inflamm Res. 2015;64(1):41–51.
16. Thaçi D, Madsen D, Saday K, Gooderham M. Minimal systemic exposure of delgocitinib cream in adults with moderate to severe chronic hand eczema in the phase 3 DELTA 2 trial. European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
17. National Institute for Health and Care Excellence. TA177: Alitretinoin for the treatment of severe chronic hand eczema. 2009 [Available from: https://www.nice.org.uk/guidance/ta177/resources/alitretinoin-for-the-treatment-of-severe-chronic-hand-eczema-pdf-82598440714693. Accessed: 16 February 2024.]
18. British Association of Dermatologists. Phototherapy – topical PUVA. [Updated March 2020. Available from: https://www.bad.org.uk/pils/phototherapy-topical-puva/. Accessed: 10 October 2024.]
19. Ennogen IP Ltd. Alitretinoin 10mg soft capsules - Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/14832. Accessed: 16 February 2024.]

20. Giménez-Arnau AM, Bewley A, Molin S, Apfelbacher C, Brignoli L, Corriveau J*, et al.*, editors. Patient characteristics and comorbidities in moderate to severe CHE: Results from the RWEAL study. European Academy of Dermatology and Venereology; 2024; Amsterdam.
21. Borg E, Munro D, Thoning H. The management of Chronic Hand Eczema: A retrospective patient record review. Contact Dermatitis. 2024;90(4):365–71.
22. Kim HJ, Bang CH, Kim HO, Lee DH, Ko JY, Park EJ*, et al.* 2020 Korean Consensus Guidelines for Diagnosis and Treatment of Chronic Hand Eczema. Ann Dermatol. 2021;33(4):351–60.
23. Rademaker M, Armour K, Baker C, Foley P, Gebauer K, Gupta M*, et al.* Management of chronic hand and foot eczema. An Australia/New Zealand Clinical narrative. Australas J Dermatol. 2021;62(1):17–26.
24. Silverberg JI, Guttman-Yassky E, Agner T, Bissonnette R, Cohen DE, Simpson E*, et al.* Chronic Hand Eczema Guidelines From an Expert Panel of the International Eczema Council. Dermatitis. 2021;32(5):319–26.
25. Molin S, Fargnoli MC, Crépy MN, Giménez-Arnau AM, Brignoli L, Dwyer B*, et al.*, editors. Self-reported disease severity and treatment of Chronic Hand Eczema from the CHECK study - A multinational study in six countries. Congress of the European Society of Contact Dermatitis (ESCD); 2024; Dresden.
26. Apfelbacher C, Bewley A, Molin S, Fargnoli MC, Giménez-Arnau AM, Brignoli L*, et al.*, editors. Prevalence of Chronic Hand Eczema in adults: A cross-sectional multi-national study of over 60,000 respondents in the general population. Congress of the European Society of Contact Dermatitis (ESCD); 2024; Dresden.
27. British Association of Dermatologists. Hand dermatis (hand eczema) - patient information leaflet. 2023 [Available from: https://www.bad.org.uk/patient-information-leaflets/. Accessed: 16 February 2024.]
28. Apfelbacher CJ, Ofenloch RF, Weisshaar E, Molin S, Bauer A, Mahler V*, et al.* Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry. Contact Dermatitis. 2019;80(1):45–53.
29. Silverberg JI, Agner T, Baranowski K, Plohberger U, Thoning H, Arbuckle R*, et al.* Validation of the Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE): a new clinician reported outcome measure of CHE severity. Arch Dermatol Res. 2024;316(4):110.
30. Scalone L, Cortesi PA, Mantovani LG, Belisari A, Ayala F, Fortina AB*, et al.* Clinical epidemiology of hand eczema in patients accessing dermatological reference centres: results from Italy. Br J Dermatol. 2015;172(1):187–95.
31. Thaçi D, Augustin M, Westermayer B, Kamps A, Hennig M. Effectiveness of alitretinoin in severe chronic hand eczema: PASSION, a real-world observational study. J Dermatolog Treat. 2016;27(6):577–83.
32. Molin S, Larsen LS, Joensson P, Oesterdal ML, Arbuckle R, Grant L*, et al.* Development and Psychometric Validation of a Patient-Reported Outcome Measure to Assess the Signs and Symptoms of Chronic Hand Eczema: The Hand Eczema Symptom Diary (HESD). Dermatol Ther (Heidelb). 2024;14(3):643–69.
33. Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population - A systematic review and meta-analysis. Contact Dermatitis. 2021;84(6):361–74.
34. Tappenden P. Conceptual modelling for health economic model development. HEDS Discussion Paper 12/05 (Unpublished). 2012; Available at: https://eprints.whiterose.ac.uk/74464/.
35. Lund T, Petersen SB, Flachs EM, Ebbehoj NE, Bonde JP, Agner T. Risk of work-related hand eczema in relation to wet work exposure. Scand J Work Environ Health. 2020;46(4):437–45.
36. Lerbaek A, Kyvik KO, Ravn H, Menne T, Agner T. Clinical characteristics and consequences of hand eczema - an 8-year follow-up study of a population-based twin cohort. Contact Dermatitis. 2008;58(4):210–6.
37. Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. Br J Dermatol. 2005;152(5):975–80.

38. Crane MM, Webb DJ, Watson E, Cunliffe T, English J. Hand eczema and steroid-refractory chronic hand eczema in general practice: prevalence and initial treatment. Br J Dermatol. 2017;176(4):955–64.
39. Dalgard FJ, Gieler U, Tomas-Aragones L, Lien L, Poot F, Jemec GBE*, et al.* The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol. 2015;135(4):984–91.
40. Ahmed A, Shah R, Papadopoulos L, Bewley A. An ethnographic study into the psychological impact and adaptive mechanisms of living with hand eczema. Clin Exp Dermatol. 2015;40(5):495–501.
41. Bewley A, Kalia S, Jonsen E, Brandi H, Gonçalves-Bradley D, Lim V*, et al.* Burden of Disease in Patients with Chronic Hand Eczema: Systematic Literature Reviews of Healthcare Resource Use and Health-Related Quality of Life. ISPOR Europe; 17–20 November 2024; Barcelona, Spain; 2024.
42. Dauden E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D*, et al.* Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. J Eur Acad Dermatol Venereol. 2009;23(12):1374–82.
43. Armstrong A, Hahn-Pedersen J, Bartlett C, Glanville J, Thyssen JP. Economic Burden of Chronic Hand Eczema: A Review. Am J Clin Dermatol. 2022;23(3):287–300.
44. Caroe TK, Ebbehoj NE, Bonde JPE, Vejlstrup SG, Agner T. Job change facilitates healing in a cohort of patients with occupational hand eczema. Br J Dermatol. 2018;179(1):80–7.
45. Cvetkovski RS, Zachariae R, Jensen H, Olsen J, Johansen JD, Agner T. Prognosis of occupational hand eczema: a follow-up study. Arch Dermatol. 2006;142(3):305–11.
46. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. Allergy. 2020;75(1):54–62.
47. Haddad EB, Cyr SL, Arima K, McDonald RA, Levit NA, Nestle FO. Current and Emerging Strategies to Inhibit Type 2 Inflammation in Atopic Dermatitis. Dermatol Ther (Heidelb). 2022;12(7):1501–33.
48. Worm M, Bauer A, Elsner P, Mahler V, Molin S, Nielsen TSS. Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study. Br J Dermatol. 2020;182(5):1103–10.
49. Xue C, Yao Q, Gu X, Shi Q, Yuan X, Chu Q*, et al.* Evolving cognition of the JAK-STAT signaling pathway: autoimmune disorders and cancer. Signal Transduction and Targeted Therapy. 2023;8(1):204.
50. Virtanen AT, Haikarainen T, Raivola J, Silvennoinen O. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. BioDrugs. 2019;33(1):15-32.
51. Christoffers WA, Coenraads PJ, Svensson A, Diepgen TL, Dickinson-Blok JL, Xia J*, et al.* Interventions for hand eczema. Cochrane Database Syst Rev. 2019;4(4):CD004055.
52. National Institute for Health and Care Excellence. Clinical Knowledge Summaries (CKS). Dermatitis - contact. [Updated January 2024. Available from: https://cks.nice.org.uk/topics/dermatitis-contact/. Accessed: 18 November 2024.]
53. Elsner P, Agner T. Hand eczema: treatment. J Eur Acad Dermatol Venereol. 2020;34 Suppl 1:13–21.
54. Wittmann M, Smith IL, Brown ST, Berekmeri A, Vargas-Palacios A, Sunderland L*, et al.* Alitretinoin versus phototherapy as the first-line treatment in adults with severe chronic hand eczema: the ALPHA RCT. Health Technol Assess. 2024;28(59):1–123.
55. Bauer A, Brans R, Brehler R, Buttner M, Dickel H, Elsner P*, et al.* S2k guideline diagnosis, prevention, and therapy of hand eczema. J Dtsch Dermatol Ges. 2023;21(9):1054–74.
56. British Photobiology Group. British Photobiology Group Position Statement: Phototherapy for skin disease. 2020 [Updated 19 April 2024. Available from: https://bpg.org.uk/wp-content/uploads/2021/08/BPG-Position-Statement-Phototherapy-for-Skin-disease-July-2020.pdf. Accessed: 31 October 2024.]

57. National Institute for Health and Care Excellence. Ruxolitinib for treating non-segmental vitiligo in people 12 years and over [ID3998]. 2024 [Updated 22 April 2024. Available from: https://www.nice.org.uk/guidance/gid-ta10893/documents/1. Accessed: 31 October 2024.]
58. Electronic Medicines Compendium. Acitretin. 2024 [Available from: https://www.medicines.org.uk/emc/product/10248/smpc. Accessed: 7 September 2024.]
59. Electronic Medicines Compendium. Azathioprine. 2022 [Available from: https://www.medicines.org.uk/emc/product/14296/smpc. Accessed: 7 September 2024.]
60. Medicines and Healthcare products Regulatory Agency. Methotrexate: advise patients to take precautions in the sun to avoid photosensitivity reactions. 2023 [Available from: https://www.gov.uk/drug-safety-update/methotrexate-advise-patients-to-take-precautions-in-the-sun-to-avoid-photosensitivity-reactions#:~:text=sun%20exposure%20during%20methotrexate%20treatment,tanning%20equipment)%20while%20taking%20methotrexate. Accessed: 6 September 2024.]
61. Electronic Medicines Compendium. Methotrexate. 2022 [Available from: https://www.medicines.org.uk/emc/product/11723/smpc. Accessed: 7 September 2024.]
62. Voorberg AN, Kamphuis E, Christoffers WA, Schuttelaar MLA. Efficacy and safety of dupilumab in patients with severe chronic hand eczema with inadequate response or intolerance to alitretinoin: a randomized, double-blind, placebo-controlled phase IIb proof-of-concept study. Br J Dermatol. 2023;189(4):400–9.
63. Simpson EL, Silverberg JI, Worm M, Honari G, Masuda K, Sygula E*, et al.* Dupilumab treatment improves signs, symptoms, quality of life, and work productivity in patients with atopic hand and foot dermatitis: Results from a phase 3, randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2024;90(6):1190–9.
64. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis. 2018 [Available from: https://www.nice.org.uk/guidance/ta534. Accessed: 19 November 2024.]
65. Rosenberg FM, Loman L, Schuttelaar MLA. Baricitinib treatment of severe chronic hand eczema: Two case reports. Contact Dermatitis. 2022;86(5):419–21.
66. Lee SD, Ahn HJ, Shin MK. Nine cases of chronic hand and foot eczema treated with baricitinib. Australas J Dermatol. 2023;64(3):408–12.
67. Bissonnette R, Worm M, Shi VY, Zhang F, Chan G, Bratt TA*, et al.* Efficacy of Abrocitinib and Dupilumab on Chronic Hand Eczema in Patients With Moderate-to-Severe Atopic Dermatitis: Results From the Phase 3 JADE DARE Study. European Academy of Dermatology and Venereology; 7–10 September 2022; Milan; 2022.
68. Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021 [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death#:~:text=FDA%20is%20requiring%20new%20and,%2C%20and%20Rinvoq%20(upadacitinib). Accessed: 16 February 2024.]
69. Chai ESX, Tey HL, Lim ZV. Are There Ethnic Differences in Hand Eczema? A Review. J Clin Med. 2023;12(6).
70. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics: Anzupgo 20 mg/g cream 2024 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/69f6d1d0fd9df92404c45454660c57b5017e1d34. Accessed: 10 December 2024.]
71. British National Formulary. Ciclosporin. 2023 [Available from: https://bnf.nice.org.uk/drugs/ciclosporin/#drug-action. Accessed: 31 October 2024.]
72. British Association of Dermatologists. Alitretinoin. 2015 [Available from: https://www.skinhealthinfo.org.uk/wp-content/uploads/2018/11/Alitretinoin-Nov-2015-lay-reviewed-Oct-20152.pdf. Accessed: 19 November 2024.]

73. Izzedine H, Launay-Vacher V, Baumelou A, Deray G. Antiretroviral and immunosuppressive drug-drug interactions: An update. Kidney International. 2004;66(2):532-41.
74. LEO Pharma. Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema (DELTA 1). 2022 [Available from: https://clinicaltrials.gov/study/NCT04871711. Accessed: 16 February 2024.]
75. LEO Pharma. Efficacy and Safety of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema (DELTA 2). 2023 [Available from: https://clinicaltrials.gov/study/NCT04872101. Accessed: 16 February 2024.]
76. LEO Pharma. Open-label Multi-site Extension Trial in Subjects Who Completed the DELTA 1 or DELTA 2 Trials (DELTA3). 2023 [Available from: https://clinicaltrials.gov/study/NCT04949841. Accessed: 16 February 2024.]
77. LEO Pharma. A 24 Week Trial to Compare the Efficacy and Safety of Delgocitinib Cream 20 mg/g Twice-daily With Alitretinoin Capsules Once-daily in Adult Participants With Severe Chronic Hand Eczema. 2023 [Available from: https://clinicaltrials.gov/study/NCT05259722. Accessed: 16 February 2024.]
78. LEO Pharma. Phase 2b Dose-ranging Trial to Evaluate Delgocitinib Cream 1, 3, 8, and 20 mg/g Compared to Delgocitinib Cream Vehicle Over a 16-week Treatment Period in Adult Subjects With Chronic Hand Eczema. 2023 [Available from: https://clinicaltrials.gov/study/NCT03683719. Accessed: 16 February 2024.]
79. LEO Pharma. Delgocitinib HTA24: Consolidated DELTA post hoc tables. 2024.
80. Leo Pharma. Delgocitinib HTA16. Efficacy endpoints stratified by Atopic and Contact HE, Sep 2024, Delta Force. Payer submission statistical appendix.; 2024.
81. Leo Pharma. Delgocitinib HTA16. Efficacy endpoints stratified by Atopic and Contact HE, Sep 2024, Delta 1 + Delta 2. Payer submission statistical appendix.; 2024.
82. Bissonnette R, Warren RB, Pinter A, Agner T, Gooderham M, Schuttelaar MLA*, et al.* Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema (DELTA 1 and DELTA 2): results from multicentre, randomised, controlled, double-blind, phase 3 trials. Lancet. 2024;404(10451):461–73.
83. LEO Pharma. DELTA 1 protocol. 2021.
84. LEO Pharma. DELTA 2 protocol. 2021.
85. LEO Pharma. DELTA 3 protocol. 2021.
86. LEO Pharma. DELTA FORCE protocol. 2022.
87. LEO Pharma. DELTA 1 clinical study report. 2023.
88. LEO Pharma. DELTA 2 clinical study report. 2023.
89. LEO Pharma. DELTA 3 clinical study report. 2023.
90. LEO Pharma. DELTA FORCE clinical study report. 2023.
91. Bissonnette R, Warren RB, Stingeni L, Baranowski K, Kurvits M, Plohberger U*, et al.* Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema: results of the Phase 3 DELTA 1 trial. European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
92. Molin S, Larsen LS, Joensson P, Oesterdal ML, Arbuckle R, Grant L*, et al.* Development and psychometric validation of a new patient-reported outcome measure to assess the signs and symptoms of Chronic Hand Eczema (CHE): the Hand Eczema Symptom Diary (HESD). European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
93. Schliemann S, Pinter A, Schuttelaar ML, Serra-Baldrich E, Baranowski K, Korn S*, et al.* Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema: results of the Phase 3 DELTA 2 trial. European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
94. Silverberg JI, Agner T, Baranowski K, Plohberger U, Thoning H, Arbuckle R*, et al.* Psychometric Validation of the Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE): a new clinician reported outcome measure. European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.

95. Giménez-Arnau AM, Pinter A, Sondermann W, Reguiai Z, Woolf R, Lynde C*, et al.*, editors. DELTA FORCE trial: A 24-week head-to-head Phase 3 trial comparing the efficacy and safety of topical delgocitinib cream with oral alitretinoin capsules in adults with severe Chronic Hand Eczema. European Academy of Dermatology and Venerology; 2024; Amsterdam.
96. LEO Pharma. Data on file, post hoc analyses of cumulative response. 2024.
97. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302–7.
98. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
99. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27–33.
100. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D*, et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
101. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets. Value Health. 2012;15(5):708–15.
102. National Institute for Health and Care Excellence. Health technology evaluations: the manual. 2022 [Available from: https://www.nice.org.uk/process/pmg36. Accessed: 31 October 2024.]
103. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337–43.
104. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
105. Worm M, Thyssen JP, Schliemann S, Bauer A, Shi VY, Ehst B*, et al.* The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial. Br J Dermatol. 2022;187(1):42–51.
106. Blank PR, Blank AA, Szucs TD. Cost-effectiveness of oral alitretinoin in patients with severe chronic hand eczema - a long-term analysis from a Swiss perspective. BMC Dermatol. 2010;10 (no pagination)(4).
107. Ruzicka T, Lynde CW, Jemec GBE, Diepgen T, Berth-Jones J, Coenraads PJ*, et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. Br J Dermatol. 2008;158(4):808–17.
108. Fowler J, Graff O, Hamedani A. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. J Drugs Dermatol. 2014;13(10):1198–204.
109. Schuttelaar ML, Bissonnette R, Worm M, Warren RB, Agner T, Gooderham M*, et al.*, editors. Efficacy and safety of delgocitinib cream in adults with moderate to severe Chronic Hand Eczema: pooled results of the Phase 3 DELTA 1 and 2 trials. European Academy of Dermatology and Venereology 2024; Amsterdam.
110. Oosterhaven JAF, Schuttelaar MLA. Responsiveness and interpretability of the Hand Eczema Severity Index. Br J Dermatol. 2020;182(4):932–9.
111. Barrett A, Hahn-Pedersen J, Kragh N, Evans E, Gnanasakthy A. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. Patient. 2019;12(5):445–59.
112. Office for National Statistics. Ethnic group, England and Wales: Census 2021. 2022 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021. Accessed: 10 September 2024.]

113. European Medicines Agency. Anzupgo - Delgocitinib. 2024 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/anzupgo#:~:text=The%20active%20substance%20of%20Anzupgo,(ATC%20code%3A%20D11AH11). Accessed: 31 October 2024.]
114. Nam J, Cho E. The cost-effectiveness of oral alitretinoin in patients with severe chronic hand eczema in the healthcare system of South Korea. Value Health. 2017;20(5):A158.
115. Paulden M, Rodgers M, Griffin S, Slack R, Duffy S, Ingram JR*, et al.* Alitretinoin for the treatment of severe chronic hand eczema. Health Technol Assess. 2010;14 Suppl 1:39–46.
116. Vicente C, Lynde C, Poulin Y, Sabapathy S, Boisjoly L, Piwko C. Cost-effectiveness of TOCTINO (Alitretinoin) versus cyclosporine in adult patients with severe chronic hand eczema unresponsive to potent topical corticosteroids. J Popul Ther Clin Pharmacol. 2012;19(2):e130.
117. Rodgers M, Griffin S, Paulden M, Slack R, Duffy S, Ingram JR*, et al.* Alitretinoin for severe chronic hand eczema: A NICE single technology appraisal. PharmacoEconomics. 2010;28(5):351–62.
118. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force–2. Med Decis Making. 2012;32(5):678–89.
119. British National Formulary. Drugs. 2024 [Available from: https://bnf.nice.org.uk/. Accessed: 31 October 2024.]
120. Jones K. WH, Birch S., Castelli A., Chalkley M., Dargan A., Forder J., Gao M., Hinde S., Markham S., Premji S., Findlay D., Teo H.,. Unit Costs of Health and Social Care 2023 Manual. 2024 [Available from: https://kar.kent.ac.uk/105685/. Accessed: 31 October 2024.]
121. NHS England. 2022/23 National Tariff Payment System. 2023 [Available from: https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23NT_Annex-A-National-tariff-workbook_Apr22.xlsx. Accessed: 31 October 2024.]
122. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ*, et al.* State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Value Health. 2012;15(6):812–20.
123. Smith IL, Brown S, Nixon J, Cowdell FC, Ersser S, Fernandez C*, et al.* Treatment of severe, chronic hand eczema: results from a UK-wide survey. Clin Exp Dermatol. 2016;42(2):185–8.
124. Brass D, Fouweather T, Stocken DD, Macdonald C, Wilkinson J, Lloyd J*, et al.* An observer-blinded randomized controlled pilot trial comparing localized immersion psoralen-ultraviolet A with localized narrowband ultraviolet B for the treatment of palmar hand eczema. Br J Dermatol. 2018;179(1):63–71.
125. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics: Alitretinoin 30 mg capsules 2024 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/9879c83434a787e88f73714b2a0d6e761720aaa3. Accessed: 10 December 2024.]
126. Bissonnette R, Worm M, Gerlach B, Guenther L, Cambazard F, Ruzicka T*, et al.* Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. Br J Dermatol. 2010;162(2):420–6.
127. Office for National Statistics. National Life Tables, United Kingdom, period expectation of life, based on data for the years 2020-2022. . 2024 [Office for National Statistics:[Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed: 2024.]
128. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011;14(4):539–45.
129. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509–18.
130. Falk Hvidberg M, Hernández Alava M. Catalogues of EQ-5D-3L Health-Related Quality of Life Scores for 199 Chronic Conditions and Health Risks for Use in the UK and the USA. PharmacoEconomics. 2023;41(10):1287–388.

131. NHS England. 2022/23 National Cost Collection Data Publication. 2024 [Available from: https://www.england.nhs.uk/publication/2022-23-national-cost-collection-data-publication/. Accessed: 16 December 2024.]
132. British National Formulary. Alitretinoin medicinal forms. 2023 [Available from: https://bnf.nice.org.uk/drugs/alitretinoin/medicinal-forms/. Accessed: 31 October 2024.]
133. British National Formulary. Alitretinoin drug. 2023 [Available from: https://bnf.nice.org.uk/drugs/alitretinoin/. Accessed: 31 October 2024.]
134. National Clinical Guideline Centre. Preoperative tests. 2015 [Available from: https://www.nice.org.uk/guidance/ng45/documents/guideline-appendices-13. Accessed: 31 October 2024.]
135. NHS England. Non-mandatory guide prices. 2023 [Available from: https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23NT_Non-mandatory-guide-prices.xlsx. Accessed: 31 October 2024.]
136. Augustin M, Kuessner D, Purwins S, Hieke K, Posthumus J, Diepgen TL. Cost-of-illness of patients with chronic hand eczema in routine care: Results from a multicentre study in Germany. Br J Dermatol. 2011;165(4):845–51.
137. British National Formulary. Tacrolimus. 2023 [Available from: https://bnf.nice.org.uk/drugs/tacrolimus/#:~:text=To%20the%20skin&text=Apply%20twice%20daily%20until%20lesion,to%200.03%25%20if%20condition%20allows. Accessed: 31 October 2024.]
138. Electronic Medicines Compendium. Dermacort Hydrocortisone Cream. Package leaflet: information for the user. 2021 [Available from: https://www.medicines.org.uk/emc/files/pil.5849.pdf. Accessed: 31 October 2024.]
139. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence Synthesis for Decision Making 6: Embedding Evidence Synthesis in Probabilistic Cost-effectiveness Analysis. Medical Decision Making. 2013;33(5):671-8.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Delgocitinib for the treatment of moderate to severe chronic hand eczema in adults [ID6408]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
[ID6408] Delgocitinib moderate to severe CHE SIP v2.0	2.0	No	19 March 2025

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's a plain English summary of their submission written for patients participating in the evaluation. It's 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's 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

1a) Name of the medicine

Generic name: Delgocitinib Brand name: Anzupgo®

1b) Population this treatment will be used by

Adults with moderate to severe chronic hand eczema: 1. That has not responded to treatment with topical corticosteroids, or 2. For whom topical corticosteroids are inadequate or inappropriate

1c) Authorisation

Delgocitinib received authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA; the regulatory body in the United Kingdom) for the treatment of moderate to severe chronic hand eczema (29th November 2024).

1d) Disclosures

Not applicable.

Section 2: current landscape

2a) The condition – clinical presentation and impact

What is the main disease that the medicine plans to treat?

Chronic hand eczema (CHE) is defined as a painful, itchy, inflammatory, non-infectious skin disorder of the hands and wrists that lasts for more than 3 months or relapses at least twice per year [1, 2]. Hand eczema (HE) is commonly associated with exposure to allergens and irritants at work [3, 4]. The most common types of HE are irritant contact dermatitis, allergic contact dermatitis, and atopic HE. These types are explained in more detail in Section 2b. Often, HE can have more than one cause. For example, irritant contact dermatitis can occur along with allergic contact dermatitis and atopic HE. Sometimes, having one type of HE can lead to developing another type. [2].

How many people have CHE?

HE affects around 10% of the general population and up to 30% of people in high-risk occupational groups such as healthcare workers. Between one third and one half of HE cases are moderate or severe [5, 6]. More than half of HE is chronic, and patients often suffer from the condition for prolonged periods [5, 7, 8]. Approximately half of CHE does not respond to treatment with potent topical steroids [9, 10].

What are the main symptoms of CHE?

CHE is characterised by core symptoms of itch and pain, and over time patients may also experience dryness, cracking, thickened skin and bleeding [2, 11]. A large LEO Pharma-funded international study (the Real-World trEatment & mAnagement of chronic hand eczema in cLinical practice [RWEAL] study) provides data on the CHE signs and symptoms recorded during patients' last clinic visit [12]. Patients had to have moderate or severe CHE and to have been treated with topical corticosteroids (TCS) in the last 12 months, or to have a contraindication to TCS (meaning they should not receive TCS). The most common symptoms and signs reported in the UK (based on 365 patients) were redness, itch, scaling and cracking [10].

Inflammatory symptoms and signs (itch, pain, redness, swelling and burning) are typically associated with flares of condition activity. Chronic features – dry skin, thickened skin and flaking – can persist between flares [11].

What is the burden of CHE and the impact on quality of life?

CHE has a persistent or fluctuating course with a poor prognosis, resulting in a major physical and psychological burden for patients [11, 13]. Patients find that symptoms are worsened by numerous triggers including exposure to various allergens or chemicals, cold or warm temperatures, excessive hand washing, and stress [11].

CHE has a substantial impact on patients' daily lives, physical functioning and personal care [11]. This is due to limited movement and difficulty touching or gripping, as well as the need to avoid certain substances and materials [11]. Persistent itch, blisters and cracking, together with the work-related nature of many CHE cases, may limit patients' ability to work [4] and affect sleep quality [11]. In the CHE Patient Impact Report, a recent survey of UK patients with CHE conducted by LEO Pharma with input from Allergy UK and healthcare professionals, most respondents considered itch and pain to have at least a moderate impact on their life [14], and relief of those symptoms is an important goal for patients with CHE. See section 2d for details on the CHE Patient Impact Report.

The visibility of the hands may contribute to a considerable psychological burden including anxiety and depression [1] – one study found that 56% of patients with severe treatment-resistant CHE had anxiety or depression [15]. In the CHE Patient Impact Report, 87% of patients agreed that eczema on their hands is particularly hard to deal with as it cannot be hidden, with 82% agreeing that it made them uncomfortable or embarrassed [14].

Overall, moderate to severe CHE has an impact on health-related quality of life (HRQoL) similar to or greater than that of moderate to severe atopic dermatitis or psoriasis [16].

What is the impact of CHE on patients' family members?

The appearance of CHE has a negative impact on personal relationships [17], causes embarrassment [11, 17] and can lead to self-isolation [17]. In the CHE Patient Impact Report, 74% of patients reported CHE having at least some impact on their relationships or ability to build relationships, and 56% said that CHE prevented them from touching their loved ones [14]. Similarly, in a survey of 1023 people with HE, 89% of respondents were embarrassed/self-conscious about their eczema, and 74% reported that their condition affects the way they handle objects or touch people [18].

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

How is CHE diagnosed?

The diagnosis of CHE is based on different types of assessments that include medical history, clinical examination, patch testing (to check for skin allergies), histopathology (looking at the appearance of skin tissue samples under a microscope) and microbiology (identifying microbes living on the skin) [4, 17, 19, 20]. The signs and symptoms of CHE can overlap with other skin conditions, such as scabies, palmoplantar pustular psoriasis & lichen planus, so some other conditions can be confused with HE [17]. Another potential obstacle to diagnosis is that there is no clear link between the signs and symptoms of CHE and its underlying cause. To be called chronic, symptoms must last for more than 3 months or relapse at least twice per year [1, 2].

What are the different subtypes of CHE?

The most common aetiological subtypes (classified by underlying cause) are irritant contact dermatitis, allergic contact dermatitis and atopic HE; in some cases, having one of these subtypes can lead to the development of a different subtype [2]:

Irritant contact dermatitis – the most common type of HE, typically caused by an irritant or hot, cold, dry or wet conditions. This type of HE is common for people in certain types of jobs which involve contact with chemicals or frequent hand washing [17].

Allergic contact dermatitis – allergens can penetrate the skin barrier and activate the immune system. With repeated, long-term exposure to allergens, the patient can develop allergic contact dermatitis, which can be more severe if the exposure continues [17].

Atopic HE – this is mainly caused by a person's immune system, but can also be caused by genetic factors that affect the development of the skin outer layers, and by environmental factors that disrupt the skin barrier. Skin barrier disruption can lead to allergic reactions. As a result, if a patient has atopic HE, they may also develop allergic contact dermatitis and/or irritant contact dermatitis [17].

2c) Current treatment options:

The latest treatment guidelines for HE were published in 2022 by the European Society of Contact Dermatitis (ESCD) Guideline Development Group [2]. There are no recognised UK treatment guidelines for HE or CHE.

Basic therapy: emollients, skin care and exposure reduction

Basic treatment of HE consists of the use of emollients (moisturisers) to maintain and/or improve skin barrier function, and the identification and avoidance of causative factors [2].

First-line therapy: TCS ± TCI

For patients for whom emollients and the reduction of exposure to substances causing skin reactions are inadequate, the first-line treatments for CHE are TCS with or without topical calcineurin inhibitors (TCIs) [2]. The high-strength TCS typically needed for the treatment of CHE is associated with a risk of skin thinning [2, 21]. Approximately half of CHE is not adequately treated by the use of strong TCS [9, 10], and data from RWEAL indicated that only 1.1% of patients in the UK used TCIs alone (i.e. without TCS) for treating moderate to severe CHE in the past 12 months [10].

Second-line therapy: phototherapy and alitretinoin

Phototherapy may be used for patients with moderate to severe CHE that has not responded to TCS [2]. Phototherapy involves exposure to ultraviolet light B (UVB) or treatment with psoralen followed by exposure to ultraviolet light A (PUVA). Phototherapy (especially PUVA) is associated with adverse events (AEs) such as reddening and burning of the skin, and long-term use increases the risk of non-melanoma skin cancer and premature skin ageing [2].

Alitretinoin is recommended by NICE as second-line treatment only for patients with severe CHE that has not responded to potent TCS [2]; it is not approved in the UK for moderate CHE. Alitretinoin is associated with AEs including headache and nausea [22]. In addition, mental health disorders such as depression have been reported in patients treated with whole-body retinoids, including alitretinoin [22]. Alitretinoin is also a powerful human teratogen which means it induces a high frequency of severe and life-threatening birth defects [22]. Consequently, in women of childbearing age alitretinoin must be used with a strict pregnancy prevention programme extending 1 month after the end of treatment [22], and is unsuitable for a significant proportion of patients with CHE [23], especially given that HE is more common in women than in men [5].

Third-line therapy: off label systemic therapies

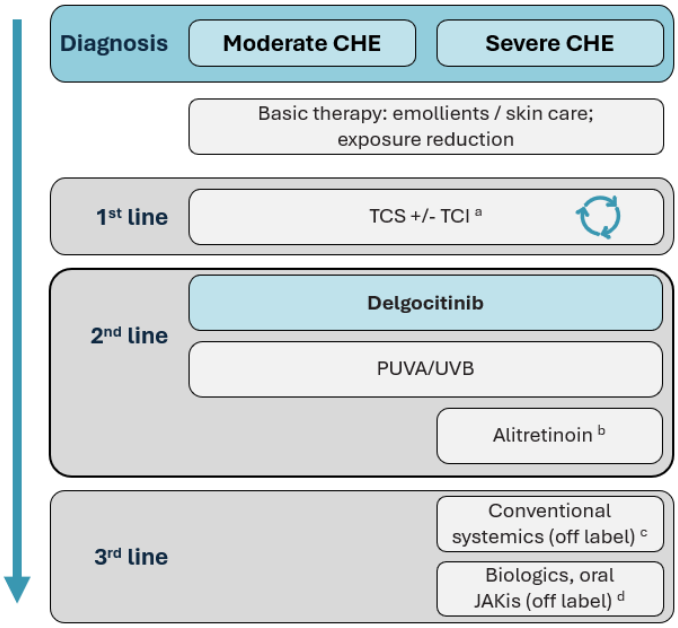
There are no licensed third-line therapies for CHE (ciclosporin is licensed for the treatment of severe atopic eczema but not specifically CHE) [2]. Some patients with severe or very severe CHE may be treated off label (i.e., outside the terms of the medication's licence) with conventional systemic treatments (acitretin, azathioprine, ciclosporin, methotrexate and oral corticosteroids), once other recommended treatments such as TCS and alitretinoin have failed [2]. However, the evidence for their efficacy (i.e., how well they work) in the treatment of CHE is limited, and they can be associated with potentially serious AEs [2]. Some patients may be treated off label with biologics (bioengineered antibodies) or oral Janus kinase inhibitors (JAKi), which are different classes of medication.

Delgocitinib

Delgocitinib works by targeting a family of proteins in the body called Janus kinases (JAKs) [24]. In human cells, inhibiting (i.e. blocking and reducing the effect of) JAK activity with

delgocitinib reduces immune and inflammatory responses in cells that are important for the development of CHE [24]. Consequently, delgocitinib is expected to be efficacious (i.e., work) across CHE aetiological subtypes. The expected position of delgocitinib in the treatment pathway, as shown in Figure 1, is as a second-line therapy for patients with moderate to severe CHE requiring long-term management, after TCS/TCI and before whole-body therapy and biologics (oral or injection therapies).

Figure 1. Anticipated treatment pathway for patients with moderate to severe CHE



[a] TCI are not indicated for non-atopic subtypes of CHE and are used as a steroid-sparing option.
[b] Alitretinoin is licensed in the UK only for severe CHE. Guidelines position alitretinoin as initial 2nd line therapy based on weight of evidence.
[c] Conventional systemics are off label, with the exception of ciclosporin, which is registered in some countries for use in atopic dermatitis but not specifically for HE (and is thus off label in HE of other aetiologies).
[d] Biologics and oral JAKis are off label; they are registered in some countries for use in atopic dermatitis but not specifically for HE (and are thus off label in HE of other aetiologies).
CHE, chronic hand eczema; JAKi, Janus kinase inhibitors; PUVA, psoralen–UV A phototherapy; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UVB, ultraviolet B.

2d) Patient-based evidence (PBE) about living with the condition

CHE Patient Impact Report

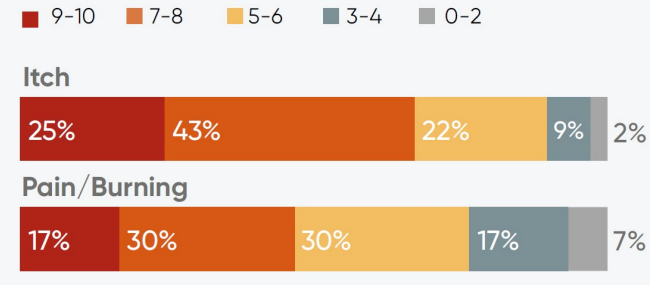
Adults with CHE were eligible to participate in the CHE Patient Impact Report if they had experienced CHE for more than a year, had previously seen a healthcare professional in relation to HE and used a medical treatment for HE, and if HE had an impact on aspects of their life [14]. The survey was completed by 152 people. The participants were aged 20–75 years, most were female (79%), lived in England (86%), and were white (British/Irish/Other, 81%) [14].

Itch and pain

In the CHE Patient Impact Report, participants rated an average itch score of 7.2 out of 10 and an average pain score of 6.2 out of 10 when assessing the impact on their lives. Around half of patients reported experiencing itchy skin as a symptom that impacted them every day or most days. In addition, 37% reported that pain impacts them at least frequently. When

asked about their future aspirations for treatment, the most frequent desire was for help with itching (75% of patients) (Figure 2) [14].

Figure 2 Impact of CHE itch and pain on UK patients' lives



Patients were asked: 'On a scale of 0–10, to what extent does itch or pain/burning from your hand eczema impact on your life?', with 0 = 'not at all' and 10 = 'significant impact'.
Source: CHE Patient Impact Report [14].

Impact of CHE on work and education

In addition to the HRQoL impact and psychological burden of CHE (section 2a), patients reported an impact on work and education. Around half of patients in the CHE Patient Impact Report said that CHE has influenced their career choice to some extent, with 72% stating that they currently experience some impact on their work due to their condition. This impact was more notable for professionals who may be required to wash their hands several times per day, such as healthcare professionals (n=24, 87% reported at least some impact), those working in the service industry (n=17, 77% reported at least some impact) and those working in education (n=14, 64% reported at least some impact) [14].

Consistent with these findings, a recent study of 395 active professionals with CHE in France found a significant occupational impact of CHE: 19.5% of participants had to change their career and 20.5% reported missing work in the past 12 months because of CHE [25].

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

About delgocitinib – its key features and how it works

Delgocitinib is a targeted therapy that blocks the activity of all four members of the JAK family of enzymes (proteins), which are involved in the development of CHE. JAK inhibitors are named after the messaging pathway that they block within cells [26]. In eczema, there is excessive inflammation in the skin [26]. When JAKs are active in the skin, they reduce the levels of antimicrobial peptides and structural proteins. Antimicrobial peptides are natural substances in the skin that help fight off bacteria and other germs. When these peptides are reduced, and the structural proteins are affected, the skin barrier stops working properly. This pathway is important for treating CHE because it affects many inflammatory processes involved in the different types of CHE. Delgocitinib targets all the JAK proteins and works by blocking the activity of specific pathways within the cells, which can cause the symptoms of CHE.

Innovation in patient care

Current treatment options for CHE have significant limitations, which are described in section 2c. As an efficacious, non-steroidal, externally applied therapy which can be used at home and which has a favourable safety profile with no major safety concerns, delgocitinib cream does not have any of issues mentioned for the existing treatments.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

Delgocitinib cream is not intended to be used in combination with other medicines.

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.

Not applicable.

3c) Administration and dosing

Delgocitinib cream is applied externally to the skin. A thin layer of the cream should be applied twice daily to clean and dry skin of the affected areas of the hands and wrists until the skin is clear or almost clear. It is recommended to apply the cream at regular intervals, approximately 12 hours apart.

Treatment with delgocitinib cream should be continued until symptoms improve or disappear, after which it can be stopped. If symptoms recur, treatment can be re-started as needed. If no improvement is seen after 12 weeks of continuous treatment, treatment should be stopped.

Periodic skin examination of the application site is recommended for all patients using delgocitinib cream, particularly those with risk factors for skin cancer.

Delgocitinib is intended to be used as a second-line treatment for CHE. The existing second-line treatments for moderate to severe CHE are phototherapy and alitretinoin. Section 2c presents additional considerations on the AEs and additional challenges posed by these therapies.

3d) Current clinical trials

The following table presents five clinical trials to date assessing delgocitinib in CHE, all of which have been completed.

Study name (ClinicalTrials.gov ID)	Phase	Location	Patient group	Number of patients	Treatments studied	Expected completion date
Phase 2b trial (NCT03683719) [27]	2	International	Adult patients with mild to severe CHE	258	Delgocitinib cream, cream vehicle [a]	Completed
DELTA 1 (NCT04871711) [28]	3	International	Adult patients with moderate to severe CHE	487	Delgocitinib cream, cream vehicle [a]	Completed
DELTA 2 (NCT04872101) [28]	3	International	Adult patients with moderate to severe CHE	473	Delgocitinib cream, cream vehicle [a]	Completed
DELTA 3 (NCT04949841) [29]	3	International	Adult patients with moderate to severe CHE (DELTA 1 and DELTA 2 extension study)	801	Delgocitinib cream	Completed
DELTA FORCE (NCT05259722) [30]	3	International	Adult patients with severe CHE	513	Delgocitinib cream, alitretinoin	Completed

[a] Cream not containing active drug.

3e) Efficacy

DELTA 1 and DELTA 2

The efficacy and safety of delgocitinib in the treatment of moderate to severe CHE has been investigated in two 16-week clinical trials, DELTA 1 and DELTA 2 [28]. Based on the approved licence delgocitinib should be stopped after 12 weeks of continuous treatment if no improvement is seen [31]; results for week 12 are also discussed.

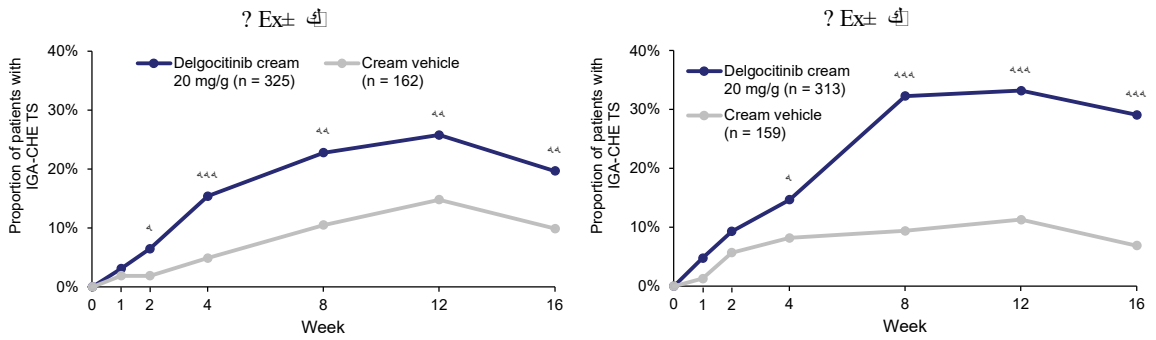
The trials included a total of 960 adults with moderate to severe CHE, with a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for TCS to have been documented to be otherwise medically inadvisable (e.g., due to important side effects or safety risks). Patients were randomly assigned to receive for 16 weeks: delgocitinib cream 20 mg/g twice daily or cream vehicle twice daily (this cream contains no active medicine).

In both studies, the main measure of effectiveness (also referred to as the primary endpoint) was the proportion of patients who achieved treatment success (TS), defined as a score of 0 (clear) or 1 (almost clear) on a 5-point scale (the Investigator's Global Assessment for CHE scale [IGA-CHE]), with an improvement of at least 2 points from baseline (the start of the study) [28]. The IGA-CHE scale is a tool used by doctors to measure the severity of CHE, and helps doctors rate how bad the eczema is, from clear skin to very severe eczema, so they can track how well treatments are working.

The results of both studies showed that patients using delgocitinib cream were more likely to achieve IGA-CHE TS (i.e., clear or almost clear skin on the hands) from as early as week 2 and throughout to weeks 8, 12 and 16, compared with the control group who received cream

vehicle (a substance similar to delgocitinib cream that contains no active medicine) [28]. These findings were statistically significant, which means they are likely to represent a real effect of delgocitinib rather than a chance occurrence.

Figure 3 Proportion of patients with IGA-CHE TS to week 16 (DELTA 1 and DELTA 2)



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ The p values represent the likelihood of the difference occurring by chance; when the p value is low as shown here, the difference is unlikely to be a chance occurrence (and is therefore likely to represent a real effect of delgocitinib).
IGA-CHE, Investigator's Global Assessment for chronic hand eczema; TS, treatment success.
Sources: Bissonnette *et al*. 2024 [28]; DELTA 1 and DELTA 2 CSRs [32, 33].

Clinical efficacy in DELTA 1 and DELTA 2 was also assessed using the Hand Eczema Severity Index (HECSI), which is used by clinicians to rate severity of CHE. The HECSI total ranges from 0 to 360 with higher scores indicating greater severity of CHE [34].Treatment responses in clinical trials are often measured as the percentage reduction in this score after treatment. Therefore, HECSI-75 and HECSI-90 represent reductions of 75% or more and 90% or more in HECSI from baseline, respectively.

In the DELTA 1 and DELTA 2 studies, patients who used delgocitinib cream were much more likely to see a 75% or 90% improvement in their HE by weeks 12 and 16 compared to those who used a cream without the active medicine. More than twice as many patients saw these improvements with delgocitinib cream compared to the control group using the inactive cream.

DELTA 3

The DELTA 1 and DELTA 2 trials were conducted for only 16 weeks. This was done because designing a long-term controlled trial would have meant some patients being treated with cream vehicle without active ingredients for an extended period. This could not be ethically justified because of the significant disease burden. Accordingly, the DELTA 3 trial was used to assess the safety and efficacy of 36 weeks of as-needed treatment with delgocitinib cream among patients who had completed DELTA 1 or DELTA 2 and agreed to participate in the extension study [35].

Treatment with delgocitinib cream 20 mg/g twice daily was initiated if a patient had an IGA-CHE score of 2 (mild) or more at any time during the trial and was stopped when an IGA-CHE score of 0 (clear) or 1 (almost clear) was achieved [35].

Among the 138 patients who used delgocitinib cream in the initial trial and then entered the DELTA 3 study after their HE improved, the average time it took for their HE to worsen again after stopping treatment was 4 weeks. For the 124 patients who started using delgocitinib cream again after their HE worsened, 80.7% saw their HE improve again by the end of the treatment period, with the average time to see improvement being 8 weeks [35].

DELTA FORCE

DELTA FORCE was a 24-week trial comparing delgocitinib cream with alitretinoin [30, 36]. Eligible patients were adults with severe CHE (an IGA-CHE score of 4) at baseline who had a recent history of inadequate response to treatment with TCS or for whom TCS were medically inadvisable (due to important side effects or safety risks that outweigh the potential treatment benefit) [36].

In the DELTA FORCE study, participants were randomly given either delgocitinib cream or alitretinoin capsules. After 12 weeks, patients taking alitretinoin could stop if their HE was clear or almost clear, or if it was severe and more treatment wouldn't help. Alitretinoin is usually taken for 12–24 weeks. Patients using delgocitinib cream continued until week 16. After that, they could stop if their HE was clear or almost clear, just like the alitretinoin group. If their HE got worse again, they could start treatment again as needed.

In DELTA FORCE, patients treated with delgocitinib cream had larger adjusted mean improvements in HECSI, compared with the alitretinoin group, at week 12 (−67.6 vs −51.5) [30]. The results also showed that patients using delgocitinib cream were more likely than those receiving alitretinoin capsules to see a 75% or 90% improvement in their HE and have clear or almost clear skin by week 12 compared with those taking alitretinoin capsules [30, 36]. This finding was statistically significant (with a *p* value below 0.001), which means it is likely to represent a real difference between delgocitinib and alitretinoin rather than a chance occurrence. Similar results were seen at week 24 [36].

3f) Quality of life impact of the medicine and patient preference information

HESD

Relieving itch and pain is very important for patients with CHE. In the DELTA trials, pain and itch were measured using the Hand Eczema Symptom Diary (HESD). Patients used this diary to record the worst severity of their symptoms over the past 24 hours. The scores range from 0 to 10, with higher scores indicating worse symptoms. These daily scores are averaged over 7 days. An improvement of 4 points in the HESD score is considered a meaningful improvement in symptoms [37].

In both the DELTA 1 and DELTA 2 studies, about twice as many patients using delgocitinib cream had at least a 4-point improvement in their itch score by week 16 compared with those using a cream without the active medicine (DELTA 1: 47% vs 23%; DELTA 2: 47% vs 20%). In the DELTA FORCE study, patients using delgocitinib cream had much larger reductions in their average itch score at weeks 12 and 24 than those taking alitretinoin capsules [36].

Similarly, in both DELTA 1 and DELTA 2, significantly more patients using delgocitinib cream had at least a 4-point improvement in their pain score by week 16 compared with those using the cream without the active medicine (DELTA 1: 49% vs 28%; DELTA 2: 49% vs 23%). In the DELTA FORCE study, patients using delgocitinib cream had much larger reductions in their average pain score at weeks 12 and 24 than those taking alitretinoin capsules [36].

HRQoL

HRQoL is an assessment of the impact of illness and treatment on a patient’s sense of overall function and wellbeing [38]. In the DELTA trials, HRQoL was assessed using the Dermatology Life Quality Index (DLQI). The DLQI comprises ten questions based on skin disease symptoms and impact on HRQoL [39]. Scores range from 0 to 30, with higher scores

indicating worse HRQoL [39]. A 4-point improvement is defined as a clinically meaningful change among patients with baseline scores of at least 4 [40].

In the DELTA 1 and DELTA 2 studies, among patients using delgocitinib cream who had DLQI scores of at least 4 at the start, 74.4% and 72.2% had an improvement of at least 4 points by week 16. This is compared with 50.0% and 45.8% of patients using a cream without the active medicine. These results are very unlikely to be due to chance.

Most patients using delgocitinib cream saw improvements in their DLQI scores within 4 weeks. More than 70% of patients with starting DLQI scores of at least 4 had an improvement of at least 4 points by week 4, with significant differences compared with the cream without the active medicine at all time points [28].

In the DELTA FORCE study, patients using delgocitinib cream had much larger average reductions in their DLQI scores at weeks 12 and 24 than those taking alitretinoin capsules [36].

Health utility

Health utility is a measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). In the DELTA trials, health utility was assessed using the EuroQol questionnaire (EQ-5D), a standardised instrument used to measure health outcomes in five different domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

In the DELTA 1 and DELTA 2 studies, patients using delgocitinib cream had a much greater improvement in their EQ-5D scores (a measure of overall health) from the start to week 16 compared with those using a cream without the active medicine [32, 33].

In the DELTA FORCE study, patients using delgocitinib cream had a numerically greater improvement in their EQ-5D scores from the start to week 12 compared with those taking alitretinoin capsules, and an even larger, statistically significant improvement from the start to week 24 [36].

3g) Safety of the medicine and side effects

In DELTA 1 and DELTA 2, delgocitinib cream was well tolerated, demonstrating a safety profile comparable to that of cream vehicle [28, 32, 33]. The most common adverse reactions were application site reactions (1.0%; 7/9 occurred within the first week of treatment) [31]. No application site reactions resulted in treatment interruption, and the median time to resolution was 3 days. No additional safety concerns were found in the DELTA 3 extension study [35].

In DELTA FORCE, the delgocitinib cream group had fewer AEs overall, lower rates of discontinuation due to AEs and substantially fewer AEs considered possibly or probably related to the study drug than the alitretinoin group. In the alitretinoin group, the most frequently reported AE was headache, affecting 32.4% of patients (vs 4.0% in the delgocitinib cream arm).

Due to safety concerns with oral JAK inhibitors, the DELTA 2 study tested if delgocitinib cream could get into the blood. The results showed that very little of the cream entered the bloodstream, meaning it is not expected to affect the rest of the body when used to treat CHE [41].

3h) Summary of key benefits of treatment for patients

There are limited options for treating moderate to severe CHE that has not responded to TCS, which may have been used with or without TCIs. Both phototherapy and alitretinoin have important limitations, which have been discussed in section 2c.

As a therapy that is applied externally to the skin and can be used at home, no issues such as time and travel required to attend specialist healthcare settings apply to delgocitinib, which are verified for phototherapy.

Contrary to alitretinoin, delgocitinib does not require a pregnancy prevention programme or monitoring for lipids or depression. Furthermore, there is a potential risk for alitretinoin from interaction with other medicinal products, namely vitamin A or other retinoids, which is not observed with delgocitinib due to its minimal systematic absorption. Alitretinoin may also require additional appointments when resuming treatment. Re-initiation of delgocitinib may require only a GP phone call, and patients may still have leftover delgocitinib cream from their previous treatment.

3i) Summary of key disadvantages of treatment for patients

Not applicable.

3j) Value and economic considerations

Introduction for patients:

Following a literature review of cost-effectiveness models in CHE, a health economic model was developed to provide an assessment of the costs and benefits of delgocitinib with other second-line treatments for moderate and severe CHE in UK clinical practice.

How the model reflects CHE

Patients in the model are treated with three different second-line treatment options: delgocitinib cream, phototherapy or alitretinoin. Based on its marketing authorisation and current NICE guidance, alitretinoin is only a treatment option for patients with severe CHE. Delgocitinib and phototherapy were treatment options for patients with moderate CHE and severe CHE. Third-line systemic treatments, such as off label immunosuppressants and biological drugs, were included only for patients who had an inadequate response to the compared second-line therapies.

The model tracks the patient's condition over 10 years based on how their condition responds to treatment. Given the fluctuating nature of CHE, loss of response (or relapse) is a key component of the condition and is reflected in the economic model. After stopping their treatment due to full response, patients can restart the treatment if their symptoms come back. Symptoms related to CHE and AEs related to treatment are included in the model.

Modelling how delgocitinib improves CHE

The model uses clinical trial data to show how well CHE responds to treatment with delgocitinib cream, phototherapy, or alitretinoin for each patient. It calculates the percentage of patients who have a full response (clear or almost clear skin) or lower levels of improvement. This is done by comparing results from several trials, including delgocitinib trials (DELTA 1, DELTA 2, DELTA FORCE, and Worm 2022), the ALPHA trial (which compared oral

alitretinoin and immersion PUVA, a type of phototherapy), and trials that assessed oral alitretinoin against a placebo pill (BACH, HANDEL).

Patients who show a response to treatment will stop using it, and the model tracks how long their improvement lasts and if their symptoms come back. If their CHE returns, they can start treatment again with the same therapy or try a different one. The model simulates this cycle of improvement and relapse, and periods of being on and off treatment, over 10 years. It measures the time spent at different levels of improvement. Healthcare costs and quality of life values are assigned to each level of improvement, and treatment and monitoring costs are counted when patients are on treatment. The effectiveness of each second-line treatment affects the time spent on treatment, the level of improvement, and the total costs and benefits of each treatment.

Cost-effectiveness results and conclusions

The analysis results suggest that delgocitinib provides health benefits for patients with moderate and severe CHE. The incremental cost-effectiveness ratio (ICER) for delgocitinib relative to other second-line treatments, when used to treat either moderate or severe CHE, was within the good value-for-money range considered by NICE in England and Wales. These results are based on assumptions made by the company and do not include any confidential discounts available for other treatments in the pathway.

This finding remained consistent across a range of sensitivity analyses, which were used to test the impact of different assumptions and data sources on the model results. The first treatment specifically licensed for both moderate and severe CHE, delgocitinib is an option with a favourable safety profile and a simple topical administration, which may help optimise the management of this condition in NHS clinical practice.

3k) Innovation

Innovation in patient care

There are limited options for treating patients with moderate to severe CHE that has not responded to TCS or for whom TCS are unsuitable. Both phototherapy and alitretinoin have important limitations.

Delgocitinib is a targeted therapy that blocks the activity of all four members of the JAK family of enzymes (proteins), which are involved in the development of CHE. Delgocitinib is expected to be efficacious across CHE aetiological subtypes. As delgocitinib cream is applied externally to the skin, it is associated with a low risk of side effects in the whole body or internal organs due to its minimal absorption into the rest of the body beyond the skin.

Benefits not captured in the QALY calculation

- Delgocitinib cream is a non-steroidal treatment applied to skin that provides long-term control without the risks of using steroid creams, like skin thinning, which can slow down recovery.
- Delgocitinib is generally safe to use and has fewer side effects compared with some whole-body treatments that are sometimes used off-label. These whole-body treatments can cause side effects like headaches and throat infections, which are not included in the quality of life calculations.

- Alitretinoin can cause birth defects, so women who can become pregnant must follow a strict pregnancy prevention programme, which can interfere with family planning. Delgocitinib does not have this requirement.
- Phototherapy can be inconvenient and expensive for patients to access. Delgocitinib can be applied at home.
- Many patients, especially those in healthcare and service jobs, find that their CHE affects their work or education. Job changes or losses due to CHE are common. Patients may also need to take a lot of time off work due to flare-ups and appointments. The benefits of avoiding these problems within effective CHE treatment are not included in the quality of life calculations.

3l) Equalities

CHE disproportionately impacts people in some job roles. In addition, there may be racial differences in susceptibility to CHE [42]. Skin type may also affect assessment of the severity of CHE, which can be more difficult in people with brown and black skin This means that some potential patients with CHE and brown or black skin may be undiagnosed, which could lead to undertreatment.

CHE may disproportionately affect patients who have co-morbidities, such as HIV or other conditions that require antivirals as a primary treatment option. Antivirals are known to have interactions which can increase the risk of drug toxicity or reduce drug efficacy, when given in adjunction with systemic immunosuppressants. Due to this, patients with moderate to severe CHE who require antivirals to treat a condition have limited treatment options after TCS [43].

Alitretinoin requires a pregnancy prevention programme (section 2C), which may lead to tokophobia (fear of becoming pregnant). The potential adoption of delgocitinib could provide women of childbearing age with an alternative licensed treatment for CHE.

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a negative impact on people protected by equality legislation, compared with the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

SECTION 4: Further information, glossary and references

4a) Further information

Patient groups, role of patients groups on health technology assessment (HTA) and charities and further information about CHE

- EUPATI guidance on patient involvement in HTA: https://www.eupati.eu/guidance-patient-involvement/
- British Skin Foundation: https://www.britishskinfoundation.org.uk/
- British Association of Dermatologists: https://www.bad.org.uk/pils/hand-dermatitis-hand-eczema/
- National Eczema Society: https://eczema.org/information-and-advice/types-of-eczema/hand-eczema/
- NHS general information: https://www.nhs.uk/conditions/atopic-eczema/
- Primary Care Dermatology Services general information: https://www.pcds.org.uk/clinical-guidance/eczema-hand-dermatitis
- Patient information: https://patient.info/skin-conditions/atopic-eczema/eczema-triggers-and-irritants

Further information on NICE and the role of patients**:**

- Public Involvement at NICE: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement
- EFPIA – Working together with patient groups (PDF): https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/

4b) Glossary of terms

Biologic therapy. A bioengineered antibody treatment that stimulates the body's immune system to fight disease.
Clinical effectiveness. The extent to which a healthcare intervention achieves the desired outcomes, such as improving health, relieving symptoms, or preventing disease, in a clinical setting.
Flares. A sudden and often temporary worsening of symptoms associated with a chronic illness or condition. It typically involves a rapid onset of symptoms that may include increased pain, inflammation, fatigue, or other manifestations of the underlying condition.
Economic model. A way to predict the costs and effects of a treatment over time in a specific population of interest.
Efficacy. The effectiveness of a treatment observed in a clinical trial.
Health-related quality of life (HRQoL). The subjective assessment of an individual's overall well-being and satisfaction with various aspects of their life, particularly as it relates to their health status and healthcare interventions. It encompasses physical, mental, emotional, and social dimensions and is influenced by factors such as health status, functional ability, symptoms, psychological well-being, social relationships, and environmental factors.
Health utility. A measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health).
Inflammation. A bodily response to injury or disease, which can lead to swelling and reddening of the skin.
Marketing authorisation. Approval by a regulatory body for a medicine or medical device to be used by patients in a specific place or country.
Patient-reported outcomes (PROs). Structured patients' feedback which includes various dimensions of patients' experiences, including symptoms, treatment satisfaction, medication adherence, and overall quality of life. These outcomes are frequently assessed in clinical trials using validated tools to gauge the treatment's impact from the patient's perspective.
Protein. A large, complex molecule composed of one or more chains of amino acids. Proteins play essential roles in the structure, function, and regulation of cells and tissues in living organisms. They are involved in various biological processes, including enzymatic reactions, cell signalling, immune response, and structural support.
Quality-adjusted life year (QALY). A comprehensive measure to assess the effectiveness of an intervention by quantifying both the improvements in quality of life and the extension of life expectancy associated with it. Incremental QALYs, compared with incremental costs, are utilised to determine the

economic value of interventions. By encompassing various domains of quality of life, QALYs enable comparability across different condition areas, facilitating broad resource allocation decisions.

4c) References

1. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J*, et al.* Guidelines for diagnosis, prevention and treatment of hand eczema--short version. J Dtsch Dermatol Ges. 2015;13(1):77–85.
2. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM*, et al.* Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis. 2022;86(5):357–78.
3. Lee GR, Maarouf M, Hendricks AK, Lee DE, Shi VY. Current and emerging therapies for hand eczema. Dermatol Ther. 2019;32(3):e12840.
4. Lynde C, Guenther L, Diepgen TL, Sasseville D, Poulin Y, Gulliver W*, et al.* Canadian hand dermatitis management guidelines. J Cutan Med Surg. 2010;14(6):267–84.
5. Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population - A systematic review and meta-analysis. Contact Dermatitis. 2021;84(6):361–74.
6. Yüksel YT, Symanzik C, Christensen MO, Olesen CM, Thyssen JP, Skudlik C*, et al.* Prevalence and incidence of hand eczema in healthcare workers: A systematic review and meta-analysis. Contact Dermatitis. 2024;90(4):331–42.
7. Lerbaek A, Kyvik KO, Ravn H, Menne T, Agner T. Clinical characteristics and consequences of hand eczema - an 8-year follow-up study of a population-based twin cohort. Contact Dermatitis. 2008;58(4):210–6.
8. Meding B, Wrangsjo K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. Br J Dermatol. 2005;152(5):975–80.
9. Crane MM, Webb DJ, Watson E, Cunliffe T, English J. Hand eczema and steroid-refractory chronic hand eczema in general practice: prevalence and initial treatment. Br J Dermatol. 2017;176(4):955–64.
10. LEO Pharma. Data on file, RWEAL study results. 2024.
11. Grant L, Seiding Larsen L, Burrows K, Belsito DV, Weisshaar E, Diepgen T*, et al.* Development of a Conceptual Model of Chronic Hand Eczema (CHE) Based on Qualitative Interviews with Patients and Expert Dermatologists. Adv Ther. 2020;37(2):692–706.
12. Giménez-Arnau AM, Bewley A, Molin S, Apfelbacher C, Brignoli L, Corriveau J*, et al.*, editors. Patient characteristics and comorbidities in moderate to severe CHE: Results from the RWEAL study. European Academy of Dermatology and Venereology; 2024; Amsterdam.
13. Tauber M, Berard E, Lourari S, Questel E, Redoules D, Paul C*, et al.* Latent class analysis categorizes chronic hand eczema patients according to skin barrier impairment. J Eur Acad Dermatol Venereol. 2020;34(7):1529–35.
14. LEO Pharma, Allergy UK. The Chronic Hand Eczema Patient Impact Report. 2024.
15. Cortesi PA, Scalone L, Belisari A, Bonamonte D, Cannavo SP, Cristaudo A*, et al.* Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. Contact Dermatitis. 2014;70(3):158–68.
16. Capucci S, Hahn-Pedersen J, Vilsboll 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.
17. Agner T, Elsner P. Hand eczema: epidemiology, prognosis and prevention. J Eur Acad Dermatol Venereol. 2020;34 Suppl 1(S1):4–12.
18. Ahmed A, Shah R, Papadopoulos L, Bewley A. An ethnographic study into the psychological impact and adaptive mechanisms of living with hand eczema. Clin Exp Dermatol. 2015;40(5):495–501.
19. Kim HJ, Bang CH, Kim HO, Lee DH, Ko JY, Park EJ*, et al.* 2020 Korean Consensus Guidelines for Diagnosis and Treatment of Chronic Hand Eczema. Ann Dermatol. 2021;33(4):351–60.
20. Rademaker M, Armour K, Baker C, Foley P, Gebauer K, Gupta M*, et al.* Management of chronic hand and foot eczema. An Australia/New Zealand Clinical narrative. Australas J Dermatol. 2021;62(1):17–26.
21. British Association of Dermatologists. Hand dermatis (hand eczema) - patient information leaflet. 2023 [Available from: https://www.bad.org.uk/patient-information-leaflets/. Accessed: 16 February 2024.]
22. Ennogen IP Ltd. Alitretinoin 10mg soft capsules - Summary of Product Characteristics. 2024 [Available from: https://www.medicines.org.uk/emc/product/14832. Accessed: 16 February 2024.]
23. Christoffers WA, Coenraads PJ, Svensson A, Diepgen TL, Dickinson-Blok JL, Xia J*, et al.* Interventions for hand eczema. Cochrane Database Syst Rev. 2019;4(4):CD004055.

24. Tanimoto A, Ogawa Y, Oki C, Kimoto Y, Nozawa K, Amano W*, et al.* Pharmacological properties of JTE-052: a novel potent JAK inhibitor that suppresses various inflammatory responses in vitro and in vivo. Inflamm Res. 2015;64(1):41–51.
25. Halioua B, Skayem C, Merhand S, BenHayoun Y, Taieb C, Richard MA. Chronic Hand Eczema in France: Occupational Impact and Work Absenteeism. Clin Exp Dermatol. 2024.
26. National Eczema Society. Upadacitinib. [Available from: https://eczema.org/information-and-advice/upadacitinib/#work. Accessed: 19 December 2024.]
27. Worm M, Thyssen JP, Schliemann S, Bauer A, Shi VY, Ehst B*, et al.* The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial. Br J Dermatol. 2022;187(1):42–51.
28. Bissonnette R, Warren RB, Pinter A, Agner T, Gooderham M, Schuttelaar MLA*, et al.* Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema (DELTA 1 and DELTA 2): results from multicentre, randomised, controlled, double-blind, phase 3 trials. Lancet. 2024;404(10451):461–73.
29. LEO Pharma. Open-label Multi-site Extension Trial in Subjects Who Completed the DELTA 1 or DELTA 2 Trials (DELTA3). 2023 [Available from: https://clinicaltrials.gov/study/NCT04949841. Accessed: 16 February 2024.]
30. Giménez-Arnau AM, Pinter A, Sondermann W, Reguiai Z, Woolf R, Lynde C*, et al.*, editors. DELTA FORCE trial: A 24-week head-to-head Phase 3 trial comparing the efficacy and safety of topical delgocitinib cream with oral alitretinoin capsules in adults with severe Chronic Hand Eczema. European Academy of Dermatology and Venerology; 2024; Amsterdam.
31. Medicines and Healthcare products Regulatory Agency. Summary of Product Characteristics: Anzupgo 20 mg/g cream 2024 [Available from: https://mhraproducts4853.blob.core.windows.net/docs/69f6d1d0fd9df92404c45454660c57b5017e1d34. Accessed: 10 December 2024.]
32. LEO Pharma. DELTA 1 clinical study report. 2023.
33. LEO Pharma. DELTA 2 clinical study report. 2023.
34. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302–7.
35. LEO Pharma. DELTA 3 clinical study report. 2023.
36. LEO Pharma. DELTA FORCE clinical study report. 2023.
37. Molin S, Larsen LS, Joensson P, Oesterdal ML, Arbuckle R, Grant L*, et al.* Development and psychometric validation of a new patient-reported outcome measure to assess the signs and symptoms of Chronic Hand Eczema (CHE): the Hand Eczema Symptom Diary (HESD). European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
38. Sitlinger A, Zafar SY. Health-Related Quality of Life: The Impact on Morbidity and Mortality. Surg Oncol Clin N Am. 2018;27(4):675–84.
39. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.
40. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27–33.
41. Thaçi D, Madsen D, Saday K, Gooderham M. Minimal systemic exposure of delgocitinib cream in adults with moderate to severe chronic hand eczema in the phase 3 DELTA 2 trial. European Academy of Dermatology and Venereology; 11–14 October 2023; Berlin; 2023.
42. Chai ESX, Tey HL, Lim ZV. Are There Ethnic Differences in Hand Eczema? A Review. J Clin Med. 2023;12(6).
43. Izzedine H, Launay-Vacher V, Baumelou A, Deray G. Antiretroviral and immunosuppressive drug-drug interactions: An update. Kidney International. 2004;66(2):532–41.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

Clarification questions

January 2025

File name	Version	Contains confidential information	Date
ID6408 delgocitinib EAG clarification letter to PM [CON]	3.0	Yes	26 February 2025

Abbreviation	Description
AE	Adverse event
AUC	Area under curve
BSC	Best supportive care
CB	Confidence band
CEAC	Cost-effectiveness acceptability curve
CHE	Chronic hand eczema
CI	Confidence interval
CS	Company submission
COVID-19	Coronavirus disease 2019
DLQI	Dermatology Life Quality Index
ESS	Efficient sample size
ECSD	European Consensus on Skin Diseases
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5-Dimension 3-Level index
EAG	Evidence Assessment Group
FE	Fixed effects
FDA	Food and Drug Administration
FAS	Full analysis set
g	Grams
HECSI	Hand Eczema Severity Index
HECSI 25	At least 25% Improvement in HECSI Score from Baseline
HECSI 75	At least 75% Improvement in HECSI Score from Baseline
HECSI 90	At least 90% Improvement in HECSI Score from Baseline
HESD	Hand Eczema Symptom Diary
HESD-ITCH	Hand Eczema Symptoms Diary - Itch
HESD-PAIN	Hand Eczema Symptoms Diary - Pain
HESD PGI-C	Hand Eczema Symptoms Diary Patient Global Impression of Change
HESD PGI-S	Hand Eczema Symptoms Diary Patient Global Impression of Severity
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
IGABLN	Investigator’s Global Assessment at Baseline
IGA-CHE	Investigator's Global Assessment for Chronic Hand Eczema
JAK	Janus kinase
kg	Kilograms
KR	Kenward-Rogers degrees of freedom method
LDA	Low disease activity
LSM	Least squares mean
MAIC	Matching adjusted indirect comparison
MAR	Missing at random
MHRA	Medicines and Healthcare products Regulatory Agency

mg	Milligrams
MI	Multiple imputation
MMRM	Mixed model for repeated measures
NMA	Network meta-analysis
NE	Not estimable
NHS	National Health Service
NR	Not reported
N	Number of subjects
OR	Odds ratio
PaGA	Patient Global Assessment of Disease Severity
PE	Primary endpoint
PGA	Physician's Global Assessment
PSA	Probabilistic sensitivity analysis
PUVA	Psoralen plus ultraviolet A
PYO	Person-years of observation
QALY	Quality-adjusted life year
R	Rates
RE	Random effects
RCT	Randomised controlled trial
RWE	Real-world evidence
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TS	Treatment success
UK	United Kingdom
WF	Workforce
WOCF	Worst observation carried forward

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

Modelling approaches

A1. Priority question. The EAG notes that worst observation carried forward (WOCF) was used to account for missing data [e.g., Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) in the DELTA trials]. Please provide tables detailing the number of patients, for each outcome at each timepoint and for each trial arm (including subgroups such as atopic/non-atopic patients), for whom data was imputed.

Table 1 DELTA 1 (LP0133-1401) Imputed patient data by outcome, timepoint, and trial arm

Analysis Visit (N)	Analysis Visit	Planned Treatment	Total All		Disease Severity - Moderate [IGA=3]		Disease Severity - Severe [IGA=4]		Hyperkeratotic Subgroup - No		Hyperkeratotic Subgroup - Yes		Atopic Subtype - No		Atopic Subtype - Yes	
			Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF
0	Baseline	Delgocitinib 20 mg/g	325		218		107		268		57		182		143	
		Vehicle	162		109		53		142		20		88		74	
30	Week 1	Delgocitinib 20 mg/g	320	5	213	5	107		263	5	57		181	1	139	4
		Vehicle	158	4	105	4	53		138	4	20		87	1	71	3
40	Week 2	Delgocitinib 20 mg/g	311	14	206	12	105	2	257	11	54	3	176	6	135	8
		Vehicle	154	8	103	6	51	2	135	7	19	1	86	2	68	6
50	Week 4	Delgocitinib 20 mg/g	310	15	206	12	104	3	254	14	56	1	177	5	133	10
		Vehicle	153	9	102	7	51	2	134	8	19	1	85	3	68	6
60	Week 8	Delgocitinib 20 mg/g	311	14	209	9	102	5	256	12	55	2	179	3	132	11
		Vehicle	144	18	97	12	47	6	126	16	18	2	81	7	63	11
70	Week 12	Delgocitinib 20 mg/g	307	18	205	13	102	5	253	15	54	3	175	7	132	11
		Vehicle	144	18	98	11	46	7	126	16	18	2	82	6	62	12
80	Week 16	Delgocitinib 20 mg/g	305	20	204	14	101	6	251	17	54	3	174	8	131	12
		Vehicle	141	21	96	13	45	8	123	19	18	2	81	7	60	14

Abbreviations: g, grams; IGA, Investigator's Global Assessment; mg, milligrams; N, number of patients; Not imp., not imputed; WOCF, worst observation carried forward.

Table 2 DELTA 2 (LP0133-1402) Imputed patient data by outcome, timepoint, and trial arm

Analysis Visit (N)	Analysis Visit	Planned Treatment	Total All		Disease Severity - Moderate [IGA=3]		Disease Severity - Severe [IGA=4]		Hyperkeratotic Subgroup - No		Hyperkeratotic Subgroup - Yes		Atopic Subtype - No		Atopic Subtype - Yes	
			Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF
0	Baseline	Delgocitinib 20 mg/g	313		238		75		227		86		231		82	
		Vehicle	159		121		38		116		43		113		46	
30	Week 1	Delgocitinib 20 mg/g	303	10	229	9	74	1	222	5	81	5	221	10	82	
		Vehicle	151	8	155	6	36	2	109	7	42	1	108	5	43	3
40	Week 2	Delgocitinib 20 mg/g	295	18	222	16	73	2	215	12	80	6	217	14	78	4
		Vehicle	151	8	114	7	37	1	109	7	42	1	109	4	42	4
50	Week 4	Delgocitinib 20 mg/g	297	16	225	13	72	3	220	7	77	9	217	14	80	2
		Vehicle	140	19	107	14	33	5	101	15	39	4	100	13	40	6
60	Week 8	Delgocitinib 20 mg/g	291	22	219	19	72	3	214	13	77	9	212	19	79	3
		Vehicle	129	30	96	25	33	5	94	22	35	8	91	22	38	8
70	Week 12	Delgocitinib 20 mg/g	295	18	223	15	72	3	218	9	77	9	216	15	79	3
		Vehicle	125	34	92	29	33	5	91	25	34	9	87	26	38	8
80	Week 16	Delgocitinib 20 mg/g	291	22	219	19	72	3	217	10	74	12	212	19	79	3
		Vehicle	121	38	89	32	32	6	87	29	34	9	84	29	37	9

Abbreviations: g, grams; IGA, Investigator's Global Assessment; mg, milligrams; N, number of patients; not imp., not imputed; WOCF, worst observation carried forward.

Table 3 DELTA FORCE (LP0133-1528) Imputed patient data by outcome, timepoint, and trial arm

Analysis Visit (N)	Analysis Visit	Planned Treatment	Total All		Disease Severity - Severe [IGA=4]		Hyperkeratotic Subgroup - No		Hyperkeratotic Subgroup - Yes		Atopic Subtype - No		Atopic Subtype - Yes	
			Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF	Not imp.	WOCF
0	Baseline	Alitretinoin	253		253		222		31		198		55	
		Delgocitinib 20 mg/g	250		250		220		30		186		64	
30	Week 1	Alitretinoin	233	20	233	20	203	19	30	1	181	17	52	3
		Delgocitinib 20 mg/g	240	10	240	10	212	8	28	2	179	7	61	3
40	Week 2	Alitretinoin	225	28	225	28	198	24	27	4	175	23	50	5
		Delgocitinib 20 mg/g	245	5	245	5	215	5	30		181	5	64	
50	Week 4	Alitretinoin	217	36	217	36	189	33	28	3	170	28	47	8
		Delgocitinib 20 mg/g	244	6	244	6	214	6	30		181	5	63	1
60	Week 8	Alitretinoin	212	41	212	41	185	37	27	4	166	32	46	9
		Delgocitinib 20 mg/g	242	8	242	8	212	8	30		181	5	61	3
70	Week 12	Alitretinoin	200	53	200	53	175	47	25	6	155	43	45	10
		Delgocitinib 20 mg/g	234	16	234	16	205	15	29	1	175	11	59	5
80	Week 16	Alitretinoin	176	77	176	77	153	69	23	8	136	62	40	15
		Delgocitinib 20 mg/g	227	23	227	23	198	22	29	1	170	16	57	7
82	Week 20	Alitretinoin	164	89	164	89	142	80	22	9	128	70	36	19
		Delgocitinib 20 mg/g	222	28	222	28	195	25	27	3	166	20	56	8
84	Week 24	Alitretinoin	153	100	153	100	132	90	21	10	120	78	33	22
		Delgocitinib 20 mg/g	219	31	219	31	195	25	24	6	162	24	57	7

Abbreviations: g, grams; IGA, Investigator's Global Assessment; mg, milligrams; N, number of patients; not imp., not imputed; WOCF, worst observation carried forward.

A2. Please outline why WOCF was selected over alternative methods for accounting for missing data (e.g., multiple imputation) and whether any testing was performed to validate this approach?

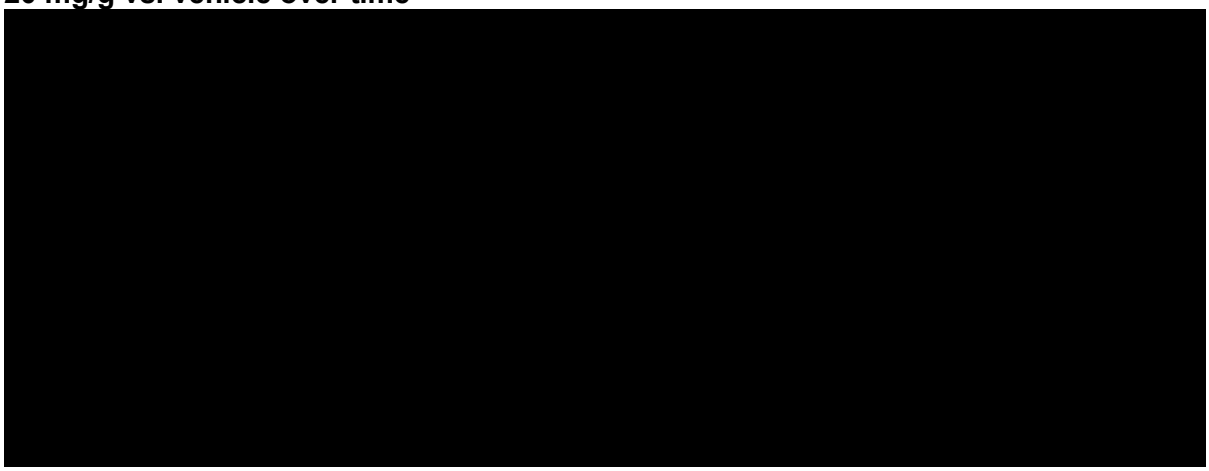
For binary outcomes, data were considered non-response after initiation of rescue treatment or after permanent discontinuation of investigational medicinal product (IMP). Missing data were also imputed as non-response. For continuous outcomes, data were considered non-response by using worst observation carried forward (WOCF; including the baseline value) after initiation of rescue treatment or after permanent discontinuation of IMP. Missing data were also imputed using WOCF (including the baseline value). These analyses reflected a “composite” estimand strategy for handling intercurrent events.

For the composite estimand, permanent discontinuation of IMP and initiation of rescue treatment was considered a failure of the randomised treatment. As illustrated by the figures (Figure 1, Figure 2 and Figure 3) and Table 4 presented below, most IMP discontinuations were caused by adverse events (AEs), lack of efficacy, or withdrawal by participant, all of which indicate treatment failure rather than random discontinuations independent of the treatment outcome. The composite estimand is therefore considered an appropriate approach. It is considered reasonable that the large difference between treatment groups in the proportion of discontinuations of IMP is reflected in the results, as presented with the composite estimand.

Figure 1 DELTA 1 Cumulative incidence of permanent discontinuation of delgocitinib 20 mg/g vs. vehicle over time

Notes: An event was defined as permanent discontinuation of IMP. Cumulative incidence functions estimated using the Aalen-Johansen estimator.
Abbreviations: g, grams; IMP, investigational medicinal product; mg, milligrams; N, number of patients.
This figure is confidential.

Figure 2: DELTA 2 Cumulative incidence of permanent discontinuation of delgocitinib 20 mg/g vs. vehicle over time



Notes: An event was defined as permanent discontinuation of IMP. Cumulative incidence functions estimated using the Aalen-Johansen estimator.
Abbreviations: g, grams; IMP, investigational medicinal product; mg, milligrams; N, number of patients.
This figure is confidential.

Figure 3 DELTA FORCE Cumulative incidence of permanent discontinuation of delgocitinib 20 mg/g vs. vehicle over time

Notes: An event was defined as permanent discontinuation of IMP. Cumulative incidence functions estimated using the Aalen-Johansen estimator

Abbreviations: g, grams; IMP, investigational medicinal product; mg, milligrams; N, number of patients.

This figure is confidential.

The breakdown of patient discontinuations from each trial and trial arm is presented in Table 4.

Table 4 Reasons for treatment discontinuation across clinical trials (DELTA 1, DELTA 2, DELTA FORCE)

Reason for discontinuation	DELTA 1		DELTA 2		DELTA FORCE	
	Delgocitinib 20 mg/g	Vehicle cream	Delgocitinib 20 mg/g	Vehicle cream	Delgocitinib 20 mg/g	Alitretinoin
Adverse events	2	6	1	6	2	24
Lack of efficacy	5	7	6	14	8	26
Patient withdrew	11	5	10	16	15	33
Personal reasons	2	0	0	0	0	0
Lost to follow up	0	2	2	1	5	1
Insufficient treatment	0	1	0	0	0	0
Discontinued during safety follow up	1	0	2	1	0	0
Not exposed to treatment	0	0	1	0	1	12
Pregnancy	0	0	2	0	0	0
Concomitant medication	0	0	1	0	0	0
Discontinuation related to Covid-19	0	0	0	0	1	0
Other	0	0	0	0	3	9

Abbreviations: g, grams; mg, milligrams.

Sensitivity testing was performed to validate this approach, under a supplementary estimand using a 'treatment policy' strategy, which attempted to quantify the effect of the randomised treatment, ignoring the occurrence of intercurrent events. This policy reflected the intention-to-treat principle. Data collected for the endpoint of interest were used regardless of whether an intercurrent event occurred. For this analysis, missing data, independent of the Coronavirus disease 2019 (COVID-19) pandemic, were imputed using multiple imputation (MI) assuming missing at random (MAR) within 2 groups defined according to treatment group. Missing/observed data due to the COVID-19 pandemic were imputed using MI assuming MAR within treatment group with data from participants without intercurrent event.

For participants with missing data after occurrence of intercurrent events, the original intention specified in the protocol was to impute the missing data based on data from other participants with intercurrent events within the same treatment arm. However, as the amount of data collected after occurrence of intercurrent events was limited, this approach was not feasible, and missing data from participants with intercurrent events were imputed based on data from all participants within the same treatment arm, both those with and without intercurrent events. This corresponds to an assumption that participants who discontinued the Investigational medicinal product (IMP) and had missing data would on average have had the same outcome on efficacy parameters as any other participant within the same treatment arm. For participants who permanently discontinued IMP due to AEs, lack of efficacy, or withdrawal by participant, this assumption does not appear reasonable and leads to an overly optimistic estimate of the treatment effect. With the large imbalance between treatment groups in the proportion of permanent IMP discontinuations, the treatment differences, as estimated by the treatment policy estimand, are therefore considered difficult to interpret and of limited relevance. The DELTA FORCE results of Hand Eczema Severity Index (HECSI) 90 and Investigator's Global Assessment for chronic hand eczema treatment success (IGA-CHE TS) at week 12 for the primary estimand (composite strategy) and secondary supplementary estimand (treatment policy strategy) can be seen in Table 5 for illustration of the testing strategy.

Table 5 Treatment response outcomes in DELTA FORCE trial: delgocitinib 20 mg/g vs. alitretinoin at week 12

Parameter	Delgocitinib 20 mg/g N = 249	Alitretinoin N = 250	Difference in percentage	P-value
	Responders, n (%)	Responders, n (%)	95% CI	
HECSI 90 at week 12				
Primary estimand (composite)	[redacted]	[redacted]	[redacted]	[redacted]
Second supplementary estimand: Treatment policy				
IGA-CHE TS at week 12				
Primary estimand (composite)	[redacted]	[redacted]	[redacted]	[redacted]
Second supplementary estimand: Treatment policy	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HECSI 90, at least 90% improvement in Hand Eczema Severity Index score from baseline; IGA-CHE TS, Investigator's Global Assessment for Chronic Hand Eczema treatment success; N, total number of participants; n, number of participants classified as responders; p-value, probability value.

Populations

A3. Priority question. Please provide baseline characteristics for both the moderate and severe subgroups (with each subgroup separated by treatment arm) in the DELTA 1, DELTA 2, and Worm 2022 trials.

Table 6 Baseline characteristics of patients in DELTA 1 and DELTA 2 trials, by disease severity at baseline

	DELTA 1				DELTA 2			
	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)		Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N =218)	Cream vehicle (N =109)	Delgocitinib cream 20 mg/g (N =107)	Cream vehicle (N =53)	Delgocitinib cream 20 mg/g (N =238)	Cream vehicle (N =121)	Delgocitinib cream 20 mg/g (N =75)	Cream vehicle (N =38)
Demographics								
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics								
IGA-CHE, n (%)								
Moderate (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HECSI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DLQI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHE characteristics								
Mean (SD) age at onset of CHE, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) duration of CHE, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkeratotic eczema, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous CHE treatments								
TCS, n (%)								

	DELTA 1				DELTA 2			
	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)		Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N =218)	Cream vehicle (N =109)	Delgocitinib cream 20 mg/g (N =107)	Cream vehicle (N =53)	Delgocitinib cream 20 mg/g (N =238)	Cream vehicle (N =121)	Delgocitinib cream 20 mg/g (N =75)	Cream vehicle (N =38)
Inadequate response last 12 months	[redacted]							
Medically inadvisable	[redacted]							
TCI, n (%)	[redacted]							
Oral retinoids, n (%)	[redacted]							
Oral corticosteroids, n (%)	[redacted]							
Oral methotrexate, n (%)	[redacted]							
Oral ciclosporin, n (%)	[redacted]							

Abbreviations: CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; g, grams; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; mg, milligrams; N, total number of participants; n, number of participants; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 7 Baseline characteristics of patients in Worm 2022 trial, by disease severity at baseline

	Moderate (IGA-CHE = 3)					Severe (IGA-CHE = 4)				
	Delgocitinib cream 1 mg/g (N =29)	Delgocitinib cream 3 mg/g (N =29)	Delgocitinib cream 8 mg/g (N = 29)	Delgocitinib cream 20 mg/g (N =31)	Cream vehicle (N = 27)	Delgocitinib cream 1 mg/g (N =10)	Delgocitinib cream 3 mg/g (N =9)	Delgocitinib cream 8 mg/g (N =12)	Delgocitinib cream 20 mg/g (N =10)	Cream vehicle (N =11)
Demographics										
Age (years), mean (SD)	[redacted]									
Female, n (%)	[redacted]									

	Moderate (IGA-CHE = 3)					Severe (IGA-CHE = 4)				
	Delgocitinib cream 1 mg/g (N =29)	Delgocitinib cream 3 mg/g (N =29)	Delgocitinib cream 8 mg/g (N = 29)	Delgocitinib cream 20 mg/g (N =31)	Cream vehicle (N = 27)	Delgocitinib cream 1 mg/g (N =10)	Delgocitinib cream 3 mg/g (N =9)	Delgocitinib cream 8 mg/g (N =12)	Delgocitinib cream 20 mg/g (N =10)	Cream vehicle (N =11)
White, n (%)	[redacted]									
Baseline characteristics										
IGA-CHE										
Moderate n (%)	[redacted]									
Severe n (%)	[redacted]									
HECSI, mean (SD)	[redacted]									
DLQI										
Mean (SD)	[redacted]									
CHE characteristics										
Mean (SD) age at onset of CHE, years	[redacted]									
Mean (SD) duration of CHE, years	[redacted]									
CHE subtype, main diagnosis, (%)										
Hyperkeratotic eczema, n (%)	[redacted]									

	Moderate (IGA-CHE = 3)					Severe (IGA-CHE = 4)				
	Delgocitinib cream 1 mg/g (N =29)	Delgocitinib cream 3 mg/g (N =29)	Delgocitinib cream 8 mg/g (N = 29)	Delgocitinib cream 20 mg/g (N =31)	Cream vehicle (N = 27)	Delgocitinib cream 1 mg/g (N =10)	Delgocitinib cream 3 mg/g (N =9)	Delgocitinib cream 8 mg/g (N =12)	Delgocitinib cream 20 mg/g (N =10)	Cream vehicle (N =11)
Atopic hand eczema, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritant contact dermatitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vesicular HE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allergic contact dermatitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; DLQI, Dermatology Life Quality Index; g, grams; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; mg, milligrams; N, total number of participants; n, number of participants; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

A4. Please provide the baseline characteristics for the pooled analyses of DELTA 1 and DELTA 2 for each trial arm for:

a) the overall population

b) the moderate subgroup and

c) the severe subgroup.

Table 8 Baseline demographics and clinical characteristics of the study population by treatment group and disease severity

	Overall population		Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N =638)	Cream vehicle (N = 321)	Delgocitinib cream 20 mg/g (N =456)	Cream vehicle (N = 230)	Delgocitinib cream 20 mg/g (N =182)	Cream vehicle (N = 91)
Demographics						
Age (years), mean (SD)	44.8 (14.5)	42.7 (14.2)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	405 (63.5)	212 (66.0)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	577 (90.4)	290 (90.3)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics						
IGA-CHE						
Moderate, n (%)	456 (71.5)	230 (71.7)	[redacted]	[redacted]	[redacted]	[redacted]
Severe, n (%)	182 (28.5)	91 (28.3)	[redacted]	[redacted]	[redacted]	[redacted]
HECSI, mean (SD)	71.1 (43.0)	72.5 (47.3)	[redacted]	[redacted]	[redacted]	[redacted]
DLQI, mean (SD)	12.4 (6.1)	12.6 (6.7)	[redacted]	[redacted]	[redacted]	[redacted]
CHE *characteristics*						
Age at onset of CHE (years), mean (SD)	35.2 (17.0)	32.8 (16.8)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of CHE (years), mean (SD)	9.6 (11.0)	10.0 (11.2)	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkeratotic eczema, n (%)	143 (22.4)	63 (19.6)	[redacted]	[redacted]	[redacted]	[redacted]
Previous CHE treatments						
TCS						
Inadequate response last 12 months, n (%)	633 (99.2)	316 (98.4)	[redacted]	[redacted]	[redacted]	[redacted]
Medically inadvisable, n (%)	127 (19.9)	68 (21.2)	[redacted]	[redacted]	[redacted]	[redacted]
TCI, n (%)	233 (36.5)	115 (35.8)	[redacted]	[redacted]	[redacted]	[redacted]
Oral retinoids, n (%)	97 (15.2)	46 (14.3)	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroids, n (%)	95 (14.9)	41 (12.8)	[redacted]	[redacted]	[redacted]	[redacted]
Oral methotrexate, n (%)	1 (0.2)	4 (1.2)	[redacted]	[redacted]	[redacted]	[redacted]
Oral ciclosporin, n (%)	1 (0.2)	3 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; g, grams; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; mg, milligrams; N, total number of participants; n, number of participants; SD, standard deviation; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

A5. Please provide the baseline characteristics and quality assessment results for the Worm *et al.* 2022 and ALPHA trials, using the same format as for the DELTA trials [Tables 8 and 10 of the company submission (CS)].

The quality assessment results for Worm 2022[1] and ALPHA[2] trials were presented in Table 149 of the company submission Appendix B.4.1. Also, the baseline data for ALPHA trial presented in the table below was presented in Tables 99 and 100 in the company submission Appendix B.1.2.4. Data from the entire randomised population in Worm 2022 were also presented in the same tables in Appendix B.

Table 9 presents the quality assessment results for ALPHA and Worm 2022 trials. In Table 10, we present the baseline characteristics for just the moderate and severe participants in this Phase 2b study, consistent with the subgroup data used in the NMA.

Table 9 Quality assessment results for ALPHA and Worm 2022

Trial	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
ALPHA	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Worm 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 10 Baseline characteristics of participants in Worm 2022 and ALPHA 2024 trials

	Worm 2022[a]					ALPHA 2024	
	Delgo cream 1 mg/g (N =39)	Delgo cream 3 mg/g (N =38)	Delgo cream 8 mg/g (N =41)	Delgo cream 20 mg/g (N =41)	Cream vehicle (N = 38)	Alitretinoin 30 mg (N =220)	Immersion PUVA (N = 221)
Demographics							
Age (years), median (range)	42.0 (20–76)	47.0 (19–72)	51.0 (25–68)	43.0 (18–70)	50.5 (20–79)	47.7 (20–81)	44.6 (18–79)
Age (years), mean (SD)	43.0 (13.6)	45.4 (15.5)	47.9 (13.0)	44.1 (15.0)	47.2 (16.8)	46.5 (14.9)	45.1 (15.2)
Female, n (%)	29 (74.4)	19 (50.0)	26 (63.4)	28 (68.3)	18 (47.4)	132 (60.0)	141 (63.8)
White, n (%)	38 (97.4)	38 (100)	39 (95.1)	40 (97.6)	38 (100)	193 (87.7)	199 (90.0)
Baseline characteristics							

	Worm 2022[a]					ALPHA 2024	
	Delgo cream 1 mg/g (N =39)	Delgo cream 3 mg/g (N =38)	Delgo cream 8 mg/g (N =41)	Delgo cream 20 mg/g (N =41)	Cream vehicle (N = 38)	Alitretinoin 30 mg (N =220)	Immersion PUVA (N = 221)
Severity	IGA-CHE					PGA	
Moderate, n (%)	29 (74.4)	29 (76.3)	29 (70.7)	31 (75.6)	27 (71.1)	0.0	0.0
Severe, n (%)	10 (25.6)	9 (23.7)	12 (29.3)	10 (24.4)	11 (28.9)	220 (100.0)	221 (100.0)
HECSI, mean (SD)	70.3 (49.4)	59.9 (37.9)	56.5 (28.4)	78.7 (60.2)	63.3 (33.3)	68.2 (47.5)	62.2 (42.0)
DLQI							
Mean (SD)	12.5 (7.0)	10.9 (6.3)	10.2 (6.2)	12.1 (6.8)	9.4 (6.3)	13.9 (6.8)	13.6 (6.0)
Median (range)	11.0 (1–29)	9.0 (0– 27)	9.0 (1– 26)	12.0 (1-29)	7.5 (1–24)	13.0 (2–30)	13.0 (2–30)
CHE characteristics							
Mean (SD) age at onset of CHE, years	30.7 (17.3)	35.2 (17.7)	36.7 (17.8)	31.1 (19.0)	33.2 (21.7)	NR	NR
Mean (SD) duration of CHE, years	12.2 (13.3)	10.2 (10.8)	11.2 (11.6)	13.0 (14.6)	13.9 (12.6)	NR[b]	NR
CHE subtype, main diagnosis							
Hyperkeratotic eczema, n (%)[c]	5 (12.8)	11 (28.9)	4 (9.8)	6 (14.6)	6 (15.8)	143 (65.0)	143 (64.7)
Atopic hand eczema, n (%)	12 (30.8)	15 (39.5)	17 (41.5)	22 (53.7)	13 (34.2)	NR	NR
Irritant contact dermatitis, n (%)	15 (38.5)	8 (21.1)	11 (26.8)	9 (22.0)	15 (39.5)	NR	NR
Vesicular HE, n (%)	4 (10.3)	1 (2.6)	5 (12.2)	2 (4.9)	2 (5.3)	62 (28.2)	62 (28.1)
Allergic contact dermatitis, n (%)	3 (7.7)	3 (7.9)	4 (9.8)	2 (4.9)	2 (5.3)	NR	NR

[a] Data reported for Worm 2022 includes only patients with moderate (IGA 3) or severe (IGA 4) CHE.

[b] Number and percentage of patients in following disease duration categories reported: < 6 months, 6-24 months and >24 months

[c] There is a lack of comparability in how hyperkeratosis was defined in the ALPHA trial compared to the delgocitinib trials; therefore, comparisons should be made with caution. Please refer to question A18 for further information on the different classification systems used.

Abbreviations: CHE, chronic hand eczema; DLQI, Dermatology Life Quality Index; g, grams; HE, hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; mg, milligrams; N, total number of participants; n, number of participants; NR, not reported; PGA, Physician's Global Assessment; PUVA, Psoralen plus ultraviolet A; SD, standard deviation.

Outcomes

A6. Priority question: Within the CS, the company stated that lower estimates of efficacy may be expected when using the IGA-CHE scale compared to the Physician's Global Assessment (PGA) scale.

a) **Please provide further information on whether IGA-CHE is validated for use as the primary outcome in clinical trials**

b) **Where trials measured both IGA-CHE and PGA, please provide the mean IGA-CHE score assigned to patients with a PGA score of 0, 1, 2, 3, and 4 and**

c) **Please provide evidence to support the assertion that efficacy may be lower when using the IGA-CHE scale compared to the PGA scale.**

a) As outlined in Appendix B.6.1, validation of the IGA-CHE is described in full in Silverberg *et al.* 2024.[3] The authors detail the evaluation of the measurement properties of the IGA-CHE tool using data from the first 280 patients completing 16 weeks of the DELTA 1 trial. The IGA-CHE was administered alongside the clinical and patient reported outcomes measures: Patient Global Assessment of Disease Severity (PaGA), HECSI, Hand eczema symptom diary (HESD) Patient Global Impression of Severity (PGI-S) and HESD Patient Global Impression of Change (PGI-C). A range of statistical methods were also used to evaluate varying aspects of the performance of IGA-CHE. All analyses were conducted by independent psychometricians who were not involved in the trial efficacy analysis and in accordance with the best practice guidance for assessing measurement properties of Clinical Outcome Assessments. The analysis included test-retest reliability, convergent validity, known-groups validity, ability to detect change, Interpretation of scores: anchor-based analyses to inform within-subject meaningful change thresholds and Interpretation of scores: distribution-based analyses. From these analyses it was concluded that IGA-CHE was a valid, reliable, and responsive measure of CHE severity, being both fit-for-purpose and suitable to be used to support clinical trial endpoints.

b) No trials included both the IGA-CHE and Physicians Global Assessment (PGA) so we cannot address this request.

c) Since no trials included both the IGA-CHE and PGA, the request cannot be met. However, by doing a side-by-side comparison of the scales, inherent differences between the IGA-CHE and PGA appear, such as PGA considering patient itch and pain and the definition of the "almost clear" category.

   The IGA-CHE "almost Clear" category includes only barely perceptible erythema and no other signs of the disease in order to clearly distinguish Treatment Success from Treatment Failure. The PGA 'almost clear' stipulates that at least one mild Erythema, Scaling and Hyperkeratosis/ lichenification covering less than 10% of the affected hand surface with the absence of vesiculation, oedema, fissures and pruritus/pain. Therefore, the PGA uses a broader definition of treatment success.

A7. Priority question: The EAG notes that the total proportion of patients with IGA-CHE treatment success (TS) varies for both the delgocitinib and cream vehicle arms between the DELTA 1 and DELTA 2 studies, although these trials were described as being identical in the CS. Please provide an explanation for the differences observed in IGA-CHE TS between these trials.

Despite efforts to control all aspects of a clinical trial, random variability persists. This variability can arise from many factors and as a result, it is unlikely that two identically designed trials, will produce replicate observations.

To evaluate the difference in treatment effect observed for IGA-CHE TS between DELTA 1 and DELTA 2, a simulation study was conducted. Using a Bayesian methodology and assuming a non-informative prior, an estimation of the distribution of the underlying probabilities using historical trial data was calculated.

This was done by assuming that p (overall population) followed a beta-distribution with the parameters Be(n+1,N-n+1), where N is the number of subjects in the treatment group and n is the number of subjects with treatment success in the historical data.

Using data from DELTA 1 and DELTA 2, the parameters in the beta-distribution were as follows:

- For delgocitinib cream 20 mg/g: [redacted]
- For cream vehicle: [redacted]

These numbers were based on the composite estimand where subjects who discontinued IMP, initiated rescue treatment, withdrew from trial, or had missing data due to other reasons are imputed as non-responders.

25,000 probabilities for delgocitinib cream 20 mg/g and 25,000 for cream vehicle were then simulated. 300 subjects sampled from the delgocitinib group, and 150 from the vehicle group were used. The proportion of responders for each treatment group represented the outcome of a future trial. The treatment difference was calculated by subtracting cream vehicle from delgocitinib cream 20 mg/g to obtain 25,000 simulated treatment differences.

The results can be seen in Figure 4 below:

Figure 4 Cumulative distribution for IGA-CHE TS at week 16 – Simulation study

Key: 1401 = DELTA 1; 1402 = DELTA 2
Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; IGA-CHE TS, IGA-CHE treatment success.
This figure is confidential.

For the cream vehicle groups, the observed proportion of responders in DELTA 1 (1401) and DELTA 2 (1402) are illustrated by the vertical orange lines. Results from DELTA 1 and DELTA 2 are placed around the centre of the distribution. For the delgocitinib groups (blue vertical lines) the DELTA 1 (1401) and DELTA 2 (1402) results are placed at the lower and upper end of the distribution. It is not unlikely, based on the distributions, to see the outcomes we have observed. By chance the

two cream vehicle outcomes are near the centre and by chance the two delgocitinib outcomes are in the outer ends of the distribution.

The simulated treatment differences are shown in Figure 5. The proportion of simulated trials with a smaller treatment effect than observed in DELTA 1 is [redacted] and the proportion of simulated trials with a larger treatment effect than observed in DELTA 2 is [redacted]

Figure 5 Cumulative distribution for treatment difference in IGA-CHE TS at week 16

Key: 1401 = DELTA 1; 1402 = DELTA 2
Abbreviations: IGA-CHE: Investigator's Global Assessment for Chronic Hand Eczema; IGA-CHE TS: IGA-CHE treatment success.
This figure is confidential.

This analysis demonstrates that the difference in the observed treatment effect between DELTA 1 and DELTA 2 is within range of what could be expected from two confirmatory trials and could be caused by statistical variability alone.

A8. The EAG notes that Molin *et al.* 2024 described how the Hand Eczema Symptoms Diary (HESD) measures were validated using data from Worm *et al.* 2022 and subsequently modified (e.g., HESD was reduced from 8 items to 6 items). This modified form of HESD was then used in the validation performed for data from the DELTA 1 trial.

a) Please provide further information how the HESD measure used in the DELTA trials differs from that used within Worm *et al.* 2022 and
b) Please outline whether HESD is comparable across Worm *et al.* 2022 and all other trials used in the network meta-analyses (NMAs)?

a) The HESD scale used in Worm 2022[1] was formed of 11 items (itch, burning, pain, cracking in skin, redness, dryness, swelling, bleeding, thickening of the skin,

flaking of skin and oozing/weeping) all of which were evaluated on a scale from 0 = none to 10 = severe. This 11-item HESD underwent initial item level and dimensionality analyses which combined with earlier qualitative findings and clinical inputs from expert dermatologists, led to the removal of three items. Following this, feedback from the Food and Drug Administration (FDA) led to the removal of two further items resulting in a 6-item HESD scale. This 6-item HESD scale, formed of itch, pain, cracking, redness, dryness and flaking with items evaluated on a scale from 0 = none to 10 = severe, was used in DELTA 1 and DELTA 2.

b) We have interpreted the question to be asking for a comparison of the HESD scores at baseline reported across the four delgocitinib trials included in the NMAs. HESD was not evaluated in the ALPHA trial, which was also included in the NMAs. The baseline scores of participants within these trials are detailed in the table below, noting that scores in Worm 2022 are based on the subgroup of patients with moderate to severe CHE at baseline (i.e. only patients with IGA-CHE score of 3 or 4 at baseline)

Across all four delgocitinib trials (Table 11), HESD itch weekly average score amongst total trial populations at baseline ranged from 5.3 (2.64) to 7.16 (1.66) in Worm 2022 and DELTA 1, respectively. HESD pain weekly average score at baseline ranged from 4.5 (2.75) to 6.83 (2.01) in Worm 2022 and DELTA 1, respectively. HESD total weekly average score at baseline ranged from 5.3 (2.17) to 7.16 (1.67) in Worm 2022 and DELTA 1, respectively. These baseline scores are slightly higher in the DELTA trials compared to Worm 2022 but are comparable overall with most baseline values being ≥4. This could be driven by the fact that both DELTA 1 and DELTA 2 trials included a baseline HESD itch score (weekly average) of ≥4 points among the inclusion criteria, whereas this was not the case for Worm 2022 nor DELTA FORCE.

DELTA FORCE only included patients with severe CHE. When considering only severe patients in Worm 2022 (N = 52), the mean (SD) baseline itch score was 6.0 (2.51), the pain score was 5.7 (2.63) and total HESD score was 6.1 (2.22). These are closely aligned and therefore comparable with those seen in DELTA FORCE.

Table 11 HESD baseline scores for severity, itch, and pain across treatment arms

Trial	Trial arm	N	HESD score (weekly average), mean (SD)	HESD itch score (weekly average), mean (SD)	HESD pain score (weekly average), mean (SD)
DELTA 1	All	486	7.16 (1.67)	7.16 (1.66)	6.83 (2.01)
	Delgocitinib 20 mg/g	324	7.15 (1.66)	7.13 (1.64)	6.83 (2.00)
	Vehicle	162	7.16 (1.68)	7.23 (1.69)	6.84 (2.03)
DELTA 2	All	469	6.95 (1.47)	6.99 (1.53)	6.56 (1.86)
	Delgocitinib 20 mg/g	312	6.97 (1.46)	6.99 (1.55)	6.62 (1.81)
	Vehicle	157	6.91 (1.51)	6.98 (1.51)	6.46 (1.96)
DELTA FORCE	Delgocitinib 20 mg/g	238	6.02 (2.26)	5.74 (2.77)	5.20 (2.90)
	Alitretinoin	238	6.23 (2.26)	5.96 (2.64)	5.80 (2.825)
Worm 2022 (only patients with IGA-CHE score of 3 or 4 at baseline)	All	197	5.3 (2.17)	5.3 (2.64)	4.5 (2.75)
	Delgocitinib 1 mg/g	39	5.9 (2.06)	5.9 (2.53)	5.4 (2.78)
	Delgocitinib 3 mg/g	38	5.1 (1.9)	4.5 (2.28)	4.5 (2.73)
	Delgocitinib 8 mg/g	41	5.0 (2.42)	5.5 (3.03)	4.4 (2.88)
	Delgocitinib 20 mg/g	41	5.3 (2.12)	5.5 (2.65)	4.4 (2.72)
	Vehicle	38	4.9 (2.29)	5.0 (2.55)	4.0 (2.58)

Abbreviations: g, grams; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; mg, milligrams; N, total number of participants; SD, standard deviation.

A9. Within the CS, the company stated that IGA-CHE was "revised for the DELTA trials".

a) Please provide further information on what the revision to IGA-CHE entailed.

b) Please outline how the IGA-CHE measure implemented in the DELTA trials differs from that used within Worm *et al.* 2022 and whether IGA-CHE is comparable across these trials.

a) The IGA-CHE underwent multiple revisions between earlier trials (e.g., Worm 2022) and the DELTA trials. The scale evolved through five iterations (Versions 1.0 to 5.0) in response to feedback from the FDA and five expert dermatologists. The main revisions included stricter treatment success criteria and the removal of subjective symptoms. Below is a list of key changes and the rationale behind them:

- Removal of pruritus and pain descriptors (2018). This increased focus on observable clinical symptoms (e.g., scaling, fissures, swelling) rather than patient-reported symptoms (e.g., pruritus, pain).

- Refinement of "almost clear" and "mild" categories (2018–2020). This improved differentiation to reduce ambiguity and overlap between categories.
- Regulatory feedback on disease severity definitions (2020). This addressed issues in distinguishing between mild and moderate cases, improving patient classification.
- Final refinement for DELTA trials (IGA-CHE v4.0 & v5.0, FDA-endorsed). This implemented a five-level IGA-CHE scale with refined clinical descriptors and stricter treatment success criteria.

b) In terms of the comparability across the trials, there are a few factors to consider. The higher stringency in DELTA trials may reduce comparability with earlier studies. The DELTA trials implemented a stricter IGA-CHE, setting a higher bar for treatment success. Consequently, efficacy estimates in DELTA may appear lower compared to Worm (2022). Finally, the differences in patient classification could impact baseline severity distribution and inclusion criteria across trials. Some patients classified as "mild" in Worm (2022) may be considered "moderate" in DELTA trials due to refined severity definitions.

A10. The EAG notes that for the DELTA 1 and DELTA 2 trials, all Hand Eczema Severity Index (HECSI) outcomes (e.g., HECSI-90 etc), and the proportion of patients with IGA-CHE TS, decline between weeks 12 and 16. Please provide an explanation for why the proportion of patients achieving IGA-CHE TS, HECSI-75, HECSI-90, or least squares mean (LSM) percentage change in HECSI from baseline declines between weeks 12 and 16?

CHE is a naturally fluctuating disease, and periods of worsening are common.[4] The IGA-CHE scale is sensitive to small changes,[3] so it is useful to look at the rate of IGA-CHE treatment success in the longer-term after the apparent drop at the end of the 16-week DELTA 1 and 2 trials.[5-7]

DELTA 3 was a 36-week extension trial that enrolled patients who completed DELTA 1 and DELTA 2, including patients from both the delgocitinib cream group and the cream vehicle group.[8] Response rates were maintained across the 36-week trial in patients who had previously received delgocitinib in DELTA 1 and DELTA 2.[8] This

was also evident across efficacy outcomes, including IGA-CHE TS, HESCI 75 and HECSI 90, and a meaningful reduction in itch and pain.[8]

A11. The EAG notes that in the DELTA trials, response was assessed at week 16; however, the summary of product characteristics (SmPC) for delgocitinib recommends that response is assessed at week 12. Please confirm how the Medicines and Healthcare products Regulatory Agency (MHRA) came to the decision to assess response at week 12 as opposed to week 16?

The European Medicines Agency (EMA) requested information on whether delgocitinib should be stopped earlier than week 16 if no improvement is observed. In response, LEO Pharma performed an early predictor analysis to evaluate whether treatment should be stopped before week 16 if no improvement had been observed. The goal was to inform on how well early improvements can predict clinical responses for IGA-CHE TS or HECSI-75 at Week 16. To evaluate the accuracy of the early improvement predictors (≥1 step improvement in IGA-CHE or ≥HECSI-25), sensitivity and negative predictive values were assessed at Weeks 4, 8 and 12.

Sensitivity was defined as the proportion of participants with an early improvement among participants with a response at Week 16. Negative predictive value was defined as the proportion of participants without an early improvement who continued to have no response at Week 16 among participants without an early improvement.

For patients treated with delgocitinib in DELTA 1, DELTA 2, and DELTA 3 (N = 638 in full analysis set [FAS]), [redacted] obtained a clinical response between weeks 8 and 52 with continued treatment.

For the same population, [redacted].

The results of this analysis illustrated that there were [redacted]

[redacted]

The MHRA did not ask any additional questions to what EMA requested and found to be satisfactory.

Subgroup analyses

A12. Priority question: The EAG notes that the cumulative response data for IGA-CHE/PGA for the delgocitinib trials was calculated *post-hoc* (section 2.10.3 of the CS) but was not provided in the CS. Please provide these *post-hoc* data for cumulative response for each trial.

These *post-hoc* data are presented in Appendix B. Tables 116 to 118 in section 2.3.3 present data for comparison at Week 16. Tables 119 to 121 in section 2.3.4 present data for comparison at week 12. Table 122 in section 2.3.5 presents data for comparison at week 24.

No trials included both the IGA-CHE and PGA so the tables referenced above only relate to IGA-CHE.

A13. Please provide the results (as shown in Table 37 of the CS) for the moderate and severe subgroups of DELTA 1 and DELTA 2 for the following outcomes:

a) percentage change in HECSI
b) Hand Eczema Symptoms Diary [HESD]-PAIN
c) HESD-ITCH
d) HESD total score
e) loss of response, measured as the time to first IGA-CHE score $\geqslant 2$ and
f) EQ-5D-3L.

As shown in the subgroup data in the tables below (Table 12 and Table 13), patients in DELTA 1 and DELTA 2 demonstrated similar results for percentage change in HECSI score, HESD-pain, HESD-itch, and total score across both moderate and severe subgroups in Weeks 12 and 16, with a higher proportion of patients treated with delgocitinib achieving these outcomes than those treated with vehicle,

regardless of severity. Treatment effects for the proportions achieving at least a 4-point reduction in these scales were higher in the severe subgroup than moderate subgroup, but all were statistically significant versus vehicle. Delgocitinib showed statistically significantly greater improvements on EQ-5D than vehicle in moderate and severe CHE.

Table 14 presents the subgroup results for time to loss of response, which is defined as the time to first IGA-CHE ≥2 in patients previously treated with delgocitinib cream in DELTA 1 and DELTA 2 who achieved IGA-CHE 0/1 at DELTA 3 baseline. The severity subgroups are according to the parent trial (DELTA 1 and DELTA 2) baseline. The median time to first IGA-CHE ≥2 was [redacted] in both moderate and severe subgroups.

Table 12 Efficacy outcomes of delgocitinib cream: improvements in HECSI, HESD scores, and quality of life by disease severity at week 12

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N = 456)	Cream vehicle (N = 230)	Delgocitinib cream 20 mg/g (N = 182)	Cream vehicle (N = 91)
HECSI score				
LSM percentage change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD pain score reduction of ≥ 4 points				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD pain score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD itch score reduction of ≥ 4 points				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD itch score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N = 456)	Cream vehicle (N = 230)	Delgocitinib cream 20 mg/g (N = 182)	Cream vehicle (N = 91)
p value	[redacted]		[redacted]	
HESD total score reduction of ≥ 4 points				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD total score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
EQ-5D-3L index				
LSM improvement (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimension 3-Level index; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; LSM, least squares mean; N, total number of participants; n, number of participants; p value, probability value; SE, standard error.

Table 13 Efficacy outcomes of delgocitinib cream: improvements in HECSI, HESD scores, EQ-5D-3L, and statistical significance by disease severity at week 16

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N = 456)	Cream vehicle (N = 230)	Delgocitinib cream 20 mg/g (N = 182)	Cream vehicle (N = 91)
HECSI				
LSM percentage change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD pain score reduction of ≥ 4 points				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD pain score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD itch score reduction of ≥ 4 points				

	Moderate (IGA-CHE = 3)		Severe (IGA-CHE = 4)	
	Delgocitinib cream 20 mg/g (N = 456)	Cream vehicle (N = 230)	Delgocitinib cream 20 mg/g (N = 182)	Cream vehicle (N = 91)
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD itch score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD total score reduction of ≥ 4 points				
Proportion of patients with response, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in % (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
HESD total score				
LSM improvement in HESD total score (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
EQ-5D-3L index				
LSM improvement (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference (95% CI)	[redacted]		[redacted]	
p value	[redacted]		[redacted]	

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimension 3-Level index; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; LSM, least squares mean; N, total number of participants; n, number of participants; p value, probability value; SE, standard error.

Table 14 Time to first IGA-CHE ≥ 2 (i.e. loss of response) – patients previously treated with delgocitinib who were IGA-CHE 0/1 at DELTA 3 baseline by disease severity at parent trial baseline

	Moderate (IGA-CHE = 3) N= 109	Severe (IGA-CHE = 4) N= 29
Cumulative incidence (%) of IGA-CHE ≥ 2 (95%CI)		
Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 20	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 28	[redacted]	[redacted]
Week 32	[redacted]	[redacted]

	Moderate (IGA-CHE = 3) N= 109	Severe (IGA-CHE = 4) N= 29
Cumulative incidence (%) of IGA-CHE ≥ 2 (95%CI)		
Week 36	[redacted]	[redacted]
Median (IQR) time to IGA-CHE ≥ 2	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; IQR, interquartile range; N, total number of participants.

Additional analyses

A14. Priority question: Although the company qualitatively discusses between-study heterogeneity, no quantitative assessments of heterogeneity are reported in the CS. Accordingly, for each endpoint and timepoint in the network meta-analyses presented in the CS, please conduct pairwise meta-analyses, for any comparisons with 2 or more studies and provide the results along with appropriate measures of heterogeneity (i.e., I^2, Cochran's Q, and tau).

A total of 22 pairwise meta-analyses were conducted, as summarised in Table 15 below. The meta-analyses were conducted for comparisons with two or more studies to quantitatively explore the level of heterogeneity between studies.

All analyses were conducted in RStudio (version 4.4.2) using the "meta" package (version 8.0-1). Both fixed and random effects models were generated. The Mantel-Haenszel method was used to pool studies under the fixed effect model while the inverse variance method was used for random effects model. All studies were included regardless of zero events; a continuity correction was added for any zero events in the studies.

Heterogeneity was assessed using I^2 statistic, tau as well as Cochran's Q. The I^2 statistic indicates the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. The generally accepted rule for its interpretation is as follows:

- 0% - 40%: may not be important
- 30% - 60%: moderate heterogeneity
- 50% - 90%: substantial heterogeneity

- 75% - 100%: considerable heterogeneity

Tau is an estimate of the variance in true effect sizes across studies; larger values of tau indicate more variation in true treatment effects. Cochran's Q tests whether observed differences between treatment effect estimates are due to chance alone. The Q statistic is often reported with a p-value and a larger Q value suggests greater heterogeneity.

The results of the conducted meta-analyses are presented in Table 15. The trends in treatment effects in terms of direction and effect size aligned with the results generated in network meta-analyses. For all efficacy endpoints, including IGA-CHE/PGA 0/1 endpoint response, IGA-CHE 0/1 cumulative response and HECSI-90 endpoint response, delgocitinib was shown to be statistically significantly more effective than vehicle cream. Similarly, delgocitinib was also significantly safer than vehicle cream in terms of discontinuation due to adverse events. Overall, the level of heterogeneity was low and does not provide evidence of clinically significant difference for the analyses conducted. Evidence of heterogeneity was moderate to substantial for several analyses (I^2 between 30-60%), especially when assessing the primary endpoint and the moderate CHE patients for IGA-CHE/PGA 0/1 endpoint response. This may be due to the inclusion of Worm 2022, which had a very small sample size (N=41 in delgocitinib arm; N=38 in vehicle cream arm) compared to DELTA 1 and DELTA 2. However, the value of tau for these analyses was relatively small, indicating limited variation in treatment effects. Moreover, the Q statistic for these analyses was not statistically significant (p-value above the significance threshold of 0.05). This means there is no evidence that the variation in effect sizes across studies is greater than what would be expected by chance.

Table 15 Pairwise meta-analyses of treatment effects

Analysis	Population	Comparison	FE (95% CI)	RE (95% CI)	I^2	Tau	Q statistic (p-value)
IGA-CHE/PGA 0/1 endpoint response							
Primary endpoint	All patients	Delgocitinib vs vehicle	3.64 (2.42, 5.47)	3.78 (1.94, 7.35)	56.4%	0.43	4.59 (0.10)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0.002	1.51 (0.47)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	38.7%	0.34	3.26 (0.20)
Week 12	All patients	Delgocitinib vs vehicle	2.87 (2.02, 4.09)	2.98 (1.71, 5.18)	46.8%	0.34	3.76 (0.15)

Analysis	Population	Comparison	FE (95% CI)	RE (95% CI)	I^2	Tau	Q statistic (p-value)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	0.50 (0.78)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	49.6%	0.39	3.97 (0.14)
IGA-CHE 0/1 cumulative response							
Primary endpoint	All patients	Delgocitinib vs vehicle	3.31 (2.44, 4.49)	3.33 (2.26, 4.92)	17.7%	0.19	2.43 (0.30)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	0.80 (0.67)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0.13	1.86 (0.39)
Week 12	All patients	Delgocitinib vs vehicle	3.14 (2.24, 4.40)	3.14 (2.24, 4.40)	0.0%	0	0.34 (0.85)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	0.72 (0.70)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	0.46 (0.80)
Week 24	All patients	Alitretinoin vs placebo	3.98 (3.03, 5.23)	3.95 (3.01, 5.20)	0.0%	0	0.85 (0.36)
HECSI 90 endpoint response							
Primary endpoint	All patients	Delgocitinib vs vehicle	3.56 (2.45, 5.16)	3.51 (2.42, 5.10)	0.0%	0	1.41 (0.49)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	30.9%	0.002	2.89 (0.24)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	0.41 (0.81)
Week 12	All patients	Delgocitinib vs vehicle	4.29 (2.96, 6.23)	4.28 (2.95, 6.22)	0.0%	0	0.39 (0.82)
	Severe patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0	1.14 (0.56)
	Moderate patients	Delgocitinib vs vehicle	[redacted]	[redacted]	0.0%	0.14	1.67 (0.43)
Discontinuation due to adverse events							
End of treatment	All patients	Delgocitinib vs vehicle	0.14 (0.042, 0.46)	0.14 (0.043, 0.46)	0.0%	0	0.15 (0.93)
		Alitretinoin vs placebo	2.22 (1.37, 3.59)	2.23 (1.38, 3.60)	0.0%	0	0.51 (0.48)
	Severe patients	Alitretinoin vs placebo	2.22 (1.37, 3.59)	2.23 (1.38, 3.60)	0.0%	0	0.51 (0.48)

Abbreviations: CI, confidence interval; FE, fixed effects; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; I^2, heterogeneity index; p value, probability value; PGA, Physician's Global Assessment; Q statistic, heterogeneity test statistic; RE, random effects; Tau, between-study variance.

A15. Priority question: The EAG notes that the company assumes that the treatment effect of delgocitinib is consistent in patients with moderate and severe CHE but no evidence is provided to support this assumption. Please provide results for comparisons of moderate versus severe CHE patients (for

all endpoints and timepoints of interest) in the delgocitinib arm of the following trials:

a) **DELTA 1**
b) **DELTA 2 and**
c) **the pooled DELTA 1 and DELTA 2 population.**

LEO Pharma assumes that the treatment effect of delgocitinib versus alitretinoin, as observed in the DELTA FORCE trial among patients with severe CHE, is consistent across moderate and severe CHE populations. By extension, LEO assumes that the treatment effect of alitretinoin versus Psoralen plus Ultraviolet A (PUVA), as observed in the ALPHA trial among patients with severe CHE, is consistent across moderate and severe CHE populations. This is informed by the observation that the difference in the treatment effects between moderate and severe subgroups in the vehicle-controlled DELTA 1 and DELTA 2 studies appear to be driven more by a difference in the vehicle arms across severity than the delgocitinib arms.

The tables below (Table 16 and Table 17) present a comparison between moderate and severe subgroups in DELTA 1 and DELTA 2 for both the delgocitinib arms (as per the EAG request) and the vehicle arms on the outcomes of IGA-CHE 0/1 and HECSI 90, the two outcomes feeding directly into the economic model. With few exceptions, the size of the difference in the vehicle arms across severity is larger than in the delgocitinib arms. This suggests that differential effect sizes between severity subgroups is more likely to be driven by a difference in the probability of response to vehicle than to delgocitinib.

We also present odds ratios for delgocitinib versus vehicle across the DELTA trials, individually and pooled, for each subgroup at week 12 and week 16 for IGA-CHE 0/1 and HECSI 90 (Table 18). In the pooled analysis, the effects are broadly similar for both severe and moderate patients at week 12, though there is a more pronounced difference at week 16. Notably, all 95% confidence intervals overlap substantially. This indicates that the differential in the vehicle arm highlighted above may be more pronounced at week 16 than week 12, which is indeed what is seen for the IGA-CHE 0/1 outcome in Table 17.

An overall similar trend is observed in a 12-week dose-finding RCT of alitretinoin (Ruzicka *et al.* 2004[9]), which notably did not include the currently licensed 30 mg/kg dose of alitretinoin and as such was not included in the submitted NMAs. The study included moderate and severe CHE patients, defined by PGA score of 3 or 4 and reported subgroup results for the outcome of proportion achieving PGA "clear or almost clear". Table 19 below presents a comparison between the moderate and severe subgroups in this study for both the placebo arm and each alitretinoin arm. The size of the difference in the placebo arm across severity is larger than in any of the alitretinoin arms. Similarly, the size of the treatment effect versus placebo is larger in the severe subgroup than the moderate subgroup, though confidence intervals overlap substantially.

LEO has not asserted that there is no difference in the absolute likelihood of response between patients with moderate and severe CHE, just that the relative effects between active comparators, e.g. delgocitinib and alitretinoin or alitretinoin and PUVA, can be assumed to be similar across severities because the underlying placebo/vehicle effects work in the same direction and are likely to net out. The NMAs used to inform treatment effects applied in the economic model use appropriate subgroup data to explore differential effects by severity in the vehicle-controlled studies of delgocitinib. The economic model also uses baseline risk estimates derived from delgocitinib arms of the included studies broken down by subgroup.

In summary, we have provided the analyses requested by the EAG, both for this question and for question B5. The data supports the assumption that relative effects for comparisons of active treatments are consistent across severity and LEO Pharma maintain that the assumptions made in the original submission and economic model are reasonable and use the available data to its fullest extent.

Table 16 Comparison of moderate and severe CHE subgroup data from delgocitinib trial arms for outcomes of IGA-CHE 0/1 and HECSI 90 at week 12 and week 16

Outcome and timepoint	Delgocitinib moderate vs severe	DELTA 1		DELTA 2		DELTA 1+DELTA 2	
		Moderate (N=218)	Severe (N=107)	Moderate (N=238)	Severe (N=75)	Moderate (N=456)	Severe (N=182)
IGA-CHE 0/1							
Week 12	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome and timepoint	Delgocitinib moderate vs severe	DELTA 1		DELTA 2		DELTA 1+DELTA 2	
		Moderate (N=218)	Severe (N=107)	Moderate (N=238)	Severe (N=75)	Moderate (N=456)	Severe (N=182)
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
Week 16	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
HECSI 90							
Week 12	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
Week 16	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; N, total number of participants; n, number of participants; OR, odds ratio.

Table 17 Comparison of moderate and severe CHE subgroup data from vehicle trial arms for outcomes of IGA-CHE 0/1 and HECSI 90 at week 12 and week 16

Outcome and timepoint	Vehicle moderate vs severe	DELTA 1		DELTA 2		DELTA 1+DELTA 2	
		Moderate (N=109)	Severe (N=53)	Moderate (N=121)	Severe (N=38)	Moderate (N=230)	Severe (N=91)
IGA-CHE 0/1							
Week 12	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
Week 16	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
HECSI 90							
Week 12	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	
Week 16	Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OR (95% CI)	[redacted]		[redacted]		[redacted]	

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; N, total number of participants; n, number of participants; OR, odds ratio.

Table 18 Comparison of moderate and severe CHE subgroup treatment effects for outcomes of IGA-CHE 0/1 and HECSI 90 at week 12 and week 16

Outcome and trial	Severity subgroup	Odds ratio (95% CI), delgocitinib vs vehicle	
		Week 12	Week 16
IGA-CHE TS			
DELTA 1	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
DELTA 2	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]

Outcome and trial	Severity subgroup	Odds ratio (95% CI), delgocitinib vs vehicle	
		Week 12	Week 16
DELTA 1+ DELTA 2	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
HECSI 90			
DELTA 1	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
DELTA 2	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]
DELTA 1+ DELTA 2	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; NE, not estimable; OR, odds ratio; TS, treatment success.

Table 19 Comparison of moderate and severe CHE subgroup data and treatment effects for outcomes of PGA 0/1 at week 12 from Ruzicka 2004

Trial arm	PGA 0/1 responders, r/n (%)		Odds ratio (95% CI)	Odds ratio (95% CI), alitretinoin vs placebo	
	Moderate	Severe	Moderate vs severe	Moderate	Severe
Placebo	17/51 (33.3)	4/27 (14.8)	2.88 (0.86, 9.65)	-	-
Alitretinoin 10 mg/kg	23/52 (44.2)	8/28 (28.6)	1.98 (0.74, 5.31)	1.59 (0.71, 3.53)	2.3 (0.6, 8.8)
Alitretinoin 20 mg/kg	22/56 (39.3)	10/24 (41.7)	0.91 (0.34, 2.4)	1.29 (0.59, 2.86)	4.11 (1.08, 15.63)
Alitretinoin 40 mg/kg	30/52 (57.7)	13/29 (44.8)	1.68 (0.67, 4.19)	2.73 (1.22, 6.08)	4.67 (1.29, 16.96)

Abbreviations: CI, confidence interval; kg, kilogram; mg, milligrams; n, number of participants; OR, odds ratio; PGA, Physician's Global Assessment; r, responders.

A16. Priority question: The EAG's clinical expert indicated that the choice of treatments for CHE is dependent on whether a patient has hyperkeratotic or non-hyperkeratotic CHE. The clinical expert suggested that PUVA and alitretinoin are predominately used to treat non-hyperkeratotic and hyperkeratotic patients, respectively. Accordingly, please provide results for comparisons of hyperkeratotic versus non-hyperkeratotic CHE patients (for all endpoints and timepoints of interest) in the DELTA FORCE trial for:

a) **patients in the delgocitinib arm and**
b) **patients in the alitretinoin arm.**

Please see the results for hyperkeratotic and non-hyperkeratotic subgroups below, for both the delgocitinib and alitretinoin arms at weeks 12 and 24, for all endpoints of interest (Table 20 and Table 21).

We acknowledge that there are observed differences between the clinician reported measures across trial arms and between the subgroups classified as hyperkeratotic or not hyperkeratotic at baseline, at both time points. In the non-hyperkeratotic population, a significantly higher proportion of patients treated with delgocitinib, achieved IGA-CHE TS, HECSI 90, HECSI 75 and change in HECSI score from baseline, than patients treated with alitretinoin across both weeks 12 and 24. In the hyperkeratotic population, a greater proportion of patients treated with alitretinoin achieved IGA-CHE-TS at both weeks 12 and 24.

The differences on HECSI endpoints were less definitive in the hyperkeratotic subgroup. Treatment effects varied by endpoint and timepoint in terms of direction, magnitude and statistical significance. A greater proportion of patients treated with alitretinoin achieved HECSI 90 at both weeks 12 and 24, a difference that was statistically significant at week 12, but no longer by week 24. For change in HECSI score from baseline and HECSI 75, results favoured alitretinoin at week 12 and favoured delgocitinib at week 24, though the differences were not found to be statistically significant at either time point.

During validation of the IGA-CHE measure (Silverberg *et al*., 2024[10]), the authors suggested that a two-level improvement in IGA-CHE was a conservative, meaningful change threshold. Their findings also suggested that a one-level improvement in IGA-CHE reflected a clinically meaningful improvement for patients. In both hyperkeratotic and non-hyperkeratotic patients participating in the DELTA FORCE trial, [redacted].

Patients with CHE report lower levels of quality of life, as well as higher levels of activity impairment and reduced work productivity levels.[11] The patient experience, the symptoms reported, and the improvements observed by patients following a successful treatment, extends beyond what can be measured in the clinician reported assessments alone. Therefore, it is essential to consider the benefits of treatments from the perspective of the patients and their reported outcomes. These include patient reported outcome measures of quality of life, pain, itch and burden of disease amongst other things. Patients who have not achieved clinician assessed endpoints of IGA-CHE TS or HECSI 90 can still have achieved clinically meaningful improvements in their CHE as assessed by patient centred outcomes.

A reduction of the Dermatology Life Quality Index (DLQI) score of ≥ 4 is widely considered to represent a clinically meaningful change in dermatological conditions and is often used in combination with clinician assessed outcomes to evaluate the success of treatments (e.g. in moderate to severe plaque psoriasis and atopic dermatitis). A study by Basra *et al.,* (2015)[12] presented an analysis of 192 patients with varying skin differences using an anchor-based method to estimate the meaningful change threshold, which was found to be an improvement of ≥ 4 points among patients with inflammatory skin diseases.[13] Within the DELTA FORCE study, a greater proportion of patients receiving delgocitinib achieved a DLQI score of ≥ 4 compared to patients treated with alitretinoin at both timepoints, for both subgroups, though the differences were only found to be statistically significant among non-hyperkeratotic patients. A similar result was observed for EQ-5D-3L change from baseline. In addition to this, in the DELTA FORCE trial, in patients with hyperkeratotic CHE, the difference in mean area under the curve (AUC) of change from baseline in DLQI up to week 24 was non-significant, showing that patients benefited from delgocitinib to the same extent as alitretinoin. For all HESD outcomes at week 12 and week 24, reductions in pain and itch sub scores were similar among hyperkeratotic patients receiving alitretinoin and delgocitinib and were significantly larger among non-hyperkeratotic patients receiving delgocitinib.

This highlights that despite differences in the clinician assessed outcomes, delgocitinib patients appear to experience meaningful improvements in patient-relevant measures of itch, pain and quality of life regardless of subgroup.

Table 20 Comparison of efficacy outcomes between delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic hand eczema at week 12 (DELTA FORCE)

Endpoint	Measure	Delgocitinib		Alitretinoin			
		N	Week 12	N	Week 12	Difference (95% CI)	p-value
Hyperkeratotic							
Change in HECSI score from baseline	Adjusted Mean Change (SE)	[redacted]					
HECSI 90	Responders, n (%)						
IGA-CHE-TS	Responders, n (%)						
	Cumulative responders, n (%)						
HECSI 75	Responders, n (%)						
Change in HESD pain sore (weekly average)	Adjusted Mean Change (SE)						
Change in HESD itch score (weekly average)	Adjusted Mean Change (SE)						
HESD score change from baseline (weekly average)	LS Mean Change (95% CI)						
Reduction of DLQI Score ≥4 points	Responders, n (%)						
EQ-5D-3L Index change from baseline	Adjusted mean change (SE)						
Non-hyperkeratotic							
Change in HECSI score from baseline	Adjusted Mean Change (SE)						
HECSI 90	Responders, n (%)						
IGA-CHE-TS	Responders, n (%)						
	Cumulative responders, n (%)						
HECSI 75	Responders, n (%)						
Change in HESD pain sore (weekly average)	Adjusted Mean Change (SE)						
Change in HESD itch score (weekly average)	Adjusted Mean Change (SE)						
HESD score change from baseline	LS Mean Change (95% CI)						
Reduction of DLQI Score ≥4 points	Responders, n (%)						
EQ-5D-3L Index change from baseline	Adjusted mean change (SE)						

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EQ-5D-3L, EuroQol 5-Dimension 3-Level index; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE,

Investigator's Global Assessment for Chronic Hand Eczema; LS, least squares; N, total number of participants; n, number of participants; NR, not reported; SE, standard error; TS, treatment success.

Table 21 Comparison of efficacy outcomes between delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic hand eczema at week 24 (DELTA FORCE)

Endpoint	Measure	Delgocitinib		Alitretinoin			
		N	Week 24	N	Week 24	Difference (95% CI)	p-value
Hyperkeratotic							
Change in HECSI score from baseline	Adjusted Mean Change (SE)	[redacted]					
HECSI 90	Responders, n (%)						
IGA-CHE-TS	Responders, n (%)						
	Cumulative responders, n (%)						
HECSI 75	Responders, n (%)						
Change in HESD pain sore (weekly average)	Adjusted Mean Change (SE)						
Change in HESD itch score (weekly average)	Adjusted Mean Change (SE)						
HESD score change from baseline	LS Mean change (95% CI)						
Reduction of DLQI Score ≥4 points	Responders, n (%)						
EQ-5D-3L Index change from baseline	Adjusted mean change (SE)						
Non-hyperkeratotic							
Change in HECSI score from baseline	Adjusted Mean Change (SE)						
HECSI 90	Responders, n (%)						
IGA-CHE-TS	Responders, n (%)						
	Cumulative responders, n (%)						
HECSI 75	Responders, n (%)						
Change in HESD pain sore (weekly average)	Adjusted Mean Change (SE)						
Change in HESD itch score (weekly average)	Adjusted Mean Change (SE)						
HESD score change from baseline	LS Mean Change (95% CI)						
Reduction of DLQI Score ≥4 points	Responders, n (%)						
EQ-5D-3L Index change from baseline	Adjusted mean change (SE)						

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; EQ-5D-3L, EuroQol 5-Dimension 3-Level index; HECSI, Hand Eczema Severity Index; HESD, Hand Eczema Symptom Diary; IGA-CHE,

Investigator's Global Assessment for Chronic Hand Eczema; LS, least squares; N, total number of participants; n, number of participants; NR, not reported; SE, standard error; TS, treatment success.

A17. Priority question: Please provide the results of indirect treatment comparisons (for all endpoints considered) that solely comprise the DELTA FORCE and ALPHA trials to derive an estimate of the effectiveness of delgocitinib relative to PUVA.

a) **For the above indirect treatment comparisons (for all endpoints considered) please perform subgroup analyses for the following populations:**

   i) **patients with hyperkeratotic CHE and**

   ii) **patients with non-hyperkeratotic CHE.**

b) **The EAG suggests that, if available for the DELTA FORCE trial, PGA should be used, in preference to IGA-CHE, to align with the outcomes reported in the ALPHA trial.**

The requested indirect comparison cannot be provided due to a lack of hyperkeratotic and non-hyperkeratotic subgroup data being presented in the ALPHA trial publication for outcomes of interest. The ALPHA trial only presents subgroup results for clinical phenotypes, including what they classify as "predominantly hyperkeratotic", for the outcome of estimated fold change in the HECSI + 1 scores. The authors conclude that the overlap of each subgroup confidence interval suggests "that there is no evidence of a differential treatment effect for any of the subgroups", including patients with "predominantly hyperkeratotic" CHE.[2] The lack of subgroup data for response outcomes from the ALPHA trial, including "clear/almost clear" on IGA-CHE or PGA or HECSI 90, makes it infeasible to perform the requested indirect comparison. In addition, for reasons outlined in the response to Question A18, it may also be problematic to assume that "hyperkeratotic" in the DELTA FORCE trial is the same as "predominantly hyperkeratotic" in the ALPHA trial.

As outlined in response to question A6, PGA was not measured in the DELTA trials or the phase 2b study reported by Worm 2022.

A18. Priority question: Please perform matching-adjusted indirect comparisons (MAICs) comparing the delgocitinib arm from the pooled DELTA 1 and DELTA 2 population to the PUVA arm of the ALPHA trial as per the advice in NICE Decision Support Unit technical support document 18 (Phillippo et al. 2016). Please conduct a fully adjusted MAIC and ensure all reported baseline characteristics are balanced between the studies and provide the following:

a) **the baseline characteristics after matching**
b) **the results for all endpoints at 12 weeks (the EAG suggests that, if available for the pooled DELTA 1 and DELTA 2 population, PGA should be used, in preference to IGA-CHE, to align with the outcomes reported in the ALPHA trial)**
c) **please comment on any factors that could not be adjusted for and the impact this lack of adjustment is expected to have on the results**
d) **please perform the above analyses (a-c) excluding disease severity as a matching covariate (i.e., include both moderate and severe patients from the pooled DELTA studies).**

An unanchored matching adjusted indirect comparison (MAIC) was performed as requested, using data for delgocitinib from DELTA 1 and DELTA 2 and for PUVA from the ALPHA trial. As per the request, we have performed two analyses: one where we include only the severe patients from DELTA 1 and DELTA 2 and one where we include both moderate and severe patients from DELTA 1 and DELTA 2. For both analyses we match on sex, race (white vs non-white), age, and HECSI score at baseline.

In addition, we performed a second set of analyses to explore the impact of including hyperkeratosis as a matching covariate. The reason this was not included in the requested analyses by default is due to the lack of comparability in how hyperkeratosis was captured in the ALPHA trial and the DELTA 1 and DELTA 2 trials. The classification of CHE by subtype is historically controversial with many different systems being used and lack of consensus in the literature.[14] As such, observed treatment responses by CHE subtype, between the ALPHA and

delgocitinib studies must be considered alongside the differences in their subtype definitions.

In the delgocitinib trials, subtype information was collected based on a classification system derived from the 2014 European Consensus on Skin Diseases (ECSD) guideline,[15] which describes three endogenous (atopic hand eczema, vesicular hand eczema, hyperkeratotic eczema) and three exogenous subtypes (irritant contact dermatitis, allergic contact dermatitis, contact urticaria/protein contact dermatitis). Investigators in the trials were asked to select a primary subtype diagnosis with the opportunity to select other secondary diagnoses, as appropriate, based on the clinical presentation. Hyperkeratotic eczema, as defined by this guideline (and the delgocitinib clinical trial protocols), is “chronic eczema with hyperkeratosis in the palms, or pulpitis, and no vesicles or pustules. No documented irritant exposure to the involved skin areas, likely to cause irritant exposure.” Vesicular hand eczema was defined as “recurrent hand eczema with vesicular eruptions. No relevant contact allergy, no documented irritant exposure likely to cause dermatitis.” These morphological subtypes are, in other words, endogenous forms of disease, which can be seen as diagnoses of exclusion when considering aetiology. A more recent update to the ECSD guidelines[14] now considers aetiological subtypes alongside morphological subtypes and mixed forms, representing a more holistic approach to the classification where multiple factors are simultaneously considered.

In the ALPHA trial protocol[16] aetiology is not considered in the CHE classification. Instead, the investigators had to classify on the basis of clinical morphology as either predominantly hyperkeratotic, predominantly vesicular, or fingertip dermatitis, with these classifications also being factored into balancing of the randomisation. Inclusion criteria in this trial were for severe CHE regardless of subtype. Given that the only basis for classification was on the defined morphologies, any associated aetiology must be assumed as potentially overlapping, since it was not possible to primarily attribute the clinical presentation of the subjects to a suspected aetiology. Since aetiology is not reflected in the ALPHA trial classification, direct comparison of results by morphologic subtype in the delgocitinib trials is therefore inappropriate and allows for limited interpretability. Due to this uncertainty, and the impact of including

this variable on the efficient sample size for the comparison, results of these additional MAICs should be considered exploratory and interpreted with caution.

The baseline characteristics for each analysis, before and after matching, are presented in the tables below along with the results for IGA-CHE response (clear/ almost clear) and absolute change in HECSI score from baseline.

First, we present the analysis as requested in A18b. In this analysis, only severe patients defined by IGA-CHE=4 are included. The efficient sample size for delgocitinib in IGA-CHE responder analysis is 84 patients and 82.1 patients in the analysis of change in HECSI (Table 22, Table 23 and Table 24) . Across both outcomes, the MAIC results indicate that delgocitinib is statistically significantly more efficacious than PUVA. When we performed the same analysis but also matched on hyperkeratosis, the efficient sample size for delgocitinib dropped to 39.4 patients in the IGA-CHE responder analysis and 38.7 patients in the analysis of HECSI (Table 25, Table 26 and Table 27). Such small sample sizes mean that these analyses are substantially underpowered and consequently the confidence intervals and p-values have increased in magnitude. However, when examining the results, these MAIC results indicate that delgocitinib is numerically better than PUVA on the outcome of absolute change in HECSI score and similar to PUVA on the outcome of proportion achieving IGA-CHE response. With such a small efficient sample size, and the limited comparability on how hyperkeratosis is captured in the different trials, the results must be interpreted with great caution.

Table 22 Baseline summary of variables that are matched on in estimation of weights: delgocitinib (DELTA 1 & 2 – severe patients) vs PUVA (ALPHA)

Variable category	Variable (baseline)	N in Alpha	Summary	Unweighted	Weighted summary
Subject counts	No. of subjects	221		N = 182	ESS = 84
Categorical (n/N [%])	Gender: Male	218	77/ 218 (35.2)	67/182 (36.8)	30/ 84 (35.3)
	Race: White	221	199/ 221 (90.0)	160/ 182 (87.9)	76/ 84 (90.0)
Numerical (mean [SD])	Age	221	45.1 (15.2)	45.5 (14.1)	45.1 (13.0)
	HECSI score	214	62.2 (42)	102 (50.3)	62.2 (26.8)

Notes: The matching is done by estimating individual weights for subjects in DELTA 1 and DELTA 2 such that weighted means of the considered baseline variables are equal to published baseline means from ALPHA trial. The efficient sample size is calculated as the squared sum of the estimated weights divided by the sum of the squared weights.

Abbreviations: ESS, efficient sample size; HECSI, Hand Eczema Severity Index; N, total number of subjects with observed baseline values of matching variables; n, number of participants; PUVA, Psoralen plus ultraviolet A; SD, standard deviation.

Table 23 MAIC on IGA-CHE 0/1: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in severe patients

IGA 0/1	Responders / subjects (crude proportions)		Estimated odds (95% CI)		Efficient sample size	Indirect comparison	
	Delgocitinib	PUVA	Delgocitinib-matched	PUVA		OR (95% CI)	p-value
Crude IC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)		[redacted]	0.027
MAIC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)	84.4	[redacted]	0.001

Abbreviations: CI, confidence interval; IC, indirect comparison; IGA 0/1, Investigator's Global Assessment for Chronic Hand Eczema score of 0 or 1; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MAIC, matching adjusted indirect comparison; OR, odds ratio; PUVA, Psoralen plus ultraviolet A; p-value, probability value.

Table 24 MAIC on HECSI change from baseline: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in severe patients

HECSI	Sample sizes			Mean (SE)			Indirect comparison	
	Delgocitinib		PUVA	Delgocitinib		PUVA	Mean difference (95% CI)	p-value
Endpoint	Original	Efficient		Not matched	Matched			
HECSI Δ from baseline	175	82.1	145	[redacted]	[redacted]	−25.8 (3.8)	[redacted]	0.041

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; MAIC, matching adjusted indirect comparison; PUVA, psoralen plus ultraviolet A; p-value, probability value; SE, standard error.

Table 25 Baseline summary of variables that are matched on in estimation of weights: delgocitinib (DELTA 1 & 2 – severe patients) vs PUVA (ALPHA) including hyperkeratosis as matching covariate

Variable category	Variable (baseline)	N in Alpha	Summary	Unweighted	Weighted summary
Subject counts	No. of subjects	221		N = 182	ESS = 39
Categorical (n/N [%])	Gender: Male	218	77/ 218 (35.3)	67/182 (36.8)	14/ 39 (35.3)
	Race: White	221	199/ 221 (90.0)	160/ 182 (87.9)	36/ 39 (90.0)
	Hyperkeratotic	221	143/ 221 (64.7)	36/ 182 (19.8)	26/ 39 (64.7)
Numerical (mean [SD])	Age	221	45.1 (15.2)	45.5 (14.1)	45.1 (13.1)
	HECSI	214	62.2 (42)	102 (50.3)	62.2 (28.3)

Notes: The matching is done by estimating individual weights for subjects in DELTA 1 and DELTA 2 such that weighted means of the considered baseline variables are equal to published baseline means from ALPHA trial. The efficient sample size is calculated as the squared sum of the estimated weights divided by the sum of the squared weights.

Abbreviations: HECSI, Hand Eczema Severity Index; N, total number of subjects with observed baseline values of matching variables; n, number of participants; ESS, Efficient sample size; SD, standard deviation.

Table 26 MAIC on IGA-CHE 0/1: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in severe patients including hyperkeratosis as matching covariate

IGA 0/1	Responders / subjects (crude proportions)		Estimated odds (95% CI)		Efficient sample size	Indirect comparison	
	Delgocitinib	PUVA	Delgocitinib-matched	PUVA		OR (95% CI)	p-value
Crude IC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)		[redacted]	0.027
MAIC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)	39.4	[redacted]	0.98

Abbreviations: CI, confidence interval; IC, indirect comparison; IGA 0/1, Investigator's Global Assessment for Chronic Hand Eczema score of 0 or 1; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MAIC, matching adjusted indirect comparison; OR, odds ratio; PUVA, psoralen plus ultraviolet A; p-value, probability value.

Table 27 MAIC on HECSI change from baseline: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in severe patients including hyperkeratosis as matching covariate

HECSI	Sample sizes			Mean (SE)			Indirect comparison	
	Delgocitinib		PUVA	Delgocitinib		PUVA	Mean difference (95% CI)	p-value
Endpoint	Original	Efficient		Not matched	Matched			
HECSI Δ from baseline	175	38.7	145	[redacted]	[redacted]	−25.8 (3.8)	[redacted]	0.22

Abbreviations: CI, confidence interval; HECSI, Hand eczema severity index; PUVA, psoralen plus ultraviolet A; p-value, probability value; SE, standard error.

Next, we present the analysis as requested in A18d. In this analysis, moderate and severe patients according to IGA-CHE from DELTA 1 and DELTA 2 are included. The efficient sample size for delgocitinib in this analysis is 609.4 patients in the IGA-CHE responder analysis and 577.5 patients in the analysis of HECSI (Table 28, Table 29 and Table 30). Across both outcomes, the MAIC results indicate that delgocitinib is statistically significantly more efficacious than PUVA. When we performed the same analysis but also matched on hyperkeratosis, the efficient sample size for delgocitinib dropped to 292 patients in the IGA-CHE responder analysis and 270 patients in the analysis of HECSI outcomes (Table 31, Table 32 and Table 33). These MAIC results indicate that delgocitinib is significantly better than PUVA for the outcome of absolute change in HECSI score and numerically better than PUVA for the outcome of proportion achieving IGA-CHE response. As the direct comparison of HK patients across the trials are inappropriate, these results should be interpreted with caution.

Table 28 Baseline summary of variables that are matched on in estimation of weights: delgocitinib (DELTA 1 & 2 – moderate and severe patients) vs PUVA (ALPHA)

Variable category	Variable (baseline)	N	Summary	Unweighted	Weighted summary
Subject counts	No. of subjects	221		N = 638	ESS = 609
Categorical (n/N [%])	Gender: Male	218	77/ 218 (35.2)	233/ 638 (36.5)	215/ 609 (35.3)
	Race: White	221	199/ 221 (90.0)	577/ 638 (90.4)	549/ 609 (90.0)
Numerical (mean [SD])	Age	221	45.1 (15.2)	44.8 (14.5)	45.1 (14.4)
	HECSI	214	62.2 (42)	71.1 (43.0)	62.2 (36.3)

Notes: The matching is done by estimating individual weights for subjects in DELTA 1 and DELTA 2 such that weighted means of the considered baseline variables are equal to published baseline means from ALPHA trial. The efficient sample size is calculated as the squared sum of the estimated weights divided by the sum of the squared weights.

Abbreviations: ESS, efficient sample size; HECSI, Hand Eczema Severity Index; N, total number of subjects with observed baseline values of matching variables; n, number of participants; PUVA, Psoralen and Ultraviolet A; SD, standard deviation.

Table 29 MAIC on IGA-CHE 0/1: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in moderate and severe patients

IGA 0/1	Responders / subjects (crude proportions)		Estimated odds (95% CI)		Efficient sample size	Indirect comparison	
	Delgocitinib	PUVA	Delgocitinib - matched	PUVA		OR (95% CI)	p-value
Crude IC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)		[redacted]	<0.001
MAIC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)	609.4	[redacted]	<0.001

Abbreviations: CI, confidence interval; IC, indirect comparison; IGA 0/1, Investigator's Global Assessment for Chronic Hand Eczema score of 0 or 1; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MAIC, matching-adjusted indirect comparison; OR, odds ratio; PUVA, Psoralen plus ultraviolet A; p-value, probability value.

Table 30 MAIC on HECSI change from baseline: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in moderate and severe patients

HECSI	Sample sizes			Mean (SE)			Indirect comparison	
	Delgocitinib		PUVA	Delgocitinib		PUVA	Mean difference (95% CI)	p-value
Endpoint	Original	Efficient		Not matched	Matched			
HECSI Δ from baseline	606	577.5	145	[redacted]	[redacted]	−25.8 (3.8)	[redacted]	<0.001

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; MAIC, matching-adjusted indirect comparison; PUVA, Psoralen plus ultraviolet A; p-value, probability value; SE, standard error.

Table 31 Baseline summary of variables that are matched on in estimation of weights: delgocitinib (DELTA 1 & 2 – moderate and severe patients) vs PUVA (ALPHA) including hyperkeratosis as matching covariate

Variable category	Variable (baseline)	N	Summary	Unweighted	Weighted summary
Subject counts	No. of subjects	221		N = 638	ESS = 292

Variable category	Variable (baseline)	N	Summary	Unweighted	Weighted summary
Categorical (n/N [%])	Gender: Male	218	77/ 218 (35.3)	233/ 638 (36.5)	103/ 292 (35.3)
	Race: White	221	199/ 221 (90.0)	577/ 638 (90.4)	263/ 292 (90.0)
	Hyperkeratotic	221	143/ 221 (64.7)	143/ 638 (22.4)	189/ 292 (64.7)
Numerical (mean [SD])	Age	221	45.1 (15.2)	44.8 (14.5)	45.1 (14.4)
	HECSI	214	62.2 (42)	71.1 (43.0)	62.2 (35.1)

Notes: The matching is done by estimating individual weights for subjects in DELTA 1 and DELTA 2 such that weighted means of the considered baseline variables are equal to published baseline means from ALPHA trial. The efficient sample size is calculated as the squared sum of the estimated weights divided by the sum of the squared weights.

Abbreviations: ESS, Efficient sample size; HECSI, Hand Eczema Severity Index N, total number of subjects with observed baseline values of matching variables; n, number of subjects; PUVA, Psoralen plus ultraviolet A; SD standard deviation.

Table 32 MAIC on IGA-CHE 0/1: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in moderate and severe patients including hyperkeratosis as a matching covariate

IGA 0/1	Responders / subjects (crude proportions)		Estimated odds (95% CI)		Efficient sample size	Indirect comparison	
	Delgocitinib	PUVA	Delgocitinib -matched	PUVA		OR (95% CI)	p-value
Crude IC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)		[redacted]	<0.001
MAIC	[redacted]	35/ 221 (15.8%)	[redacted]	0.19 (0.13, 0.27)	292.0	[redacted]	0.20

Abbreviations: CI, confidence interval; IC, indirect comparison; IGA 0/1, Investigator's Global Assessment for Chronic Hand Eczema score of 0 or 1; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MAIC, matching-adjusted indirect comparison; OR, odds ratio; PUVA, Psoralen plus ultraviolet A; p-value, probability value.

Table 33 MAIC on HECSI change from baseline: delgocitinib (DELTA 1 & 2) vs PUVA (ALPHA) at week 12 in moderate and severe patients including hyperkeratosis as a matching covariate

HECSI	Sample sizes			Mean (SE)			Indirect comparison	
	Delgocitinib		PUVA	Delgocitinib		PUVA	Mean difference (95% CI)	p-value
Endpoint	Original	Efficient		Not matched	Matched			
HECSI Δ from baseline	606	270.0	145	[redacted]	[redacted]	−25.8 (3.8)	[redacted]	0.011

Abbreviations: CI, confidence interval; HECSI, Hand Eczema Severity Index; MAIC, matching-adjusted indirect comparison; PUVA, Psoralen plus ultraviolet A; p-value, probability value; SE, standard error.

Adverse events

A19. Please provide a breakdown by grade of adverse events (AEs) for each AE in each trial arm in the DELTA FORCE (the number and proportion of patients

experiencing each grade of each AE) and describe how AEs were categorised as serious or not.

The breakdown by grade for each AE in each trial arm within DELTA FORCE can be seen below (Table 34, Table 35 and Table 36). We have only presented the breakdown for the AEs reported in Table 49 of the submission, which represented the most frequent TEAEs (≥ 2% in any treatment group).

An adverse event was categorised as serious[17] if it:

- Resulted in death
- Was life-threatening – the patient was at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Required in-patient hospitalisation or prolongation of existing hospitalisation.
- Resulted in persistent or significant disability or incapacity.
- Was a congenital anomaly of birth defect
- Was a medically important condition. Events that were not immediately life-threatening or resulted in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.
- Was a malignancy including any skin malignancies

Table 34 Summary of adverse events by severity for delgocitinib 20 mg/g vs. alitretinoin: Mild

Events: Grade Mild	Delgocitinib 20mg/g N = 253				Alitretinoin N = 247			
	n	%	E	R	n	%	E	R
Infections and infestations								
Nasopharyngitis	21	8.3	25	20.7	27	10.9	35	33.7
Upper respiratory tract infection	4	1.6	6	5	7	2.8	7	6.7
COVID-19	3	1.2	3	2.5	7	2.8	7	6.7
Urinary tract infection	0				6	2.4	7	6.7
Skin and subcutaneous tissue disorders								
Dry skin	3	1.2	3	2.5	7	2.8	7	6.7
Eczema	2	0.8	2	1.7	5	2	5	4.8

Events: Grade Mild	Delgocitinib 20mg/g N = 253				Alitretinoin N = 247			
	n	%	E	R	n	%	E	R
Erythema	1	0.4	1	0.8	6	2.4	7	6.7
Hand dermatitis	1	0.4	1	0.8	1	0.4	1	1
Dermatitis atopic	0				2	0.8	2	1.9
Investigations								
Blood triglycerides increased	1	0.4	1	0.8	5	2	6	5.8
Musculoskeletal and connective tissue disorders								
Back pain	1	0.4	1	0.8	3	1.2	3	2.9
Gastrointestinal disorders								
Nausea	1	0.4	1	0.8	9	3.6	10	9.6
Diarrhoea	0				4	1.6	4	3.8
Lip dry	0				8	3.2	8	7.7
Nervous system disorders								
Headache	5	2	10	8.3	52	21.1	72	69.2
Migraine	1	0.4	1	0.8	2	0.8	3	2.9
Dizziness	0				3	1.2	3	2.9
Respiratory, thoracic and mediastinal disorders								
Epistaxis	1	0.4	1	0.8	3	1.2	3	2.9
Vascular disorders								
Flushing	0				4	1.6	5	4.8
Eye disorders								
Dry eye	0				5	2	5	4.8
Metabolism and nutrition disorders								
Hypercholesterolaemia	0				8	3.2	9	8.7
Hypertriglyceridaemia	0				4	1.6	5	4.8

Abbreviations: E, number of events; N, total number of participants; n, number of participants with events; R, rates = (E/PYO)*100; % = percentage of participants.

Table 35 Summary of adverse events by severity for delgocitinib 20 mg/g vs. alitretinoin: Moderate

Events: Grade Moderate	Delgocitinib 20mg/g N = 253				Alitretinoin N = 247			
	n	%	E	R	n	%	E	R
Infections and infestations								
Nasopharyngitis	12	4.7	13	10.7	9	3.6	11	10.6
COVID-19	2	0.8	2	1.7	2	0.8	2	1.9
Upper respiratory tract infection	2	0.8	2	1.7	1	0.4	1	1
Urinary tract infection	1	0.4	1	0.8	4	1.6	4	3.8
Nervous system disorders								
Headache	5	2	9	7.4	31	12.6	36	34.6
Dizziness	1	0.4	1	0.8	3	1.2	3	2.9
Migraine	1	0.4	1	0.8	4	1.6	4	3.8
Musculoskeletal and connective tissue disorders								
Back pain	1	0.4	1	0.8	3	1.2	3	2.9

Skin and subcutaneous tissue disorders								
Dermatitis atopic	1	0.4	1	0.8	3	1.2	3	2.9
Hand dermatitis	1	0.4	2	1.7	3	1.2	3	2.9
Dry skin	0				2	0.8	2	1.9
Eczema	0				1	0.4	1	1
Erythema	0				3	1.2	3	2.9
Investigations								
Blood triglycerides increased	1	0.4	1	0.8	2	0.8	2	1.9
Metabolism and nutrition disorders								
Hypertriglyceridemia	3	1.2	3	2.5	2	0.8	2	1.9
Hypercholesterolaemia	0				1	0.4	1	1
Gastrointestinal disorders								
Diarrhoea	0				1	0.4	1	1
Nausea	0				4	1.6	4	3.8
Respiratory, thoracic and mediastinal disorders								
Epistaxis	0				2	0.8	3	2.9
Eye disorders								
Dry eye	0				2	0.8	2	1.9
Vascular disorders								
Flushing	0				1	0.4	1	1

Abbreviations: E, number of events; N, total number of participants; n, number of participants with events; R, rates = (E/PYO)*100; % = percentage of participants.

Table 36 Summary of adverse events by severity for delgocitinib 20 mg/g vs. alitretinoin: Severe

Events: Grade Severe	Delgocitinib 20mg/g N = 253				Alitretinoin N = 247			
	n	%	E	R	n	%	E	R
Skin and subcutaneous tissue disorders								
Hand dermatitis	0				1	0.4	1	1
Gastrointestinal disorders								
Nausea	0				1	0.4	1	1
Nervous system disorders								
Headache	0				5	2	6	5.8

Abbreviations: E, number of events; N, total number of participants; n, number of participants with events; R, rates = (E/PYO)*100; % = percentage of participants.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model ("ModelSettings" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario.

Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

As a note on our responses to the questions in section B, we have performed each scenario requested within the submitted model in order to illustrate the individual impact of the change on the base case results. This was considered reasonable given that none of the errors identified by the EAG had a substantial impact on the submitted results. With our final set of responses, we will provide a full executable, updated model which corrects for any errors identified and allows for the EAG to further explore the individual scenarios. At the end of this document, we also present updated results of the base case, sensitivity and submitted scenario analyses.

Baseline characteristics

B1. In Table 53 of the CS, baseline characteristics are presented by subgroups but are not used in the model. For both populations in the model, the mean age is 44.1 years and the percentage male is 35.6%. The EAG considers that the company's description in the CS to use subgroup baseline characteristics is appropriate. Please clarify if the company's intention was to use the values presented in Table 53 of the CS and amend the model as necessary.

Thank you for identifying this error in the submitted model. The intention was to use the values presented in Table 53, i.e. the mean age and percentage male by subgroup. We have amended the model. On its own, this correction reduces the ICER of delgocitinib versus alitretinoin in patients with severe CHE to £8,219 from £8,221 and does not change the results versus PUVA in patients with moderate or severe CHE, i.e. delgocitinib is still dominant.

We have corrected this in the re-submitted model accompanying these responses.

B2. Please clarify the assumption that 15% of females in the model are of childbearing potential, given that 64.4% of the model population is female and the mean age is 44.1 years?

To clarify, the assumption is not that 15% of females in the model are of childbearing potential. Rather the assumption is that 15% of the population in the model are females of childbearing potential. This was borrowed from NICE TA177 (2012)[18] on alitretinoin; however, the original technology appraisal does not explicitly reference or provide a calculation supporting this assumption.

To derive an alternative estimate, the following considerations were made:

- Definition of childbearing potential: The UK does not have a universally established definition of "women of childbearing potential." However, various sources provide guidance. For example, the Office for National Statistics (ONS) defines the childbearing period for cohort fertility analyses as ages 15–45.
- Baseline estimate based on UK population data: Using ONS population estimates, the proportion of women in the UK aged 15–45 relative to the total female population is:

  P(childbearing potential)=Women aged 15-45 in the UK/ Total female population in the UK
  =12,244,541/ 31,018,735
  =39.5%

- Application to the model population: The population in the DELTA trials population has a mean age of 44.1 years and a normal distribution assumption was considered.
- Using a normal distribution with mean (μ) = 44.1 years and standard deviation (σ) = 15 years (based on ONS UK 2021 census data), an estimated 49.8% of females in the model population are expected to fall within the 15–45 age range.
- Applied in the model, this means that 49.8% of the female population in the model, which makes up 64.4% of the overall population in the base case submitted model, are of childbearing potential. The revised proportion is

therefore 32.1% of the entire model population are females of childbearing potential.

To test the impact of this change on the model results, we amended the variable "proportion of childbearing women" on "c_Treatment_BE" cell G48 to 49.8% * (1-pop_male). The impact on the base case results presented in the submission is to reduce the ICER for delgocitinib versus alitretinoin in the severe CHE population to £7,922 from £8,221.

It is important to highlight that increasing the proportion of women classified as being of childbearing age would be advantageous for delgocitinib compared to alitretinoin, as the latter would be associated with increased monitoring costs.

Treatment comparisons

B3. Priority question. Using only the DELTA FORCE trial please conduct a direct treatment comparison between delgocitinib and alitretinoin for severe patients. Please use only DELTA FORCE to inform:

- **initial treatment response**
- **probability of relapse**
- **re-treatment response**
- **on-treatment discontinuation**
- **re-treatment discontinuation**
- **utilities**
- **consumption**

To conduct this scenario analysis in the originally submitted model, we applied the following changes. All values listed in Table 37 are derived directly from DELTA FORCE. Values in the base case that were already based on DELTA FORCE were unchanged in the scenario.

Table 37 Treatment response, relapse, and discontinuation probabilities for delgocitinib and alitretinoin

Parameter	Delgocitinib	Alitretinoin	Variable reference
Probability of IGA-CHE 0/1 at week 12	27.2%	16.6%	e_Resp!H32:H33

Distribution across non full response states at week 12	[redacted]	[redacted]	e_Resp!H44:J45
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)	e_Resp!J56:K57
Per-cycle probability of relapse (to mild CHE)	[redacted]% (as per base case)	[redacted]% (as per base case)	NA
Per-cycle probability of full response with re-treatment	[redacted]% (based on 8-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)	e_Resp!H66:H67
Per-cycle probability of permanent discontinuation from continued initial treatment and retreatment	[redacted]% (as per base case)	[redacted]% (as per base case)	NA
Proportion of patients opting not to re-initiate initial treatment following relapse	[redacted]%	[redacted]%	e_discontinuation!F27:F28
Utilities	Baseline: 0.674 FR: [redacted] PR: [redacted] LR: [redacted] InR: [redacted]	Same as delgo due to the structural assumption that all active treatments are associated with the same utilities.	Utilities!E19 Utilities!E24:E27
Delgocitinib dose (g/week)	FR: [redacted]g PR: [redacted]g LR: [redacted]g InR: [redacted]g	NA	TreatmentSettings!F16:F19

Abbreviations: FR, full response; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

The incremental costs and benefits between delgocitinib and alitretinoin in this scenario are increased from £312 to £1,487 and from 0.038 QALYs to 0.093 QALYs, resulting in an ICER of £16,040 (compared to £8,221 in the submitted base case).

In a further scenario where we substitute the week 12 results from the treatment policy estimand instead of the composite estimand ([redacted]% for delgocitinib and [redacted]% for alitretinoin) but leave all other values in the scenario as outlined in the table above, the ICER for delgocitinib versus alitretinoin in severe CHE increases further to £16,744. This is to illustrate the impact of the testing strategy highlighted in response to question A2.

Though it may be helpful to look at this scenario based solely on the results of the head-to-head DELTA FORCE trial, the base case analysis presented in the original submission makes the best use of all evidence available for delgocitinib, alitretinoin and PUVA.

We have programmed this scenario as described in Table 37 into the updated economic model submitted as part of our response to clarification questions (described at the end of this document). The impact on incremental costs and benefits between delgocitinib and alitretinoin in this scenario are increased from £336 to £1,474 and from 0.039 QALYs to 0.089 QALYs, resulting in an ICER of £16,639 (compared to £8,526 in the revised base case). Where the treatment policy estimand is used instead of the composite estimand, the ICER for delgocitinib versus alitretinoin in severe CHE increases to £16,680.

B4. Priority question. Please conduct a scenario analysis comparing delgocitinib to alitretinoin in severe patients using DELTA FORCE to inform the initial treatment effects. The treatment effects from other trials can be used to inform treatment-related outcomes other than initial treatment effects; i.e. rate of relapse, re-treatment, etc., as in the company base case.

To conduct this scenario analysis in the originally submitted model, we applied the following changes on the e_Resp tab of the economic model, as presented in Table 38. All values listed are derived directly from DELTA FORCE.

Table 38 Probability and distribution of treatment response at week 12

Parameter	Delgocitinib	Alitretinoin
Probability of IGA-CHE 0/1 at week 12	[redacted]%	[redacted]%
Distribution across non full response states at week 12	PR: [redacted]% LR: [redacted]% InR: [redacted]%	PR: [redacted]% LR: [redacted]% InR: [redacted]%
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; PR, partial responder; LR, late responder; InR, incomplete responder; wk, week.

The incremental costs and benefits of delgocitinib over alitretinoin in this scenario are increased from £312 to £492 and from 0.038 QALYs to 0.044 QALYs, resulting in an ICER of £11,106 (compared to £8,221 in the submitted base case).

In a further scenario where we substitute the week 12 results from the treatment policy estimand instead of the composite estimand ([redacted]% for delgocitinib and [redacted]% for alitretinoin), but leave all other values in the scenario unchanged, the

ICER for delgocitinib versus alitretinoin in severe CHE increases to £12,725. This is to illustrate the impact of the testing strategy highlighted in response to question A2.

As part of our response to clarification questions, we have built user selections into the updated model (described at the end of this document) to allow the EAG to explore this scenario as described in Table 38. The impact on incremental costs and benefits between delgocitinib and alitretinoin in this scenario are increased from £336 to £494 and from 0.039 QALYs to 0.046 QALYs, resulting in an ICER of £10,720 (compared to £8,526 in the revised base case). Where the treatment policy estimand is used instead of the composite estimand, the ICER for delgocitinib versus alitretinoin in severe CHE increases to £12,283.

B5. Priority question. Using the initial treatment outcomes of the DELTA FORCE trial and the relative efficacy of delgocitinib in severe and moderate patients demonstrated in clarification question A15, please conduct a scenario analysis comparing delgocitinib to alitretinoin in moderate patients.

We understand that the EAG wish to see the results of a scenario in which delgocitinib is compared with alitretinoin in moderate patients, but we do not think it is strictly appropriate to run this scenario by simply adjusting the settings outlined in Question B4 for the severe CHE population using the data presented in our response to Question A15. This is because of the structural differences regarding the handling of patients who achieve an IGA-CHE 3 in the model. For patients with severe CHE at baseline, an IGA-CHE 3 represents a “low response” in the model. For patients with moderate CHE at baseline, an IGA-CHE 3 represents an “insufficient response” in the model. To ensure that these are accurately accounted for, this scenario must be run using the moderate CHE settings. The model provides the flexibility to include alitretinoin in a moderate CHE population; therefore, we have used this as our starting point for this scenario. The user can do this by setting the model population to “Moderate” and selecting for the inclusion of alitretinoin under “comparators” on the Model Settings page.

With the model set to the moderate population, we set the probabilities of response equal to the probabilities from DELTA FORCE (27.2% and 16.6% for delgocitinib and alitretinoin, respectively) adjusted by the odds ratio presented in our response to Question A15 ([redacted], pooled DELTA 1 and DELTA 2 IGA-CHE 0/1 data

at week 12). This produces probabilities of response of [redacted]% and [redacted]% for delgocitinib and alitretinoin, respectively. The distribution of non-responders across partial and insufficient response (the only two non-responder states relevant to moderate patients) from the base case was applied. The per-cycle probability of achieving full response from partial response from DELTA FORCE (11.6%, presented in settings outlined for Question B4) was applied. All other base case settings applicable to the moderate CHE population were unchanged.

The results of this scenario in which alitretinoin is used to treat patients with moderate CHE, simulated using adjusted results from DELTA FORCE, show that delgocitinib is expected to generate 0.033 more QALYs than alitretinoin at an incremental cost of £422. The ICER for delgocitinib compared to alitretinoin is £12,721 in this scenario.

For the EAG's reference, we have also run the scenario where alitretinoin is included in the moderate CHE base case using the results of the NMA. As outlined in our response to Question A15, we believe that this is a relevant scenario to consider if alitretinoin is considered a relevant comparator to delgocitinib and PUVA in moderate CHE. Under this setting, with no other changes, delgocitinib is £310 more costly and generate 0.035 more QALYs for an ICER versus alitretinoin of £8,754.

B6. Priority question. As discussed in clarification question A16, the EAG's clinical experts have suggested that the choice of treatments for CHE may depend on patient aetiology, as such please:

- **conduct a scenario analysis comparing delgocitinib to alitretinoin, informing the treatment effects (initial response, probability of relapse, response to retreatment and discontinuation) using the hyperkeratotic patients from DELTA FORCE as requested in clarification question A16.**

- **conduct a scenario analysis comparing delgocitinib to alitretinoin, informing the treatment effects (initial response, probability of relapse, response to retreatment and discontinuation) using the non-hyperkeratotic patients from DELTA FORCE as requested in clarification question A16.**

- **conduct a scenario analysis comparing delgocitinib to PUVA, informing the delgocitinib treatment effects (initial response, probability of relapse, response to retreatment and discontinuation) using the non-hyperkeratotic patient treatment effects as requested in clarification question A17**.

Scenario analysis comparing delgocitinib to alitretinoin using the hyperkeratotic patients from DELTA FORCE as requested in clarification question A16

To conduct this scenario analysis in the originally submitted model, we applied the following changes on the e_Resp tab of the economic model. All values listed in Table 39 are derived directly from DELTA FORCE and wherever possible, from the hyperkeratotic population specifically. Where data from DELTA FORCE were not available or could not be used, subgroup data from DELTA 3 was considered. Where no data were available, we provided a rationale for why the base case values were considered plausible.

Table 39 Parameters for patients with severe hyperkeratotic CHE from DELTA FORCE

Parameter	Delgocitinib	Alitretinoin	Notes
Probability of IGA-CHE 0/1 at week 12	[redacted]%	[redacted]%	DELTA FORCE; Hyperkeratotic subgroup specific
Distribution across non full response states at week 12	PR: [redacted]% LR: [redacted]% InR: [redacted]%	PR: [redacted]% LR: [redacted]% InR: [redacted]%	DELTA FORCE; Hyperkeratotic subgroup specific
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	DELTA FORCE; Hyperkeratotic subgroup specific
Discontinuation	[redacted]% (based on 12-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)	DELTA FORCE; Hyperkeratotic subgroup specific
Loss of IGA-CHE 0/1 response	[redacted]% (calculated by applying risk ratio of [redacted] to base case risk)	[redacted]% (based on median time to relapse of [redacted] weeks)	See paragraph below
Response to re-treatment	Base case	Base case	See paragraph below

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

DELTA FORCE subgroup data for hyperkeratotic patients were available to inform the following parameters for delgocitinib and alitretinoin: initial response (at week 12 and up to week 24) and discontinuation during initial treatment.

For the outcome of loss of IGA-CHE 0/1 response, there were insufficient subgroup data to produce results for delgocitinib. The limited data available for this outcome for alitretinoin suggested that the median time to relapse (i.e. IGA-CHE ≥ 2) was shorter in the hyperkeratotic subgroup than in the overall population of DELTA FORCE ([redacted] weeks versus [redacted] weeks). The corresponding per-cycle probability of relapse in the hyperkeratotic subgroup was [redacted] times higher than in the overall population ([redacted]% vs [redacted]%). This risk ratio was applied to the base case probability of relapse for delgocitinib to approximate a risk of relapse in the hyperkeratotic subgroup.

For the outcome of response to re-initiated treatment, there was insufficient subgroup data to produce results for delgocitinib or alitretinoin. This was due to very small patient numbers and the brevity of the observation period between relapse and the end of the trial at Week 24. Instead, rates of response to re-treatment from the base case were used for both delgocitinib and alitretinoin. This is considered a reasonable assumption given that the initial morphology of CHE does not reliably reflect the aetiological cause and can change over time.[14, 19] Even though a patient might present initially with a particular clinical subtype, such as hyperkeratosis, it does not mean that this will be the predominant clinical subtype at the point of relapse. In addition, the re-initiation of delgocitinib at the point of a mild relapse (e.g. IGA-CHE 2) may mean that even if hyperkeratosis is present, a patient may respond better to re-treatment than initial treatment when their disease was severe due to earlier intervention. The data from DELTA 3, which is used in the base case, is assumed to be applicable to this scenario.

Original submitted model

In this scenario, delgocitinib is in the southwest quadrant of the cost-effectiveness plane relative to alitretinoin. Alitretinoin provides 0.024 more QALYs than delgocitinib at an incremental cost of £223, with an ICER versus delgocitinib of £9,226. In a comparison with PUVA, assuming no changes to its base case values, delgocitinib is still dominant, producing 0.015 more QALYs at a savings of £1,216.

We tested the following additional scenarios where we have assumed base case values.

- Decreasing the probability of response to re-treatment with delgocitinib to an arbitrary 10% (from 20.2% in the base case) increases the ICER for alitretinoin versus delgocitinib to £9,863.
- Increasing the probability of discontinuation from re-initiated delgocitinib to an arbitrary 20% (from [redacted]% in this scenario) increases the ICER of alitretinoin versus delgocitinib to £12,068.

Updated model

We have programmed this scenario as described in Table 39 into the updated economic model submitted as part of our response to clarification questions (described at the end of this document). Delgocitinib is in the southwest quadrant of the cost-effectiveness plane relative to alitretinoin. Alitretinoin provides 0.026 more QALYs than delgocitinib at an incremental cost of £217, with an ICER versus delgocitinib of £8,507. In a comparison with PUVA, assuming no changes to its base case values, delgocitinib is still dominant, producing 0.017 more QALYs at a savings of £1,170.

In addition to the settings described in Table 39, we have assessed the additional impact of delgocitinib consumption in the hyperkeratotic patient subgroup (see response to Question B34). For this, we have assumed that the hyperkeratotic subgroup consumption data applies only during the initial period and that the consumption during the re-treatment period is aligned with the base case settings. This aligns with the arguments provided above about the morphology of CHE not reliably reflecting the aetiological cause, that it can change over time and that the predominant morphological subtype at relapse may be different from the predominant morphological subtype at baseline.

Under this scenario, delgocitinib generates 0.026 fewer QALYs at an incremental cost of £1,148 compared to alitretinoin. Compared to PUVA, delgocitinib generates 0.017 more QALYs at an additional cost of £195, giving it an ICER of £11,193 per QALY gained.

Overall, the model shows that delgocitinib is expected to generate fewer QALYs at a lower cost compared to alitretinoin in a population with severe hyperkeratotic CHE and where delgocitinib consumption is assumed to be similar to patients without

hyperkeratosis. If patients with hyperkeratotic CHE use more delgocitinib during their initial treatment, then the total costs of delgocitinib treatment may exceed the total costs of alitretinoin treatment. The benefits in the model are driven mainly by the proportion of patients achieving IGA-CHE 0/1 within 12 and 24 weeks of starting treatment, which are endpoints that hyperkeratotic patients treated with alitretinoin achieve more often than hyperkeratotic patients treated with delgocitinib. However, as outlined in response to question A16, there are a number of clinical and patient-reported outcomes where the differences between delgocitinib and alitretinoin at week 12 and week 24 are not statistically significant (see Table 20 and Table 21) in this subgroup. Though these are not incorporated directly into the economic model, they are important considerations in clinical practice and point to meaningful benefits that hyperkeratotic patients report even as they do not achieve “clear or almost clear” status. In addition, the fact that the primary morphology of hyperkeratosis, which primarily occurs on the palms of the hands, may co-exist with other clinical signs, such as fissures and lichenification on the dorsal aspect of the hand; therefore, the full clinical picture needs to be considered when treating patients with CHE. Finally, the model accounts for some differences in the safety profile between alitretinoin and delgocitinib by reflecting the higher incidence of headaches and including the costs of pregnancy prevention and lipid monitoring; however, these may not capture the full impact on patient HRQoL or healthcare resource use considering that alitretinoin is a powerful human teratogen which induces a high frequency of severe and life-threatening birth defects.

As outlined in section 1.3.3.5 and section 1.4 of the original submission, there are a number of reasons why alitretinoin may not be an acceptable treatment for some patients, including those with a hyperkeratotic clinical presentation. For these patients, delgocitinib offers a more convenient and cost-effective treatment than PUVA, the only other recommended second-line therapy.

Scenario analysis comparing delgocitinib to alitretinoin using the non-hyperkeratotic patient treatment effects as requested in clarification question A16

To conduct this scenario analysis, we applied the following changes on the e_Resp and e_discontinuation tabs of the economic model updated in response to the EAG

clarification questions (described at the end of this document). As this question was asked after we had submitted the updated economic model, we have not gone back to implement the scenario in the originally submitted model as we have for other questions.

All values listed in Table 40 are derived directly from DELTA FORCE and wherever possible, from the non-hyperkeratotic population specifically. Where data from DELTA FORCE were not available or could not be used, subgroup data from DELTA 3 was considered. Where no data were available, we provided a rationale for why the base case values were considered plausible.

Table 40 Parameters for patients with severe non-hyperkeratotic CHE from DELTA FORCE

Parameter	Delgocitinib	Alitretinoin	Notes
Probability of IGA-CHE 0/1 at week 12	[redacted]%	[redacted]%	DELTA FORCE; Non-hyperkeratotic subgroup specific
Distribution across non full response states at week 12	PR: [redacted]% LR: [redacted]% InR: [redacted]%	PR: [redacted]% LR: [redacted]% InR: [redacted]%	DELTA FORCE; Non-hyperkeratotic subgroup specific
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	DELTA FORCE; Non-hyperkeratotic subgroup specific
Discontinuation	[redacted]% (based on 12-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)	DELTA FORCE; Non-hyperkeratotic subgroup specific
Loss of IGA-CHE 0/1 response	Base case	Base case	See paragraph below
Response to re-treatment	Base case	Base case	See paragraph below
Delgocitinib dose (g/week)	FR: [redacted] g PR: [redacted] g LR: [redacted] g InR: [redacted] g	NA	DELTA FORCE; Non-hyperkeratotic subgroup specific

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

DELTA FORCE subgroup data for non-hyperkeratotic patients were available to inform the following parameters for delgocitinib and alitretinoin: initial response (at week 12 and up to week 24) and discontinuation during initial treatment.

For the outcome of loss of IGA-CHE 0/1 response, data from the base case were used. Only 1.8% of the delgocitinib patients and 25.6% of the alitretinoin patients contributing to this data point had hyperkeratotic CHE at baseline; therefore, this was considered a reasonable assumption. For the same reasons as outlined in the

section above, the rates of response to re-treatment from the base case were used for both delgocitinib and alitretinoin. Similarly, the non-hyperkeratotic subgroup consumption data (see response to Question B34), is assumed to apply only during the initial period and that the consumption during the re-treatment period is aligned with the base case settings.

The updated model shows that among patients with severe non-hyperkeratotic CHE, delgocitinib is cost effective compared to alitretinoin, generating 0.054 more QALYs at an incremental cost of £577 for an ICER of £10,605 (compared to £8,526 in the base case). Among severe non-hyperkeratotic CHE patients, delgocitinib dominates PUVA, costing £267 less and generating 0.061 more QALYs.

Scenario analysis comparing delgocitinib to PUVA using the non-hyperkeratotic patient treatment effects as requested in clarification question A17

As outlined in the response to question A17, the requested indirect comparison cannot be provided due to a lack of hyperkeratotic and non-hyperkeratotic subgroup data being presented in the ALPHA trial publication for response outcomes, including "clear/almost clear" on IGA-CHE or PGA or HECSI 90.

B7. Priority question. Please conduct 2 scenario analyses comparing delgocitinib to PUVA using the initial treatment effects calculated using the results of the MAICs conducted as requested in clarification question A18.

We have applied the MAIC results presented in our response to Question A18 in the originally submitted economic model to compare delgocitinib and PUVA in the moderate CHE and severe CHE populations. For this, we have set the PUVA risk of response to 15.8% across all scenarios and derived the risk of delgocitinib by applying the odds ratio from each individual MAIC. Results for moderate CHE and severe CHE populations are calculated by changing the population on the ModelSettings tab. Results for the scenarios using each MAIC are presented in Table 41.

Across all scenarios, delgocitinib remains the dominant strategy, generating more QALYs at a lower cost than PUVA. These results indicate that delgocitinib is more cost effective than PUVA in a population with a similar baseline severity, based on

either IGA-CHE and HECSI or based on HECSI alone, and a similar case mix of patients with and without hyperkeratosis, acknowledging the limitations of the morphological classification as outlined in response to question A18.

Table 41 Matching-adjusted indirect comparison outcomes: delgocitinib vs. PUVA – originally submitted model

Scenario	Matched on		PUVA risk	MAIC OR (95% CI) Delgocitinib vs PUVA	Model severity	Incremental		ICER
	Disease severity	Hyper-keratosis				Cost	QALY	
MAIC 1a	Severe only	N	15.8%	[redacted]	Moderate	-£438	0.048	Delgocitinib dominates
					Severe	-£483	0.053	Delgocitinib dominates
MAIC 1b	Severe only	Y	15.8%	[redacted]	Moderate	-£763	0.033	Delgocitinib dominates
					Severe	-£754	0.032	Delgocitinib dominates
MAIC 2a	Moderate and severe	N	15.8%	[redacted]	Moderate	-£490	0.046	Delgocitinib dominates
					Severe	-£529	0.050	Delgocitinib dominates
MAIC 2b	Moderate and severe	Y	15.8%	[redacted]	Moderate	-£673	0.037	Delgocitinib dominates
					Severe	-£692	0.039	Delgocitinib dominates

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; N, no; OR, odds ratio; PUVA, Psoralen plus Ultraviolet A; QALY, quality-adjusted life year; Y, yes.

We have programmed this scenario into the updated economic model submitted as part of our response to clarification questions (described at the end of this document). Table 42 presents the results of the scenarios as implemented in the updated economic model.

Table 42 Matching-adjusted indirect comparison outcomes: delgocitinib vs. PUVA – Updated model

Scenario	Matched on		PUVA risk	MAIC OR (95% CI) Delgocitinib vs PUVA	Model severity	Incremental		ICER
	Disease severity	Hyper-keratosis				Cost	QALY	
MAIC 1a	Severe only	N	15.8%	[redacted]	Moderate	-£454	0.052	Delgocitinib dominates
					Severe	-£443	0.054	Delgocitinib dominates
MAIC 1b	Severe only	Y	15.8%	[redacted]	Moderate	-£769	0.035	Delgocitinib dominates
					Severe	-£722	0.035	Delgocitinib dominates
MAIC 2a	Moderate and severe	N	15.8%	[redacted]	Moderate	-£505	0.050	Delgocitinib dominates
					Severe	-£489	0.051	Delgocitinib dominates
MAIC 2b	Moderate and severe	Y	15.8%	[redacted]	Moderate	-£688	0.040	Delgocitinib dominates
					Severe	-£651	0.040	Delgocitinib dominates

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; N, no; OR, odds ratio; PUVA, Psoralen plus Ultraviolet A; QALY, quality-adjusted life year; Y, yes.

B8. The EAG considers the company's rationale for preferring the fixed effects NMA results over the random effects NMA results to be insufficient. Given the clinical and methodological heterogeneity identified in the company's network of evidence, the EAG would consider the random effects NMA results to be preferred. Please provide additional justification for why the fixed effect model should be preferred in the company base case. As a scenario, please assume the random effect model treatment effects.

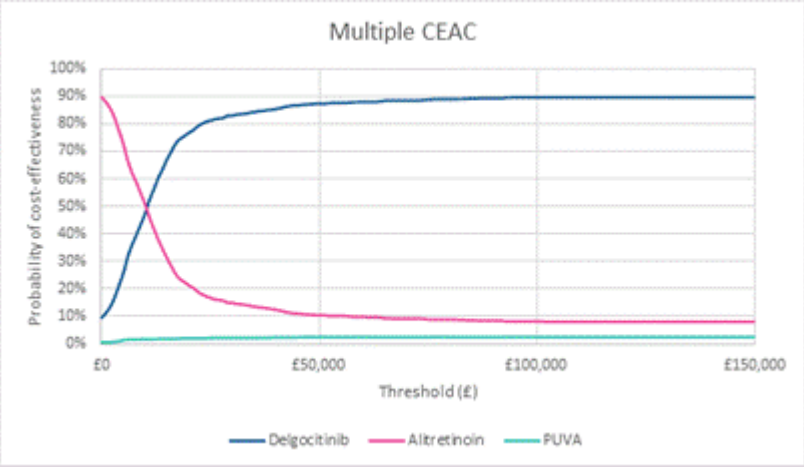
As outlined in Appendix B.2.7, the model diagnostics for the NMAs did not point to a clear recommendation for selecting one model over another based on model fit statistics alone. For all outcomes, the total residual deviance and DIC were similar in the FE and RE models, with a difference in DIC of less than 5 for all analyses. Due to the small number of trials included in the network, the treatment effects estimated in the RE models were associated with implausibly wide 95% credible intervals (CrIs)

compared to the FE models. Considering the sparsity of the network and resulting imprecise treatment effect estimates generated by the RE model, the FE model was preferred.

As the EAG has expressed a preference for the RE NMA results, we have performed a scenario analysis including the RE model treatment effects in the economic model. As the mean and median values are broadly similar, we have focused our response on the impact of the RE model results on the probabilistic sensitivity analysis (PSA).

For patients with severe CHE, the mean ICER from the PSA for delgocitinib compared with alitretinoin was £12,135 per QALY (versus £8,177 per QALY in the deterministic analysis using median point estimates from the RE model). PUVA was dominated by both delgocitinib and alitretinoin. Cost-effectiveness acceptability curves are shown in Figure 6. At cost-effectiveness thresholds of £20,000 and £30,000 per QALY, delgocitinib has the highest likelihood of the comparators of being cost effective (76.6% and 82.8%), followed by alitretinoin (21.4% and 15.0%). Delgocitinib was dominant (i.e., less costly and more effective) in 16.2% of simulations compared to alitretinoin and in 90.9% of simulations compared to PUVA.

Figure 6 Multiple CEAC – severe CHE

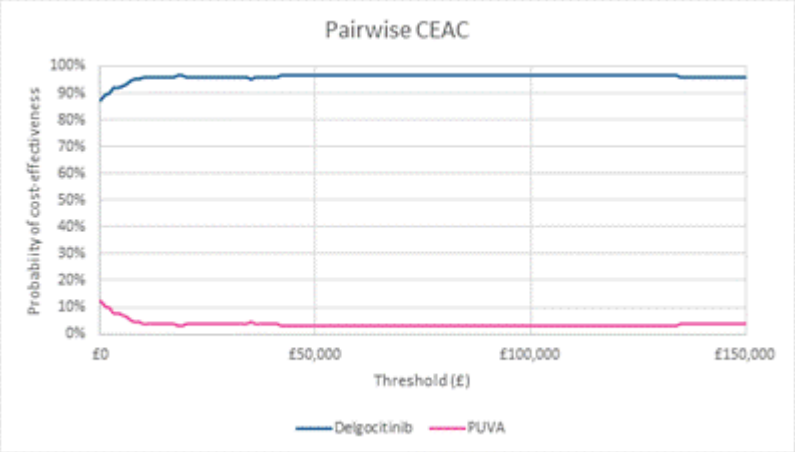


Abbreviations: CEAC, cost-effectiveness acceptability curve; PUVA, psoralen plus ultraviolet A; £, British Pound (GBP).

For patients with moderate CHE, delgocitinib dominated PUVA. Cost-effectiveness acceptability curves are shown in Figure 7. Delgocitinib had a 97.7% and 98.5% likelihood of being more cost effective than PUVA at cost-effectiveness thresholds of

£20,000 and £30,000 per QALY, respectively, and dominated PUVA in 88.4% of simulations.

Figure 7 Pairwise CEAC – moderate CHE



Abbreviations: CEAC, cost-effectiveness acceptability curve; PUVA, psoralen plus ultraviolet A; £, British Pound (GBP).

Despite the additional uncertainty, these results are similar to those from the base case using the FE NMA results. Due to time constraints, we have only explored this scenario for the base case and not for other scenarios for which NMA results are available, (e.g. using HECSI responses instead of IGA-CHE responses or using week 16 endpoints instead of week 12 endpoints). We expect that the use of RE models in these scenarios would have a similarly minimal impact on the results.

Initial treatment

B9. Priority question. The EAG is concerned that using the company's approach, the proportion of full responders by 24 weeks in the model may be overestimated. For example, compared to DELTA 3 and DELTA FORCE which recorded 31% and 27% of delgocitinib patients achieving a full response by week 24 respectively, the EAG calculates that in the model when using the NMA treatment effects, approximately 36% of delgocitinib patients achieved a full response by week 24 (26.35% by week 12 and 10.3% of the moderate and mild patients over the next 12 weeks). Please can the company confirm if the

EAG's calculations are correct and if so, explain the difference between the trial and modelled treatment outcomes.

We can confirm that the EAG's calculations of the model are correct: by week 24, the model predicts that around 36% of severe CHE patients treated with delgocitinib will have achieved full response. However, we are unable to confirm the responder figures that the EAG has provided from DELTA 3 and DELTA FORCE because we are not sure of how they were estimated or from where they were sourced. We would be happy to follow-up if the EAG is able to provide further context to the numbers in their question. As an exercise in validation though, we have worked through an example from DELTA FORCE where we compare values presented in section 2.6.9 of the submission to those generated by the economic model.

DELTA FORCE data on the cumulative incidence of IGA-CHE 0/1 at week 12 and week 24 are presented in Table 30 of the submission and suggest that [redacted]% of delgocitinib patients will have achieved IGA-CHE 0/1 at week 24. However, this is not a perfect representation of what we have included in the submitted model, as we have included the following stopping rules which differ somewhat from the clinical trial:

- the proportion with IGA-CHE 0/1 at week 12 stop treatment
- the proportion who achieved an IGA-CHE 2 or IGA-CHE 3 with 1-point improvement at week 12, continue treatment until they achieve IGA-CHE 0/1 or by week 24
- the proportion with no change in their IGA-CHE score from baseline at week 12 discontinue treatment, in line with approval from MHRA.

In the DELTA FORCE trial, patients with no improvement at week 12 could still continue treatment if, in the opinion of the investigator, there was still an opportunity to benefit from further treatment.

Based on these stopping rules, crude values were estimated: [redacted]% of delgocitinib-treated patients from DELTA FORCE achieved IGA-CHE 0/1 at week 12 and [redacted]% experienced no improvement. Of those who remain on treatment ([redacted]%), the data shows that a cumulative [redacted]% of them will go on to achieve IGA-CHE 0/1 by week 24 (a pooling of the DELTA FORCE values presented in section 3.3.1.3 of the submission), which amounts to a further [redacted]%. Added to the week 12 responders,

this suggests that [redacted]% of delgocitinib-treated patients in DELTA FORCE would achieve IGA-CHE 0/1 by week 24 according to the submitted model's protocol.

When we programme this scenario into the submitted economic model (see settings in Table 43), the proportion of patients in full response at week 24 is [redacted]%.

Table 43 Delgocitinib treatment parameters

Parameter	Value used for delgocitinib (DELTA FORCE)
Probability of IGA-CHE 0/1 at week 12	[redacted]%
Non-responder distribution	PR: [redacted]% LR: [redacted]% InR: [redacted]%
Per-cycle probability of full response from partial and low response	[redacted]% (cycle-adjusted from [redacted]%)
Loss of response/relapse	0% (to see accumulation of full responders)

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand eczema; InR, incomplete responder; LR, late responder; PR, partial responder.

B10. Priority question. The EAG is concerned that while treatment outcomes are assumed to be the same between 12 week and 24 week full responders, there may be a difference in future outcomes between these patients given the treatment waning between weeks 12 and 16 (in DELTA 1 and 2). Please conduct a subgroup analysis between the patients that responded to initial treatment by week 12 and by week 24, assessing:

- **per cycle probability of relapse**
- **per cycle probability of full response on re-treatment**
- **proportion of patients opting not to re-initiate treatment after relapse.**

Please comment on the differences and similarities between the subgroups and conduct a scenario analysis exploring these differences.

During development of the model, we investigated whether the future outcomes among patients with early (week 12) versus later (beyond week 12) achievement of full response might differ. The evidence suggested that future outcomes were broadly similar.

Figure 8 presents the data on time to loss of response (IGA-CHE ≥ 2) for patients who were treated with delgocitinib in DELTA 1 and DELTA 2 and entered DELTA 3

in full response (i.e. IGA-CHE 0/1). Figure 9 presents the data on time to loss of response among patients who were treated with delgocitinib in DELTA 1 and DELTA 2, entered DELTA 3 not in full response and subsequently achieved full response.

The figures present a comparison of the rate of loss of response following the first off-treatment period vs second off-treatment period within these subgroups of patients. These data suggest that a patient's risk of relapse following an off-treatment period is generally consistent whether it is the first or second time a patient has responded and whether they had started DELTA 3 in response or achieved it at some point after that.

Figure 8 Time to relapse at first off-treatment period vs. time to relapse at second off-treatment period. Patients that have previously been on delgocitinib in the parent trial and entered DELTA 3 in response (IGA-CHE 0/1)

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.

Figure 9 Time to relapse at first off-treatment period vs. time to relapse at second off-treatment period. Patients that have previously been on delgocitinib in the parent trial and entered DELTA 3 in not in response (IGA-CHE ≥2)

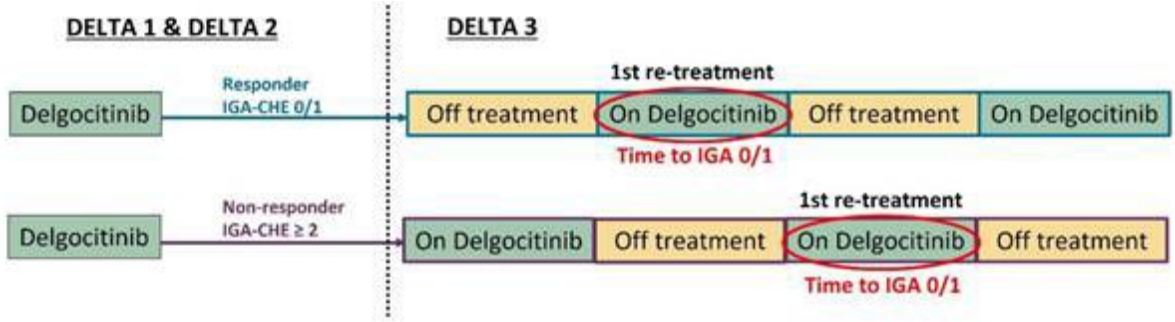
Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.

To evaluate the probability of response following first treatment re-initiation based on baseline IGA-CHE TS, an analysis of data from DELTA 3 was performed and presented in section 2.6.5.3 of the original company submission. Figure 10 illustrates

the subgroups being compared and we present the results visually in Figure 11 below.

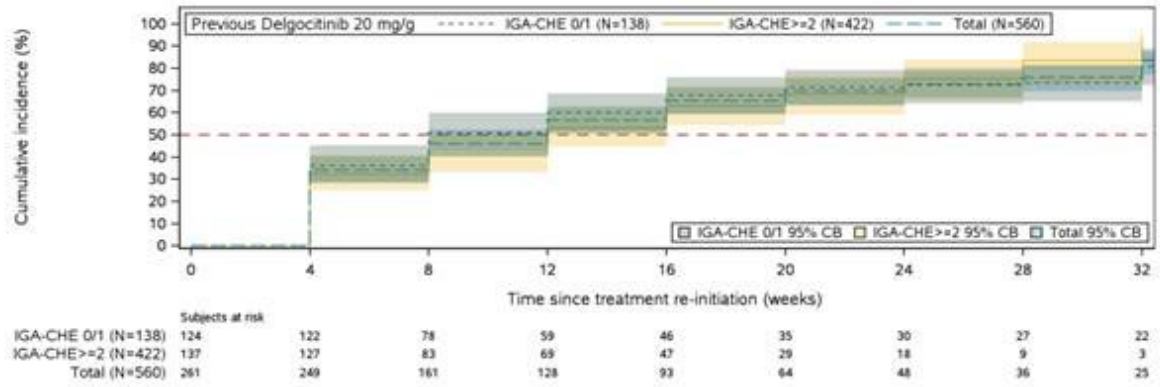
The results illustrate that the likelihood of regaining response following treatment re-initiation was not dissimilar between patients who entered DELTA 3 either as responders or not responders. Therefore, the base case of the model pools across these two groups. The estimated cumulative proportion of subjects having regained an IGA-CHE score of 0/1 after having re-initiated treatment was 83.6% (95% CI: 77.2%-89.1%) at the end of the treatment period.

Figure 10 Treatment re-initiation after the first off-treatment period: 2 scenarios – subjects previously treated with delgocitinib cream 20 mg/g in parent trial



Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.

Figure 11 Time to response (IGA-CHE 0/1) following first treatment re-initiation by baseline IGA-CHE TS – subjects in safety analysis set previously treated with delgocitinib cream 20 mg/g in parent trial



Notes: Cumulative incidence (%) = 1 minus the Kaplan Meier estimate of having event at week X expressed as a percentage. An event is defined as achieving response IGA-CHE O/1) following first treatment re-initiation. Subjects completing treatment period discontinuing IMP or initiating rescue treatment are censored at the date of the event, whichever occurs first.
Abbreviations: CB, confidence band; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.; IGA-CHE TS, Investigator's Global Assessment for Chronic Hand Eczema treatment success; IMP, investigational medicinal product; N, number of subjects; SAS, safety analysis set.

To inform the estimate for the proportion of patients opting not to re-initiate delgocitinib following relapse, we used information about censored patients at week 0 for the outcome of time to response following the first treatment re-initiation in DELTA 3. These data indicated that [redacted]% ([redacted]) of patients who entered DELTA 3 with IGA-CHE 0/1 response were censored at week 0 compared to [redacted]% ([redacted]) of patients who achieved IGA-CHE 0/1 response at some point during DELTA 3. Using this as a proxy for the decision not to re-initiate initial treatment, it suggests that patients who experienced a response by week 12 may be more likely to re-initiate treatment than patients who experienced a response later than week 12.

The model is not built to allow for differentiation by responders at week 12 versus responders after week 12; therefore, we have tried to approximate the impact of such a difference. To do this, we have estimated a weighted average probability of opting not to re-initiate delgocitinib based on the proportion in the model who achieved early (week 12) response compared to later response (after week 12). Of all delgocitinib responders by week 24 in the model, 71.9% had achieved full response by week 12 and 28.1% between week 13 and 24. Using these proportions as weights, the weighted mean probability of not re-initiating delgocitinib was 3.2%. Applying this value to the delgocitinib arm only, the ICER for delgocitinib versus

alitretinoin increases to £8,992 (from £8,221 in the submitted base case) in severe CHE and delgocitinib remains dominant over PUVA in moderate and severe CHE.

B11. Priority question. The EAG's clinical expert stated that of their patients who have been treated with alitretinoin, approximately 30% have continued to relapse and be re-treated for 2+ years. Comparatively in the model, only 2% of patients are assumed to still be treated with alitretinoin. Can the company discuss the modelling factors that have contributed to time on treatment in the model misaligning with clinical practice and discuss the consequences of the difference between the model and clinical practice in terms of cost-effectiveness?

There are many uncertainties in how the EAG's clinical expert has framed their description of clinical practice; therefore, it is difficult to properly address this question. For example, is the 30% to which the clinical expert refers a proportion across all patients to whom alitretinoin has been administered or only among the proportion who achieved IGA-CHE 0/1 by week 24?

According to the submitted model, which is based on an NMA of the best available and comparable RCT evidence, only 25.6% of alitretinoin-treated patients will achieve full response by week 24. Based on data from the ALPHA trial, only about half of patients will re-initiate alitretinoin following a relapse within the first 52 weeks of achieving response. If we assume instead that 100% of relapsed patients re-initiate alitretinoin at the point of relapse, the 2% described by the EAG increases to 8.3% still being treated with alitretinoin at 2 years. This represents 32.4% of the original 25.6% of patients who had responded to initial alitretinoin by week 24. We present this as an illustration of how the model can approximate the description of clinical practice described by the clinical expert, depending on the interpretation.

The factors that affect time on treatment in the model include the initial response rate, the stopping rules, rates of discontinuation, rates of relapse, probability of re-initiating treatment at relapse and the rates of response to reinitiated treatment. If, in clinical practice, more alitretinoin-treated patients are likely to require treatment beyond week 12 or the rates of discontinuation are lower or more patients re-initiate treatment at the point of relapse, then the time on treatment with alitretinoin (and associated costs) will increase. The acquisition costs of alitretinoin will increase at a

higher rate than the QALYs gained from staying on treatment which is likely to decrease the ICER of delgocitinib versus alitretinoin and improve the relative cost-effectiveness of delgocitinib.

Finally, the model includes some alitretinoin use in the next-line treatment basket to account, albeit indirectly, for the use of alitretinoin beyond initial discontinuation. The approach to this basket, as outlined in the response to Question B12, is as a cohort whereby a proportion of patients at any given time are receiving a range of treatments, including alitretinoin.

Next line treatments

B12. Priority question. Please justify the assumption that 39.8% of patients who fail on alitretinoin will go on to receive alitretinoin. As a scenario, please assume that patients who fail on alitretinoin do not receive alitretinoin as a next-line treatment. In this scenario, please estimate the effectiveness of this next line of treatment based on the most commonly used option for patients that have failed on alitretinoin.

Though it is not referenced in the question, we assume the figure of 39.8% to which the EAG refer is from the scenario in which data from the ALPHA trial is used to inform the distribution of treatments in the next-line treatment basket. To note, the value from the RWEAL study, which is used in the base case analysis, is 23.8%.

The next-line basket uses a cohort approach, a simplification of what patients might receive following the discontinuation of their initial treatment (e.g. delgocitinib, alitretinoin or PUVA). It is worth noting that not all patients who discontinue initial treatment have failed to respond to treatment. Patients can discontinue any of the initial treatments for reasons other than lack of efficacy. They can also decide not to re-initiate the same treatment immediately at the point of relapse. For example, a woman who previously responded to alitretinoin could decide to discontinue because she wished to become pregnant. Or there could be a patient who could not attend twice weekly PUVA sessions for 12 weeks despite showing early signs of response. It is not unreasonable to assume that these patients might try alitretinoin or PUVA again in the future if their circumstances have changed.

As outlined in the submission, CHE is a complex, multifactorial disease; there can be more than one underlying cause or clinical presentation which can change over time. By including alitretinoin and PUVA in the next-line basket, we have captured the range of options from which patients and their dermatologists may choose, even where these treatments have been tried previously.

No reliable data was available to inform the efficacy of the treatments in the next-line basket, therefore the percentage of alitretinoin patients in low disease activity reported in the RWEAL study was used as a proxy and varied in sensitivity analysis.

For the scenario requested, we have revised the distribution of treatments in the basket for the alitretinoin arm only. The proportion of patients who would move on to alitretinoin in the basket have been split evenly between ciclosporin, methotrexate and dupilumab. This increases the cost of the next-line basket after alitretinoin to £262.25. Under these assumptions and in the absence of any changes to the expected efficacy of the next-line basket (since no evidence was available), delgocitinib dominates alitretinoin. To explore alternative efficacy assumptions, the efficacy of this alternative next-line basket was increased to 80% and delgocitinib still dominated alitretinoin.

B13. The company has estimated next-line treatment efficacy using the ongoing and stopped alitretinoin in the RWEAL study. Please can the company show how the efficacy has been calculated using the data and tables from the RWEAL study?

Unfortunately, it seems that some of the RWEAL study data that has informed the model was unintentionally omitted from our reference pack. The table presented on page 14-15 (of the PDF) of the RWEAL_UK_Tables.pdf in the reference pack (Table 59 – Reasons for stopping Alitretinoin or TCS treatment, overall and by treatment [focus population]) presents only half of the calculations. The other half, based on alitretinoin that is ongoing, is presented below (Table 44).

To calculate the probability of low disease activity (LDA) in each group (the ongoing and stopped populations), we took the number reported as achieving LDA out of the total responses, recognising that multiple were possible). We then estimated a weighted average across the ongoing and stopped populations where weights were based on the sample size.

Table 44 Judgment on the current alitretinoin or TCS treatments outcome, overall and by treatment family

Base: Alitretinoin or TCS treatments that are ongoing	Overall, N = 1552	Treatment					
		Alitretinoin, N = [redacted]	TCS, N = [redacted]	uhTCS, N = [redacted]	hTCS, N = [redacted]	mTCS, N = [redacted]	ITCS, N = [redacted]
Achieved low disease activity state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure to maintain a low disease activity state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of treatment adherence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events or side effects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: hTCS: high potency topical corticosteroids, ITCS: low potency topical corticosteroids, mTCS: moderate potency topical corticosteroids, N: number of subjects, TCS: topical corticosteroids, uhTCS: ultra-high potency topical corticosteroids.

Discontinuation

B14. As a scenario, please derive the probability of re-treatment discontinuation using DELTA 3. The EAG considers that applying the initial treatment discontinuation rates to patients being re-treated may overestimate discontinuation given these patients have previously achieved a full response.

Unfortunately, there was insufficient time to be able to generate these data from DELTA 3. However, we call attention to a scenario analysis presented in Table 77 where we have already tested this for exactly the reasons the EAG has outlined. In this scenario, we have assumed that the discontinuation rate from re-treatment is half of the discontinuation rate applied between week 12 and week 24 of initial treatment ([redacted]% vs [redacted]%). As outlined in Table 77, this increases the ICER of delgocitinib vs alitretinoin to £9,587 from £8,221 in the base case.

Health-related quality of life

B15. Priority question: In the CS, the company referenced the Van Hout algorithm to crosswalk EQ-5D-5L data to the EQ-5D-3L. In section 4.3.16 of the NICE health technology evaluations manual, it states that, "*The mapping function developed by the Decision Support Unit (Hernández Alava* et al. *2017),*

***using the 'EEPRU dataset' (Hernández Alava* et al. *2020), should be used for reference-case analyses*". Therefore, please amend the EQ-5D data used to estimate utility values in the model to be based on the mapping function developed by the Decision Support Unit and provide updates to Table 63 of the CS and Tables 248 and 249 of Appendix J.2 and include standard errors for each utility value provided. Please ensure that the updated utility data are referenced in response to the remainder of the clarification questions on health-related quality of life.**

Many thanks to the EAG for highlighting the preference of NICE for the Hernández Alava mapping formula for EQ-5D-5L to EQ-5D-3L values. We have amended the EQ-5D data used to estimate utility values in the model and present the updated values in the same format as Table 63. For the avoidance of doubt, as per question B18, we have presented values for the IGA-CHE defined health states that were originally presented in Table 63 and for use in the base case along with values for the HECSI defined health states for use in a scenario analysis (Table 45). We have also provided updates to Table 248 and Table 249 presented in Appendix J.2 (Table 46 and Table 47). Please note that we have not presented standard errors with the health state utility values as the precision of these values is a function of the uncertainty in the MMRM regression outputs and parameter values which are either presented in the table below or in the submission.

After including the revised utility values in the economic model, the base case ICER for delgocitinib versus alitretinoin in severe CHE decreases to £8,037 compared to £8,221 in the submitted base case. Delgocitinib remains less costly and more effective than PUVA in moderate and severe CHE.

Table 45 Health state utility values used in the model

	IGA-CHE defined health states			HECSI defined health states		
Health state	Active treatment	Vehicle treatment	Common effect [a]	Active treatment	Vehicle treatment	Common effect [a]
Severe CHE						
Baseline	0.617	0.617	0.617	0.617	0.617	0.617
Full response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate CHE						

	IGA-CHE defined health states			HECSI defined health states		
Health state	Active treatment	Vehicle treatment	Common effect [a]	Active treatment	Vehicle treatment	Common effect [a]
Baseline	0.665	0.665	0.665	0.665	0.665	0.665
Full response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Used in a scenario analysis and applied to response states independent of treatment received.

Abbreviations: CHE, Chronic hand eczema; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.

Table 46 Parameter coefficients from MMRM model using IGA-CHE and HECSI response definitions, including treatment effects

	IGA-CHE		HECSI	
	Coefficient	SE	Coefficient	SE
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
EQ5D baseline	[redacted]	[redacted]	[redacted]	[redacted]
HECSI score	[redacted]	[redacted]	[redacted]	[redacted]
HESD pain score	[redacted]	[redacted]	[redacted]	[redacted]
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]
Vehicle	Reference	Reference	Reference	Reference
Full response	[redacted]	[redacted]	Reference	Reference
Partial response	[redacted]	[redacted]	[redacted]	[redacted]
Low response	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient response	Reference	Reference	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; EASI, eczema area severity index; EQ-5D, EuroQol 5 dimension; HECSI, hand eczema severity index; HESD, hand eczema symptom diary; IGA-CHE Investigator's Global Assessment for Chronic Hand Eczema; MMRM, mixed model with repeated measures; SE, standard error.

Table 47 Parameter coefficients from MMRM model using IGA-CHE and HECSI response definitions, excluding treatment effects

	IGA-CHE		HECSI	
	Coefficient	SE	Coefficient	SE
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
EQ5D baseline	[redacted]	[redacted]	[redacted]	[redacted]
HECSI score	[redacted]	[redacted]	[redacted]	[redacted]
HESD pain score	[redacted]	[redacted]	[redacted]	[redacted]
Full response	[redacted]	[redacted]	Reference	Reference
Partial response	[redacted]	[redacted]	[redacted]	[redacted]
Low response	[redacted]	[redacted]	[redacted]	[redacted]

	IGA-CHE		HECSI	
	Coefficient	SE	Coefficient	SE
Insufficient response	Reference	Reference	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; EASI, eczema area severity index; EQ-5D, EuroQol 5 dimension; HECSI, hand eczema severity index; HESD, hand eczema symptom diary; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MMRM, mixed model with repeated measures; SE, standard error.

B16. Priority question: Please provide the mean EQ-5D-3L utilities from DELTA 1, DELTA 2 and FORCE (severe CHE only) for each health state (based on IGA-CHE response definitions) requested in the below table. For each utility value, please also provide the number of EQ-5D responses informing the health state.

a) **Please compare and discuss the utility values provided in the table below with the utility values derived from the mixed model with repeated measures (MMRM) regression.**

b) **Please conduct a scenario for both the moderate and severe CHE subgroups using the overall utility values (non-treatment specific utilities) each health state provided in the below table.**

c) **Please conduct a scenario where the overall utility values for each health state (not split by baseline severity or treatment) are used for both the moderate and severe subgroups.**

Table 48 Mean EQ-5D-3L utilities from DELTA trials

Health state	Severe CHE (DELTA 1, 2 & FORCE)				Moderate CHE (DELTA 1 & 2)			Overall (no split by baseline severity)			
	delgocitinib n=409	Alitretinoin (DELTA FORCE only) n=236	Vehicle treatment (D1&D2 only) n=90	Overall n=735	Delgo n=452	Vehicle treatment n=227	Overall n=679	delgocitinib (D1, D2 & DFORCE) n=861	Alitretinoin (DELTA FORCE only) n=236	Vehicle (D1 & D2) n=317	Overall n=1414
Baseline	0.617 (n=735)				0.665 (n=679)			0.640 (n=1414)			
IGA-CHE 0/1	[redacted]										
IGA-CHE 2	[redacted]										
IGA-CHE 3	[redacted]										
IGA-CHE 4	[redacted]										

Abbreviations: CHE, Chronic hand eczema; D1, DELTA 1 trial; D2, DELTA 2 trial; DFORCE, DELTA FORCE trial; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; n = number of patients

a) In the severe CHE population, the mean EQ-5D-3L utilities from DELTA 1, DELTA 2 and DELTA FORCE (severe only) (reported in Table 48) are higher for delgocitinib and lower for vehicle. This indicates that the MMRM regression values may underestimate the gains associated with achieving improvement on IGA-CHE on delgocitinib and overestimate the gains associated with achieving the same improvements with vehicle. A comparison of the treatment independent utilities based on the MMRM regression excluding a treatment effect against the overall severe CHE utilities shows that the MMRM regression values may slightly underestimate utility gains associated with improvements on IGA-CHE.
   In the moderate CHE, the differences between the utilities generated by the MMRM regression and the summary statistics from DELTA 1 and DELTA 2 only were less pronounced, particularly for health states of IGA-CHE 2 and IGA-CHE 0/1. The values for patients with IGA-CHE 3 or 4 were slightly higher using the MMRM regression than the summary statistics. A comparison of the treatment independent utilities based on the MMRM regression excluding a treatment effect against the overall moderate CHE utilities shows that the MMRM regression values may slightly underestimate utility gains associated with achieving IGA-CHE 0/1 or 2 and overestimate utility gains associated with non-response.
b) In the severe population, after implementing the overall utility values reported in the summary statistics (DELTA 1, 2 & FORCE) to both the active arms and BSC, the ICER for delgocitinib versus alitretinoin was £10,671. This is slightly higher than the ICER for a similar scenario presented in the original submission where the treatment-independent utilities values were used. In that scenario, delgocitinib had an ICER of £9,873 versus alitretinoin in severe CHE. In both scenarios, delgocitinib remained dominant over PUVA.
   In the moderate population, after implementing the overall utility values reported in the summary statistics (DELTA 1& 2), delgocitinib remains dominant over PUVA.
c) A scenario where the overall utility values for each health state (not split by baseline severity or treatment) was explored. These alternative utility values were applied to both active arms and BSC in the economic model.
   In the severe population, the ICER increased to £10,667 from £9,873 and delgocitinib dominated PUVA. In the moderate population, delgocitinib remained dominant over PUVA.

B17. Priority question: Please provide a scenario where the age adjustment for utilities is based on the approach developed by the NICE Decision Support Unit (Hernández Alava *et al.,* 2022).

a) **The NICE Decision Support Unit report recommends that the Health Survey for England (HSE) 2014 dataset is used for the age adjustment of utilities as it is the most up to date information available that has direct observation of EQ-5D-3L. Please justify the use of the method described by Ara and Brazier, for the age-adjustment of utilities in the company base case.**

Thank you for sharing the latest recommendation from the NICE DSU. The age-adjustment based on the HSE 2014 data set reported by Hernández Alava et al., 2022 has now been applied in the model and submitted as part of our response to clarification questions. This can be found in the economic model on the worksheet "e_UtilitiesBE" from rows 155 onwards.

After implementing this approach, and independent of any other changes discussed in the clarification questions, the ICER for delgocitinib versus alitretinoin drops slightly to £8,202 in severe CHE. Delgocitinib remains dominant over PUVA in both moderate CHE and severe CHE.

B18. Priority question: In Appendix J.2, results of utility analyses using IGA-CHE response definitions were presented.

a) Given that the structure of the model is based on IGA-CHE definitions of response, please clarify why the regressions which uses IGA-CHE response were not used to estimate utilities for the company base case?

b) Please provide utility values and standard errors for the moderate and severe CHE subgroups as well as overall (no split by severity) based on the utility regression model that uses IGA-CHE response definitions and provide scenarios using these values.

The utility values presented in Table 63 of the submission are applied in the model base case which uses IGA-CHE response definitions. These values are derived using the regression covariates reported under the IGA-CHE headings of Table 248

in Appendix J.2. These can be found in the economic model on the worksheet "UitilitesBE" in cells K13:U25. In the scenario where health states are defined by HECSI response, utility values are derived using the regression covariates reported under the HECSI headings of Table 248 in Appendix J.2.

The utility values for moderate CHE and severe CHE subgroups used in the base case model where health states are defined by IGA-CHE response are reported in Table 64 of the main submission. Any estimates of uncertainty around these utility values are a function of the uncertainty captured in the regression covariates and parameter values which are described in Table 72, Table 248 and Table 250. Covariance matrices to preserve correlation in the regression using the Cholesky decomposition in the probabilistic sensitivity analysis are presented in cells K29:T38 of UtilitiesBE for the base case and were provided in the reference pack at submission.

Health state utility values based on IGA-CHE response definitions for an overall moderate to severe population with a split of 57.8% moderate patients and 42.2% severe patients, informed by RWEAL, are provided in Table 49.

Table 49 Health state utilities for an overall moderate to severe population

Health state	Active treatment	Best Supportive Care	Common effect*
Baseline	0.637	0.637	0.637
Full response	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states	[redacted]	[redacted]	[redacted]
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]

*Used in a scenario analysis and applied to response states independent of treatment received.
Abbreviations: CHE, Chronic hand eczema.

B19. Please provide the mean EQ-5D-3L utilities from DELTA 3 for each health state (based on IGA-CHE response definitions) requested in the below table. For each utility value, please also provide the number of EQ-5D responses informing the health state.

a) Please discuss how the long-term utility data (36 weeks) from DELTA 3 compares to the short-term utility data (16 weeks) from DELTA 1 and DELTA 2

The table below (Table 50) presents a summary of the EQ-5D-3L utility values (mapped from EQ-5D-5L using the Hernandez Alava algorithm) broken down by IGA-CHE health state measured at week 36 in the DELTA 3 study among patients who received delgocitinib for 16 weeks in the DELTA 1 and DELTA 2 parent trials. All patients in the DELTA 3 study received delgocitinib; therefore, we amended the table to reflect this.

Table 50 EQ-5D-3L Health state utilities for delgocitinib by severity (DELTA 3)

Health state	Delgocitinib					
	Severe CHE		Moderate CHE		Overall (not split by baseline severity)	
	N	EQ-5D-3L	N	EQ-5D-3L	N	EQ-5D-3L
Full response (IGA-CHE 0/1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response (IGA-CHE 2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low response (IGA-CHE 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient response (IGA-CHE 4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; EQ-5D-3L, EuroQol 5-Dimension 3-Level index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; N, number of subjects.

A comparison of these long-term utility data from DELTA 3 with the short-term utility data from DELTA 1, DELTA 2 and DELTA FORCE (presented in response to Question B16, page 83) indicates that the utility values for full and partial response (IGA-CHE 0/1 or 2) are stable, with values appearing to be similar after 12 weeks and 52 weeks of treatment. The long-term vs short-term utility data for moderate and severe CHE health states (IGA-CHE 3 or 4) are more differentiated, with utility values in the short term reported as being lower than the values in the long term. The patient numbers for the severe CHE health state (IGA-CHE 4) are very small and should therefore be interpreted with some caution. What is not captured in this snapshot at week 36 is how the patients in the moderate or severe states have fluctuated over time with as-needed delgocitinib. Though they are classified as having moderate or severe CHE at week 36, they could have experienced full or partial response at some point during the prior 36 weeks. Similarly, these values reflect observed cases at week 36. This could inflate the values observed in the more severe health states if the missing patients discontinued treatment with delgocitinib for reasons related to efficacy. These factors could explain the higher utility values reported here than after just 12 weeks of treatment.

B20. Please clarify if the utility data from DELTA 1 and DELTA 2 was pooled and then split by severity in the MMRM regression.

Data were pooled on subject level and several effects were added to the MMRM regression model. Severity (IGA-CHE) was among other variables added, but since other time dependent variables were also added, the subject's severity was expressed through covariates such as time dependent covariates pain, HECSI and baseline EQ5D.

The mixed model was reduced in steps using a backward selection process and only significant variables were kept in the regression. The final model did not include baseline severity.

B21. Please describe the backward selection process used to specify the final regression model to estimate the utility values applied in the economic model.

a) The EAG considers that the HECSI score, HECSI pain score and IGA-CHE are likely to be correlated. Please explain why HECSI score and HECSI pain score were included as variables for inclusion in the selection process for both the regression models based on IGA-CHE and HECSI response definitions?

b) Please explain why it is appropriate to include age in the regression model given that an age adjustment to utilities is included in the economic model?

The DELTA 1 and DELTA 2 data were used to inform the MMRM model.

The starting model included the following parameters:

igache_01_rest*AVISITN igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN STUDYID HKSTATUS EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN

- STUDYID: Study Identifier
- igache_01_rest: Responder (0,1) vs rest (2, 3, 4)
- AVISITN: Analysis Visit (Numerical)
- TRT01PN: Treatment
- REGION1: Geographic Region

- SEX: Gender
- RACE: Race
- IGABLN: IGA at baseline
- HKSTATUS: Hyperkeratotic Status
- EQ5D_base: EQ-5D at baseline
- AGE: Age
- Hecsi: HECSI score
- W_HESD: HESD score
- W_HD301: HESD itch score
- W_HD302: HESD pain score

By backwards elimination the model including the IGACHE_01_rest (The IGA responders) was reduced by removing variables according to their p-value. The steps (W_HD301 and W_HD302 are the Itch and Pain domains of the HESD, respectively):

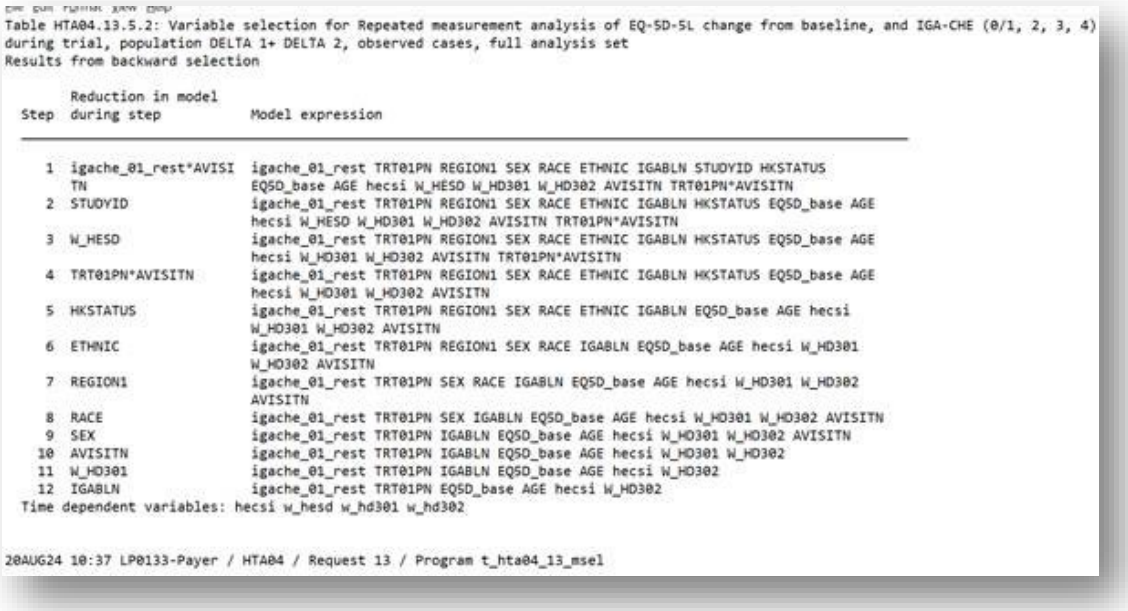


Table HTA04.13.5.2: Variable selection for Repeated measurement analysis of EQ-5D-5L change from baseline, and IGA-CHE (0/1, 2, 3, 4) during trial, population DELTA 1+ DELTA 2, observed cases, full analysis set
Results from backward selection

Step	Reduction in model during step	Model expression
1	igache_01_rest*AVISITN	igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN STUDYID HKSTATUS EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN
2	STUDYID	igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN HKSTATUS EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN
3	W_HESD	igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN HKSTATUS EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN TRT01PN*AVISITN
4	TRT01PN*AVISITN	igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN HKSTATUS EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
5	HKSTATUS	igache_01_rest TRT01PN REGION1 SEX RACE ETHNIC IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
6	ETHNIC	igache_01_rest TRT01PN REGION1 SEX RACE IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
7	REGION1	igache_01_rest TRT01PN SEX RACE IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
8	RACE	igache_01_rest TRT01PN SEX IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
9	SEX	igache_01_rest TRT01PN IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
10	AVISITN	igache_01_rest TRT01PN IGABLN EQ5D_base AGE hecsi W_HD301 W_HD302
11	W_HD301	igache_01_rest TRT01PN IGABLN EQ5D_base AGE hecsi W_HD302
12	IGABLN	igache_01_rest TRT01PN EQ5D_base AGE hecsi W_HD302

Time dependent variables: hecsi w_hesd w_hd301 w_hd302

20AUG24 10:37 LP0133-Payer / HTA04 / Request 13 / Program t_hta04_13_msel

Similar for the model that included the HECSI responder criteria:

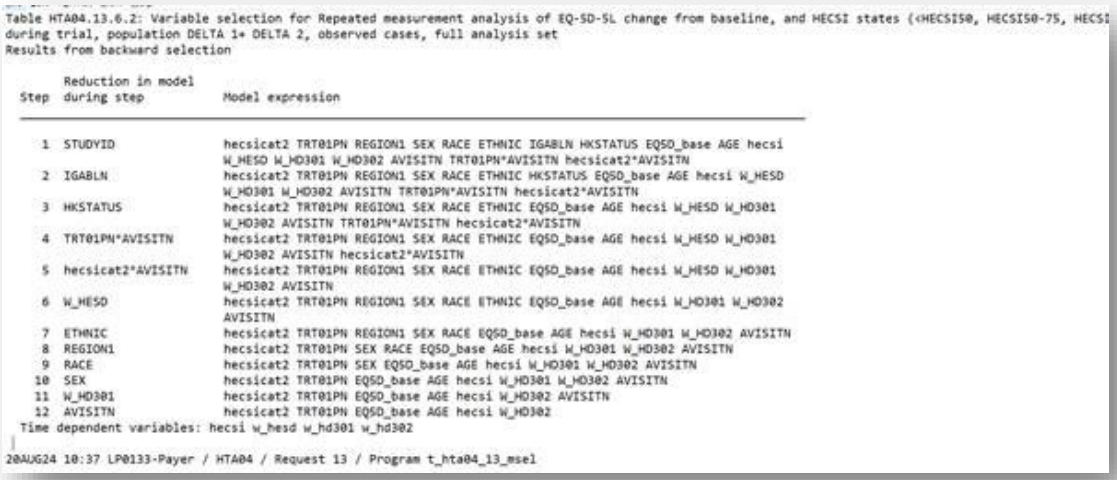


Table HTA04.13.6.2: Variable selection for Repeated measurement analysis of EQ-5D-5L change from baseline, and HECSI states (<HECSI50, HECSI50-75, HECSI
during trial, population DELTA 1+ DELTA 2, observed cases, full analysis set
Results from backward selection

Step	Reduction in model during step	Model expression
1	STUDYID	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC IGABLN HKSTATUS EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN hecsicat2*AVISITN
2	IGABLN	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC HKSTATUS EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN hecsicat2*AVISITN
3	HKSTATUS	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN TRT01PN*AVISITN hecsicat2*AVISITN
4	TRT01PN*AVISITN	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN hecsicat2*AVISITN
5	hecsicat2*AVISITN	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC EQ5D_base AGE hecsi W_HESD W_HD301 W_HD302 AVISITN
6	W_HESD	hecsicat2 TRT01PN REGION1 SEX RACE ETHNIC EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
7	ETHNIC	hecsicat2 TRT01PN REGION1 SEX RACE EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
8	REGION1	hecsicat2 TRT01PN SEX RACE EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
9	RACE	hecsicat2 TRT01PN SEX EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
10	SEX	hecsicat2 TRT01PN EQ5D_base AGE hecsi W_HD301 W_HD302 AVISITN
11	W_HD301	hecsicat2 TRT01PN EQ5D_base AGE hecsi W_HD302 AVISITN
12	AVISITN	hecsicat2 TRT01PN EQ5D_base AGE hecsi W_HD302

Time dependent variables: hecsi w_hesd w_hd301 w_hd302

20AUG24 10:37 LP0133-Payer / HTA04 / Request 13 / Program t_hta04_13_msel

a) We had originally explored the inclusion of HECSI score for the regression based on HECSI response states, which are defined by a percentage change from baseline. Drawing on experience from other dermatological conditions, such as atopic dermatitis where EASI is used, indicated that it can be helpful to include the actual score when estimating utilities for these health states defined by relative improvement. By extension, we tested the inclusion of HECSI score in the IGA-CHE responder state model, and indeed the covariate was found to be statistically significant, so it was included.
   As neither the IGA-CHE scale nor HECSI capture pain as a CHE symptom, we looked to assess whether the inclusion of HESD pain (not HECSI pain) would be meaningful. The backwards selection process indicated that it was a statistically significant covariate; therefore, it was included in the final model.
b) We included age in the original specification of the model and it was not excluded through the backwards selection process; therefore, it was included.

B22. In the economic model, tab “UtilitiesBE” cell N128, the best supportive care (BSC) utility value is weighted based on response at Week 12 to vehicle treatment and the associated response utility values. However, in section 3.3.7.4 of the CS, it is described that patients in the BSC health state return to their baseline utility.

Please clarify if the approach in the economic model is what was intended for the company base case analysis (as presented in Table 64 of the CS)?

At the start of section 3.3.7.4 we state that “In the base case, efficacy of BSC was assumed to be equivalent to the efficacy of the vehicle arm in the NMA.” This is consistent with the base case settings in the economic model. The return to baseline utility for patients in the BSC health state is modelled in a scenario analysis only.

B23. Please clarify if the utility values used for the company base case were validated against relevant utility values in the published literature [for instance against studies identified in the health-related quality of life (HRQoL) systematic literature review or related technology appraisals] or with clinical experts. If external validation of the utility values was performed, please describe the findings.

a) In particular, the EAG considers that the baseline utility value for the moderate subgroup is relatively low. Thus, please discuss how the baseline utility value for the moderate subgroup compares to published values for CHE or other similar skin conditions.

b) Please provide any relevant scenario analyses based on findings of the utility value validation exercise.

a) The utility values used for the base case were compared with relevant values identified in the health-related quality of life (HRQoL) systematic literature review and other technology appraisals. The systematic literature review (SLR), as outlined in appendix F, identified multiple studies that reported health utility values for CHE. The primary sources included studies using the EQ-5D and time trade-off (TTO) approaches. Studies reported between 2010 and 2018 reported baseline utility values ranging from 0.50 to 0.94, depending on severity, time of data collection and methodology. The NICE TA177 (2008) appraisal mapped DLQI scores to EQ-5D values, producing utility estimates for different severity levels of CHE.

   Utility values for CHE in the literature may be overestimated due to factors such as adaptation to chronic symptoms, underreporting of disease burden, and differences in utility measurement methods (e.g., mapped vs. directly collected EQ-5D values). There may also be differences between studies in terms of the

way they define disease severity. The baseline utility value of 0.665 (Table 45) for the moderate subgroup was calculated based on data from DELTA 1 and DELTA 2 trials and represents the best available estimate for the economic model. This value is lower but relatively consistent with reported values in the SLR of health-related quality of life (HRQoL) studies, which are presented in Table 199 and Table 200 in Appendix F of the submission. The NICE TA177 used a utility of 0.713 for moderate CHE, which is slightly higher than the value used in this submission but, as mentioned above, it was derived by mapping from DLQI rather than direct EQ-5D elicitation. The value of 0.761 from Blank 2010 includes both mild and moderate patients, making it an overestimate for moderate patients alone, while Lindberg 2013 and Ofenloch 2014 reported 0.74 and 0.84, respectively, for CHE of unspecified severity.

The value of comparing the impact of CHE on quality of life to other dermatological conditions (Balieva et al. 2017) may be limited, as CHE, even in milder forms, can profoundly impact the various domains of HRQoL measures. Patients often report that the visibility of lesions, the intense itch and painful fissures can significantly impair their quality of life and interfere with their everyday activities, including their ability to work. For these reasons, the reported utility values in the model may appear low but are likely to be a realistic reflection of the impact that CHE has on patients.

b) We have not performed any scenario analysis to specifically validate the utilities generated in the clinical trials as these were considered to be the most robust, comprehensive and appropriate for the appraisal.

Resource use and costs

B24. Priority question: The EAG considers there is a lack of detail around the estimation of the mean weekly dose of delgocitinib used for each health state in the model.

a) **Please describe how delgocitinib consumption data were collected in DELTA1, DELTA 2 and FORCE (i.e. describe how grams per week was measured).**

b) **Please clarify if consumption was a variable for which missing data was imputed. If so, please clarify the imputation method used and the number of patients for which these data were imputed.**

c) **Please clarify if subgroup data by severity from DELTA 1 and 2 was used to estimate the weekly dose presented in tab "c_Treatment_BE" as it is described in the model as the full analysis set.**

    i) **If the full analysis set has been used, please provide a justification as to why that is appropriate for the moderate and severe subgroups.**

d) **On page 141 of the CS, it states that mean weekly usage for the severe subgroup is derived from an average over the first 12 weeks from DELTA 1, DELTA 2 and FORCE.**

    a. **In the model, the average for IGA-CHE 2-4 is taken from the first 20 weeks. Please justify the approach used in the model.**

    b. **Please provide a scenario where the weekly mean usage for all IGA-CHE categories is taken from the first 12 weeks from DELTA 1, DELTA 2 and FORCE, as described in the CS.**

e) **Week 0 data are included in the model for IGA-CHE 3 and 4 for both the moderate and severe CHE subgroups but are not included in the calculation of the weekly mean usage. Please justify this approach.**

f) **In tab "c_Treatment_BE", the week 16 mean weekly usage from DELTA 1, DELTA 2 and FORCE for IGA-CHE 0 and 1 is [redacted]. Please justify these results.**

g) **Please provide details on the MMRM regression used for the estimation of the delgocitinib doses, including which variables were considered for the MMRM regression and the approach to the final selection of variables included in the MMRM regression (including the final model specification).**

a) To determine the data concerning consumption, the total IMP used in a specified period was determined. Initially the mean weight of an unopened tube was calculated (21.9 g). The amount used per tube was calculated based on the weight of the returned tubes. If the weight of the returned tube was less than 6.9 g (but was not a missing tube) the amount used was set to 15 g (the entire content of a tube [21.9 - 6.9 = 15]). If the weight of the tube was between 6.9 g and 21.9 g the amount used is equal to the difference of the unopened tube and the returned tube. If a returned tube was greater than the mean weight of an unopened tube, the amount was set to 0 g. In any other case, the amount used is set to missing for the given tube.
In addition to the weight of returned tubes, additional data was collected on the dispense day: (date of dispensing – treatment start date) + 1, return day (date of return – treatment stat date) + 1, day of last IMP from tube: The treatment end day or day before date of return whichever is first and the average daily use per tube: amount used per tube divided by the number of days between dispense day and the day of last IMP from the tube (both included so counting as one day if two days are the same).

The total amount of IMP used between trial days was calculated as follows:

Relevant records about average daily use per tube was selected (return day > X and dispense day < Y). For each record, the last day is set to be the minimum of: Y the treatment end day, and the day of the last IMP from the tube. The first day is set to the maximum of X and the dispense day. The average daily use is multiplied by the number of days in the period between X and Y when the tube was 'in use'. This calculation assumes that the IMP in

the tube was used uniformly across all days between date of dispense and last day of IMP use. The total amount of IMP used between trial days X and Y is then derived for each subject by adding the total amount of IMP used per tube between days X and Y.

The average weekly amount of IMP used between trial days X and Y is the total amount used in the interval per subject, divided by the number of days in the interval, multiplied by 7.

b) A total of 36,458 of tubes were dispensed and 36,035 were returned. This means that 423 were not returned, corresponding to approximately 1%. Consumption for missing tubes was not imputed; they were excluded from the consumption calculations.

c) The full analysis sets were used. This was considered a reasonable approach when the analysis was undertaken.

d) i) In DELTA FORCE, patients in IGA-CHE ≥2 at week 16 continued treatment until they achieved IGA-CHE 0/1. We therefore included these estimates of consumption as they represented the situation in the model when patients would continue applying delgocitinib. This was intended to be described as the base case in the submission as it made the most use of available data.
ii) By restricting the estimates of usage to the first 12 weeks (and correcting the model as per item e below), as stated in the submission, the weekly usage in the severe CHE subgroup increases to [redacted] g/week, [redacted] g/week and [redacted] g/week among patients in partial, low and insufficient response, respectively. Delgocitinib remains dominant over PUVA, and the ICER for the comparison with alitretinoin increases to £10,907 from the intended base case described above.

e) Thank you for identifying this error. These Week 0 values should have been included in the average. After correcting this value, the mean weekly usage in the severe subgroup of patients is [redacted] g in the low response state and [redacted] g in the insufficient response state. In the moderate subgroup of patients, mean weekly usage is [redacted] g in the low response state and [redacted] g in the insufficient response state. The correction increases the ICER of delgocitinib versus

alitretinoin to £8,564. Delgocitinib remains dominant over PUVA in moderate and severe CHE. This has been corrected in the model.

f) The weekly usage data beyond week 16 is drawn from the DELTA FORCE study, which had a duration of 24 weeks. The reduction in weekly usage at week 16 is a function of the trial protocol which had patients who achieved an IGA-CHE 0 (clear) or 1 (almost clear) discontinue delgocitinib. They would only restart treatment if they lost response (IGA-CHE ≥2) off treatment. The reduction in consumption reflects this pause in treatment and is the reason why data beyond week 16 are excluded from the calculation of the average weekly usage for full responders.

g) Two mixed-model repeated measures (MMRM) analyses that differ in how the investigator's global assessment (IGA) are coded:

   a. **First Model (Using IGA as a numeric variable)**

      Conceptually, it can be written as:

      $$wmimp\_ij = \beta_0 + \beta_1(studyid_i) + \beta_2(igabase_i) + \beta_3(trt01p_i \times iga_{ij}) + \beta_4(trt01p_i \times weekn_{ij} \times iga_{ij}) + \varepsilon_{ij}$$

      where:

      - i indexes the subject,
      - j indexes the time point (week),
      - wmimp_ij is the consumption (g/week) for subject i at time j,
      - $studyid_i$ indicates which study subject i belongs to,
      - $igabase_i$ is the baseline IGA score for subject i,
      - $trt01p_i$ is the treatment group for subject i,
      - iga_{ij} is the IGA score for subject i at time j,
      - $weekn_{ij}$ is the numeric week index (0, 1, 2, etc.) for subject i at time j,
      - ε_{ij} is the within-subject error term.

      The random (within-subject) component uses a repeated statement with a compound symmetry covariance structure, meaning each subject has a constant variance across time points and a single correlation parameter for all time points.

2. **Second Model (Using IGA grouped into categories)**

In this version, the categorical variable (statec) is used, classifying each observation as “Responder” (IGA 0/1), “Partial responder” (IGA 2), or “Non-responder” (IGA 3/4). The same model structure applies:

$$wmimp\_ij = \beta_0 + \beta_1(studyid_i) + \beta_2(igabase_i) + \beta_3(trt01p_i \times statec_{ij}) + \beta_4(trt01p_i \times weekn_{ij} \times statec_{ij}) + \varepsilon_{ij}$$

Here, iga_{ij} is replaced by $statec_{ij}$ (the categorical “responder status” at time j).

Key Points:

- The outcome variable is wmimp (grams of consumption per week).
- studyid and igabase are included as covariates.
- trt01p (treatment group) interacts with time (weekn) and IGA (either numeric or categorical).
- A compound symmetry (CS) covariance structure is assumed for repeated measurements within each subject, meaning a constant variance over time and a single correlation for any two time points.
- Kenward-Roger degrees of freedom (ddfm=kr) are used, which refines the standard errors and degrees of freedom estimates for small or unbalanced samples.

This approach allows examination of how treatment effects on consumption may vary over time and how they differ by IGA-CHE level or IGA-CHE responder category.

B25. Priority question: Please provide descriptive statistics (including 95% confidence intervals and the number of patients informing each data point) on the mean weekly consumption by IGA-CHE response based on data from DELTA 1, DELTA 2, DELTA 3 and FORCE (severe CHE only) using the below

tables as a template. Please provide supportive mean weekly consumption based on 24-week data for the severe CHE subgroup.

a) **Please compare the mean weekly consumption of delgocitinib based on descriptive data with the data derived from the MMRM regression and discuss the results.**

b) **Please run a scenario analysis using the delgocitinib 12-week data provided in the below table for DELTA 1, DELTA 2 and FORCE.**

Table 51, Table 52, Table 53 present the 12- ,24- and 36-week delgocitinib consumption data on IGA-CHE categories by treatment and severity.

Table 51 12-Week delgocitinib consumption data on IGA-CHE categories by treatment and severity

IGA-CHE category	Severe CHE		Moderate CHE (DELTA 1 & 2)		Overall (not split by baseline severity)	
	Delgocitinib (D1, D2 & DFORCE)	Vehicle treatment (D1 & D2 only)	Delgocitinib	Vehicle treatment	Delgocitinib (D1, D2 & DFORCE)	Vehicle treatment (D1 & D2)
0		-				
1						
2						
3						
4						
All response categories (IGA-CHE 0-4)						

Abbreviations: CHE, Chronic hand eczema; D1, DELTA 1 trial; D2, DELTA 2 trial; DFORCE, DELTA FORCE trial; g, grams; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; n, number of subjects.

Table 52 24-Week delgocitinib consumption data on IGA-CHE categories by treatment and severity

IGA-CHE category	Severe CHE	
	Delgocitinib (DELTA 1, 2 & FORCE)	Vehicle treatment (D1 & D2 only)
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
All response categories (IGA-CHE 0-4)	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; D1, DELTA 1 trial; D2, DELTA 2 trial; DFORCE, DELTA FORCE trial; g, grams; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; n, number of subjects.

Table 53 36-Week delgocitinib consumption data on IGA-CHE categories by treatment and severity

IGA-CHE category	Delgocitinib		
	Severe CHE	Moderate CHE	Overall (no split by severity)
0/1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
Missing	N=30	N=59	N=89

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; N, total number of subjects; n, number of subjects.

a) We have pulled together a summary table below to aid a comparison of the mean weekly consumption of delgocitinib based on descriptive data with the data derived from the MMRM regression (Table 54). All MMRM estimates reflect the correction made in response to Question B24.e to include usage at week 0.

Table 54 IGA-CHE category: treatment outcomes across trials

IGA-CHE category	Severe CHE			Moderate CHE	
	Descriptive statistics (DELTA 1, DELTA 2 and DELTA FORCE)	MMRM (all timepoints [B24.d.i])	MMRM (up to week 12 only [B24.d.ii])	Descriptive statistics (DELTA 1 and DELTA 2)	MMRM (up to week 12 only)
0/1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; DELTA 1, Clinical trial evaluating delgocitinib in moderate and severe CHE; DELTA 2, Clinical trial evaluating delgocitinib in moderate and severe CHE; DELTA FORCE, Clinical trial evaluating delgocitinib vs. alitretinoin; g, grams; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; MMRM, mixed model for repeated measures.

Among patients with severe CHE at baseline, the descriptive statistics at week 12 suggest that weekly usage is higher on average than the outputs of the MMRM model. The only exception to this is for the insufficient response health state (IGA-CHE 4) where the expected usage according to the MMRM model (based only on estimates to week 12) is higher than the descriptive statistics once data have been adjusted for the modelled IGA-CHE health states (i.e. after pooling Clear and Almost Clear categories).

Among patients with moderate CHE at baseline, the descriptive statistics at week 12 suggest that weekly usage is lower on average than the outputs of the MMRM, except in the case of patients who experience a worsening to IGA-CHE 4.

The appropriateness of the different sources depends on what one considers to be the most relevant driver of usage in both the short and longer term. The descriptive statistics are a function of the total usage by patients who achieve a particular outcome at week 12. It assumes that the outcome at week 12 is the most relevant feature by which to define usage in the economic model, both during the initial 12 weeks and any time after that when a patient occupies an on-treatment state (e.g. IGA ≥2).

The MMRM outputs are a reflection of the usage by patients whilst they are experiencing a given level of CHE severity. It assumes that the severity at any given time is the most relevant feature by which to define usage in the model.

As such, it represents a more appropriate approach to the way that usage is built into the model, both for the initial 12-week period and beyond, where patients use delgocitinib in an as-needed fashion based on their signs and symptoms.

LEO Pharma argue that the MMRM output remains the best available source for estimating delgocitinib consumption and that the scenario using the descriptive statistics represents a more conservative approach that could overestimate delgocitinib consumption in the longer term.

b) The model was run for the severe CHE population using the descriptive statistics at week 12 from DELTA 1, DELTA 2 and DELTA FORCE for delgocitinib. A weighted average ([redacted] g/week) was calculated for the full response health state (IGA-CHE 0/1) using the values for IGA-CHE 0 and IGA-CHE 1 with weights defined by the number of patients informing each data point. The results of this scenario increase the incremental cost of delgocitinib to £608 compared to alitretinoin for an ICER of £16,011. Delgocitinib remains dominant over PUVA. Using the same approach but applying the usage values reported in Table 52 (at week 24 [from DELTA FORCE] or week 16 [from DELTA 1 and DELTA 2]), results in an ICER of £15,959.

B26. Priority question: Please provide a scenario where tube wastage is assumed for delgocitinib (i.e. delgocitinib cost is based on number of whole tubes per model cycle and not by cost per gram)

To approximate this scenario, we have assumed that patients will require 2 x 60 g tubes over 12 weeks of treatment with delgocitinib. This translates to one-sixth of a tube per week or 10 g/week. By inflating the weekly usage, we are crudely simulating wastage to be around [redacted] to [redacted] grams per week, or around [redacted] to [redacted] grams of delgocitinib wasted per dispensed tube relative to the base case. At this level of usage by all patients, the ICER of delgocitinib vs alitretinoin in severe CHE increases to £19,134 and delgocitinib still dominates PUVA in moderate and severe CHE.

The company considers the inclusion of wastage to represent an overly conservative scenario as the label for delgocitinib recommends that treatment be used as needed in the event of recurrence of the signs and symptoms of CHE. Given the fluctuating nature of the condition (the time to loss of response observed in the clinical trials falls

well within 1 year), the experience that these patients have with the self-management of their condition, along with the ease of use and the shelf life of the product (1 year), there is good reason to expect that wastage will be minimal. It is unlikely that the product would expire between two treatment phases. Therefore, a patient who has experienced a loss of response is likely to be able to apply unused cream from a prior course.

In addition, this scenario only explored the wastage of delgocitinib and assumed that alitretinoin would not be wasted. Alitretinoin is distributed in packs of 30 capsules, but the model estimates the costs of alitretinoin based on the number of capsules consumed. For example, in the first 12 weeks of treatment, 84 capsules are consumed by one patient for a cost of £1,382.40, but the patient would be expected to require 3 packs for a cost of £1,481.20. This could represent a wastage if patients discontinue treatment, and the ICER delgocitinib versus alitretinoin would likely decrease if this wastage was considered in the model.

B27. According to the EAG's clinical experts, 30 minutes of nurse time would be required per administration of PUVA. Please conduct a scenario analysis including this cost.

For this scenario, we added the cost of 30 minutes of dermatologist nurse time (£29.00) to the cost per session of PUVA (£94.00) to get a total cost per PUVA session of £123.00. This brings the cost per 4-week cycle of PUVA to £984.00.

This increases the expected total cost of PUVA to £10,881 in severe CHE (compared to £9,849 in the base case) and to £9,764 in moderate CHE (compared to £8,809 in the base case). In both severe and moderate CHE and consistent with the base case, delgocitinib is less costly and more effective than PUVA. The impact of the increased PUVA cost in this scenario reduces the ICER for delgocitinib versus alitretinoin in severe CHE to £8,218 from £8,221 in the base case. This change is due to the inclusion of PUVA in the next-line treatment basket.

B28. The EAG could not validate the following healthcare resource groups (HRG) cost codes used in the model against the NHS cost sources. Please clarify if the costs included in the model are correct and also provide further details on the service

descriptions and service codes, as well as any other information that will help to locate the costs.

a) JC47Z (£140.12) used for PUVA cost (Table 65 of the CS).

b) DAPS08 (£6.63) used for lipid monitoring cost (Table 67 of the CS).

c) WF01A (£90) used for a dermatologist visit cost (Table 68 of the CS).

i) Please note that in the model, a dermatologist visit cost of £148 has been used in the model but also could not be verified against the NHS cost source. Please clarify what should be the correct cost for a dermatologist visit in the company's base case.

Thank you for identifying these inconsistencies in the submitted model.

a) JC47Z is the code for "Phototherapy or Photochemotherapy". We took the cost from its use as an outpatient procedure independent of service. We incorrectly took the cost (£140.12) from the National Health Service (NHS) Reference Costs for 2021/22 instead of the cited NHS Reference Costs for 2022/23. The correct cost, using the same code, description and service type, based on the cited 2022/23 source is £145.03.
b) DAPS08 is the code for Phlebotomy under "Total Other Currencies" in the NHS Reference Costs 2022/23 workbook (Cell reference: 'Total Other Currencies'!C67).
c) The cost listed in Table 68 for the dermatologist visit (£90) was listed erroneously. The correct cost, which is used in the economic model, is £148, which was sourced from the 2023/35 NHS Payment Scheme workbook for WF01B (first attendance – single professional) under the Dermatology Service (330).

As none of the incorrect values were used in the base case, the base case results are not expected to change following these corrections.

B29. In Table 71 of the CS, the company presents the utilisation data from RWEAL. Please clarify which table from the supplied reference document the data were taken

from or provide more information on how the data from RWEAL were used to estimate the utilisation of next line treatment.

Unfortunately, it seems that some of the RWEAL study data that has informed the economic model was unintentionally omitted from our reference pack. Please find the full table from the RWEAL study, looking at the UK focus population broken down by CHE severity in Table 55. The split between providers was not relevant to the economic model but reflects how the data was presented.

In the economic model, patients classified as “Severe” and “Very severe” in RWEAL were grouped together as Severe; patients classified as “Moderate” were categorised as Moderate. From the comprehensive list of treatments taken in the past 12 months, we selected a subset that were likely to be reserved for patients requiring second- and third-line care for inclusion in the next-line treatment basket. These have been highlighted in green, along with TCS and TCIs which were included in the BSC treatment basket.

Table 55 Treatment history in the UK focus population

Base: All patients in the UK with completed census forms and focus forms from complete physicians	Dermatologist				GPwER			
	N = 183	Moderate, N = 98	Severe, N = 74	Very severe, N = 11	N = 182	Moderate, N = 113	Severe, N = 63	Very severe, N = 6
All treatments taken in the past 12 months (multiple responses possible), n (%)								
Abrocitinib	[redacted]							
Acitretin	[redacted]							
Adalimumab	[redacted]							
Alclometasone dipropionate	[redacted]							
Alitretinoin	[redacted]							
Azathioprine	[redacted]							
Betamethasone dipropionate	[redacted]							
Baricitinib	[redacted]							
Betamethasone valerate	[redacted]							
Bimekizumab	[redacted]							
Brodalumab	[redacted]							
Clobetasol propionate	[redacted]							
Corticosteroids (orally taken)	[redacted]							
Crisaborole	[redacted]							
Cyclosporine	[redacted]							
Dupilumab	[redacted]							
Emollients	[redacted]							
Etanercept	[redacted]							
Fluocinolone	[redacted]							

Base: All patients in the UK with completed census forms and focus forms from complete physicians	Dermatologist				GPwER			
Fluocinonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Guselkumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydrocortisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mometasone furoate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other topical treatments[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pimecrolimus cream	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus ointment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tralokinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Triamcinolone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ultraviolet B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upadacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All treatments (per family) taken in the past 12 months (multiple responses possible), n (%)								
JAK inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base: All patients in the UK with completed census forms and focus forms from complete physicians	Dermatologist				GPwER			
TCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topical treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emollients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All treatments (per subfamily) taken in the past 12 months (multiple responses possible), n (%)								
JAK inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITCS:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
hTCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mTCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
uhTCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topical treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TCIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emollients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Phototherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] either oral or parenteral

[b] iontophoresis, tar, potassium, permanganate, aluminium, acetate, etc.

Abbreviations: CHE, Chronic hand eczema; GPwER, General Practitioner with Extended Role; hTCS, high-potency topical corticosteroids; JAK, janus kinase; ITCS, low-potency topical corticosteroids; mTCS, moderate-potency topical corticosteroids; N, total number of subjects; n, number of subjects; PUVA, Psoralen plus ultraviolet A; TCIs, topical calcineurin inhibitors; TCS, topical corticosteroids; uhTCS, ultra-high potency topical corticosteroids.

B30. The SmPC for dupilumab states the recommended dose for treating atopic dermatitis in adults is “an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection”. However, in the model the dose assumed is 300 mg every other week.

a) Please clarify why the 600 mg loading dose has not been included in the cost calculation.

b) Please provide a scenario where the cost of the loading dose of dupilumab (600 mg) is included in the total costs of next line treatment.

The loading dose was not included as we had focused on the maintenance dose given that patients receiving dupilumab in the next-line basket were assumed to use it continuously (i.e. 100% of the time).

For the requested scenario analysis, we have re-estimated the cost of dupilumab based on an assumption of 27 x 300 mg doses per year. This amounts to a per-cycle cost of £1,313.54 instead of £1,264.89. Including this extra dose increases the per-cycle cost of the next-line basket from £170.45 to £175.86 in the severe CHE subgroup and from £152.40 to £157.37 in the moderate CHE subgroup.

In the requested scenario where the loading dose of dupilumab is included in the costing for the next-line treatment basket, PUVA remains dominated by delgocitinib in both moderate and severe CHE. The ICER of delgocitinib versus alitretinoin in the severe CHE population decreases to £8,208 from £8,221 in the base case.

B31. Please clarify the source used to estimate the median duration of next line treatments and BSC, as presented in Table 71 of the CS.

As mentioned in section 3.3.7.1 of the submission, the duration of therapy for each treatment family was based on data from the RWEAL study.

Oral therapies (e.g. acitretin, alitretinoin, azathioprine, ciclosporin, methotrexate, and oral corticosteroids) were grouped into a treatment family, as were phototherapies (e.g. PUVA and NB-UVB), various potency TCS, TCIs and emollients. Dupilumab was included on its own. Data on the mean and median duration of therapy with each treatment or treatment family was derived from the RWEAL study. For oral therapies and for dupilumab, the data for a UK population was used. For other

treatments, data from the overall RWEAL study population was used. Values are based on treatment duration for treatments that were not ongoing.

A comparison of the mean and median days of treatment suggested a right skew of the data generally, so the median values were used to estimate a percent of time on treatment within a given year. Table 56 presents the values from RWEAL which informed the economic model base case. For a sensitivity analysis, we have also provided data from the overall population for oral therapies and dupilumab and from the UK population for phototherapy and TCIs. In this analysis the ICER of delgocitinib versus alitretinoin in the severe population would increase to £8,409 from £8,221.

Table 56 Treatment duration in days, used in economic model to inform next-line treatment and best supportive care

Treatment family	N	Mean (95% CI), days	Median (IQR), days	% of year using treatment (based on median)	Source
Values used in economic model					
Oral therapy	35	280.1 (204.8, 355.4)	221.0 (39.5, 531.0)	60.5%	UK
Phototherapy	38	190.4 (127.9, 252.9)	88.0 (61.3, 264.8)	24.1%	Overall
Dupilumab	6	472.3 (349.4, 595.2)	530.5 (529.3, 537.8)	145.3%[a]	UK
TCI	39	213.0 (150.2, 275.8)	122.0 (62.0, 437.0)	33.4%	Overall
Emollients	7	178.7 (75.1, 282.3)	151.0 (93.5, 273.5)	41.4%	Overall
TCS	522	286.3 (224.7, 347.9)	122.0 (58.3, 316.3)	33.4%	Overall
Alternative values for sensitivity analysis					
Oral therapy	139	174.0 (143.9, 204.1)	111.0 (48.5, 218.5)	30.4%	Overall
Phototherapy	17	256.3 (141.8, 370.8)	84.0 (62.0, 531.0)	23.0%	UK
Dupilumab	15	295.1 (200.6, 389.6)	180.0 (155.5, 529.5)	49.3%	Overall
TCI	8	538.0 (534.2, 541.8)	538.5 (534.8, 542.3)	147.5%	UK

[a] Since the median duration of dupilumab exceeds a year, the model assumes that the proportion of patients receiving dupilumab in the next-line treatment cohort are on it 100% of any unit of time

Abbreviations: CI, confidence interval; IQR, interquartile range; N, number of subjects; TCI, topical calcineurin inhibitor; TCS, topical corticosteroids; UK, United Kingdom.

Systematic literature review

B32. Priority question: Appendix F.2 appears to be missing sections. For example, both Appendix E.2 and G.2 have information on data extraction and

quality assessment. Please clarify if Appendix F.2 is incomplete and if so, please provide the missing sections.

The following paragraph describes the data extraction and quality assessment performed for studies included in the review of HRQoL presented in appendix F.

All extractions were performed by one reviewer and quality checked by a second reviewer. Any discrepancies were resolved by consensus across both reviewers. For included studies, relevant information was collected on summary of study design (e.g. methods, setting, objectives of the study), patient population (including disease severity) and HRQoL outcomes reported (including patient-reported outcomes). The quality of included studies was not formally assessed (e.g. using a critical appraisal tool).

B33. Please clarify why the quality assessment of HRQoL and costs studies was not performed for the systematic literature review?

For the HRQoL studies, we consulted Technical Support Document 9 (TSD9) from NICE DSU, specifically Box 3, which outlines key criteria for assessing the quality of health state utility value (HSUV) studies. These include sample size, selection and recruitment of respondents and their rates of response, inclusion/exclusion criteria, loss to follow-up and missing data and any other issues, e.g. geographic applicability. Each of these aspects was extracted and summarised in our reporting.

For the cost studies, no standardised reference checklist was identified for quality assessment. However, key methodological aspects were reviewed:

- Study perspective (e.g., healthcare payer, societal)
- Costing methodology (e.g., sources of cost data, transparency in calculations)
- Time horizon and discounting (alignment with NICE's 3.5% discount rate)
- Use of sensitivity analyses (e.g., deterministic, probabilistic)
- Consistency with best-practice economic evaluation frameworks (e.g., Drummond et al., CHEERS checklist)

B34. Can the company provide the breakdown in consumption data between non and hyperkeratotic patients from DELTA FORCE?

Table 57 presents the average weekly consumption data for delgocitinib broken down by IGA-CHE severity categories and by hyperkeratotic status at baseline. The size of the hyperkeratotic CHE population is very small, with just 29 patients, therefore caution should be taken when interpreting the results. On average, the data show that regardless of the level of IGA-CHE response achieved by week 12, [redacted].

These data have been incorporated into scenarios conducted in response to Question B6. For this, we have assumed that the hyperkeratotic subgroup consumption data applies only during the initial period and that the consumption during the re-treatment period is aligned with the base case settings for the overall patient population. This is considered a reasonable assumption given that the initial morphology of CHE does not reliably reflect the aetiological cause and can change over time.[14, 19] Even though a patient might present initially with a particular clinical subtype, such as hyperkeratosis, it does not mean that this will be the predominant clinical subtype at the point of relapse. In addition, the re-initiation of delgocitinib at the point of a mild relapse (e.g. IGA-CHE 2) may mean that even if hyperkeratosis is present, a patient may need to use less delgocitinib during re-treatment than initial treatment when their disease was severe due to earlier intervention.

Table 57 12-Week delgocitinib consumption data on IGA-CHE categories by hyperkeratotic status from DELTA FORCE

IGA-CHE category	Severe CHE	
	Hyperkeratotic	Non-hyperkeratotic
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]

IGA-CHE category	Severe CHE	
All response categories (IGA-CHE 0-4)	[redacted]	[redacted]

Abbreviations: CHE, Chronic hand eczema; g, grams; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; n, number of subjects.

Section C: Textual clarification and additional points

C1. The BSC moderate cost in Table 69 of the CS is £585.52, but in the model it is £584.52. Please check and correct as necessary.

This was a typo in Table 69. The correct value is £584.52.

Updated results of cost-effectiveness analysis

Deterministic base-case results

Base-case cost-effectiveness results for patients with severe CHE and with moderate CHE are shown in Table 58. Delgocitinib was less costly and more effective than PUVA in both populations. The ICER for delgocitinib compared with alitretinoin was £8,526 per QALY. Delgocitinib is ranked first in terms of net health benefit at the £20,000 and £30,000 per QALY thresholds across both moderate and severe CHE populations.

Table 58 Base case results for severe and moderate CHE subgroups

Treatment		Severe CHE			Moderate CHE	
		Alitretinoin (reference)	Delgocitinib	PUVA	Delgocitinib (reference)	PUVA
Total	Costs (£)	8,875	9,211	9,811	8,282	8,812
	LYs	8.362	8.362	8.362	8.375	8.375
	QALYs	5.725	5.765	5.714	5.847	5.795
Incremental vs reference	Costs (£)	-	336	936	-	529
	LYG	-	0	0	-	0
	QALYs	-	0.039	−0.011	-	−0.051
ICER (£/QALY)	vs reference	-	8,526	Dominated	-	Dominated
	Fully incremental	-	8,526	Dominated	-	Dominated
NHB at	£20,000	5.28	5.30	5.22	5.43	5.35
	£30,000	5.43	5.46	5.39	5.57	5.50
Rank based on NHB		2	1	3	1	2

ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALY, quality-adjusted life year.

Probabilistic sensitivity analysis

PSA results are shown in Table 59. For patients with severe CHE, the mean ICER for delgocitinib compared with alitretinoin was £10,858 per QALY. PUVA was dominated by both delgocitinib and alitretinoin. Cost-effectiveness acceptability curves are shown in Figure 12. At cost-effectiveness thresholds of £20,000 and £30,000 per QALY, delgocitinib has the highest likelihood of the comparators of being cost effective (83.8% and 92.2%), followed by alitretinoin (16.2% and 7.8%). Delgocitinib was dominant (i.e., less costly and more effective) in 8.7% of simulations compared to alitretinoin and in 92.9% of simulations compared to PUVA.

For patients with moderate CHE, delgocitinib dominated PUVA. Cost-effectiveness acceptability curves are shown in Figure 13. Delgocitinib had a 99.5% and 99.8%%

likelihood of being more cost effective than PUVA at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, respectively, and dominated PUVA in 89.9% of simulations.

Table 59 PSA results for severe and moderate CHE subgroups

Treatment	Total, mean (95% CrI)		Total NHB, mean (95% CrI)		Incremental vs reference, mean (95% CrI)		iNHB vs reference, mean (95% CrI)	
	Costs (£)	QALYs	£20k	£30k	Costs (£)	QALYs	£20k	£30k
Severe CHE								
Alitretinoin	8857 (7838, 9952)	5.752 (5.580, 6.011)	5.31 (5.12, 5.6)	5.46 (5.28, 5.74)	-	-	-	-
Delgocitinib	9237 (8273, 10295)	5.787 (5.607, 6.044)	5.33 (5.15, 5.59)	5.48 (5.31, 5.75)	380 (−117, 980)	0.035 (0.003, 0.060)	0.016 (−0.028, 0.044)	0.022 (−0.015, 0.045)
PUVA	9784 (8672, 10889)	5.740 (5.569, 5.991)	5.25 (5.06, 5.54)	5.41 (5.23, 5.70)	926 (687, 1078)	−0.012 (−0.028, −0.004)	−0.059 (−0.076, −0.044)	−0.043 (−0.059, −0.033)
Moderate CHE								
Delgocitinib	8303 (7509, 9135)	5.88 (5.656, 6.183)	5.46 (5.25, 5.79)	5.60 (5.39, 5.92)	-	-	-	-
PUVA	8745 (7595, 9653)	5.832 (5.617, 6.135)	5.39 (5.17, 5.75)	5.54 (5.32, 5.88)	442 (−400, 966)	−0.048 (−0.074, −0.023)	-0.07 (−0.095, −0.026)	−0.063 (−0.085, −0.03)

CHE, chronic hand eczema; CrI, credible interval; iNHB, incremental net health benefit; NHB, net health benefit; PSA, probabilistic sensitivity analysis; PUVA, psoralen–UV A phototherapy; QALYs, quality-adjusted life years.

Figure 12 PSA cost-effectiveness acceptability curve of all comparators for severe CHE

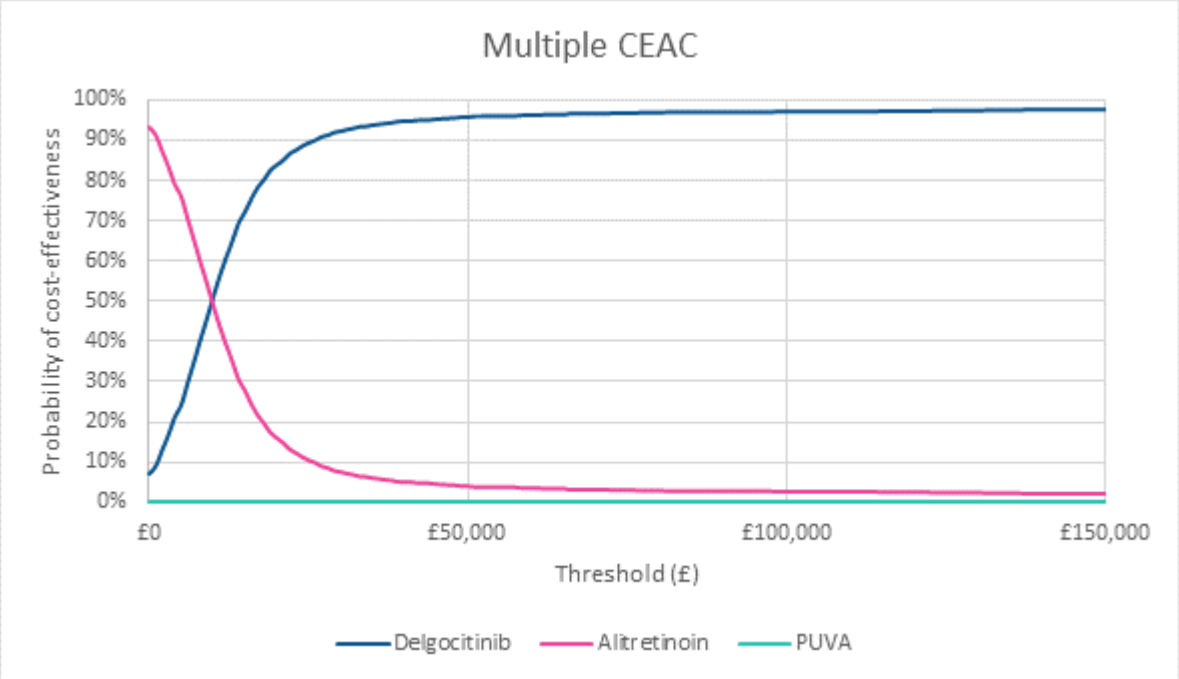
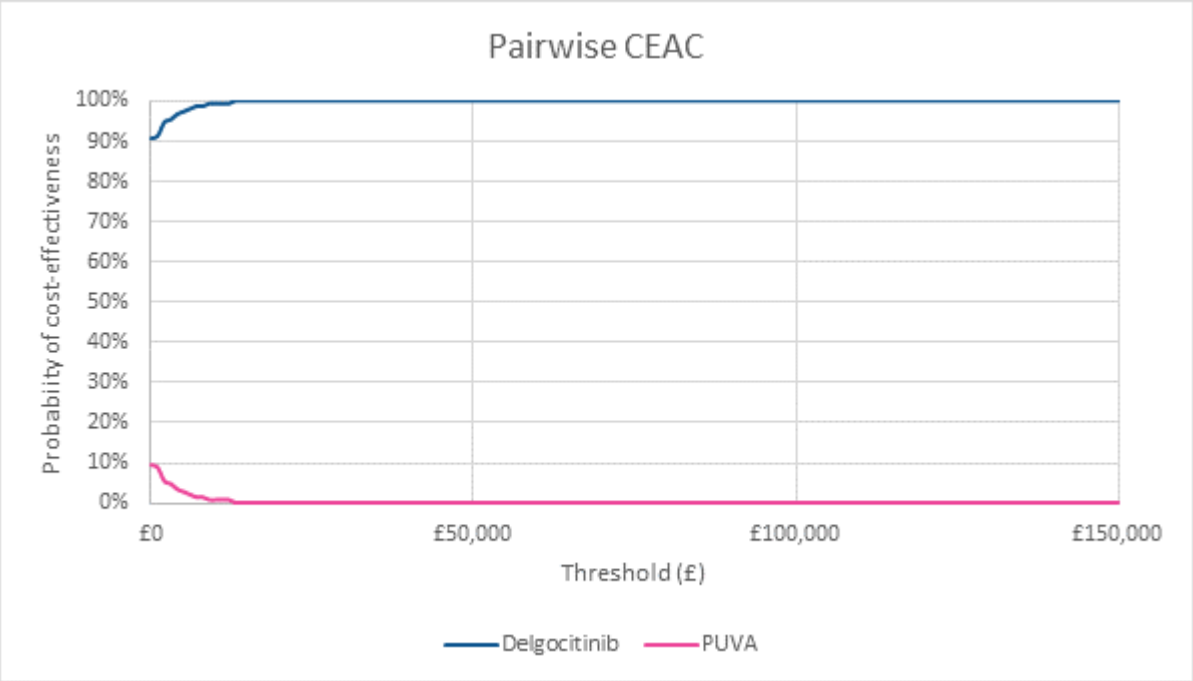


Figure 13 PSA cost-effectiveness acceptability curve for moderate CHE



Scenario analysis

Table 60 Scenario analyses for severe CHE and moderate CHE

Scenario	Severe CHE		Moderate CHE
	Delgocitinib vs alitretinoin ICER	Delgocitinib vs PUVA ICER	Delgocitinib vs PUVA ICER
Base case	£8,526	Dominates	Dominates
Time horizon			
1 year	Dominates	Dominates	Dominates
3 years	£5,324	Dominates	Dominates
5 years	£7,780	Dominates	Dominates
30 years	£8,550	Dominates	Dominates
Stopping rules			
Scenario 1	£15,378	£1,956	£2,395
Scenario 2	£19,965	£7,258	£2,395
Scenario 3	£21,938	£14,314	£12,045
Delgocitinib usage (g/week)			
Overall average ([redacted])	£7,030	Dominates	Dominates
DELTA 2 ([redacted])	£402	Dominates	Dominates
DELTA FORCE ([redacted])	£17,750	Dominates	Dominates
As-needed initial treatment	£8,256	Dominates	Dominates
Health state definition			
HECSI responses (< 50, 50, 75, 90)	£9,377	Dominates	Dominates
NMA results			
Primary endpoint NMA	£6,583	Dominates	Dominates
Cumulative response NMA	£9,766 [a]	Dominates [a]	Dominates [b]
Distribution of non-responders at week 12			
Equal for all treatments based on delgocitinib	£4,289	Dominates	NA
ALPHA for alitretinoin and PUVA (severe only) – NRI	£9,714	Dominates	NA

Scenario	Severe CHE		Moderate CHE
	Delgocitinib vs alitretinoin ICER	Delgocitinib vs PUVA ICER	Delgocitinib vs PUVA ICER
ALPHA for alitretinoin and PUVA (severe only) - OC	£4,529	Dominates	NA
Relapse			
Delgocitinib informed by D3	£10,657	Dominates	Dominates
Risk of relapse with alitretinoin and PUVA assumed to be 50% of risk with delgocitinib	£18,500	Dominates	Dominates
Alternative re-initiation assumptions			
All reinitiate at IGA-CHE ≥ 2	£7,919	Dominates	Dominates
All reinitiate at IGA-CHE ≥ 3	£6,463	Dominates	Dominates
Alitretinoin non-reinitiation: 12%	Dominates	Dominates	Dominates
Response and discontinuation from retreatment			
Differential probabilities of response by treatment [c]	£7,496	Dominates	Dominates
Retreatment discontinuation 50% of initial continued treatment discontinuation	£9,790	Dominates	Dominates
Utilities			
Response-dependent and treatment-independent utilities from DELTA 1, 2 and FORCE	£10,412	Dominates	Dominates
Health state costs			
Health state costs increase with IGA-CHE severity based on data from Augustin 2011	£6,992	Dominates	Dominates
Adverse effects			
No utility decrement	£8,668	Dominates	Dominates
No cost impact	£8,801	Dominates	Dominates
No cost nor utility decrement	£8,948	Dominates	Dominates
Dermatologist visit for AEs	£7,970	Dominates	Dominates
Next-line and BSC assumptions			
Next-line progression and basket composition from ALPHA	£7,951	Dominates	Dominates
Next-line efficacy: 75% in LDA	£8,666	Dominates	Dominates
Percent move to next-line treatment: 75%	£8,264	Dominates	Dominates
LDA defined as full response [d]	£8,626	Dominates	Dominates
Patients on BSC revert to baseline CHE severity	£5,302	Dominates	Dominates

[a] In this scenario, [redacted], [redacted], [redacted] and [redacted] of delgocitinib, alitretinoin, PUVA and BSC patients, respectively, achieve full response at week 12.

[b] In this scenario, [redacted], [redacted] and [redacted] of delgocitinib, PUVA and BSC patients, respectively achieve full response at week 12.

[c] In this scenario, probabilities of response to retreatment for alitretinoin and PUVA were adjusted by the odds ratios from the initial period; the resulting per-cycle response rates were 20.2% for delgocitinib, [redacted]% for alitretinoin and [redacted]% for PUVA.

[d] In this scenario, the NL treatment HS costs equals £460.77 and the utility equals 0.776

BSC, best supportive care; CHE, chronic hand eczema, g, gram; HECSI; hand eczema severity index; ICER, incremental cost-effectiveness ratio; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; NMA, network meta-analysis; NRI, non-responder imputation; OC, observed case; PUVA, psoralen–UV A phototherapy.

Deterministic sensitivity analysis

Figure 14 Tornado plot of delgocitinib vs alitretinoin for severe CHE

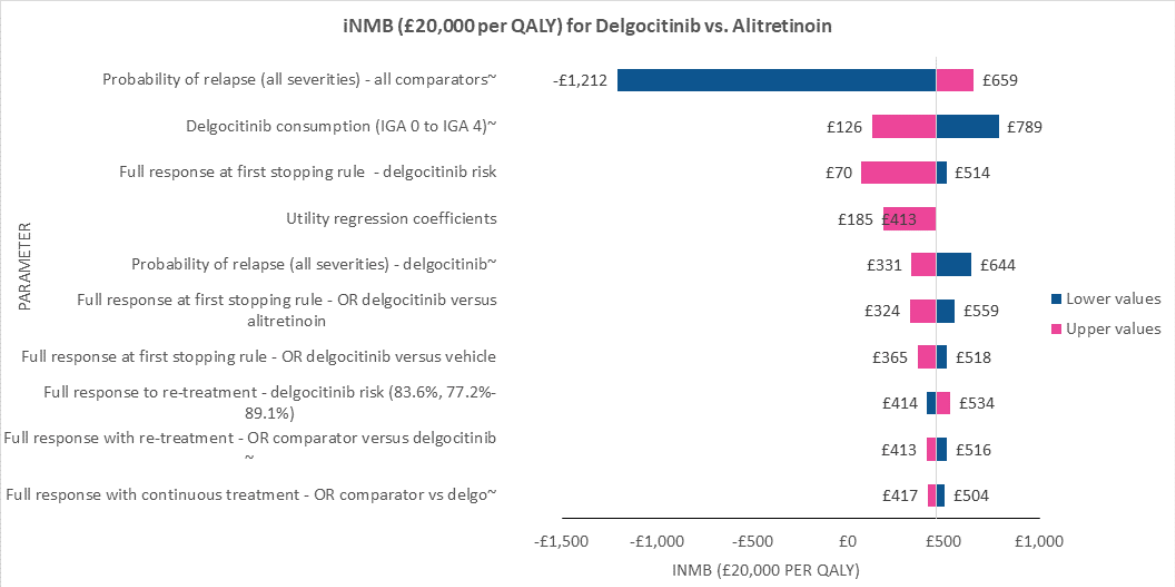


Figure 15 Tornado plot of delgocitinib vs PUVA for severe CHE

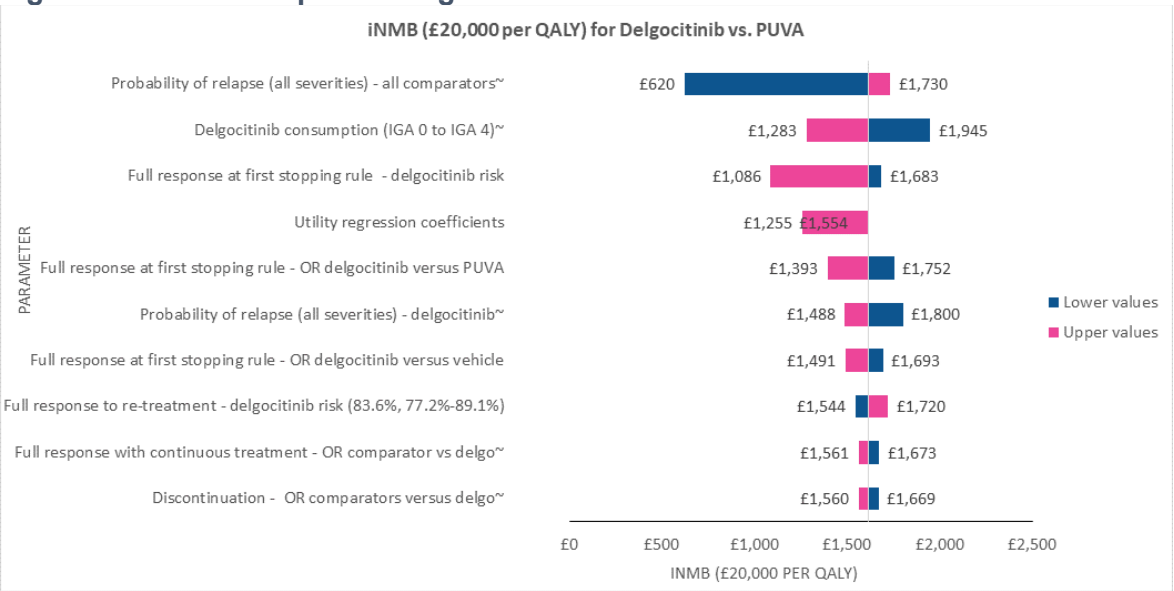


Figure 16 Tornado plot of delgocitinib vs PUVA for moderate CHE

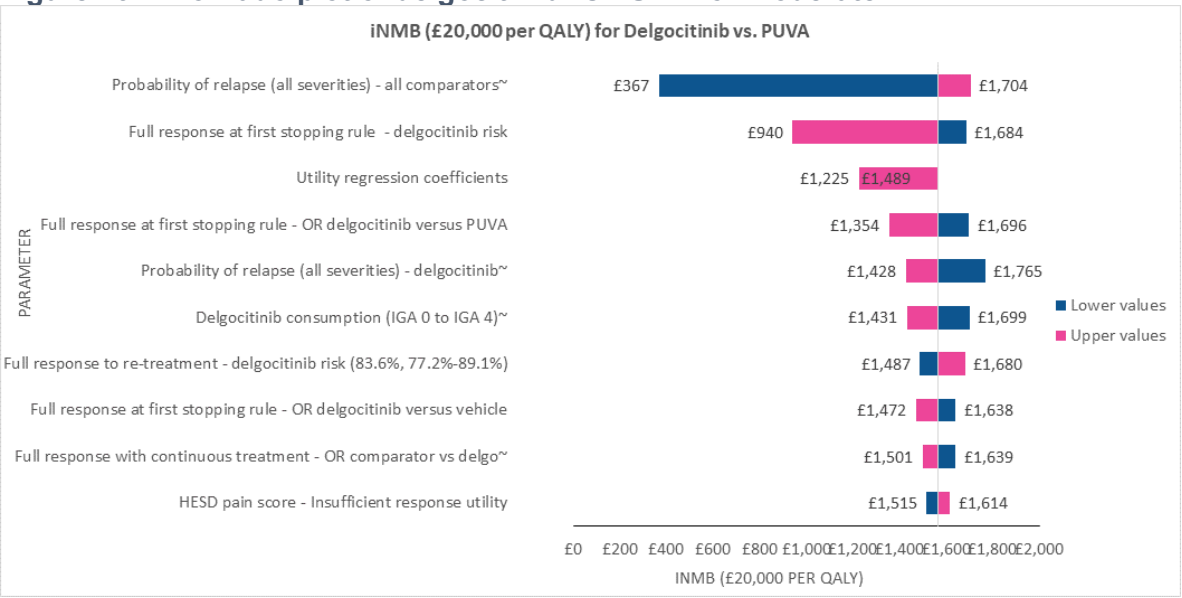


Table 61 Net monetary benefit of delgocitinib vs alitretinoin at £20,000 per QALY threshold – severe CHE

Parameter	Low	High	Difference
Probability of relapse (all severities) – comparators [a]	-£1,212	£659	£1,870
Delgocitinib consumption (IGA 0 to IGA 4) [a]	£789	£126	£662
Full response at first stopping rule - delgocitinib risk [a]	£514	£70	£443
Utility regression coefficients [a]	£413	£185	£318
Probability of relapse (all severities) - delgocitinib [a]	£644	£331	£313
Full response at first stopping rule - OR delgocitinib versus alitretinoin [a]	£559	£324	£235
Full response at first stopping rule - OR delgocitinib versus vehicle [a]	£518	£365	£153
Full response to re-treatment - delgocitinib risk (83.6%, 77.2%-89.1%) [a]	£414	£534	£120
Full response with re-treatment - OR comparator versus delgocitinib [b]	£516	£413	£104
Full response with continuous treatment - OR comparator vs delgocitinib [b]	£504	£417	£87
Comparator proportion of patients opting not to re-initiate treatment [a]	£483	£436	£47
Baseline utility [a]	£476	£441	£35
Partial response with continued treatment - delgocitinib risk [a]	£475	£440	£35
Delgocitinib proportion of patients opting not to re-initiate treatment [a]	£444	£471	£28
All comparators AE frequency [a]	£449	£468	£19
HESD pain score - insufficient response [a]	£449	£467	£18
Discontinuation from NL [b]	£472	£454	£18
Discontinuation - OR comparators versus delgocitinib [a]	£467	£450	£17
Monitoring costs [c]	£450	£466	£16
Low response with continued treatment - delgocitinib risk [a]	£465	£449	£15
Health care unit costs [c]	£451	£466	£15
Efficacy of NL basket [a]	£466	£451	£15
Delgocitinib AE frequency [a]	£464	£452	£13
HECSI score - Insufficient response [a]	£452	£464	£11

HESD pain score - full response [a]	£453	£463	£10
HESD pain score - Partial response [a]	£462	£454	£8
Proportion of childbearing women [c]	£455	£461	£6
AEs disutilities [c]	£456	£460	£4
HESD pain score - Low response [a]	£456	£460	£4
Delgocitinib risk of discontinuation [a]	£460	£456	£3
HECSI score - Partial response [a]	£459	£458	£1
Proportion of patients discontinuing treatment directly to BSC [a]	£459	£458	£1
HECSI score - Low response [a]	£458	£459	£1
HECSI score - Full response [a]	£458	£458	£0
Vehicle average weekly consumption in grams [a]	£458	£458	£0
Alitretinoin percentage patients on the lower dose [c]	£458	£458	£0
Proportion of patients discontinuing 2L directly to BSC [c]	£458	£458	£0

[a] Varied to limits of 95% confidence interval.

[b] Standard error assumed to be 20% of the mean.

[c] Lower and upper limits are 85% and 115% of the mean.

Table 62 Net monetary benefit of delgocitinib vs PUVA at £20,000 per QALY threshold – severe CHE

Parameter	Low	High	Difference
Probability of relapse (all severities) – comparators [a]	£620	£1,730	£1,110
Delgocitinib consumption (IGA 0 to IGA 4) [a]	£1,945	£1,283	£662
Full response at first stopping rule - delgocitinib risk [a]	£1,683	£1,086	£596
Utility regression coefficients [a]	£1,554	£1,255	£419
Full response at first stopping rule - OR delgocitinib versus PUVA [a]	£1,752	£1,393	£359
Probability of relapse (all severities) - delgocitinib [a]	£1,800	£1,488	£313
Full response at first stopping rule - OR delgocitinib versus vehicle [a]	£1,693	£1,491	£202
Full response to re-treatment - delgocitinib risk (83.6%, 77.2%-89.1%) [a]	£1,544	£1,720	£176
Full response with continuous treatment - OR comparator vs delgocitinib [b]	£1,673	£1,561	£112
Discontinuation - OR comparators versus delgocitinib [a]	£1,669	£1,560	£109
Delgocitinib risk of discontinuation [a]	£1,669	£1,572	£97
Partial response with continued treatment - delgocitinib risk [a]	£1,639	£1,587	£52
Baseline utility [a]	£1,638	£1,590	£48
Delgocitinib proportion of patients opting not to re-initiate treatment [a]	£1,600	£1,627	£28
HESD pain score - Insufficient response [a]	£1,602	£1,626	£24
Low response with continued treatment - delgocitinib risk [a]	£1,624	£1,601	£23
Discontinuation from NL [b]	£1,632	£1,609	£23
Comparators proportion of patients opting not to re-initiate treatment [a]	£1,625	£1,604	£21
Efficacy of NL basket [a]	£1,624	£1,605	£19
HECSI score - Insufficient response [a]	£1,607	£1,622	£15
Health care unit costs [c]	£1,608	£1,621	£13
Delgocitinib AE frequency [a]	£1,621	£1,608	£13
HESD pain score - Full response [a]	£1,608	£1,621	£13
HESD pain score - Partial response [a]	£1,618	£1,611	£7

Full response with re-treatment - OR comparator versus delgocitinib [b]	£1,618	£1,612	£6
AEs disutilities [c]	£1,616	£1,612	£4
HESD pain score - Low response [a]	£1,613	£1,616	£3
Proportion of patients discontinuing treatment directly to BSC [a]	£1,616	£1,614	£1
HECSI score - Partial response [a]	£1,615	£1,614	£1
HECSI score - Low response [a]	£1,614	£1,615	£1
HECSI score - Full response [a]	£1,614	£1,615	£1
Vehicle average weekly consumption in grams [a]	£1,614	£1,614	£0

[a] Varied to limits of 95% confidence interval.

[b] Standard error assumed to be 20% of the mean.

[c] Lower and upper limits are 85% and 115% of the mean.

Table 63 Net monetary benefit of delgocitinib vs PUVA at £20,000 per QALY threshold – moderate CHE

Parameter	Low	High	Difference
Probability of relapse (all severities) - comparators [a]	£367	£1,704	£1,337
Full response at first stopping rule - delgocitinib risk [a]	£1,684	£940	£744
Utility regression coefficients [a]	£1,489	£1,225	£416
Full response at first stopping rule - OR delgocitinib versus PUVA [a]	£1,696	£1,354	£342
Probability of relapse (all severities) - delgocitinib [a]	£1,765	£1,428	£337
Delgocitinib consumption (IGA 0 to IGA 4) [a]	£1,699	£1,431	£267
Full response to re-treatment - delgocitinib risk (83.6%, 77.2%-89.1%) [a]	£1,487	£1,680	£193
Full response at first stopping rule - OR delgocitinib versus vehicle [a]	£1,638	£1,472	£166
Full response with continuous treatment - OR comparator vs delgocitinib [b]	£1,639	£1,501	£138
HESD pain score - Insufficient response [a]	£1,515	£1,614	£98
Discontinuation - OR comparators versus delgocitinib [a]	£1,596	£1,534	£62
Partial response with continued treatment - delgocitinib risk [a]	£1,589	£1,536	£52
Delgocitinib risk of discontinuation [a]	£1,593	£1,543	£49
Baseline utility [a]	£1,587	£1,542	£46
HECSI score - Insufficient response [a]	£1,543	£1,586	£43
Delgocitinib proportion of patients opting not to re-initiate treatment [a]	£1,550	£1,578	£28
All comparators proportion of patients opting not to re-initiate treatment [a]	£1,578	£1,552	£26
HESD pain score - Low response [a]	£1,574	£1,556	£18
Efficacy of NL basket [a]	£1,574	£1,556	£18
Discontinuation from NL [b]	£1,576	£1,561	£15
Health care unit costs [c]	£1,558	£1,571	£13
Delgocitinib AE frequency [a]	£1,571	£1,558	£12
HESD pain score - Full response [a]	£1,560	£1,570	£10
Full response with re-treatment - OR comparator versus delgocitinib [b]	£1,569	£1,562	£7
HECSI score - Low response [a]	£1,567	£1,562	£5
AEs disutilities [c]	£1,567	£1,563	£4
HESD pain score - Partial response [a]	£1,563	£1,566	£3
Proportion of patients discontinuing treatment directly to BSC [a]	£1,566	£1,565	£1
HECSI score - Full response [a]	£1,564	£1,565	£0
HECSI score - Partial response [a]	£1,564	£1,565	£0
Vehicle average weekly consumption in grams [a]	£1,565	£1,565	£0
Proportion of patients discontinuing 2L directly to BSC [a]	£1,565	£1,565	£0

[a] Varied to limits of 95% confidence interval.

[b] Standard error assumed to be 20% of the mean.

[c] Lower and upper limits are 85% and 115% of the mean.

References

Ara, R. and J. E. Brazier (2010). "Populating an economic model with health state utility values: moving toward better practice." Value Health 13(5): 509-518.

Hernández Alava, M., et al. (2023). "Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study." PharmacoEconomics 41(2): 199-207.

Molin S, Larsen LS, Joensson P, Oesterdal ML, Arbuckle R, Grant L, et al. Development and Psychometric Validation of a Patient-Reported Outcome Measure to Assess the Signs and Symptoms of Chronic Hand Eczema: The Hand Eczema Symptom Diary (HESD). Dermatology and Therapy. 2024 Mar;14(3):643-69.

Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE. 2016.

References

1. Worm M, Thyssen JP, Schliemann S, et al. The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial. Br J Dermatol 2022;187:42–51.

2. Wittmann M, Smith IL, Brown ST, et al. Alitretinoin versus phototherapy as the first-line treatment in adults with severe chronic hand eczema: the ALPHA RCT. Health Technology Assessment (Winchester, England) 2024;28:1.

3. Silverberg JI, Agner T, Baranowski K, et al. Validation of the Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE): a new clinician reported outcome measure of CHE severity. Arch Dermatol Res 2024;316:110.

4. Grant L, Seiding Larsen L, Burrows K, et al. Development of a Conceptual Model of Chronic Hand Eczema (CHE) Based on Qualitative Interviews with Patients and Expert Dermatologists. Adv Ther 2020;37:692–706.

5. Bissonnette R, Worm M, Shi VY, et al. Efficacy of Abrocitinib and Dupilumab on Chronic Hand Eczema in Patients With Moderate-to-Severe Atopic Dermatitis: Results From the Phase 3 JADE DARE Study. European Academy of Dermatology and Venereology. Milan, 2022.

6. Langan SM, Stuart B, Bradshaw L, et al. Measuring long-term disease control in patients with atopic dermatitis: A validation study of well-controlled weeks. J Allergy Clin Immunol 2017;140:1580-1586.

7. Schliemann S, Pinter A, Schuttelaar ML, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema: results of the Phase 3 DELTA 2 trial. European Academy of Dermatology and Venereology. Berlin, 2023.

8. Gooderham M, et al. Long-term safety and efficacy of delgocitinib cream for up to 36 weeks in adults with Chronic Hand Eczema: results of the Phase 3 open-label extension DELTA-3 trial. AAD Anual Meeting. San Diego, USA, 2024.

9. Ruzicka T, Larsen F, Galewicz D, et al. Oral alitretinoin (9-cis-retinoic acid) therapy for chronic hand dermatitis in patients refractory to standard therapy: results of a randomized, double-blind, placebo-controlled, multicenter trial. Arch Dermatol 2004;140:1453-1459.

10. Silverberg JI, Agner T, Baranowski K, et al. Validation of the Investigator Global Assessment of Chronic Hand Eczema (IGA–CHE): a new clinician reported outcome measure of CHE severity. Archives of Dermatological Research 2024;316:110.

11. Fowler JF, Ghosh A, Sung J, et al. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. Journal of the American Academy of Dermatology 2006;54:448-457.

12. Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology 2015;230:27-33.

13. Barrett A, Hahn-Pedersen J, Kragh N, et al. Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults. Patient 2019;12:445-459.

14. Thyssen JP, Schuttelaar MLA, Alfonso JH, et al. Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis 2022;86:357–378.

15. Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema--short version. J Dtsch Dermatol Ges 2015;13:77–85.

16. Smith IL, Gilberts R, Brown S, et al. Comparison of ALitretinoin with PUVA as the first-line treatment in patients with severe chronic HAnd eczema (ALPHA): study protocol for a randomised controlled trial. BMJ Open 2022;12:e060029.

17. LEO Pharma. DELTA FORCE protocol, 2022.

18. National Institute for Health and Care Excellence. TA177: Alitretinoin for the treatment of severe chronic hand eczema, 2009.

19. Weidinger S, Novak N. Hand eczema. The Lancet 2024;404:2476-2486.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

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].

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 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 and publications. 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 LEO Pharma has been a corporate member of National Eczema Society for several years and the membership agreement complies with the ABPI code of practice. The annual corporate membership fee paid by the company is £15,000 plus VAT. The charity's Corporate Membership Scheme allows company partners to demonstrate public support for the important work of the Society. The funding helps

amount, and purpose of funding.	pay for the charity's core operating costs with the purpose of helping the Society achieve its overall objective of making life better for people affected by eczema and their families. Regarding manufacturers of comparator products: Almirall is a corporate member of National Eczema Society and pays a corporate membership fee £20,000 plus VAT. Almirall also provided unrestricted funding of €10,000 under the company's Global 'You Feel Well' Challenge initiative. Lilly is a corporate member of National Eczema Society and pays an annual fee for this of £15,000 plus VAT. AbbVie is a corporate member of National Eczema Society and pays an annual fee for this of £20,000 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?	We are very engaged with our charity members and wider eczema community through our charity magazine, e-newsletters, events, general email enquiries, social media engagement and patient surveys. As well, we run a number of health information webinars for people affected by eczema and respond to enquiries raised by our members. Until March 2024, National Eczema Society operated an eczema helpline service, responding to telephone enquiries from people affected by eczema who were seeking advice either on their own behalf or for a loved

	one. 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 in 2020 with over 1,000 patients and carers in the UK, 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 further 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 various ways, such as through difficulty in sleeping, 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?	Hand eczema (HE) is a painful skin condition that primarily affects the hands and wrists, causing itching and inflammation. This condition is influenced by external factors like irritants and allergens, as well as internal factors such as problems with the skin barrier, immune system, and imbalances in the skin's natural microbiome. HE often follows a chronic course with cycles of flare-ups and remission, and when it lasts three months or more, or when flare-ups occur at least twice a year, it is classified as chronic hand eczema (CHE). CHE can significantly affect physical and mental health, daily activities, and work/occupational capabilities, creating substantial personal and economic burdens. The intense itching associated with eczema is one of the most challenging symptoms, making those affected feel self-conscious about their condition and reluctant to engage in social activities. Patients report that CHE impacts their daily routines, work, and studies. Since hands are essential for communication and are often visible, this condition can take a toll on mental health and emotional well-being, potentially straining personal relationships. The itchiness can also disrupt sleep, leading to difficulties in concentration and the ability to perform tasks effectively during the day. Frequent scratching can damage the skin and increase the risk of infections. Managing eczema requires significant time and effort, as patients must apply treatments multiple times a day. Those who scratch and bleed during the night may find themselves needing to wash their bedding daily. Many individuals with eczema also face mental health challenges, making it especially difficult to maintain an effective care routine, while even those without diagnosed issues may find daily management burdensome. Caring for someone with eczema can be both physically and emotionally draining. Caregivers often need to apply treatments frequently, provide emotional support, and accompany the person to medical appointments. They may also experience sleep disturbances due to the challenges faced by the person in their care, leading to their own lack of sleep.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Many patients with moderate to severe chronic hand eczema (CHE) and their carers feel that available treatments are still limited in both number and effectiveness. Currently, no topical treatment has been specifically developed and approved for CHE, and the UK lacks specific treatment guidelines for this condition. As a result, clinicians may refer to the European Society of Contact Dermatitis (ESCD) guidelines, which recommends the oral vitamin A derivative (retinoid), alitretinoin as the only approved option for severe CHE, typically used as a second-line treatment after topical corticosteroids. Most CHE patients are initially prescribed topical corticosteroids, with topical calcineurin inhibitors as a backup if corticosteroids are not effective. However, many are hesitant to use topical steroids regularly due to concerns about long-term safety and potential side effects, particularly the risk of topical steroid withdrawal (TSW), a concern amplified by recent media coverage. Access to calcineurin inhibitors is also limited, as they are generally prescribed only for sensitive skin areas. CHE also poses a higher risk for skin infections, often requiring antibiotic treatment. For more severe cases, phototherapy and immunosuppressant drugs like azathioprine, ciclosporin, methotrexate, and mycophenolate mofetil may be considered. Phototherapy, however, requires a demanding schedule of two to three hospital visits per week over several months, making it impractical for many. Immunosuppressants can carry serious risks of long-term side effects, leading to understandable concerns among patients. The recent MHRA warning regarding systemic JAK inhibitors has added to the apprehension among some patients and dermatologists about using or prescribing these treatments.

8. Is there an unmet need for patients with this condition?	Currently, alitretinoin, an oral retinoid, is the only approved treatment for severe chronic hand eczema (CHE) that does not respond to topical corticosteroids in several countries, including parts of the EU, Canada, Israel, and South Korea. However, alitretinoin treatment often requires regular medical and lab monitoring, as well as a pregnancy prevention programme for women of childbearing age. These limitations make managing CHE challenging and often leave patients unsatisfied with their treatment options. There is a clear need for safe and effective treatments specifically designed for the long-term management of CHE. CHE is a complex condition, and individual responses to treatments vary. Expanding the range of treatments available for long-term management will increase the chances that patients with moderate to severe CHE can find a treatment - or a combination of treatments -that works well for them.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Delgocitinib provides a non-steroidal, convenient, and effective option for managing chronic hand eczema (CHE), especially for those concerned about the long-term risks of traditional steroid treatments. By targeting inflammation in the skin, delgocitinib can potentially deliver longer-lasting relief from the severe itching, redness, and cracking associated with CHE. Better inflammation management also reduces scratching and skin damage, which can lower the risk of secondary infections that often require antibiotics. CHE significantly impacts individuals in jobs involving frequent hand-washing, exposure to chemicals, irritants and allergens, or prolonged glove use in both domestic and work environments. The economic cost of sick days, reduced productivity to even job loss and/or early retirement due to CHE affects not only patients and their employers but also the broader economy, highlighting the importance of effective treatment. By helping control symptoms more effectively, delgocitinib can enable individuals to maintain daily activities, work, and social interactions without the discomfort and disruptions caused by CHE flare-ups.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients receiving treatment in primary care usually do not have access to systemic treatments, which are typically started and monitored in secondary care setting. Thus, if delgocitinib can only be prescribed by a dermatologist in secondary care, patients must be under a dermatologist's care to access this treatment.

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.	Women of childbearing age would significantly benefit from an additional treatment option, as alitretinoin necessitates medical and laboratory monitoring, along with a pregnancy prevention programme. The limitations of current treatments make managing chronic hand eczema (CHE) challenging and often unsatisfactory, especially for this patient group. Diagnosing the severity of symptoms of CHE in individuals with brown and black skin can be more challenging because signs like skin reddening are harder to assess visually. This may result in some patients with chronic hand eczema (CHE) going undiagnosed and undertreated. Moreover, the lack of access to certain diagnostic tools, like patch testing for allergic contact dermatitis, creates disparities in diagnosis across different regions in the UK.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes, women of childbearing age a need viable treatment option for CHE. The possible introduction of delgocitinib which does not necessitate a pregnancy prevention programme, could offer women of childbearing age a licensed treatment option for CHE without the added anxiety related to pregnancy concerns. Diagnosing the severity of symptoms in individuals with brown and black skin can be more challenging, as signs like skin reddening (erythema) are harder to visually assess. This may lead to some patients with CHE being undiagnosed and subsequently undertreated. Additionally, people of Asian descent may have more sensitive skin due to a thinner outer layer and a higher density of sweat glands. Furthermore, some diagnostic tools, such as patch testing for allergic contact dermatitis, are not available in certain areas, resulting in unequal access to diagnoses across different regions in the UK.

Other issues

13. Are there any other issues that you would like the committee to consider?	We believe that treatment outcomes should fully reflect the patient experience, utilising tools like the Patient Oriented Eczema Measure (POEM). Patients report that CHE significantly affects their daily activities, work, and studies. A patient experience measure would help capture these various impacts. It's important to note that traditional measures of disease severity, such as the Eczema Area and Severity Index (EASI), can be more difficult to apply to chronic hand eczema, which typically affects a smaller area.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chronic hand eczema significantly impacts quality of life, disrupting daily activities, work, mental health, and social interactions, particularly in occupations requiring frequent hand-washing or chemical exposure, and imposes economic burdens through sick days and reduced productivity. • CHE treatment options are limited; while topical corticosteroids are commonly prescribed, concerns over long-term side effects and limited access to alternatives like alitretinoin underscore the need for more options. • The intense itching and pain from CHE disrupt sleep, concentration, and increases infection risk, while daily management - including multiple treatments, frequent bedding changes, and healthcare visits, if available, places a heavy physical and emotional strain on patients and caregivers. • Managing CHE is especially challenging for women of childbearing age due to the need for treatment options without pregnancy-related precautions, and diagnosing the condition in individuals with darker skin tones can be difficult as traditional signs like redness may be less visible, potentially resulting in underdiagnosis and undertreatment. • Delgocitinib, a non-steroidal treatment targeting inflammation, provides patients with an effective option for long-term relief from CHE, particularly benefiting women of childbearing age and those without access to secondary care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

NICE National Institute for Health and Care Excellence

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

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] on behalf of the British Association of Dermatologists' Therapy & Guidelines Sub-committee and [redacted] on behalf of the British Society for Cutaneous Allergy
2. Name of organisation	British Association of Dermatologists (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 ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
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 reduce the severity of chronic hand eczema (CHE) to allow usual function at work and at home.
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.)	To reduce Investigator's Global Assessment (IGA) severity for CHE to 'clear' or 'almost clear'.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	A proportion of patients fail to respond to repeated, intermittent courses of topical corticosteroids (TCS), and topical calcineurin inhibitors (TCI) if tried; second-line options may carry higher risk or cost (e.g. alitretinoin).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Soap substitutes, emollients, TCS, TCI, oral alitretinoin or localised psoralen-UVA (PUVA) or narrowband UVB (NBUVB) therapies, if more severe. Patch testing is indicated for persistent disease.
9a. Are any clinical guidelines used in the	No.

treatment of the condition, and if so, which?	
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.)	Generally, patients receive soap substitutes, emollients and TCS in primary care and are then referred to secondary care for persistent cases; generally, patients should be referred for patch testing if failing to respond to TCS.
9c. What impact would the technology have on the current pathway of care?	Reduced secondary care review activity.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, some patients with persistent CHE will improve after failing TCS and TCI therapy. It is worth mentioning that the evidence demonstrates treatment with topical delgocitinib can produce meaningful outcomes. The DELTA1 and DELTA2 studies reported % reduction in HESCI scores, and % of people who achieved HESCI-75 and HESCI-90 (75% and 90% reduction in the HECSI score, respectively). The proportion who had clear or almost clear hand eczema at week 16 was 20% in DELTA1 and 29% in DELTA2. At the European Academy of Dermatology and Venereology's Congress in 2024, data from the phase III DELTA FORCE compared topical delgocitinib with subcutaneous dupilumab for chronic hand eczema, and there were greater improvements seen in HESCI scores at week 12 in the topical delgocitinib group. To put this in context, there was a clinic trial (ALPHA RCT) of oral alitretinoin versus topical PUVA for hand eczema (https://pubmed.ncbi.nlm.nih.gov/39364555/) which showed a greater reduction in HESCI in the alitretinoin group (30 points [IQR 10-61]) versus the topical PUVA group (20 points [2-47]) at week 12. The proportion who had clear or almost clear hands at week 12 was 27.6% in the alitretinoin group versus 23.6 in the topical PUVA group. Essentially, topical delgocitinib's efficacy outcomes are comparable with those for treatment modalities that might be more inconvenient and labour-intensive (hence greater cost) such as topical hand PUVA, or with systemic therapy such as oral alitretinoin or subcutaneous dupilumab. There is a place for effective topical therapy (if conventional topical therapy such as TCS or TCI have not controlled people's hand eczema adequately), especially in those who have relative/absolute contraindications to or are unable to tolerate other systemic therapy.
11a. Do you expect the technology to increase length of life more than current care?	No.
11b. Do you expect the technology to increase	Yes, especially in patients whose hand eczema have not been adequate controlled with TCS/TCI and/or have relative/absolute contraindications to or are unable to tolerate other systemic therapy. The DELTA 1 and 2 phase III trials have reported the proportion of participants whose Dermatology Life Quality Index (DLQI) scores have

health-related quality of life more than current care?	decreased by at least 4 points at week 16, and also absolute DLQI score reduction - 7.6 in DELTA1 and 7.0 in DELTA 2. The reduction in DLQI can be compared to the data in the ALPHA RCT of oral alitretinoin vs. topical hand PUVA.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, people who might be poorly adherent to or find it difficult to tolerate topical treatments.

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.)	I think ease of use of topical delgocitinib cream would be no different to TCS/TCI. It would be more convenient to patients than attending phototherapy appointments. It is likely that there would be less baseline investigations required and blood test monitoring required for delgocitinib, although it was stated in the paper (Bissonnette *et al.* 2024) that further work might be needed to "understand the systemic effects of delgocitinib cream".
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Severity assessments, e.g. the Hand Eczema Severity Index (HECSI). Additionally, DLQI and perhaps physicians global assessment (PGA), as per NICE TA 177 (alitretinoin in chronic severe hand eczema). HESCI and the modified Total Lesion Symptom Score (mTLSS) are outcome measures often used in clinical trials but rarely used in normal clinical practice.

include any additional testing?	
15. 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?	Yes, skin-related quality of life may not be adequately captured in QALY calculations but reduction in pain and discomfort and ability to self-care with reduction in severity of hand eczema might be captured to some extent.
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?	Yes, it is – first JAK inhibitor for chronic hand eczema and may result in reduction in severity of hand eczema that is comparable to phototherapy and systemic therapy.
16a. Is the technology a 'step-change' in the management of the condition?	It is the first topical Janus kinase (JAK) inhibitor available for CHE.
16b. Does the use of the technology address any particular unmet need of the patient population?	
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?	If the treatment is not tolerated then other treatments would need to be considered.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, prior treatment failure with TCS/TCI.
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?	Improvement of IGA assessment scores to ‘clear’ or ‘almost clear’; yes, these were measured. - and DLQI score reduction of at least 4
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that we are aware of.
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)	No.

since the publication of NICE technology appraisal guidance [TA177]?	
21. How do data on real-world experience compare with the trial data?	We have no real-world experience with the use of topical delgocitinib.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Under-estimation of severity of erythema when assessing more richly pigmented skin More difficult for people who are unable to read/understand English to complete English-language questionnaires that enquire about their skin-related quality of life, even with the help of interpreters
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• The first topical Janus kinase (JAK) inhibitor available for CHE • New treatment option for people with CHE unresponsive to or are intolerant of TCS and TCI • Improves CHE severity, as measured by IGA scores, to 'clear' or 'almost clear' • No risk of skin thinning compared with TCS – or other potential adverse effects of TCS

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

BMJ TAG

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174560.

Title:	Delgocitinib for treating moderate to severe chronic hand eczema
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Archie Walters, Health Economist, BMJ-TAG, London Ben Burgess, Clinical Evidence Analyst, BMJ-TAG, London Tracey Jhita, Senior Health Economist, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	14/03/2025
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174560.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Leila Ferguson, Consultant Dermatologist, St George's Hospital NHS Foundation Trust; Dr Charles Mitchell, Consultant Dermatologist, Portsmouth Hospitals University NHS Trust; and Dr Mili Shah, Consultant Dermatologist, Wrightington, Wigan and Leigh Trust for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
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.
Report reference:	Steve Edwards, Ben Burgess, Archie Walters, Victoria Wakefield, Tracey Jhita. Delgocitinib for treating moderate to severe chronic hand eczema: A Single Technology Appraisal. BMJ Technology Assessment Group, 2025.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Ben Burgess	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event
BD	Twice a day
CHE	Chronic hand eczema
CI	Confidence interval
CS	Company's submission
CSR	Clinical study report
DIC	Deviance Information Criterion
DLQI	Dermatology Life Quality Index
EAG	External Assessment Group
ECSD	European Consensus on Skin Diseases
EQ-5D	European Quality of Life 5 Dimensions
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
FDA	US Food and Drug Administration
FE	Fixed-effect
HE	Hand eczema
HECSI	Hand Eczema Severity Index
HECSI-50	Hand Eczema Severity Index score 50% reduction
HECSI-75	Hand Eczema Severity Index score 75% reduction
HECSI-90	Hand Eczema Severity Index score 90% reduction
HEIS	Hand Eczema Impact Scale
HESD	Hand Eczema Symptom Diary
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratios
IGA	Investigator's Global Assessment
IGA-CHE	Investigator's Global Assessment for chronic hand eczema
IGA-CHE TS	Investigator's Global Assessment for chronic hand eczema treatment success
IL	Interleukin
ITC	Indirect treatment comparison
JAK	Janus kinase
JAKi	Janus kinase inhibitor
MAIC	Matching adjusted indirect comparison
MD	Mean difference
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute of Health and Care Excellence
NMA	Network meta-analysis
NUVB	Narrowband ultra-violet B
MAIC	Matching adjusted indirect comparison
NHS	National Health Service

OR	Odds ratio
PGA	Physician's Global Assessment
PUVA	Psoralen-UV A
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial
RE	Random-effect
RR	Risk ratio
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse events
TOST	Two one-sided tests
UK	United Kingdom
UVB	Ultra-violet B
WOCF	Worst observation carried forward

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 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, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of EAG's key issues

ID	Summary of issue	Report sections
Issue 1	Inappropriate choice of indirect treatment comparisons.	Section 3.4
Issue 2	Assumption of equivalence in the relative treatment effects between moderate and severe patients.	Section 3.3.1.1.2 and 4.2.5.2
Issue 3	No consideration of hyperkeratotic status.	Sections 2.3.5; 3.3.1.1.3; 3.3.2 and 4.2.3
Issue 4	Use of worst observation carried forward approach.	Sections 3.2 and 4.2.5
Issue 5	Time on treatment may be underestimated in the model compared to clinical practice	Section 4.2.6

Abbreviations: EAG, External Assessment Group

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The sources used to inform treatment effects;
- The sources used to inform delgocitinib usage;
- The sources used to inform health state utility values.

1.2 Overview of key model outcomes

NICE technology appraisals compare 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.

Overall, the technology is modelled to affect QALYs by:

- Increasing the probability of achieving a full response to treatment;
- Increasing the probability of achieving a full response to re-treatment;
- Less adverse events;
- Reduced discontinuation to next-line treatments and best supportive care (BSC).

Overall, the technology is modelled to affect costs by:

- Less time spent in high-cost health states;
- Lower demand for health care resource use;
- Less adverse events;
- No monitoring costs (compared to alitretinoin).

The modelling assumptions that have the greatest effect on the ICER are:

- The assumed treatment effects (hyperkeratotic vs non-hyperkeratotic, moderate symptoms at baseline vs severe symptoms at baseline);
- The assumed usage of delgocitinib;
- The assumed health state utility values.

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

Table 2. Issue 1: Inappropriate choice of indirect treatment comparisons.

Report section	Section 3.4
Description of issue and why the EAG has identified it as important	The EAG has serious concerns regarding the network meta-analyses (NMAs) provided by the company. Firstly, the EAG notes that there is substantial clinical and methodological heterogeneity reported among the studies included in the NMAs. For instance, some trials only included patients with severe CHE, while others included patients with both moderate and severe CHE. Likewise, for NMAs of IGA-CHE TS, three different endpoints were assumed to be sufficiently similar for inclusion in a single NMA. Secondly, the EAG has serious concerns regarding the company's preference for the fixed-effect (FE) NMAs over the random-effects (RE) NMAs. The company noted that the deviance information criterion (DIC) for the RE and FE models were similar, allowing the company to use their judgement to select the most appropriate model. Given the above issues with methodological and clinical heterogeneity, the EAG suggests that RE NMAs would be the most appropriate. However, the company selected the FE NMAs on the basis that 'the RE model SDs are large' and ultimately selecting the FE NMAs that demonstrated statistically significant outcomes in favour of delgocitinib. [redacted] The EAG considers that the presented NMAs are inappropriate when more robust comparisons are available (see below).
What alternative approach has the EAG suggested?	The EAG notes that indirect comparisons are only required for the comparison of delgocitinib to PUVA as direct evidence exists for the comparison of delgocitinib to vehicle cream and alitretinoin. Through a clarification question, the EAG requested that the company perform a MAIC to compare the PUVA population from the ALPHA trial to the delgocitinib population from the pooled DELTA 1 and DELTA 2 trials. This was provided by the company.
What is the expected effect on the cost-effectiveness estimates?	The EAG base cases inform treatment effects using DELTA FORCE and a MAIC between DELTA 1 and 2 and ALPHA, which led to an increase in the ICER compared to using the NMA treatment effects.
What additional evidence or analyses might help to resolve this key issue?	This issue was addressed by the company through the provision of MAICs comparing IGA-CHE TS and HECSI-90 in the PUVA population of the ALPHA trial to the delgocitinib population from the pooled DELTA 1 and DELTA 2 trials. However, a comparison of additional endpoints (e.g., EQ-5D-3L, HECSI-75, HECSI-50, etc) may be beneficial to aid the comparison of delgocitinib to PUVA.

Abbreviations: CHE, chronic hand eczema; CS, company's submission; EAG, External Assessment Group; FE, fixed-effects; HECSI-50, Hand Eczema Severity Index score 50% reduction; HECSI-75, Hand Eczema Severity Index score 75% reduction; ICER, ICER, incremental cost effectiveness ratio; IGA-CHE TS, Investigator's Global Assessment for chronic hand eczema treatment success; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PUVA, Psoralen-UV A; RE, random-effects; SD, standard deviation.

Table 3. Issue 2: Assumption of equivalence in the relative treatment effects between moderate and severe patients.

Report section	Section 3.3.1.1.2
Description of issue and why the EAG has identified it as important	The EAG has concerns regarding the assumption of an equivalence in the relative treatment effect between moderate and severe patients with CHE. Only the DELTA FORCE and ALPHA trials considered alitretinoin and/or PUVA; however, these trials only included patients with severe CHE. As such, there is no direct, or indirect, evidence for the efficacy or safety of alitretinoin or PUVA in patients with moderate CHE. Within the CS, the company has assumed that the relative treatment effect of delgocitinib to alitretinoin and delgocitinib to PUVA in moderate patients is consistent with that observed in severe patients. In response to a clarification question, the company provided analyses to support the assertion that treatment effects are consistent across patients with moderate and severe CHE. However, it is the opinion of the EAG that these analyses are insufficient to confirm whether the relative treatment effects between moderate and severe patients are consistent. Furthermore, the EAG notes that the effect estimates for delgocitinib are numerically different across the moderate and severe populations.
What alternative approach has the EAG suggested?	The EAG suggests that equivalence testing (e.g., two one-sided tests [TOST] procedure) may potentially be used to determine whether the relative treatment effects between patients with moderate CHE and severe CHE are equivalent. This would provide a statistically robust approach to assessing whether it can be assumed that relative treatment effects would be consistent across these subgroups.
What is the expected effect on the cost-effectiveness estimates?	The EAG has provided exploratory scenarios around the EAG's base case results to assess the cost-effectiveness of delgocitinib in patients with moderate symptoms at baseline. Compared to patients with severe symptoms at baseline, the ICER was found to be greater in the moderate population when comparing delgocitinib to alitretinoin. When compared to PUVA, the incremental costs and QALYs were smaller compared to the severe population, however, delgocitinib continued to dominate PUVA. The EAG considers the outcomes of these scenarios to be uncertain, given the reliance on the assumption of an equal relative treatment effect between moderate and severe populations between delgocitinib, alitretinoin and PUVA.
What additional evidence or analyses might help to resolve this key issue?	Due to a paucity of data for patients with moderate CHE receiving either alitretinoin or PUVA, there are limited options for obtaining additional evidence or analyses to support the company's assertion. As such, the EAG suggests that a form of equivalence testing may provide an avenue for the company to determine whether the relative treatment effects are consistent across patients with moderate and severe CHE.

Abbreviations: CHE, chronic hand eczema; CS, company's submission; EAG, External Assessment Group; ICER, ICER, incremental cost effectiveness ratio; PUVA, Psoralen-UV A; QALY, Quality-adjusted life year; TOST, two one-sided tests.

Table 4. Issue 3: No consideration of hyperkeratotic status.

Report section	Sections 2.3.5; 3.3.1.1.3; and 3.3.2.
Description of issue and why the EAG has identified it as important	The EAG's clinical experts have indicated that the presence of hyperkeratosis is a treatment effect modifier and that treatment decisions will be dependent on how a patient presents. Patients with hyperkeratotic CHE are likely to receive alitretinoin, while patients with non-hyperkeratotic CHE are likely to receive PUVA. Despite hyperkeratotic status being a stratification factor for one of the key trials (DELTA FORCE), analyses of hyperkeratotic, and non-hyperkeratotic, subgroups were not provided by the company. Furthermore, the potential impact of hyperkeratosis was not reported by the company within the CS.
What alternative approach has the EAG suggested?	Through clarification questions, the EAG requested that the company perform subgroup analyses, for hyperkeratotic and non-hyperkeratotic subgroups, for the comparison of delgocitinib to alitretinoin. Additionally, the EAG requested that the company perform MAICs to assess the relative efficacy of delgocitinib to PUVA. When performing these MAICs, the EAG requested that all treatment effect modifiers or prognostic variables (including hyperkeratotic status) were accounted for in the matching. As the only trial to consider PUVA (ALPHA) did not report subgroup results for hyperkeratotic status, subgroup analyses were not feasible.
What is the expected effect on the cost-effectiveness estimates?	The company and the EAG have conducted scenario analyses using the hyperkeratotic subgroup treatment effects. In hyperkeratotic patients, delgocitinib was found to be dominated by alitretinoin, while in non-hyperkeratotic patients delgocitinib was to have an ICER below the £20,000 to £30,000 threshold typically employed by NICE. As ALPHA did not report subgroup results, it was not possible to conduct the same analyses with PUVA, however, matching by hyperkeratotic status in an indirect treatment comparison led to a decrease in the estimated relative treatment effect compared to the company base case.
What additional evidence or analyses might help to resolve this key issue?	Subgroup analyses have provided direct evidence for the relative efficacy of patients with hyperkeratotic, or non-hyperkeratotic, severe CHE between delgocitinib and alitretinoin. Likewise, indirect comparisons of PUVA to delgocitinib in patients with severe CHE have been matched to account for hyperkeratotic status between the two treatment arms from different trials. However, the MAIC allows for the estimation of the efficacy of delgocitinib to PUVA assuming the proportions of hyperkeratotic and non-hyperkeratotic patients as present in the ALPHA trial. Unfortunately, a lack of subgroup analyses from ALPHA prohibits evaluating the two subtypes independently.

Abbreviations: CHE, chronic hand eczema; EAG, External Assessment Group; MAIC, matching adjusted indirect comparison; NICE, National Institute of Health and Care Excellence; PUVA, Psoralen-UV A.

Table 5. Issue 4: Use of worst observation carried forward approach.

Report section	Sections 3.2 and 4.2.5
Description of issue and why the EAG has identified it as important	The EAG is concerned that the use of the worst observation carried forward (WOCF) approach to account for missing data has the potential to bias comparisons of delgocitinib to either vehicle cream or alitretinoin in favour of delgocitinib. This is due to the WOCF approach generating bias against the treatment arm in which the dropout rate is highest; accordingly, the WOCF approach may be conservative if the dropout rate is greatest in the arm for the new treatment. Within the DELTA 1, DELTA 2, and DELTA FORCE trials dropout rates are greater in the vehicle cream and alitretinoin arms compared to the delgocitinib arms of these trials. For instance, at the end (Week 24) of the DELTA FORCE trial, the dropout rate in the alitretinoin arm was 39.5% compared to 12.4% in the delgocitinib arm. In response to a clarification question, the company noted that multiple imputation, with a missing at random assumption, was performed to account for missing data in a sensitivity analyses 'which attempted to quantify the effect of the randomised treatment, ignoring the occurrence of intercurrent events'. The company noted that this approach led to overly optimistic treatment effects at Week 12 for the DELTA FORCE trial. However, the company did not present similar results for other timepoints or trials.
What alternative approach has the EAG suggested?	The EAG suggests that multiple imputation, with a missing not a random assumption, should be used, over WOCF, to impute missing data as it is likely to be associated with a lower risk of bias.
What is the expected effect on the cost-effectiveness estimates?	Given the use of WOCF, and that the delgocitinib comparators have more missing data, the EAG considers that the treatment effectiveness of comparators may be underestimated in the model, leading to the underestimation of the ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that it would be preferable, due to the high risk of bias resulting from the use of the WOCF approach, to impute missing data using multiple imputation with a missing not at random assumption. However, the EAG notes that due to the high dropout rate in the latter stages of some trials, there may still be limitations with using a multiple imputation approach.

Abbreviations: EAG, External Assessment Group; WOCF, worst observation carried forward.

Table 6. Issue 5: Time on treatment does not reflect clinical practice

Report section	Section 3.4
Description of issue and why the EAG has identified it as important	The EAG's clinical expects outlined that in clinical practice, approximately 25% of alitretinoin patients would continue to cycle through the resolution and relapse of symptoms for up to two years of treatment. Conversely in the model, only [redacted] of alitretinoin patients are still on treatment by two years. The EAG therefore considers that time on treatment for delgocitinib and alitretinoin may be underestimated in the model, with the proportion of patients on delgocitinib being potentially more underestimated given that delgocitinib is more effective than alitretinoin in specific patient populations.
What alternative approach has the EAG suggested?	At clarification the company was asked to discuss the modelling factors that contributed to time on treatment in the model misaligning with that of the EAG's clinical experts' opinion, and to discuss the consequences of the difference between the model and clinical practice in terms of cost-effectiveness. The company discussed the consequences of time on treatment being underestimated for alitretinoin in the model, without considering that delgocitinib may also be underestimated, and its impact to the decision of cost-effectiveness. No scenario was conducted exploring alternative times on treatment.
What is the expected effect on the cost-effectiveness estimates?	If times on treatment are longer for both alitretinoin and delgocitinib, it's expected that the ICER will increase, as delgocitinib is more costly than alitretinoin, leading to higher incremental costs. However, the extent to which the ICER will increase is dependent on the difference in proportions of patients remaining on treatment, which is unknown. The EAG expects the ICER to be highly sensitive to the difference in the proportions of patients remaining on treatment.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that additional opinions from clinical experts on the expected time on treatment for patients that achieved a full response on treatment and scenario analyses exploring these opinions would resolve this issue.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio.

1.4 Summary of EAG's preferred assumptions, base cases and scenario analyses around the base cases

Table 7. EAG preferred model assumptions, delgocitinib vs alitretinoin

Scenario	Incremental costs (£)	Incremental QALYs	ICER (change from company base case [£/QALY])
Company base case	[redacted]	[redacted]	8,526
Delgocitinib dosing (DELTA FORCE)	[redacted]	[redacted]	22,419 (+13,893)
Next line treatment discontinuation pathway (ALPHA)	[redacted]	[redacted]	7,951 (-575)
Next line treatment basket and reduce next-line treatment efficacy (No alitretinoin, efficacy assumed at 25.6%) *	[redacted]	[redacted]	7,986 (-540)
Probability of full response at 12 weeks (DELTA FORCE)	[redacted]	[redacted]	9,627 (+1,101)

Per-cycle probability of full response for continued treatment (DELTA FORCE)	[redacted]	[redacted]	9,719 (1,193)
Per-cycle probability of full response for retreatment (DELTA FORCE)	[redacted]	[redacted]	8,823 (+297)
Proportion of patients opting not to re-initiate initial treatment following relapse (DELTA FORCE)	[redacted]	[redacted]	2,327 (-6,199)
Not including AEs	[redacted]	[redacted]	8,948 (+422)
HSUVs derived from pooled DELTA trials	[redacted]	[redacted]	11,551 (+3,025)
HCRU according to EAG's clinical experts	[redacted]	[redacted]	7,441 (-1,085)

*Includes previous assumption

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 8. EAG preferred model assumptions, delgocitinib vs PUVA

Scenario	Incremental costs (£)	Incremental QALYs	ICER (change from company base case [£/QALY])
Company base case	[redacted]	[redacted]	PUVA dominated
Delgocitinib dosing (12- and 24-week weighted dosing from DELTA 1,2 and FORCE)	[redacted]	[redacted]	PUVA dominated
Next line treatment discontinuation pathway (ALPHA)	[redacted]	[redacted]	PUVA dominated
Next line treatment basket and reduce next-line treatment efficacy (No alitretinoin, efficacy assumed at 25.6%) *	[redacted]	[redacted]	PUVA dominated
Probability of full response at 12 weeks (MAIC matching by severe symptoms and HK status)	[redacted]	[redacted]	PUVA dominated
Per-cycle probability of relapse (DELTA 3)	[redacted]	[redacted]	PUVA dominated
Not including AEs	[redacted]	[redacted]	PUVA dominated
HSUVs using pooled DELTA trials	[redacted]	[redacted]	PUVA dominated
HCRU according to EAG clinical expert	[redacted]	[redacted]	PUVA dominated

*Includes previous assumption

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 9. EAG base case, delgocitinib vs alitretinoin, severe symptoms at baseline

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	18,541
Probabilistic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	19,017

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 10. EAG base case, delgocitinib vs PUVA, severe symptoms at baseline

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Probabilistic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 11. EAG base case scenario analyses

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Delgocitinib vs alitretinoin in patients with moderate symptoms at baseline					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	20,425
Delgocitinib vs PUVA in patients with moderate symptoms at baseline					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Delgocitinib vs alitretinoin in patients with hyperkeratosis					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	Delgocitinib dominated
Delgocitinib vs alitretinoin in patients with non-hyperkeratosis					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	8,165

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of delgocitinib (Anzupgo®, LEO Pharma) for the treatment of adults with moderate to severe chronic hand eczema (CHE) that has not responded to treatment with topical corticosteroids (TCS) or for whom TCS are inadequate or inappropriate. The Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for delgocitinib in this indication is, "for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate".[1]

2.2 Background

The company submission (CS) provides an overview of CHE, including the causes, prevalence, diagnosis, pathology, and symptom burden (Section 1.3 of the CS). It also provides a description of delgocitinib, its mechanism of action, indication, and methods of administration and dosage (Section 1.2 of the CS). Included below is the EAG's summary of the key background information presented in the CS, supplemented by information provided by the EAG's clinical experts.

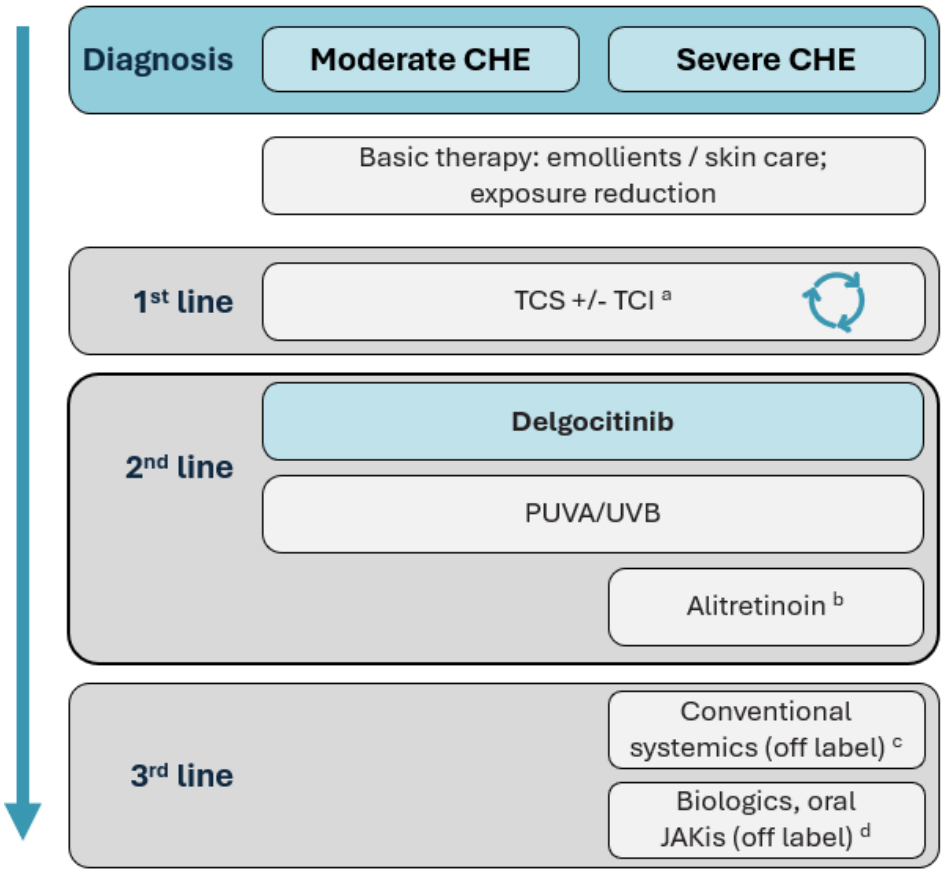
CHE is defined as hand eczema that has persisted for more than 3 months or hand eczema that has relapsed two or more times per year.[2, 3] A recent meta-analysis estimated the one-year global prevalence of CHE to be 9.7%.[4] The core symptoms of CHE are considered to be itching and pain, though CHE may also be associated with bleeding, cracking, dryness, and hyperkeratosis (thickened skin).[3, 5] Additionally, a large chart review study (RWEAL) identified that the most common symptoms associated with CHE for patients in the United Kingdom (UK) were erythema, fissures, pruritus, and scaling.[6] CHE may be limited to specific parts of a patient's hands (e.g., fingertips or palms) or effect most of the surface area of a patient's hands and wrists.[3] Likewise, the symptoms of CHE are not necessarily consistent over time, with the severity of CHE symptoms prone to fluctuation.[3, 5] Several different measures exist to classify the severity of CHE, including the Physician's Global Assessment (PGA), Investigator's Global Assessment (IGA), Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) or Hand Eczema Severity Index (HECSI). Typically, these measures may be used to assess a patient as being clear of CHE, almost clear of CHE, or having mild, moderate, or severe CHE. The EAG's clinical experts indicated that within UK clinical practice, PGA is the most widely used measure for assessing the severity of CHE, although one clinical expert indicated that they do not currently use this measure.

Usually, the first line treatment for patients with CHE is topical corticosteroids (TCSs) with, or without, topical calcineurin inhibitors (TCIs). However, many patients have an inadequate response to, or are unsuitable to be prescribed, TCSs and require further treatment. Within UK clinical practice, patients are typically prescribed either psoralen-UV A (PUVA) phototherapy or alitretinoin as a second-line therapy. In TA177[7], NICE recommended that alitretinoin can be prescribed to patients with severe eczema. In contrast, PUVA may be prescribed to patients with either moderate or severe CHE. However, the EAG's clinical experts noted that approximately 50% of patients with moderate CHE may receive alitretinoin on an off-label basis.

CHE has multiple different aetiological forms including irritant contact dermatitis, allergic contact dermatitis, and atopic hand eczema. Irritant contact dermatitis is associated with a patient coming into contact with a known irritant that exacerbates their symptoms, it is known to be common for people who work with chemicals or whose occupation involves frequent hand washing. Allergic contact dermatitis is caused by a sensitive individual coming into contact with an allergen (e.g., nickel or latex). Atopic hand eczema normally occurs as a result of a patient's immune system. Importantly, it is possible for patient to have more than one aetiological form of CHE. CHE may take on different morphological forms such as bleeding, dryness, or hyperkeratosis. As such, the EAG's clinical experts indicated that the treatment a patient receives may be dependent on the morphological characteristic of hyperkeratosis. Specifically, the EAG's clinical experts indicated that patients with hyperkeratotic CHE may be more likely to receive alitretinoin, while patients with non-hyperkeratotic CHE may be more likely to receive PUVA.

Delgocitinib is proposed as a second-line therapy in patients, with either moderate or severe CHE, for whom TCS are inappropriate or produce an inadequate response. The Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for delgocitinib in this indication is, "for the treatment of moderate to severe chronic hand eczema (CHE) in adults for whom topical corticosteroids are inadequate or inappropriate".[1] Additionally, one of the EAG's clinical experts considered that they would expect delgocitinib to be primarily used to treat patients with non-hyperkeratotic CHE, although it was noted that clinicians may seek to use delgocitinib in both hyperkeratotic and non-hyperkeratotic patients. The company's proposed positioning of delgocitinib is outlined in Figure 1.

Figure 1. Proposed positioning of delgocitinib within UK clinical practice (taken from Figure 2 of the CS).



[a] TCI are not indicated for non-atopic subtypes of CHE and are used as a steroid-sparing option.
[b] Alitretinoin is licensed in the UK only for severe CHE. Guidelines position alitretinoin as initial 2nd line therapy based on weight of evidence.
[c] Conventional systemics are off label, with the exception of ciclosporin which is registered in some countries for use in AD but not specifically for HE (and is thus off label in HE of other aetiologies).
[d] Biologics and oral JAKis are off label; they are registered in some countries for use in atopic dermatitis but not specifically for HE (and are thus off label in HE of other aetiologies).

Abbreviations: JAKis, Janus kinase inhibitor; PUVA, Psoralen-UV A; UVB, ultra-violet B; TCI, Topical calcineurin inhibitors; TCS, topical corticosteroids.

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

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE), together with a rationale for any deviations from the decision problem. The CS covers the full marketing authorisation for delgocitinib and matches most of the NICE final scope[8], with some differences in the comparators. Overall, the EAG considers that the CS appears appropriate and justified. A summary of the final scope issued by NICE, the decision problem

addressed in the CS, and the EAG's critique of this is provided in Table 12. Further detail about the EAG's critique is provided in Sections 2.3.1 to 2.3.5.

Table 12. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with moderate to severe chronic hand eczema that has not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate	Per final scope	N/A	The population covered in the CS and the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials match the NICE final scope and draft SmPC. However, the EAG notes that the DELTA FORCE and ALPHA trials only consider patients with severe chronic hand eczema. Accordingly, the EAG notes that the trials allowing a direct, or indirect, comparison of delgocitinib to alitretinoin and PUVA are in a narrower population than stated in the NICE final scope and draft SmPC. See Section 2.3.1 for further discussion.
Intervention	Delgocitinib cream (20mg g^{-1})	Per final scope	N/A	The intervention covered in the CS and the DELTA 1, DELTA 2, and DELTA FORCE trials matches the NICE final scope and draft SmPC. See Section 2.3.2 for further discussion.
Comparator(s)	• Alitretinoin (in severe hand eczema); • Topical calcineurin inhibitors;	• Alitretinoin (in severe hand eczema); and • Ultraviolet light therapy (PUVA)	Feedback from clinical experts and real-world study data suggest that TCIs are used as part of a first line optimisation strategy alongside topical	Based on feedback from the EAG's clinical experts, the EAG is satisfied that the only relevant comparators are alitretinoin and PUVA. However, the EAG notes that data are only available

	• Ultraviolet light therapy (PUVA, narrowband UVB); and • Systemic immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil)		corticosteroids in the treatment of CHE, and not as a monotherapy for patients in the target patient population. TCIs have therefore been excluded as comparators in the presented decision problem due to their positioning and frequent use as first line treatment. Within the guidelines from the European Society of Contact Dermatitis (ESCD), systemic immunosuppressants are positioned in CHE patients who are refractory or contraindicated to first and second line options and are therefore positioned at a different point in the treatment pathway (third line+). Ciclosporin is a "suggested" treatment in the ESCD guidelines, so it has a higher grade of recommendation than the other systemic immunosuppressants; however, ciclosporin is also positioned as a third line treatment. Methotrexate and azathioprine have the lowest grade of recommendation and are positioned as third line treatments. Mycophenolate mofetil is not included in the	for these comparators in patients with severe CHE. The EAG's clinical experts have asserted that patients with moderate CHE would still be expected to receive alitretinoin (on an off-label basis) and PUVA. As such, the EAG has concerns regarding the lack of data for the efficacy of alitretinoin and PUVA in moderate patients. See Section 2.3.3 for further discussion.

			ESCD guidelines. Additionally, a survey of 194 UK dermatologists reported that mycophenolate mofetil is rarely used as the first, second or third choice of treatment for CHE, with the majority of those surveyed indicating that they would never or rarely use mycophenolate mofetil for the treatment of CHE. For these reasons, the decision problem addressed in this submission excludes azathioprine, ciclosporin, methotrexate and mycophenolate mofetil as comparators as they are used in a different line of therapy. In the absence of comparative evidence, PUVA was assumed to serve as a proxy for NBUVB. This assumption may be conservative given that the limited available evidence suggested that NBUVB may be less effective than PUVA though their unit costs in the UK National Health Service (NHS) are the same.	
Outcomes	• Measures of disease severity;	• Measures of disease severity (Investigator's Global	N/A	All four outcomes listed in the NICE final scope are covered in the DELTA

	• Measures of symptom control, including improvement in itch; • Time to relapse/prevention of relapse; • Adverse effects of treatment; and • Health-related quality of life	Assessment for Chronic Hand Eczema [IGA-CHE] treatment success [TS], Hand Eczema Severity Index [HECSI]-75, HECSI-90 and HECSI score reduction); • Measures of symptom control, including improvement in itch (Hand Eczema Symptoms Diary [HESD]-PAIN and HESD-ITCH); • Time to relapse/prevention of relapse (loss of response, measured as the time to first IGA-CHE score ≥2); • Adverse effects of treatment; and • Health-related quality of life (Dermatology Life Quality Index [DLQI] >4-point improvement, change from baseline in DLQI, EQ-5D and HEIS)		trials. However, the EAG's clinical experts noted that the endpoints of IGA-CHE, HECSI, HESD, and HEIS, are not routinely assessed in clinical practice. See Section 2.3.4 for further discussion.
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	The analysis performed is in line with the NICE reference case, and the NICE 2022 health technology evaluation manual; the economic analysis is a cost-utility analysis. Costs and QALYs are considered over a lifetime horizon and will be conducted from the perspective of the National Health Service (NHS)	In line with the NICE reference case.	The EAG considers that the model evaluates the cost-effectiveness of treatments according to costs and QALYs with an ICER reported, in line with the NICE reference case. Appropriate time horizons have been assumed with an NHS and PSS perspective taken.

	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 of any managed access arrangement for the intervention will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	and Personal Social Services (PSS). The main output of the economic analysis is the incremental cost-effectiveness ratio (ICER). Certain treatments included in the economic analysis have confidential PASs in the form of simple discounts. The economic analysis has allowed for inclusion of these simple discounts, but the base case analysis reflects list prices for these treatments.		The base cases reported reflect the list price of treatments, with the discounts for relevant treatments included in the confidential appendix.
Subgroups to be considered	• Primary cause of hand eczema (atopic or contact); • Moderate vs severe disease; and • Inadequate response to topical corticosteroids vs topical corticosteroids inadequate or inappropriate	• Primary cause of hand eczema (atopic or contact); and • Moderate vs severe disease	In DELTA 1 and DELTA 2, the pivotal trials for delgocitinib versus cream vehicle, 99% of patients across both arms had an inadequate response to TCS in the last 12 months and 20.3% of patients across both treatment arms were inappropriate for treatment with TCS. This means that there is a significant overlap between these two populations within the key clinical studies. Additionally, the DELTA trials were not	The EAG is satisfied with the company's rationale for not performing a subgroup analysis of patients who had an inadequate response to TCS compared to patients who had either an inadequate response to TCS or for those patients where TCS was deemed inappropriate. Subgroup analyses for disease severity and the primary cause of CHE are provided in the CS. For the subgroup analysis of moderate and severe CHE patients, this subgroup analysis was not feasible for the

			powered to look at efficacy differences in those subgroups. Therefore, subgroup analyses based on ineligibility for TCS versus inadequate response to TCS would not provide a meaningful comparison regarding the relative clinical efficacy of delgocitinib in these two subgroups.	comparisons of delgocitinib to either alitretinoin or PUVA as these trials (DELTA FORCE and ALPHA) only considered severe patients. Additionally, the EAG requested that the company performed subgroup analyses for patients based on whether they had hyperkeratotic CHE or non-hyperkeratotic CHE. Data for this subgroup was not presented in the CS or requested in the NICE final scope. However, the EAG's clinical experts indicated that patients may be treated differently based upon whether they experienced hyperkeratotic CHE. As such, the EAG considers patients with hyperkeratotic CHE and non-hyperkeratotic CHE important subgroups to consider. See Section 2.3.5 for further discussion.
Special considerations, including issues related to equity or equality	Nothing outlined in the NICE final scope	Nothing outlined by the company in the submission	N/A	N/A
Abbreviations: EAG, External Assessment Group				

2.3.1 Population

Alignment to NICE final scope

The population focused on by the company in this submission, including the economic model, is adult patients with moderate to severe chronic hand eczema that has not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate. The EAG considers this population to be aligned with the NICE final scope and MHRA marketing authorisation.

Alignment to UK population

When assessing the efficacy of delgocitinib to comparator treatments, the company performed several trials. DELTA 1[9] and DELTA 2[10] are described as being identical trials that compared delgocitinib to a vehicle cream. Patients who were enrolled on the DELTA 1 and DELTA 2 trials were eligible to be enrolled on the DELTA 3[11] open-label extension in which patients received delgocitinib regardless of whether they previously received delgocitinib or vehicle cream in the DELTA 1 or DELTA 2 trials. The company also performed the DELTA FORCE[12] trial that compared delgocitinib to alitretinoin. There were no studies performed that sought to compare delgocitinib to PUVA. Overall, the DELTA 1, DELTA 2, and DELTA FORCE trials are considered to be the key clinical trials for delgocitinib used in the CS.

The EAG notes that within the DELTA 1 trial, 24 of the 487 patients (4.9%) were from the UK, while in the DELTA 2 trial no patients were from the UK.[13] However, within the DELTA 1 and DELTA 2 trials, 80.1% and 79.5% of patients were from Europe, respectively. Likewise, for the DELTA FORCE trial, six of the 513 patients (1.2%) were from the UK, though 89.5% of patients were from Europe. The EAG's clinical experts noted that across the DELTA trials, approximately 65% of patients were female, aligning with UK clinical practice. Likewise, across all the DELTA trials, the median age of patients varied from 42 to 46 years, which aligns with UK clinical practice. However, the EAG's clinical experts noted that, across all the DELTA trials, a relatively small number of patients had prior phototherapy, which does not necessarily align with UK clinical practice. The EAG noted that there were substantial differences in the prevalence of severe CHE across the DELTA 1, DELTA 2, and DELTA FORCE trials. While the DELTA FORCE trial only considered patients with severe CHE, ~32.8% and ~23.9% of patients had severe CHE in the DELTA 1 and DELTA 2 trials, respectively. As such, the EAG's clinical

experts noted that the prevalence of severe CHE in the DELTA 2 trial is lower than would typically be expected in UK clinical practice.

The EAG notes that there are within-trial differences for several baseline characteristics including prior treatments and aetiological or morphological subgroups each of which is detailed below:

- Prior oral corticosteroids were received by 14.2% of patients in the delgocitinib arm and 8.0% of patients in the vehicle cream arm of the DELTA 1 trial;
- Prior TCIs were received by 37.2% of patients in the delgocitinib arm and 32.7% of patients in the vehicle cream arm of the DELTA 1 trial;
- Prior phototherapy was received by 19.1% of patients in the delgocitinib arm and 24.5% of patients in the vehicle cream arm of the DELTA 2 trial;
- Other previous treatments for CHE (e.g., treatments other than TCIs, phototherapy, oral retinoids, oral corticosteroids, oral methotrexate, oral ciclosporin, and oral azathioprine) were received by 19.7% of patients in the delgocitinib arm and 28.2% of patients in the alitretinoin arm of the DELTA FORCE trial;
- Hyperkeratotic CHE was reported for 17.5% of patients in the delgocitinib arm and 12.3% of patients in the vehicle cream arm of the DELTA 1 trial;
- Allergic contact dermatitis was reported for 15.7% of patients in the delgocitinib arm and 20.4% of patients in the vehicle cream arm of the DELTA 1 trial;
- Allergic contact dermatitis was reported for 9.0% of patients in the delgocitinib arm and 14.0% of patients in the vehicle cream arm of the DELTA 2 trial;
- Vesicular CHE (pompholyx) was reported for 14.0% of patients in the delgocitinib arm and 6.0% of patients in the vehicle cream arm of the DELTA 2 trial;
- Pompholyx was reported for 8.7% of patients in the delgocitinib arm and 13.9% of patients in the alitretinoin arm of the DELTA FORCE trial.

Overall, the EAG's clinical experts indicated that differences in the prevalence of prior treatments between groups would not be expected to significantly impact trial results or affect the reported outcomes. However, the EAG's clinical experts noted that the difference in the proportion of patients with hyperkeratotic eczema in the DELTA 1 trial would be the most likely subtype imbalance to affect reported outcomes or trial results, although this is expected to bias the results in favour of vehicle cream. However, one of the EAG's clinical experts indicated that they were unsure whether

the imbalance in the proportion of patients with hyperkeratotic eczema would bias the results in favour of vehicle cream.

In response to a clarification question, the company provided HESD score, HESD itch score, and HESD pain scores at baseline for the DELTA 1, DELTA 2, DELTA FORCE, and Worm *et al.* 2022[14] trials. In response to this clarification question, the company noted that there was substantial variation, in all three measures, across the trials. For patients who received delgocitinib, the highest HESD score (7.15), HESD itch score (7.13), and HESD pain score (6.83) were all reported in the DELTA 1 trial, while the lowest HESD score (5.3), HESD itch score (5.5), and HESD pain score (4.4) were all reported in the Worm *et al.* 2022 trial. Overall, the highest HESD were reported for the DELTA 1 and DELTA 2 trials, while the lowest scores were reported for the DELTA FORCE and Worm *et al.* 2022 trial. Given the considerable differences between HESD scores at baseline across the trials, the company suggested that the differences may be caused by the DELTA 1 and DELTA 2 trials implementing an inclusion criterion that stipulated that patients must have an HESD itch score of ≥4 at baseline. As this criterion was not implemented in the DELTA FORCE or Worm *et al.* 2022 trials, the company suggested that this may explain the disparities in HESD scores observed between these trials.

The EAG's clinical experts noted that several baseline characteristics are likely to be prognostic indicators for the treatment of CHE, each of which is noted below:

- Severity of CHE (patients with moderate CHE were considered more likely to respond to treatment than patients with severe CHE);
- Hyperkeratosis (patients with hyperkeratotic CHE are generally considered more challenging to treat than patients with non-hyperkeratotic CHE);
- Age (older patients are considered more likely to have poorer outcomes);
- Duration of CHE (patients with longer time since diagnosis are considered more likely to have poorer outcomes);
- Prior treatments (patients who have failed either phototherapy or systemic treatment are considered more likely to have poor outcomes);
- Prior TCS (patients for whom TCS produced an inadequate response, or patients for whom TCS are inappropriate, [namely the population of interest for this appraisal] would be expected to have a poorer response to treatment [although one of the EAG's clinical experts indicated that they did not consider this to be the case]).

Alongside the above prognostic variables, the EAG's clinical experts indicated that CHE morphology is likely to be a treatment effect modifier. Firstly, the EAG's clinical experts indicated that alitretinoin is more likely to be effective in patients with hyperkeratotic CHE compared to either vesicular or atopic hand eczema. In contrast, PUVA is thought to be effective in patients with vesicular or atopic hand eczema compared to hyperkeratotic CHE.

Additionally, the EAG's clinical experts noted that occupation is likely an important covariate to consider. For instance, patients who work in 'hands-on' occupations (e.g., manual labourers, nail technicians, or hairdressers) are more likely to have CHE compared to patients in other industries (e.g., office workers). Furthermore, the EAG's clinical experts noted that the number of young children that a patient has is a potential covariate to consider. For example, the greater number of young children that a patient has, the greater their exposure to conditions or substances that may trigger, or worsen symptoms of, CHE. However, the EAG notes that these variables are not routinely captured in clinical trials and as such cannot be explored within this assessment.

2.3.2 Intervention

The intervention matches that stated in the NICE final scope. Delgocitinib (brand name Anzupgo®) received UK (Medicines and Healthcare products Regulatory Agency [MHRA]) regulatory approval on 29 November 2024 for patients with moderate to severe CHE for whom TCS are inadequate or inappropriate. As such, the administration and dose of delgocitinib used in the DELTA 1, DELTA 2, DELTA 3, and DELTA FORCE trials aligns with that described in the SmPC, which is for a thin layer of delgocitinib (20mg g^{-1}) to be applied twice daily (at regular intervals, approximately 12 hours apart) to the affected skin of the hands and wrists, until the skin is clear or almost clear of CHE.

Delgocitinib is a pan Janus kinase inhibitor (JAKi) that targets the activity of the four members of the Janus kinase (JAK) family of enzymes (JAK1, JAK2, JAK3, and tyrosine kinase 2). In human cells, delgocitinib lessens the signalling of multiple pro-inflammatory cytokines (e.g., interleukin (IL)-2, IL-4, IL-6, IL-13, IL-21, IL-23). As such, delgocitinib suppresses the relevant immune and inflammatory response of cells within the CHE pathology.

Within the DELTA 1, DELTA 2, DELTA FORCE trials, efficacy and safety outcomes were assessed at 16 weeks, although DELTA 3 also considers such outcomes up to 52 weeks. The EAG's clinical experts considered 16 weeks to be a sufficient time over which to assess a patient's response to treatment. Given that the dose, method of administration, and assessment time points reflect what the clinical

experts would expect in practice, the intervention used in the trials appears suitable to address the decision problem.

2.3.3 Comparators

Of the comparators listed in the NICE final scope, the company has covered comparisons against alitretinoin and ultraviolet light therapy (namely PUVA). The EAG's clinical experts confirmed that for patients with CHE for whom TCS are inappropriate or inadequate, alitretinoin and PUVA would be considered the main comparators for patients who would be eligible for delgocitinib. Alitretinoin received a positive recommendation from NICE, for treating patients with severe CHE in 2009 (TA177). Accordingly, any patients with moderate CHE who receive alitretinoin would be doing so on an off-label basis. However, the EAG's clinical experts asserted that an estimated 50% of patients with moderate CHE would be prescribed alitretinoin as second-line treatment on an off-label basis. In contrast to alitretinoin, PUVA does not hold marketing authorisation in the UK, though it is routinely prescribed on an off-label basis to treat patients with either moderate or severe CHE. PUVA has two distinct forms, the first is a localised topical gel or immersion allowing PUVA to only be applied to the target areas. The second is in a tablet form, although given the non-localised nature of this formulation, the tablet form of PUVA is associated with compliance issues including the need to wear sunglasses, both indoors and outside, for 24 hours. Accordingly, within UK clinical practice, the EAG's clinical experts noted that the immersion or topical gel form of PUVA is generally prescribed to patients with CHE. The EAG's clinical experts additionally noted that treatment with alitretinoin or PUVA depended on whether the patient presented with hyperkeratotic or atopic CHE. Accordingly, the EAG's clinical experts noted that patients with atopic CHE were more likely to prescribed PUVA, while patients with hyperkeratotic CHE were more likely to be prescribed alitretinoin.

In contrast to alitretinoin and PUVA, the other comparisons listed in the NICE final scope (topical calcineurin inhibitors [TCIs], narrowband UVB [NUVB], and systemic immunosuppressive therapies) have not been included as a comparator within the CS. With regards to NUVB, the EAG's clinical experts suggested that PUVA is a much more widely used form of ultraviolet light therapy in UK clinical practice for treating CHE. The EAG's clinical experts outlined that this is primarily due to NUVB requiring a whole-body machine, whereas PUVA is administered with a dedicated machine for targeting just hand and foot skin. Accordingly, the EAG considers the exclusion of NUVB from the CS to be reasonable.

For TCIs, the EAG's clinical experts agreed with the company's assertion that TCIs are not regularly used as a monotherapy for patients with CHE. Instead, the EAG's clinical experts indicated that TCIs are broadly used to either augment a patient's response to TCS, as a top-up treatment, or as a steroid-sparing agent in patients who would otherwise require long-term daily TCS. Accordingly, the EAG considers the exclusion of TCIs from the CS to be reasonable.

For systemic immunosuppression therapies, the EAG's clinical experts agreed with the company's assertion that these treatments were not relevant comparators for the population of interest. The company indicated that systemic immunosuppression therapies were predominantly used as third-line (or later) treatment for patients with CHE. Likewise, the EAG's clinical experts indicated that systemic immunosuppressive therapies are not routinely used for patients with CHE. However, one of the EAG's clinical experts indicated that systemic immunosuppressive therapies are routinely used for patients who fail on earlier stage treatments (although the clinical expert noted that this may represent a smaller group of patients). Of the treatments listed in the NICE final scope, the EAG's clinical experts indicated that in UK clinical practice:

- Azathioprine is not used to treat patients with CHE;
- Ciclosporin is rarely used by dermatologists and is not used to treat CHE;
- Methotrexate is only used occasionally to treat CHE but is contraindicated by pregnancy and is additionally associated with issues with both alcohol and obesity; and
- Mycophenolate mofetil is very occasionally used to treat CHE but, similar to methotrexate, is contraindicated by pregnancy and issues with both alcohol and obesity.

Accordingly, the EAG considers the exclusion of systemic immunosuppression therapies from the CS to be reasonable.

The EAG's clinical experts noted that they did not consider any other comparators to be missing from the CS. However, the EAG's clinical experts also noted that there are some case studies or case series of oral JAK inhibitors being used to treat patients with CHE, although these are not considered standard clinical practice in the UK. When performing the SLR, the company identified the following randomized controlled trials (RCTs) that evaluated an oral JAK inhibitor:

- Two RCTs (Measure Up 1 and Measure Up 2) that compared upadacitinib to placebo in patients with atopic dermatitis and were included in the SLR;
- One RCT (Jiminez *et al.* 2023) that compared gusacitinib to placebo in patients with CHE, although this was excluded from the SLR due to the product not holding marketing authorisation in Europe or Canada; and
- One RCT (JADE DARE) that compared dupilumab to abrocitinib in patients with atopic dermatitis and was included in the SLR.

Within the CS, the company also noted that baricitinib, a JAK inhibitor, has been approved for the treatment of moderate to severe atopic dermatitis who have not responded to conventional systemic immunosuppressants. Likewise, the company notes that baricitinib has been described in case reports for patients with severe CHE, but that no RCTs for patients with CHE have been undertaken. Additionally, the EAG noted that within the treatment pathway provided by the company, oral JAK inhibitors are only considered on an off-label basis as a third line treatment in the population of interest. As such, despite the identification of trials that investigated oral JAK inhibitors in patients with CHE, the EAG considers the exclusion of oral JAK inhibitors from the CS to be appropriate.

Overall, the EAG notes that direct evidence is only available for the comparison of delgocitinib to alitretinoin, although the DELTA FORCE trial only considers patients with severe CHE. Accordingly, indirect treatment comparisons are required to assess the relative efficacy of delgocitinib to PUVA (Section 3.4).

2.3.4 Outcomes

The outcomes in the CS are aligned to those specified in the NICE final scope. Within the NICE final scope, outcomes measures were required to assess disease severity, symptom control, time to relapse or prevention of relapse, adverse events, and health-related quality of life.

Within the DELTA 1, DELTA 2, and DELTA FORCE trials, disease severity was assessed using the measures of Investigator Global Assessment Chronic Hand Eczema (IGA-CHE) and Hand Eczema Severity Index (HECSI). IGA-CHE is a recently published measure, that was developed with resources from the company, for specific use in patients with hand eczema in contrast to other broad-use dermatological assessment tools such as the Physician Global Assessment (PGA). Using IGA-CHE patients are assigned a score of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), or 4 (severe).

Within the DELTA trials, the primary outcome was IGA-CHE treatment success (IGA-CHE TS), which was measured as the proportion of patients who achieved an IGA-CHE score of either 0 or 1 following treatment. When using HECSI, patients are assigned a score of between 0 and 360 based on the severity of their symptoms. Accordingly, across all DELTA trials, the proportion of patients who achieved a reduction in HECSI scores of 50% (HECSI-50), 75% (HECSI-75), and 90% (HECSI-90) were measured. Additionally, the DELTA 1 and DELTA 2 trials measured percentage change in HECSI, while the DELTA FORCE trial measured mean change in HECSI.

The EAG notes that not all clinical outcomes used within the DELTA trials are commonly used within UK clinical practice. The EAG's clinical experts noted that IGA-CHE, the primary outcome in the DELTA trials, is not routinely used to measure clinical response in the UK, with PGA more commonly used. Likewise, the EAG's clinical experts noted that HECSI is a measure of clinical response that is more widely used by European dermatologists, as opposed to those working in the UK. However, despite not being used in UK clinical practice, the EAG's clinical experts indicated that they considered that all clinical outcomes were appropriate for assessing the outcomes listed in the NICE final scope. Although IGA-CHE was measured in the DELTA trials, it was not measured within the ALPHA trial that compared alitretinoin and PUVA. Instead, the ALPHA trial used PGA to determine the severity of a patient's hand eczema. In response to clarification questions, the company confirmed that PGA was not measured within the DELTA trials. Accordingly, when performing indirect treatment comparisons, the company assumed that the measures of IGA-CHE and PGA are clinically equivalent. Within the CS, the company acknowledged that this was a strong assumption to make, which the EAG is likewise concerned by. However, the company has justified the assumption by indicating that patients would be required to meet more stringent criteria to be deemed as either clear or almost clear when using IGA-CHE compared to PGA, an assertion supported by the EAG's clinical experts.

Within the DELTA trials, symptom control was assessed through the use of the patient-reported outcome measure of the Hand Eczema Symptom Diary (HESD), a new measure that was developed with resources from the company. HESD combines scores from multiple different elements; however, within the DELTA trials, HESD total score, HESD pain score, and HESD itch score were all measured to assess symptom control. As with the clinical outcomes, the EAG's clinical experts noted that HESD is an outcome that is not currently used within UK clinical practice; however, the EAG's clinical experts noted that the Dermatology Life Quality Index (DLQI) may be more commonly used in UK clinical practice. However, the EAG's clinical experts likewise noted that symptom control is not

commonly measured quantitatively in UK clinical practice and qualitative descriptions are used due to time constraints in dermatology clinics. In response to clarification questions, the company outlined that the form of the HESD used within the Worm *et al.* 2022 trial differed to that used in the DELTA trials. Within the Worm *et al.* 2022 trial an 11-item version of the HESD was used, although this was subsequently revised to a 6-item version following consultations with the US Food and Drug Administration (FDA) and expert dermatologists. This 6-item version of the HESD was subsequently used in the DELTA trials.

Time to relapse was not assessed in the DELTA trials. DELTA 1, DELTA 2, and DELTA 3 did not assess any form of relapse. However, while the DELTA FORCE trial did not measure time to relapse, the trial reported the percentage of patients who relapsed and was measured as a patient having an IGA-CHE score of ≥2 after previously having an IGA-CHE score of 0 or 1. Time to relapse was reported in three of the trials (ALPHA, BACH, and HANDEL trials) included in the SLR; however, the company noted that time to relapse was defined differently across these trials. As such, the EAG is concerned that methodological heterogeneity between the trials may prevent time to relapse from being directly comparable across these trials.

Within the DELTA trials, health-related quality of life (HRQoL) was assessed using DLQI, EuroQol Group 5-Dimension Five Level Questionnaire (EQ-5D-5L), and the Hand Eczema Impact Scale (HEIS). DLQI and EQ-5D-5L were both measured in the DELTA 1, DELTA 2, DELTA 3, and DELTA FORCE trials. EQ-5D-5L was subsequently crosswalked to the EuroQol Group 5-Dimension Three Level Questionnaire (EQ-5D-3L) prior to performing any analyses.[15] HEIS, which was developed with resources from the company, was only measured in the DELTA 1, DELTA 2, and DELTA 3 trials.[16] Of these HRQoL outcomes, the EAG's clinical experts noted that only DLQI is routinely used in UK clinical practice. Additionally, the EAG's clinical experts agreed with the company's assertion that a 4-point improvement in DLQI would be considered a clinically meaningful change in HRQoL. However, the EAG's clinical experts noted that DLQI is generic dermatology measure and is not tailored to CHE. Of the three measures used to assess HRQoL, only EQ-5D-3L was used within the economic model.

For safety outcomes, the company provided information on patients with treatment-emergent adverse events (TEAEs), mild TEAEs, moderate TEAEs, severe TEAEs, and serious TEAEs for the DELTA 1, DELTA 2, and DELTA FORCE trials. The most common TEAEs were reported in the CS for the DELTA

1 and DELTA 2 trials and, in response to the EAG's clarification questions, the company provided the same information for the DELTA FORCE trial.

2.3.5 Subgroups

Within the NICE final scope, one listed subgroup comparison of interest was patients with inadequate response to TCS compared to patients for whom TCS were inappropriate or inadequate. The company stated that as, within the DELTA 1 and DELTA 2 trials, ~99% of patients had an inadequate response to TCS and ~20% were inappropriate for treatment with TCS, there would be substantial overlap between the patients included in these subgroups. The EAG also noted that, for the DELTA FORCE trial, there was a substantial overlap between the patients included in these subgroups, although TCS were considered inappropriate for only ~10% of patients in the DELTA FORCE trial. Additionally, the company noted that the DELTA 1 and DELTA 2 trials were not powered to consider differences in outcomes between these subgroups. Given these points, the company concluded that a subgroup analysis of patients with inadequate response to TCS compared to patients for whom TCS were inappropriate or inadequate would not provide a meaningful comparison of these subgroups and did not perform these analyses. As such, the EAG accepts the rationale provided by the company and agrees that it is not appropriate to perform a subgroup analysis of patients with inadequate response to TCS compared to patients for whom TCS were inappropriate or inadequate. As in the DELTA 1 and DELTA 2 trials, ~99% of patients were ineligible for TCSs, the EAG anticipates that the overall assessment will likely only be valid for this subgroup. As such, given the absence of any subgroup analysis, the EAG is concerned that the results of this overall assessment may not necessarily hold for patients for whom TCS were inappropriate. However, the EAG is uncertain as to what the likely difference in treatment effect between patients for whom TCS are inappropriate or inadequate would be.

The company performed subgroup analyses for CHE aetiological subtype across the DELTA 1, DELTA 2, and DELTA FORCE trials. Subgroup group analyses were performed for:

- Patients with atopic CHE compared to patients with non-atopic CHE; and
- Patients with contact CHE compared to patients with non-contact CHE.

These subgroup analyses, based on CHE aetiological subtype, align with the subgroup analyses specified in the NICE final scope. Additionally, within the CS, the company noted that patch testing is required to identify and classify the contact subtype of CHE. As such, the company noted that based

on the CHECK patient survey[17] and RWEAL physician survey[18], patch testing was only performed for 16.1% or 41% of patients with CHE in the UK, respectively. However, the EAG's clinical experts stated that patch testing was routinely performed for all patients with CHE within UK clinical practice. As such, the EAG understands that most patients should have had patch testing to confirm whether their CHE is the allergic contact dermatitis subtype.

The company additionally performed subgroup analyses for patients who had moderate or severe forms of CHE, in alignment with the NICE final scope. In the CS, subgroup analyses for moderate and severe patients with CHE were presented for the pooled data from the DELTA 1 and DELTA 2 trials, although as the DELTA FORCE trial solely comprised patients with severe CHE, a subgroup analysis of moderate and severe CHE patients was not possible for this trial. Within the CS, the company presented subgroup results, for moderate and severe patients, for the outcomes of IGA-CHE TS, HECSI-75, and HECSI-90. In response to a clarification question, the company provided the results of subgroup analyses for HECSI change from baseline, HESD pain score reduction of ≥4 points, HESD pain score improvement, HESD itch score reduction of ≥4 points, HESD itch score improvement, HESD total score reduction of ≥4 points, HESD total score improvement, and EQ-5D-3L. Additionally, in response to a clarification question, the company provided the results of a subgroup analysis comparing outcomes in the DELTA 1 and DELTA trials across moderate and severe patients who received delgocitinib.

Despite not being stated as a subgroup of interest in the NICE final scope, the company performed subgroup analyses of patients based upon whether they had previously been treated with TCIs. In the CS, subgroup analyses for patients who had previously been treated with a TCI, and those who had not, were presented for the pooled data from the DELTA 1 and DELTA 2 trials (comparing delgocitinib to a vehicle cream) and the DELTA FORCE trial (comparing delgocitinib to alitretinoin).

Although not stated as a subgroup of interest in the NICE final scope, the EAG's clinical experts noted that the prescribed treatments are likely to vary depending on whether the patient has hyperkeratotic or non-hyperkeratotic CHE. The EAG's clinical experts indicated that patients with hyperkeratotic CHE were more likely to be prescribed alitretinoin, while patients with non-hyperkeratotic CHE were more likely to be treated with PUVA. Accordingly, despite not being stated as a subgroup of interest within the NICE final scope, the EAG requested, through clarification questions, that subgroup analyses be performed for patients with hyperkeratotic CHE and non-hyperkeratotic hand eczema. However, the EAG noted that the presence of hyperkeratotic CHE or

non-hyperkeratotic CHE was considered at stratification for the DELTA FORCE trial, but not for the DELTA 1 or DELTA 2 trials.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR) to identify randomised controlled trials (RCTs) that assessed the efficacy and safety of treatments for moderate to severe chronic hand eczema in patients that have not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate.

The External Assessment Group (EAG) summarises the SLR methods in Table 9. The EAG considers the company SLR to be appropriate, and notes that the SLR was broader than would have been necessary given the final scope issued by the National Institute for Health and Care Excellence (NICE) and the decision problem addressed by the company in the company submission (CS). The latest update to the SLR was performed in October 2024, i.e., approximately three months prior to the submission, suggesting that most, if not all, relevant evidence was captured in the CS.

Table 13. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix B1.1	**Appropriate** The following databases were searched: • EMBASE; • MEDLINE® and Epub Ahead of print, In-Process, In-Data-Review, and Other Non-Indexed Citations, Daily and Versions • Cochrane Central Register of Controlled Trials; and • Cochrane Database of Systematic Reviews. In addition, the following trial registries were searched: • US National Institute of Health Database (clinicaltrials.gov); • World Health Organisation Internation Clinical Trials Registry Platform; and • European Union Drug Regulating Authorities Clinical Trials Database. In addition, the abstracts of the following six dermatology conferences were searched from 2020 to 2024: • American Academy of Allergy, Asthma, and Immunology; • American Academy of Dermatology; • British Association of Dermatologists; • European Academy of Dermatology and Venereology; • European Academy of Allergy and Clinical Immunology; and

		• World Congress of Dermatology. In addition, grey literature searches were performed for the websites of HTA agencies in Canada, Germany, and the United Kingdom. However, only English language documents were considered after the first update to the SLR. Bibliographic reviews of an unknown number of systematic reviews, meta-analyses, indirect treatment comparisons, and trials.
Search strategies	Appendix B1.1	**Appropriate** Searches were broad, while limits were defined using both keywords and subject heading terms. The original SLR was performed in 2022, with update searches subsequently performed in April 2024 and October 2024. Accordingly, the most recent update search was performed approximately three months prior to the company's submission.
Inclusion criteria	Appendix B1.1.3	**Appropriate** The EAG considers the inclusion criteria to be broader than the final scope issued by NICE and the decision problem addressed by the company in the CS. Hence, the EAG considers it unlikely any studies relevant to the decision problem have been missed.
Screening	Appendix B1.1.3 and Appendix B1.2.2	**Appropriate** Title/abstract review and full-text review were completed by two independent reviewers. Discrepancies were resolved through discussion or through input of a third reviewer who also performed a quality check of 25% of records.
Data extraction	Appendix B1.1.4	**Appropriate** Data extraction was performed by a single reviewer, while a quality assessment was performed by a second independent reviewer. Any discrepancies were resolved by consensus across both reviewers. No information is provided in the CS regarding the quality assessment of the extracted data. During the factual accuracy check, the company confirmed that the entire extracted dataset was reviewed by a second reviewer.
Tool for quality assessment of included study or studies	Appendix B4.1	**Some concerns** Quality assessments for trials identified in the SLR were completed using the Cochrane tool for assessing risk of bias. However, free-text justifications were not provided for the quality assessment of the trials, making it difficult to assess the appropriateness of the judgements.
Abbreviations: EAG, External Assessment Group		

After the *de novo* SLR performed in April 2022, a total of 1,794 records were identified; of these records, 60 met the inclusion criteria reporting on 31 trials. After the first SLR update, performed in April 2024, 263 new records were identified; of these records, 56 were eligible for inclusion. Finally, after the most recent SLR update, performed October 2024, 73 new records were identified, with 22 records being deemed eligible for inclusion in the SLR. As such, 128 records corresponding to 44

primary studies included in the final SLR update. Of the 44 included studies, 15 were deemed suitable for inclusion within the indirect treatment comparisons based on the reporting of outcomes and an absence of major sources of heterogeneity. The CS outlined that a further six records were linked to pooled data for the DELTA 1 and DELTA 2 trials, but that the company requested the exclusion of these records as separated trial data was available. Of the 15 studies deemed suitable for inclusion in an indirect treatment comparison:

- Three studies compared delgocitinib to a vehicle cream;
- One study compared delgocitinib to alitretinoin;
- One study compared alitretinoin to PUVA;
- Two studies compared alitretinoin to placebo;
- Two studies compared alitretinoin to immunosuppressant therapies;
- Two studies compared upadacitinib to placebo;
- One study compared two different forms of ultraviolet light therapy;
- Two studies compared dupilumab to placebo; and
- One study compared dupilumab to abrocitinib.

For the 29 studies that were deemed unsuitable for inclusion in an indirect treatment comparison:

- Two studies compared alitretinoin to placebo;
- Six studies compared TCIs to a vehicle cream, vehicle ointment, or steroid ointment;
- Two studies compared topical JAK inhibitors (including one study that considered delgocitinib) to vehicle cream or vehicle ointment;
- One study compared an oral SYK/JAK inhibitor to placebo;
- 14 studies compared ultraviolet light therapy to:
    - another form of ultraviolet therapy (8);
    - calcipotriol (1);
    - betamethasone valerate cream (1);
    - placebo light (2); or
    - x-rays (2).
- Three studies compared immunosuppressants to steroids; and
- One study compared a phosphodiesterase inhibitor with a steroid to only a steroid.

Based on the available evidence, the EAG agrees that the direct evidence is the most relevant for assessing the comparison between delgocitinib and vehicle cream and between delgocitinib and alitretinoin. Given the absence of direct evidence comparing delgocitinib and PUVA, the company

performed ITCs to allow for a comparison between these treatments. However, the company noted that there were several limitations for these analyses (e.g., differences in reported outcomes and patient characteristics), which appear to be justified and are discussed in more detail in Section 3.4.

3.2 Critique of trials of the technology of interest

Five randomised clinical trials (RCTs) provided the clinical evidence base for delgocitinib for treating patients with moderate to severe CHE who have not responded to treatment with topical corticosteroids or for whom topical corticosteroids are inadequate or inappropriate in the CS. An overview of each trial is given as follows:

- DELTA 1 (NCT04871711): a randomised, double-blind, parallel-group, phase 3 trial to assess the efficacy and safety of delgocitinib compared with a cream vehicle in patients with moderate or severe CHE. DELTA 1 is described in the CS as being identical in trial design to DELTA 2;
- DELTA 2 (NCT04872101): a randomised, double-blind, parallel-group, phase 3 trial to assess the efficacy and safety of delgocitinib compared with a cream vehicle in patients with moderate to severe CHE. DELTA 2 is described in the CS as being identical in trial design to DELTA 1;
- DELTA 3 (NCT04949841): an open-label extension for patients from the DELTA 1 and DELTA 2 trials to assess the long-term safety of delgocitinib in patients with moderate or severe CHE. All patients in this extension received delgocitinib;
- DELTA FORCE (NCT05259722): a randomised, assessor-blinded, parallel-group, phase 3 trial to compare the efficacy and safety of delgocitinib with oral alitretinoin in adults with severe CHE; and
- Worm *et al.* 2022 (NCT03683719): a randomised, double-blind, vehicle-controlled, phase 2b, dose-ranging trial in adults with mild to severe CHE. The trial considered four dosages (1, 3, 8, 20 mg g^{-1}) of delgocitinib.

Of the above trials, DELTA 1, DELTA 2, DELTA 3, and DELTA FORCE are considered by the EAG to be the pivotal trials for delgocitinib. For each of these trials, the EAG has summarised the trial design, conduct, and analysis below. As the company describes the DELTA 1 and DELTA 2 trials as being identical, and with DELTA 3 being an extension of DELTA 1 and DELTA 2, these three trials are jointly summarised. Worm *et al.* 2022 was not considered to be a pivotal trial by the EAG for several reasons. Firstly, Worm *et al.* 2022 was a dose-ranging trial and considered multiple different dosages

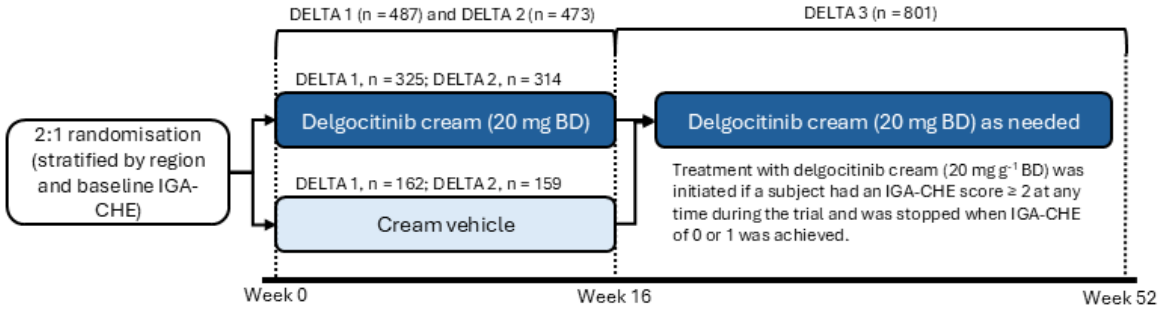
of delgocitinib that have not received approval from MHRA. Secondly, several measures that were implemented in the Worm *et al.* 2022 trial were subsequently adjusted prior to their use in the DELTA trials. For instance, IGA-CHE, HESD, and HEIS all underwent modifications following their implementation in the Worm *et al.* 2022 trial. Additionally, in response to a clarification question, the company noted that the changes in IGA-CHE between the Worm *et al.* 2022 trial and subsequent DELTA trials may limit the comparability of these trials. Likewise, the EAG has similar concerns for outcomes based on the measures of HESD and HEIS.

3.2.1 DELTA 1, DELTA 2, and DELTA 3 trials

DELTA 1 and DELTA 2 were identical double-blind, multi-centre, phase 3, randomised trials designed to determine the efficacy and safety of delgocitinib relative to a vehicle cream. To be eligible to be included in either trial, patients must have been adults with moderate to severe CHE (an IGA-CHE score of 3 or 4), who had an inadequate response to treatment with TCS, or for whom TCS were inappropriate. The DELTA 1 and DELTA 2 trials were each performed over a 16-week period, with patients randomised 2:1 to either delgocitinib 20 mg g^{-1} bd or vehicle cream bd. DELTA 1 and DELTA 2 were conducted over a 16-week treatment period, with patients randomised 2:1 to continuous delgocitinib cream 20 mg/g bd or cream vehicle bd.

Following the conclusion of the 16-week DELTA 1 and DELTA 2 trials, all patients who completed these trials were eligible to enrol in the DELTA 3 phase 3 open-label extension study. All patients who enrolled in the DELTA 3 trial were given delgocitinib 20mg g^{-1} bd regardless of whether they received delgocitinib or the vehicle cream in the DELTA 1 and DELTA 2 trials. The DELTA 3 trial lasted for 36 weeks with patients only applying delgocitinib if they had an IGA-CHE of ≥2, and pausing treatment if they had an IGA-CHE score of 0 or 1. The trial design for the DELTA 1, DELTA 2, and DELTA 3 trials is shown below in Figure 2.

Figure 2. Trial design for the DELTA 1, DELTA 2, and DELTA 3 trials (reproduced from Figure 3 of the CS).



Abbreviations: BD, twice a day; IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

The company provided an overview of the risk of bias for the DELTA 1 and DELTA 2 trials, although not the DELTA 3 trial, in Table 149 of the CS. Overall, the company concluded that there was a low risk of bias for the DELTA 1 and DELTA 2 trials across all attributes considered as part of the Cochrane Risk of Bias Tool.[19] The EAG has conducted its own risk of bias assessments for DELTA 1, DELTA 2, and DELTA 3 that is provided in Table 14 below. Following the risk of bias assessments, the EAG has some minor concerns. Firstly, the EAG notes that some outcomes, across all three trials, were only specified *post-hoc*; accordingly, the EAG considers that these outcomes are at a higher risk of bias compared to those that were pre-specified in each trial's protocol.

Secondly, across all trials, no calculations of sample size or statistical power were performed for subgroups (e.g., moderate and severe CHE patients), as such the EAG has concerns that any subgroup analyses performed from these trials will be insufficiently powered to detect differences between such groups.

Finally, the EAG notes that, for the DELTA 1 and DELTA 2 trials, the rates of treatment discontinuation (both all-cause and discontinuation due to AEs) is substantially higher in patients who received the vehicle cream as opposed to delgocitinib. As such, the EAG is concerned that this may lead to potential biases in any comparisons between these treatment arms. Likewise, for the DELTA 2 trial, 23.0% of patients who received vehicle cream discontinued treatment; as such, the EAG is concerned that this high drop-out rate may bias the results of any analysis of this patient population. Additionally, the all-cause treatment discontinuation rate in the DELTA 3 was high at 17.0%, though only 0.9% of patients discontinued treatment due to adverse events. Accordingly, the EAG has some concerns that this high drop-out rate may bias any interpretation of the results of the DELTA 3 trial.

For the DELTA 1, DELTA 2, and DELTA 3 trials, the EAG is concerned that the high dropout rate has the potential to introduce bias into the results. Given the disparity in dropout rates between the trial

arms, the potential for selective dropouts would result in the patients assessed for outcomes, at a given timepoint, would no longer represent balanced groups despite being balanced at baseline. Additionally, the EAG is concerned that the use of the worst observation carried forward (WOCF) approach to account for missing data has the potential to bias against vehicle cream in favour of delgocitinib. The use of the WOCF approach generates bias against the treatment arm in which the dropout rate is highest. As such, the WOCF approach may be considered to be conservative if the dropout rate is greatest in the arm for the new treatment. However, within the DELTA 1 and DELTA 2 trials, the dropout rate is greatest in the vehicle cream arm, not the delgocitinib arm, as such it may result in a bias in favour of delgocitinib (within the pooled DELTA 1 and DELTA 2 trials, WOCF was used to estimate data at Week 16 for 6.6% and 18.4% for delgocitinib and vehicle cream, respectively). Furthermore, the EAG notes that when higher dropout rates are expected for one treatment arm, use of the WOCF approach may result in an exaggerated treatment effect for the treatment arm with the lower dropout rate. As such, within the DELTA 1 and DELTA 2 trials, discontinuation rates may have been assumed to be greater in the vehicle cream arm, compared to the delgocitinib arm, *a priori*, due to lower efficacy expected in the vehicle cream arm. Likewise, a reduced rate of dropouts, due to a lack of efficacy, may have been expected for patients receiving delgocitinib in the DELTA 1 and DELTA 2 trials, based on efficacy data from prior trials of delgocitinib (e.g., Worm *et al.* 2022). As such, the EAG is concerned that the use of the WOCF approach may have resulted in the relative effectiveness for delgocitinib being overstated relative to vehicle cream.

Table 14. EAG's summary of the design, conduct and analysis of the DELTA 1, DELTA 2, and DELTA 3 trials

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 2.3.1.2	**DELTA 1 and DELTA 2** **Appropriate** Randomised 2:1 to receive delgocitinib or vehicle cream using an interactive response technology. Randomisation was stratified by: • Region (North America or Europe); and • Baseline IGA-CHE score. **DELTA 3** **Appropriate** As an open-label extension study with a single arm, no randomisation was performed.

Concealment of treatment allocation	Section 2.3.1.2	**DELTA 1 and DELTA 2** **Appropriate** An interactive response technology was used for randomisation. Although there is not an explicit statement to support this, it is likely that the randomised allocation sequence was concealed from study investigators/recruiters when deciding if patients met eligibility criteria for the trial. If this concealment was not in place, there is a risk of selection bias in terms of which patients are ultimately included in the trial. The company's submission also notes that the packaging and labelling of the treatment provided to patients in each arm provided no evidence of the identity of the product, while sensory evaluation could also not distinguish between the products. **DELTA 3** **Appropriate** As an open-label extension study with a single arm, no concealment of treatment allocation was needed.
Eligibility criteria	Section 2.3.1.3	**DELTA 1, DELTA 2, and DELTA 3** **Appropriate** The EAG's clinical experts agreed that the eligibility criteria of the DELTA 1 and DELTA 2 trial were reasonably reflective of patients who would be considered for treatment in clinical practice.
Blinding	Section 2.3.1.2	**DELTA 1 and DELTA 2** **Appropriate** The DELTA 1 and DELTA 2 trials were double-blind trials, as such the EAG considers the blinding of these trials to be appropriate. **DELTA 3** **Appropriate** To preserve the blinding of the DELTA 1 and DELTA 2 trials, patient treatment assignments were not revealed when patients commenced the DELTA 3 trial.
Baseline characteristics	Section 2.3.3	**DELTA 1** **Some differences between groups but no major concerns** The baseline characteristics of the DELTA 1 trial aligned with what would be expected for patients with moderate to severe CHE. However, the EAG's clinical experts noted that the difference in the prevalence of hyperkeratotic CHE between the delgocitinib (17.5%) and vehicle cream (12.3%) arms may potentially impact trial results. Likewise, the EAG's clinical experts also noted that the difference in the prevalence of allergic contact dermatitis between the delgocitinib (15.7%) and vehicle cream (20.4%) arms may impact trial results. **DELTA 2**

		Some differences between groups but no major concerns The baseline characteristics of the DELTA 2 trial aligned with what would be expected for patients with moderate to severe CHE. However, the EAG's clinical experts also noted that the difference in the prevalence of allergic contact dermatitis between the delgocitinib (9.0%) and vehicle cream (14.0%) arms may impact trial results. Additionally, the EAG's clinical experts noted that a higher proportion of patients had prior phototherapy in the vehicle cream arm (24.5%) compared to the delgocitinib arm (19.1%). As such, those patients who have failed phototherapy may be more treatment-resistant and therefore potentially impact the trial results in favour of the delgocitinib arm. **DELTA 3** **Some differences between groups but no major concerns** The DELTA 3 trial comprises patients from both the DELTA 1 and DELTA 2 trials. Overall, the baseline characteristics of the DELTA 3 trial align with what would be expected for patients with moderate to severe CHE. However, as for the DELTA 1 and DELTA 2 trials, there is a difference in the prevalence of allergic contact dermatitis between the delgocitinib (13.2%) and vehicle cream (18.7%) arms may impact trial results.
Dropouts	Appendix Section B1.2.7.2; DELTA 3 CSR Table 1.1.2	**DELTA 1** **Some differences between groups but no major concerns** The EAG notes that there is a difference in the proportion of patients that discontinued treatment in the trial, with discontinuation due to AEs (5.6% vs 0.9%) and all-cause discontinuation (13.0% vs 6.0%) being greater for vehicle cream compared to delgocitinib. **DELTA 2** **Some concerns** The EAG notes that there is a difference in the proportion of patients that discontinued treatment in the trial due to AEs, with patients who received delgocitinib (0.3%) have lower discontinuation rates that patients who received a vehicle cream (3.1%). However, all-cause treatment discontinuation was substantially greater in patients who received vehicle cream (23.0%) compared to delgocitinib (7.0%). It is unclear why all-cause treatment discontinuation is substantially higher in patients who received the vehicle cream in DELTA 2 trial or compared to all patient groups in the DELTA 1 trial. The EAG is concerned that the all-cause discontinuation of 23.0% of patients has the potential to skew the results. **DELTA 3** **Some concerns**

		The EAG noted that the number of dropouts within the DELTA 3 trial is not provided in the CS. However, based on the CSR, 17.5% of patients who started on the DELTA 3 trial did not complete the trial. However, only 0.9% of patients in the DELTA 3 trial discontinued treatment due to an adverse event. Overall, the discontinuation rates reported in the DELTA 3 trial are aligned with those observed in the DELTA 1 and DELTA 2 trials.
Statistical analysis		
Sample size and power	DELTA 1 Protocol Section 14.1; DELTA 2 Protocol Section 14.1	**DELTA 1** **No concerns for primary analyses, some concerns for subgroup analyses** Approximately 470 patients were expected to be randomised into DELTA 1, with 487 patients ultimately randomised to treatment. The sample size required to demonstrate efficacy, with regards to the primary efficacy endpoint (IGA-CHE TS) were based on the following points based on assumptions from the phase 2b dose-ranging trial (Worm *et al.* 2022): • Overall one-sided significance level of 2.5% in the overall population; and • 99% power to detect a treatment difference for the primary endpoint, assuming an IGA-CHE TS, at week 16, of 40% for delgocitinib and 10% for vehicle cream. No discussions of sample size or power were presented for subgroup analyses. As such, it is unclear whether these analyses are adequately powered to detect differences between subgroups. **DELTA 2** **No concerns for primary analyses, some concerns for subgroup analyses** Approximately 450 patients were expected to be randomised into DELTA 1, with 473 patients ultimately randomized to treatment. The sample size required to demonstrate efficacy, with regards to the primary efficacy endpoint (IGA-CHE TS) were based on the following points based on assumptions from the phase 2b dose-ranging trial (Worm *et al.* 2022): • Overall one-sided significance level of 2.5% in the overall population; and • 99% power to detect a treatment difference for the primary endpoint, assuming an IGA-CHE TS, at week 16, of 40% for delgocitinib and 10% for vehicle cream. No discussions of sample size or power were presented for subgroup analyses. As such, it is unclear whether these analyses are adequately powered to detect differences between subgroups. **DELTA 3** **Appropriate**

		All patients who completed the DELTA 1 or DELTA 2 trials were eligible for inclusion within the DELTA 3 trial. As the DELTA 3 assessed the long-term efficacy of delgocitinib, no between-arm comparisons are made. Accordingly, the EAG noted that the DELTA 3 protocol did not consider, nor perform, calculations relating to sample size or statistical power.
Handling of missing data	Appendix Section B2.5.1; DELTA 1 Protocol Section 14.3.6.1; DELTA 2 Protocol Section 14.3.6.1; DELTA 3 Protocol Section 14.3.13	**DELTA 1 and DELTA 2** **Some concerns** The protocols for DELTA 1 and DELTA 2 trials indicate that missing data is accounted for differently depending on the following attributes: • Binary or continuous endpoints; • Discontinuation was related, or unrelated, to the Covid-19 pandemic; and • Occurrence, or absence, of intercurrent event (e.g., initiation of rescue treatment) The protocols for the DELTA 1 and DELTA 2 trials indicate that multiple different approaches to account for missing data were implemented including multiple imputation (following an assumption of data being missing at random) or worst observation carried forward. The CSRs for the DELTA 1 and DELTA 2 trials indicate that for all endpoints, multiple different sensitivity analyses are provided where differing approaches are used for the estimation of averages. However, the EAG has some concerns regarding the substantially greater discontinuation rates for patients receiving vehicle cream, as opposed to delgocitinib, in both the DELTA 1 and DELTA 2 trials. The proportion of patients lost to follow-up in the vehicle cream arm is much greater than that reported for the delgocitinib arm in the DELTA 1 trial. For the DELTA 1 trial, at Week 18, ~13% of patients in the vehicle cream arm discontinued compared to ~6% of patients in the delgocitinib arm. For the DELTA 2 trial, at Week 18, ~23% of patients in the vehicle cream arm discontinued compared to ~7% of patients in the delgocitinib arm. Accordingly, the EAG is concerned that, given the imbalance in discontinuation rates between the arms, the use of worst observation carried forward as an imputation method for missing data has the potential to underestimate the treatment effect in the vehicle cream arms. **DELTA 3** **Appropriate** The DELTA 3 protocol stated that for binary response tabulations, any patients who discontinued treatment, withdrew from the trial, or initiated rescue treatment were imputed as non-responders. For all other outcomes, missing values were not imputed.
Outcome assessment	Section 2.2	**DELTA 1 and DELTA 2** **Appropriate**

		The DELTA 1 and DELTA 2 trials report the following outcomes: • IGA-CHE TS (primary outcome); • HECSI-50 (*post-hoc* analysis; not predefined in DELTA 1 or DELTA 2 trials); • HECSI-75; • HECSI-90; • Percentage change in HECSI; • HESD total score; • HESD itch score; • HESD pain score; • DLQI; • EQ-5D-3L; • HEIS; and • AEs **DELTA 3** **Appropriate** The DELTA 3 trial reported the following outcomes: • IGA-CHE TS; • HECSI-50 (*post-hoc* analysis; not predefined in DELTA 3 trial); • HECSI-75; • HECSI-90; • Mean change in HECSI; • HESD total score; • HESD itch score; • HESD pain score; • DLQI; • EQ-5D-3L; • AEs (primary outcome); and • Time to loss of response. Accordingly, the EAG consider the outcomes reported within the DELTA 1, DELTA 2, and DELTA 3 trials to be appropriate and cover those outcomes listed in the NICE final scope. Additionally, the EAG's clinical experts noted that of the endpoints listed above, only DLQI is routinely measured in UK clinical practice, with PGA being preferred to IGA-CHE for outcome assessments while symptom control is not regularly measured. Additionally, the EAG noted that HECSI-50 was not pre-specified and as such only considered *post-hoc*. As such, the EAG considers HECSI-50 as being of a higher risk of bias compared to the pre-specified outcomes.

Abbreviations: EAG, External Assessment Group

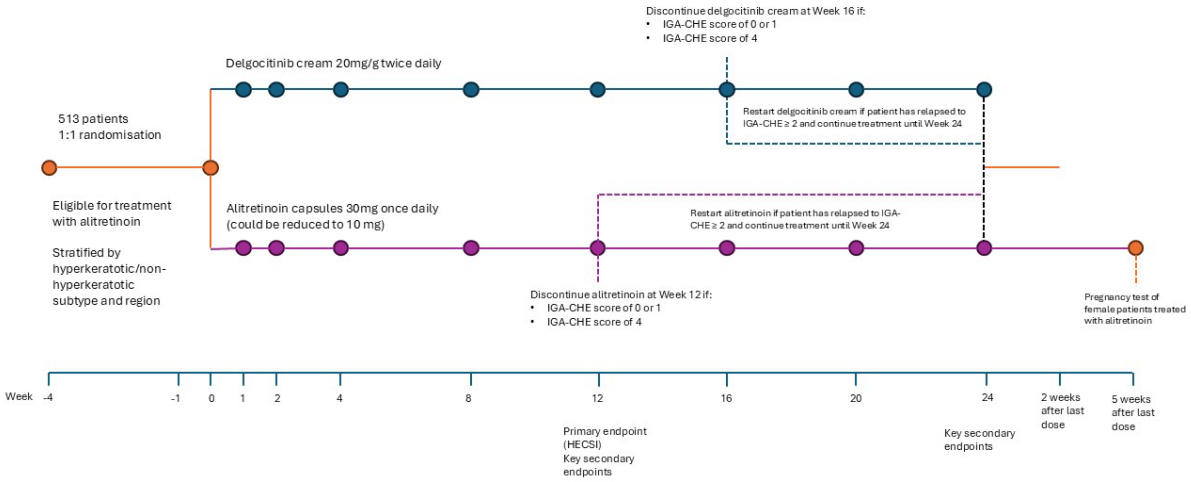
The matching trial design, population, interventions, comparators and outcomes of the DELTA 1 and DELTA 2 trials meant that the company chose to present two sets of analyses. The first being to

present results for each trial separately, and the second to pool the analysis of the two trials. For subgroup analyses, only the pooled results of the DELTA 1 and DELTA 2 trials was presented. Given the similar baseline characteristics between the two trials, the EAG considers that the pooling of the DELTA 1 and DELTA 2 trials an acceptable approach for outcome assessment. The pooled baseline characteristics were similar between the delgocitinib and vehicle cream arms and the EAG's clinical experts considered them to be reflective of patients who would be eligible for delgocitinib in clinical practice in England. The EAG notes that alongside the DELTA 1 and DELTA 2 trials, a further trial (Worm *et al.* 2022) that compared delgocitinib (20mg g^{-1}) to vehicle cream was included within ITCs performed by the company. However, within the CS the results of a pairwise meta-analysis combining data from all three studies was not performed by the company. In response to a clarification question, the company provided the results of pairwise meta-analyses for the comparison of delgocitinib to vehicle cream in which included data from the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials. The results of these pairwise meta-analyses are discussed in Section 3.3 below.

3.2.2 DELTA FORCE trial

The DELTA FORCE trial was a randomised, assessor-blinded, phase 3 trial to assess the efficacy and safety of delgocitinib cream (20 mg g^{-1} bd) compared to oral alitretinoin (30mg od). All patients included in the trial had severe CHE (assessed as an IGA-CHE score of 4) and either an inadequate response to treatment with TCS or for whom TCS were inappropriate. DELTA FORCE was conducted over a 24-week treatment period, with patients randomised 1:1 to continuous delgocitinib cream 20 mg/g bd or oral alitretinoin 30mg od. Patients receiving alitretinoin were started on a dose of 30mg but had the option to reduce the dosage to 10mg if they experienced adverse reactions. As the recommended duration of treatment for alitretinoin is 12 to 24 weeks, the primary endpoint in the DELTA FORCE trial was assessed at week 12 to align with the minimum continuous treatment period for alitretinoin. In contrast, patients in the delgocitinib arm were treated continuously until week 16. After week 16, patients were required to stop treatment with delgocitinib if they had an IGA-CHE score of 0 or 1 and would subsequently resume treatment with delgocitinib if they had an IGA-CHE score ≥2. The trial design for the DELTA FORCE trial is shown below in Figure 3.

Figure 3. Trial design for the DELTA FORCE trial (reproduced from Figure 4 of the CS).



Abbreviations: HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

The company provided an overview of the risk of bias for the DELTA FORCE trial in Table 149 of the CS. Overall, the company concluded that there was a low risk of bias for the DELTA FORCE trial across all attributes considered as part of the Cochrane Risk of Bias Tool, the single exception to this was the blinding of participants and personnel which was considered to have a high risk of bias. The EAG has conducted its own risk of bias assessments for the DELTA FORCE trial that is provided in Table 15 below. Following the risk of bias assessment, the EAG has some concerns regarding the DELTA FORCE trial. Firstly, in line with the assessment of the company, the EAG has concerns regarding the lack of blinding of participants and investigators within the DELTA FORCE trial, given the different manner of application for delgocitinib and alitretinoin. While the EAG notes that trial assessors were blinded, the EAG is concerned that the lack of blinding and allocation concealment may have introduced biases into the trial.

Secondly, the EAG notes that some outcomes were only specified *post-hoc*; accordingly, the EAG considers that these outcomes are of a higher risk of bias compared to those that were pre-specified in the trial's protocol. Thirdly, the EAG notes that there is uncertainty surrounding the power and sample size calculations for the DELTA FORCE trial. Given the limited data on the primary outcome of change from baseline HECSI for alitretinoin, the trial design was based on assumed treatment differences for IGA-CHE. Accordingly, the EAG is concerned with whether the assumption of equivalent treatment effects across outcomes is appropriate and, consequently, whether the trial has sufficient power to detect treatment differences in the primary endpoint.

Finally, the EAG notes that for the DELTA FORCE trial the rates of treatment discontinuation (both all-cause and discontinuation due to AEs) is substantially higher in patients who received alitretinoin

as opposed to delgocitinib. As such, the EAG is concerned that this may lead to potential biases in any comparisons between these treatment arms. For the DELTA FORCE trial, the EAG is concerned that the high dropout rate has the potential to introduce bias into the results. Given the disparity in dropout rates between the trial arms, the potential for selective dropouts would result in the patients assessed for outcomes, at a given timepoint, would no longer represent balanced groups despite being balanced at baseline. Additionally, the EAG is concerned that the use of the WOCF approach to account for missing data has the potential to bias against alitretinoin in favour of delgocitinib. The use of the WOCF approach generates bias against the treatment arm in which the dropout rate is highest. As such, the WOCF approach may be considered to be conservative if the dropout rate is greatest in the arm for the new treatment. However, within the DELTA FORCE trial the dropout rate is greatest in the alitretinoin arm, not the delgocitinib arm, as such it may result in a bias in favour of delgocitinib (within the DELTA FORCE trial, WOCF was used to estimate data at Week 24 for 12.4% and 39.5% of patients for delgocitinib and alitretinoin, respectively).

Furthermore, the EAG notes that when higher dropout rates are expected for one treatment arm, use of the WOCF approach may result in an exaggerated treatment effect for the treatment arm with the lower dropout rate. As such, within the DELTA FORCE trial, discontinuation rates may have been assumed to be greater in the alitretinoin arm, compared to the delgocitinib arm, *a priori*, due to the known potential for adverse events to occur when patients receive alitretinoin. Likewise, a reduced rate of dropouts, due to adverse events, may have been expected for patients receiving delgocitinib in the DELTA FORCE trial, based on adverse event data from prior trials of delgocitinib (e.g., Worm *et al.* 2022). As such, the EAG is concerned that the use of the WOCF approach may have resulted in the relative effectiveness for delgocitinib being overstated relative to alitretinoin.

Table 15. EAG's summary of the design, conduct and analysis of DELTA FORCE

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 2.3.1.2	**Appropriate** Randomised 1:1 to receive delgocitinib or alitretinoin using an interactive response technology. Randomisation was stratified by: • Region (North America or Europe); and • CHE subtype (hyperkeratotic/non-hyperkeratotic).

Concealment of treatment allocation	Section 2.3.1.2	**Moderate concerns** The EAG noted that delgocitinib and alitretinoin are administered through contrasting routes. Accordingly, both participants and clinical experts were not blinded to each patient's treatment assignment. The use of a double-dummy design was not considered appropriate as there were concerns that the application of a vehicle cream may increase the clinical effect of alitretinoin. However, any evaluation of efficacy was performed by a blinded assessor.
Eligibility criteria	Section 2.3.1.3	**Appropriate** The EAG's clinical experts agreed that the eligibility criteria of the DELTA FORCE trial were reasonably reflective of patients who would be considered for treatment in clinical practice.
Blinding	Section 2.3.1.2	**Moderate concerns** The EAG noted that the DELTA FORCE trial was unblinded due to the different administration routes for delgocitinib and alitretinoin. A double-dummy design was not implemented due to concerns that a vehicle cream may increase the clinical effectiveness of alitretinoin. Although the trial was unblinded, any evaluation of efficacy was performed by a blinded assessor.
Baseline characteristics	Section 2.3.3	**Some differences between groups but no major concerns** The baseline characteristics of the DELTA FORCE trial aligned with what would be expected for patients with moderate to severe CHE. However, the EAG's clinical experts noted that a higher proportion of patients had prior treatment with an 'other' therapy in the alitretinoin arm (28.2%) compared to the delgocitinib arm (19.7%). In this context, 'other' therapies are therapies other than TCSs, TCIs, phototherapy, oral retinoids, oral corticosteroids, oral methotrexate, oral ciclosporin, and oral azathioprine. As such, those patients who have previously failed on another treatment may be more treatment-resistant and therefore potentially impact the trial results in favour of the delgocitinib arm.
Dropouts	Appendix Section B1.2.7.2; DELTA FORCE CSR Section 10.1	**Some concerns** The EAG notes that there is a difference in the proportion of patients that discontinued treatment in the trial due to AEs, with patients who received delgocitinib (1.2%) have lower discontinuation rates that patients who received alitretinoin (10.1%). However, of the 254 randomised to the delgocitinib arm, 34 discontinued treatment for any reason (13.4%). In contrast, of the 259 patients randomised to the alitretinoin arm, 93 discontinued treatment for any reason (35.9%). As such, the EAG notes that the substantially higher all-cause discontinuation, and discontinuation due to AEs, in the alitretinoin arm compared to the delgocitinib arm, has the potential to skew the results of any analysis.
Sample size and power	DELTA FORCE Protocol Section 9.5	**Some concerns** Approximately 510 patients were expected to be randomised into DELTA FORCE, with 513 patients ultimately randomised to treatment.

		The sample size required to demonstrate efficacy, with regards to the primary efficacy endpoint (change from baseline HECSI) were based on the following points: • Overall one-sided significance level of 2.5% in the overall population; and • 80% power to detect a treatment difference for the primary endpoint, assuming a difference of 7.5 (with a standard deviation of 30) in change from baseline HECS, at week 16, between the delgocitinib and alitretinoin arms. Given the limited data on HECSI for alitretinoin, anticipated treatment differences were based on IGA scales from Worm *et al.* 2022. The EAG has some concerns as to whether there is sufficient power for the DELTA FORCE trial given the assumption of 80% power is based upon endpoint that differs to the primary endpoint considered here.
Handling of missing data	Appendix Section B2.5.1; DELTA FORCE Protocol Section 9.3.6.1	**Some concerns** The protocols for the DELTA FORCE trial indicated that missing data is accounted for differently depending on the following attributes: • Binary or continuous endpoints; • Discontinuation was related, or unrelated, to the Covid-19 pandemic; and • Occurrence, or absence, of intercurrent event (e.g., initiation of rescue treatment) The protocols for the DELTA FORCE trial indicated that multiple different approaches to account for missing data were implemented including multiple imputation (following an assumption of data being missing at random) or worst observation carried forward. The CSRs for the DELTA FORCE trial indicated that that for all endpoints, multiple different sensitivity analyses are provided where differing approaches are used for the estimation of averages. However, the EAG has some concerns regarding the substantially greater discontinuation rates for patients receiving alitretinoin, as opposed to delgocitinib, in the DELTA FORCE trial. At Week 24, ~36% of patients in the alitretinoin arm discontinued compared to ~13% of patients in the delgocitinib arm. Accordingly, the EAG is concerned that, given the imbalance in discontinuation rates between the arms, the use of worst observation carried forward as an imputation method for missing data has the potential to underestimate the treatment effect in the alitretinoin arm.
Outcome assessment	Section 2.2	**Appropriate** The DELTA FORCE trial reported the following outcomes: • IGA-CHE TS; • HECSI-50 (*post-hoc* analysis; not predefined in DELTA FORCE trial); • HECSI-75; • HECSI-90; • Mean change in HECSI (primary outcome); • HESD total score;

		• HESD itch score; • HESD pain score; • DLQI; • EQ-5D-3L; • AEs; and • Time to loss of response (*post-hoc* analysis; not predefined in DELTA FORCE trial). Accordingly, the EAG consider the outcomes reported within the DELTA FORCE trial to be appropriate and cover those outcomes listed in the NICE final scope. Additionally, the EAG's clinical experts noted that of the endpoints listed above, only DLQI is routinely measured in UK clinical practice, with PGA being preferred to IGA-CHE for outcome assessments while symptom control is not regularly measured. Additionally, the EAG noted that several outcomes were not pre-specified and as such only considered *post-hoc*. As such, the EAG considers these outcomes as being of a higher risk of bias compared to the pre-specified outcomes.

Abbreviations: EAG, External Assessment Group

As the DELTA FORCE trial was the only trial comparing delgocitinib and alitretinoin, no pairwise meta-analyses were required. As such, the EAG is satisfied that the direct comparison data reported for the DELTA FORCE trial is appropriate for the comparison of delgocitinib and alitretinoin.

3.3 Critique of the clinical effectiveness analysis and interpretation

The EAG presents results for the key outcomes from the DELTA 1, DELTA 2, and DELTA FORCE in the sections that follow. Of the efficacy outcomes, IGA-CHE TS, HECSI-90, HECSI-75, and HECSI-50 (from all three trials) are used in the economic model. Additionally, HESD pain scores from the DELTA 1 and DELTA 2 trials as well as both adverse events and time to loss of response from the DELTA FORCE trial, are included in the economic model and discussed below. Results for EuroQol Group 5-Dimension Questionnaire (EQ-5D) are also briefly discussed given these results were mapped for inclusion in the economic model and AEs are also covered. Issues related to the clinical effectiveness as implemented in the economic model are discussed in Section 4.2.5.

3.3.1 Primary outcome

3.3.1.1 IGA-CHE TS

Across the DELTA 1 and DELTA 2 trials, the primary outcome was the Investigator Global Assessment of Chronic Hand Eczema treatment success (IGA-CHE TS). Furthermore, IGA-CHE TS was a key secondary endpoint in the DELTA FORCE trial. IGA-CHE TS was defined as the proportion of patients, in each arm, that, following treatment, were either clear (corresponding to an IGA-CHE score of 0) or

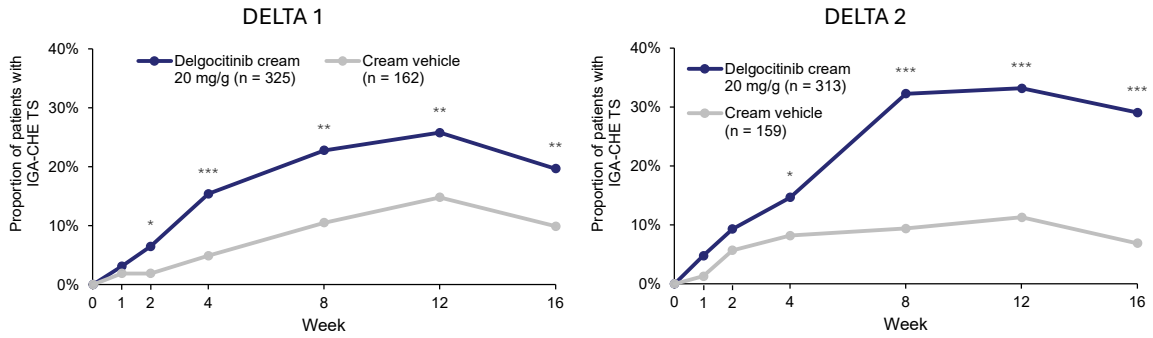
almost clear (corresponding to an IGA-CHE score of 1). Below, IGA-CHE is discussed for the DELTA 1, DELTA 2, and DELTA FORCE trials for the overall population, severity subgroups, and hyperkeratotic subgroups.

3.3.1.1.1 Overall population

Across both the DELTA 1 and DELTA 2 trials, the proportion of patients achieving IGA-CHE TS was greater in the delgocitinib arm compared to the vehicle cream arm, at all timepoints considered after Week 0 (Figure 4). For the DELTA 1 trial, this difference was statistically significant for all timepoints (aside from Week 1), while for the DELTA 2 trial this difference was statistically significant for all timepoints aside from Weeks 1 and 2. When measured at Week 16, 19.7% and 29.1% of patients receiving delgocitinib in the DELTA 1 and DELTA 2 trials achieved IGA-CHE TS, respectively. In contrast, of the patients receiving vehicle cream 9.9% and 6.9% achieved IGA-CHE TS in the DELTA 1 and DELTA 2 trials respectively. As such, the difference in patients achieving IGA-CHE TS between the delgocitinib and vehicle cream arms was statistically significant for both the DELTA 1 ($p = 0.006$) and DELTA 2 ($p < 0.0001$) trials.

Despite being described as identical trials, there is a considerable difference in the results of the DELTA 1 and DELTA 2 trials at later time points. For instance, at Weeks 8–16, the proportion of patients, who received delgocitinib, who achieved IGA-CHE TS was substantially greater in the DELTA 2 trial compared to the DELTA 1 trial. For instance, at Weeks 8 the proportion of patients, who received delgocitinib, was 22.8% in the DELTA 1 trial and 32.3% in the DELTA 2 trial, representing an absolute difference of ~10%. Overall, the EAG is uncertain as to why two trials, described as being identical, reported substantially different results for the primary outcome. Additionally, the EAG noted that the proportion of patients who achieved IGA-CHE TS declined, in the DELTA 1 and DELTA 2 trials, between Weeks 12 and 16 (Figure 4). In response to a clarification question, the company outlined that CHE is a naturally fluctuating disease and that periods of worsening are common. While the EAG acknowledges that symptoms associated with CHE may vary over time, the EAG is unclear why the proportion of patients achieving IGA-CHE TS consistently declines, in patients receiving delgocitinib, between Week 12 and Week 16 in the DELTA 1 and DELTA 2 trials despite still receiving treatment.

Figure 4. Proportion of patients achieving IGA-CHE TS in the DELTA 1 (left panel) and DELTA 2 (right panel) trials up to 16 weeks (taken from Figure 8 of the CS).



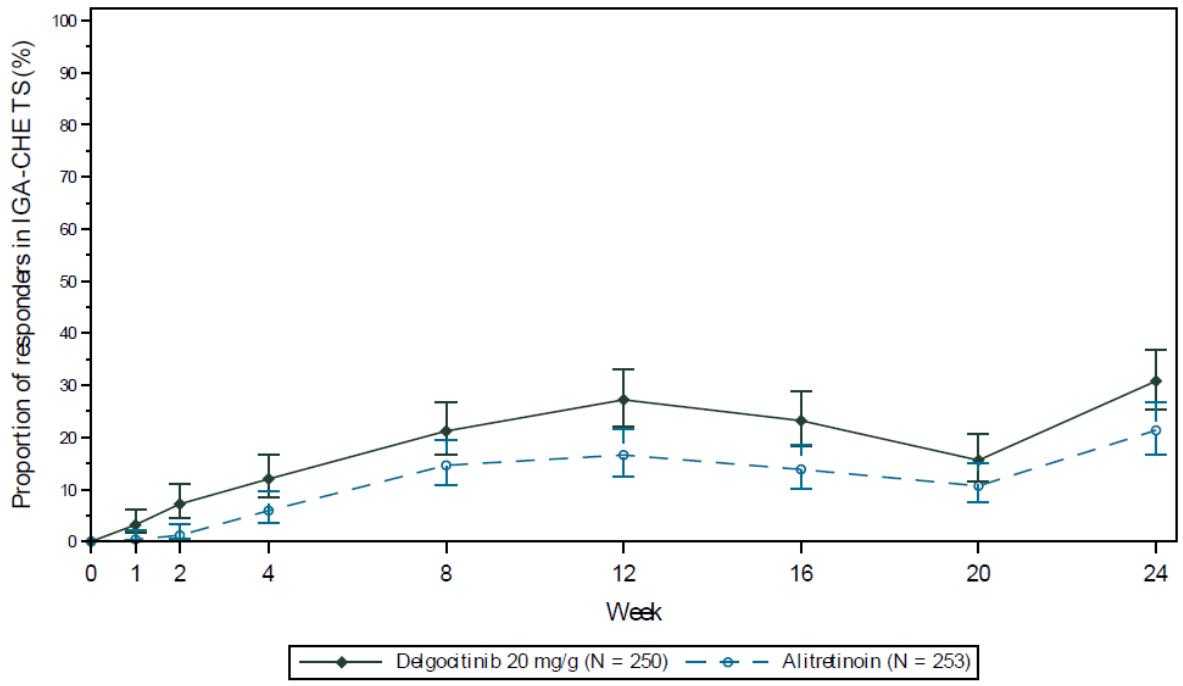
Abbreviations: IGA-CHE TS, Investigator's Global Assessment for chronic hand eczema treatment success.

In response to a clarification question, the company provided the results of pairwise meta-analyses for the difference in IGA-CHE TS between patients who received delgocitinib and vehicle cream in the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials. At Week 12, the random effects (RE) meta-analysis indicated that [redacted] although this result was associated with moderate heterogeneity (I^2 = 46.8%) indicating that the network of evidence is unlikely to be homogenous. At Week 16, the RE meta-analysis indicated that [redacted] although this result was associated with moderate heterogeneity (I^2 = 56.4%) indicating that the network of evidence is unlikely to be homogenous.

For the DELTA FORCE trial, IGA-CHE was measured at Week 12 and Week 24 for both the delgocitinib and alitretinoin arms. At Week 12, there was a statistically significant (p = 0.004) difference in the percentage of patients who achieved IGA-CHE TS, with 27.2% and 16.6% of patients in the delgocitinib and alitretinoin arms achieving IGA-CHE TS, respectively. Likewise, at Week 24, a statistically significant (p = 0.016) difference was reported between the percentage of patients who achieved IGA-CHE TS in the delgocitinib (30.8%) and alitretinoin (21.3%) arms. As for the DELTA 1 and DELTA 2 trials, the proportion of patients who achieved IGA-CHE TS declined between Week 12 and Week 16 for both patients receiving alitretinoin and delgocitinib (Figure 5). A further decline in the proportion of patients who achieved IGA-CHE TS was observed, for both arms, between Weeks 16 and 20, before increasing between Weeks 20 and 24. Within the alitretinoin arm, the decline in

the proportion of patients who achieved IGA-CHE TS between Week 12 and Week 16 may be explained by the relapse of some patients who stopped treatment with alitretinoin at Week 12 (due to having achieved IGA-CHE score of 0 or 1) in line with the trial design. However, as patients receiving delgocitinib were only required to stop treatment at Week 16, the decline in the proportion of patients receiving delgocitinib who achieved IGA-CHE TS between Week 12 and Week 16 is not explained by the cessation of treatment.

Figure 5. Proportion of patients achieving IGA-CHE TS in the DELTA FORCE trial up to 24 weeks (taken from CSR for the DELTA FORCE trial[12]).



Abbreviations: IGA-CHE TS, Investigator's Global Assessment for chronic hand eczema treatment success.

3.3.1.1.2 Severity subgroups

Within the CS, and in response to clarification questions, the company provided the results of subgroup analyses that considered patients with either moderate or severe CHE at baseline in the DELTA 1 and DELTA 2 trials. As the DELTA FORCE trial only considered patients with severe CHE (as assessed by IGA-CHE), subgroup analyses comparing patients with moderate and severe CHE was not possible for this trial.

Within the CS, the company performed subgroup analyses comparing delgocitinib to vehicle cream in patients with moderate CHE and severe CHE in the pooled DELTA 1 and DELTA 2 trials.

*[redacted]

[redacted] As the DELTA FORCE only considered patients with severe CHE (as assessed by IGA-CHE), subgroup analyses to determine whether the relative efficacy of delgocitinib compared to alitretinoin varied across patients with moderate and severe CHE was not possible.

In response to a clarification question, the company provided the results of subgroup analyses that compared IGA-CHE TS between patients with moderate and severe CHE in the DELTA 1 and DELTA 2 trials. Such results were provided separately for patients who received delgocitinib and vehicle cream.

[redacted] In response to a clarification question, the company provided odds ratios comparing IGA-CHE TS in patients who received delgocitinib and vehicle cream in either the moderate or severe subgroups.

[redacted]

[redacted] In contrast to the analyses presented by the company, the EAG notes that the assumption of equivalence in the relative treatment effects between moderate and severe patients may potentially be examined through the use of alternative statistical tests such as equivalence testing (e.g., TOST procedure).[20]

In response to a clarification question, the company provided the results of pairwise meta-analyses for the difference in IGA-CHE TS between patients who received delgocitinib and vehicle cream in the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials.

[redacted] The results of the RE model were associated with moderate heterogeneity (I^2 = 49.6%) indicating that the network of evidence is unlikely to be homogenous.

[redacted] although this result was associated with moderate heterogeneity (I^2 = 38.7%) indicating that the network of evidence is unlikely to be homogenous.

[redacted] The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

[redacted]

[redacted] As with the results at Week 12 The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

3.3.1.1.3 Hyperkeratotic subgroups

Within the CS, the company did not provide any subgroup analyses for patients based on whether they had hyperkeratotic, or non-hyperkeratotic, CHE. As such, despite not being listed as a subgroup of interest in the NICE final scope, subgroup analyses relating to the hyperkeratotic subgroup were requested by the EAG following discussions with the EAG's clinical experts. The EAG notes that the DELTA 1 and DELTA 2 trials were not stratified for hyperkeratotic status; however, the DELTA FORCE trial was stratified for hyperkeratotic status.

In response to a clarification question, the company provided the results of subgroup analyses comparing delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic patients in the DELTA FORCE trial.

[redacted]

3.3.1.1.4 Aetiological subgroups

The company provided the results of subgroup analyses that compared delgocitinib and vehicle cream between patients with contact or non-contact CHE in the pooled DELTA 1 and DELTA 2 trials. The results of such subgroup analyses were also provided for patients with atopic or non-atopic CHE in the pooled DELTA 1 and DELTA 2 trials.

[redacted]

[redacted]

The company provided the results of subgroup analyses that compared delgocitinib and alitretinoin between patients with contact or non-contact CHE in the DELTA FORCE trial. The results of such subgroup analyses were also provided for patients with atopic or non-atopic CHE in the DELTA FORCE trial.

[redacted]

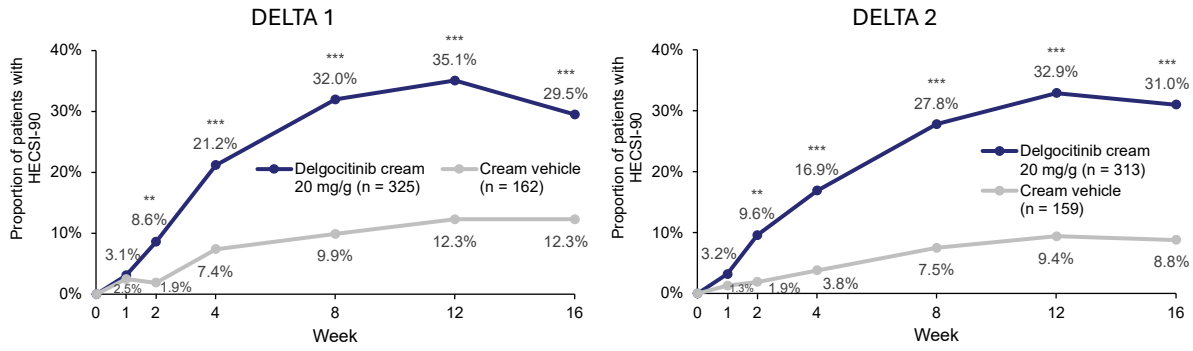
3.3.2 Secondary outcomes

3.3.2.1 HECSI-90

HECSI-90 was measured across the DELTA 1, DELTA 2, and DELTA FORCE trials and is defined as the proportion of patients who achieved a 90% reduction in HECSI scores. For the DELTA FORCE trial, HECSI-90 was measured at Week 12, while in the DELTA 1 and DELTA 2 trials, the primary timepoint for HECSI-90 was Week 16. Within the DELTA 1 and DELTA 2 trials, there was a statistically significant

difference in the proportion of patients who achieved HECSI-90 responses between patients receiving delgocitinib and vehicle cream (Figure 6). Overall, a higher proportion of patients who received delgocitinib had HECSI-90 responses compared to patients who received vehicle cream. However, as for IGA-CHE TS, the DELTA 1 trial reported that the proportion of patients who had HECSI-90 responses declined between Week 12 and Week 16.

Figure 6. Proportion of patients with HECSI-90 in the DELTA 1 (left panel) and DELTA 2 (right panel) trials up to 24 weeks (taken from Figure 10 of the CS).



Abbreviations: HECSI-90, Hand Eczema Severity Index score 90% reduction.

In response to a clarification question, the company provided the results of pairwise meta-analyses for the difference in HESCI-90 between patients who received delgocitinib and vehicle cream in the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials. At Week 12, the RE meta-analysis indicated that there was a statistically significant difference in the proportion of patients who achieved HECSI-90 (OR 4.28; 95% CI: 2.95 to 6.22). The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model. At Week 16, the RE meta-analysis indicated that there was a statistically significant difference in the proportion of patients who achieved HECSI-90 (OR 3.51; 95% CI: 2.42 to 5.10). As with the results at Week 12, The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

Within the CS, the company performed subgroup analyses comparing delgocitinib to vehicle cream in patients with moderate CHE and severe CHE in the pooled DELTA 1 and DELTA 2 trials.

[redacted]

[redacted]

In response to a clarification question, the company provided the results of subgroup analyses that compared HECSI-90 between patients with moderate and severe CHE in the DELTA 1 and DELTA 2 trials. Such results were provided separately for patients who received delgocitinib and vehicle cream. In response to a clarification question, the company provided comparisons between moderate and severe patients for HECSI-90.

[redacted]

In response to a clarification question, the company provided odds ratios comparing the proportion of patients who achieved HECSI-90 in patients who received delgocitinib and vehicle cream in either the moderate or severe subgroups.

[redacted]

The company provided the results of subgroup analyses that compared delgocitinib and vehicle cream between patients with contact or non-contact CHE in the pooled DELTA 1 and DELTA 2 trials. The results of such subgroup analyses were also provided for patients with atopic or non-atopic CHE in the pooled DELTA 1 and DELTA 2 trials.

[redacted]

[redacted]

In response to a clarification question, the company provided the results of pairwise meta-analyses for the difference in the proportion of patients who achieved HECSI-90 between patients who received delgocitinib and vehicle cream in the DELTA 1, DELTA 2, and Worm *et al.* 2022 trials.

[redacted] The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

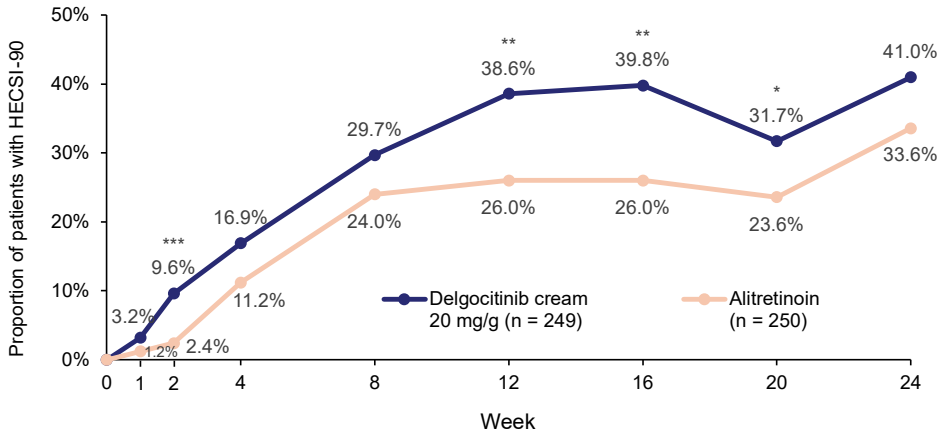
[redacted] As with the results at Week 12, The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

[redacted] The results of the RE model were not associated with any heterogeneity (I^2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.

[redacted] The results of the RE model were associated with moderate heterogeneity (I^2 = 30.9%) indicating that the network of evidence is unlikely to be homogenous.

Results from the DELTA FORCE trial indicated that a greater proportion of patients had HECSI-90 responses in the delgocitinib arm compared to the alitretinoin arm. However, there was only a statistically significant difference in the proportions who achieved a HECSI-90 response, between the arms, at Weeks 2, 12, 16, and 20 (Figure 7). The proportion of patients who achieved an HECSI-90 response declined between Week 16 and Week 20 in the delgocitinib arm, with this decline likely being due to the patients who stopped treatment with delgocitinib at Week 16 experiencing a relapse in symptoms.

Figure 7. Proportion of patients with HECSI-90 in the DELTA FORCE trial up to 24 weeks (taken from Figure 23 of the CS).



Abbreviations: HECSI-90, Hand Eczema Severity Index score 90% reduction.

In response to a clarification question, the company provided the results of subgroup analyses comparing delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic patients in the DELTA FORCE trial.

[redacted]

The company provided the results of subgroup analyses that compared delgocitinib and alitretinoin between patients with contact or non-contact CHE in the DELTA FORCE trial. The results of such

subgroup analyses were also provided for patients with atopic or non-atopic CHE in the DELTA FORCE trial.

[redacted]

3.3.2.2 HECSI-75

HECSI-75 was measured across the DELTA 1, DELTA 2, and DELTA FORCE trials and is defined as the proportion of patients who achieved a 75% reduction in HECSI scores. For the DELTA FORCE trial, HECSI-75 was measured at Week 12, while in the DELTA 1 and DELTA 2 trials, the primary timepoint for HECSI-75 was Week 16. Within the DELTA 1 and DELTA 2 trials, there was a statistically significant difference in the proportion of patients who achieved HECSI-75 responses between patients receiving delgocitinib and vehicle cream. Overall, at every time point (except for Week 1 in the DELTA 1 trial) there was a statistically significant difference in the proportion of patients who achieved a HECSI-75 response across the delgocitinib and vehicle cream arms (Figure 8). Overall, a higher proportion of patients who received delgocitinib had HECSI-75 responses compared to patients who received vehicle cream.

[redacted]

[redacted]

The company provided the results of subgroup analyses that compared HECSI-75 between patients with contact or non-contact CHE in the pooled DELTA 1 and DELTA 2 trials. The results of such subgroup analyses were also provided for patients with atopic or non-atopic CHE in the pooled DELTA 1 and DELTA 2 trials.

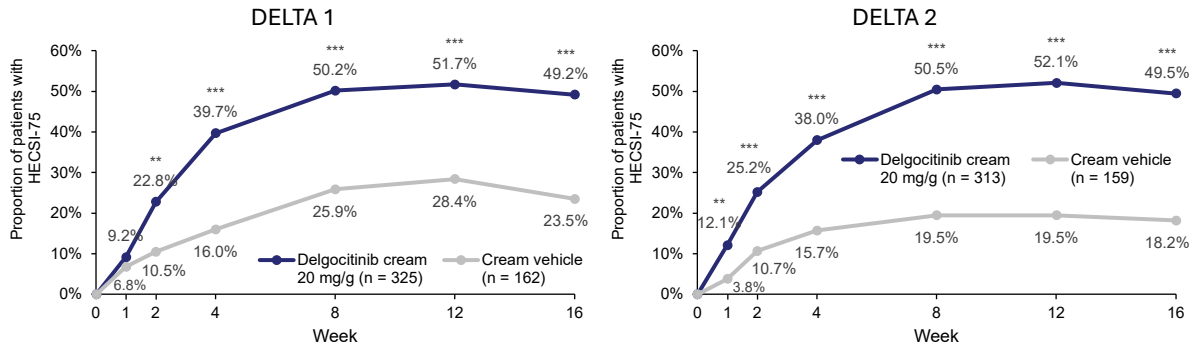
[redacted]

The company provided the results of subgroup analyses that compared delgocitinib and alitretinoin between patients with contact or non-contact CHE in the DELTA FORCE trial.

[redacted]

[redacted]

Figure 8. Proportion of patients with HECSI-75 in the DELTA 1 (left panel) and DELTA 2 (right panel) trials up to 24 weeks (taken from Figure 9 of the CS).



Abbreviations: HECSI-75, Hand Eczema Severity Index score 75% reduction.

Within the CS, the company performed subgroup analyses comparing delgocitinib to vehicle cream in patients with moderate CHE and severe CHE in the pooled DELTA 1 and DELTA 2 trials. [redacted]

In response to a clarification question, the company provided the results of subgroup analyses comparing delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic patients in the DELTA FORCE trial.

[redacted]

[redacted]

3.3.2.3 HECSI-50

HECSI-50 was measured *post-hoc* across the DELTA 1, DELTA 2, and DELTA FORCE trials and is defined as the proportion of patients who achieved a 50% reduction in HECSI scores. For the DELTA FORCE trial, HECSI-50 was measured at Week 12, while in the DELTA 1 and DELTA 2 trials, the primary timepoint for HECSI-50 was Week 16.

[redacted]

3.3.2.4 HESD Pain Score

HESD pain score was included in the economic model, using data from the DELTA 1 and DELTA 2 trials. However, rather than being incorporated into the models through the variables of either the proportion of patients achieving a ≥4-point reduction in HESD pain score or change in HESD pain score from baseline (endpoints reported for the DELTA 1, DELTA 2, and DELTA FORCE trials), raw HESD pain scores were incorporated into the economic model. As such, a brief overview of the outcome of mean change in HESD pain score from baseline is provided. In both the DELTA 1 and DELTA 2 trials, there was a statistically significant difference in the least squares mean difference, at Week 16, in change in HESD pain score from baseline between patients receiving delgocitinib or a vehicle cream. For the DELTA 1 trial, patients who received delgocitinib had a greater mean reduction in HESD pain score from baseline (−3.4) than patients who received (−1.8) with this

difference being statistically significant (p < 0.0001). Likewise, for the DELTA 2 trial, patients who received delgocitinib had a greater mean reduction in HESD pain score from baseline (−3.3) than patients who received (−1.3) with this difference being statistically significant (p < 0.0001).

In response to a clarification question, the company performed subgroup analyses comparing delgocitinib to vehicle cream in patients with moderate CHE and severe CHE in the pooled DELTA 1 and DELTA 2 trials.

[redacted]

Within the DELTA FORCE trial, there was a statistically significant difference, at Week 12, between the mean change in HESD pain score from baseline in the delgocitinib (−2.9) and alitretinoin (−2.3) arms (p = 0.018). Likewise, there was a statistically significant difference, at Week 24, between the mean change in HESD pain score from baseline in the delgocitinib (−2.5) and alitretinoin (−1.6) arms (p < 0.001).

3.3.2.5 Time to loss of response

Time to loss of response was include in the economic model using data from the DELTA 3 and DELTA FORCE trials. Within the DELTA FORCE trial, [redacted] and [redacted] of patients discontinued delgocitinib (at Week 16) and alitretinoin (at Week 12), respectively, due to achieving IGA-CHE TS. However, of these patients, [redacted] of delgocitinib patients and [redacted] of alitretinoin patients had restarted their respective treatments due to a loss of response (i.e., an IGA-CHE score of ≥2).

Within the DELTA 3 trial, all patients received delgocitinib regardless of whether they had previously received delgocitinib or vehicle cream in the DELTA 1 or DELTA 2 trials. For the overall population, patients achieved a response (i.e., an IGA-CHE score of <2) for a mean of 18.16% of days in the trial. However, substantial differences were observed depending on whether patients achieved a response at the start of the DELTA 3 trial. Of those patients who had previously received delgocitinib in either the DELTA 1 or DELTA 2 trials, patients with a response at baseline spent a mean of 46.45%

of days in response, while patients without a response at baseline spent a mean of 9.87% of days in response. Likewise, of those patients who had previously received vehicle cream in either the DELTA 1 or DELTA 2 trials, patients with a response at baseline spent a mean of 59.15% of days in response, while patients without a response at baseline spent a mean of 12.13% of days in response.

The EAG notes that while the definition of loss of response was consistent across the DELTA 3 and DELTA FORCE trials, time to loss of response was not measured in a consistent manner across these trials.

3.3.3 Quality of life

EQ-5D-3L was reported in the DELTA 1, DELTA 2, and DELTA FORCE trials, with data from all three trials being included in the economic model. For the DELTA 1 and DELTA 2 trials, this endpoint was primarily measured at Week 16, while in the DELTA FORCE trial it was primarily measured at Week 12. For the DELTA 1 trial, there was a statistically significant difference, between patients who received delgocitinib and vehicle cream, in mean change in EQ-5D-3L index from baseline at Week 16 (MD 0.103; 95% CI: 0.067 to 0.140; $p < 0.001$). Likewise, for the DELTA 2 trial, there was a statistically significant difference, between patients who received delgocitinib and vehicle cream, in mean change in EQ-5D-3L index from baseline at Week 16 (MD 0.108; 95% CI: 0.0701 to 0.145; $p < 0.001$).

[redacted]

In response to a clarification question, the company performed subgroup analyses comparing delgocitinib to vehicle cream in patients with moderate CHE and severe CHE in the pooled DELTA 1 and DELTA 2 trials.

[redacted]

[redacted]

In response to a clarification question, the company provided the results of subgroup analyses comparing delgocitinib and alitretinoin in hyperkeratotic and non-hyperkeratotic patients in the DELTA FORCE trial.

[redacted]

3.3.4 Safety

The company presented data on treatment-emergent adverse events (TEAEs) for the DELTA FORCE trial in the CS and in response to a clarification question. Overall, no deaths were reported for either the delgocitinib or alitretinoin arms of the DELTA FORCE trial. The rate of all TEAEs in the DELTA FORCE trial (defined as the event rate per 100 patient years of observation) was 231.5 in the delgocitinib arm and 596.1 in the alitretinoin arm. Likewise, the rate of serious adverse events was greater in the alitretinoin arm (11.5) compared to the delgocitinib arm (4.1). The rate of TEAEs that possibly, or probably, related to the study drug was greater in the alitretinoin arm (299.0) compared to the delgocitinib arm (24.8). Furthermore, the rate of TEAEs that lead to a permanent discontinuation of the study drug was greater in the alitretinoin arm (43.3) compared the delgocitinib arm (3.3).

For the DELTA FORCE trial, the rate of mild TEAEs was greater in the alitretinoin arm (381.7) compared to the delgocitinib arm (138.9). The rates of individual mild TEAEs, for which the rate was ≥ 1 event per 100 person years in one or more treatment arms, are shown in Table 16. For all TEAEs that occurred in both arms, the rate was greater in the alitretinoin arm compared to the delgocitinib arm. There was a substantially greater rate of headaches in the alitretinoin arm (69.2) compared to the delgocitinib arm (8.3). Likewise, there greater rates of nasopharyngitis in the alitretinoin arm

(33.7) compared to the delgocitinib arm (20.7). Additionally, the rate of nausea was greater in the alitretinoin arm (9.6) compared to the delgocitinib arm (0.8).

Table 16. Rate of mild TEAEs reported for patients in the delgocitinib and alitretinoin arms of the DELTA FORCE trial.

Mild TEAEs	Delgocitinib (Rate)	Alitretinoin (Rate)
Nasopharyngitis	20.7	33.7
Upper respiratory tract infection	5	6.7
COVID-19	2.5	6.7
Urinary tract infection	–	6.7
Dry skin	2.5	6.7
Eczema	1.7	4.8
Erythema	0.8	6.7
Hand dermatitis	0.8	1
Dermatitis atopic	–	1.9
Blood triglycerides increased	0.8	5.8
Back pain	0.8	2.9
Nausea	0.8	9.6
Diarrhoea	–	3.8
Lip dry	–	7.7
Headache	8.3	69.2
Migraine	0.8	2.9
Dizziness	–	2.9
Epistaxis	0.8	2.9
Flushing	–	4.8
Dry eye	–	4.8
Hypercholesterolaemia	–	8.7
Hypertriglyceridaemia	–	4.8
Abbreviations: TEAEs, treatment-emergent adverse events.		

Only TEAEs for which the rate was ≥1 event per 100 person years in one or more treatment arms are shown.

Rate is defined as the number of events that occurred per 100 patient years.

For the DELTA FORCE trial, the rate of moderate TEAEs was greater in the alitretinoin arm (190.4) compared to the delgocitinib arm (89.3). The rates of individual moderate TEAEs, for which the rate was ≥ 1 event per 100 person years in one or more treatment arms, are shown in Table 17. For all TEAEs that occurred in both arms, the rate was greater in the alitretinoin arm compared to the delgocitinib arm, with the exceptions of hypertriglyceridemia and upper respiratory tract infections. There was a substantially greater rate of headaches in the alitretinoin arm (34.6) compared to the delgocitinib arm (7.4). Otherwise, the rates of the moderate TEAEs were broadly comparable between the arms.

Table 17. Rate of moderate TEAEs reported for patients in the delgocitinib and alitretinoin arms of the DELTA FORCE trial.

Moderate TEAEs	Delgocitinib (Rate)	Alitretinoin (Rate)
Nasopharyngitis	10.7	10.6
COVID-19	1.7	1.9
Upper respiratory tract infection	1.7	1
Urinary tract infection	0.8	3.8
Headache	7.4	34.6
Dizziness	0.8	2.9
Migraine	0.8	3.8
Back pain	0.8	2.9
Dermatitis atopic	0.8	2.9
Hand dermatitis	1.7	2.9
Dry skin	–	1.9
Eczema	–	1
Erythema	–	2.9
Blood triglycerides increased	0.8	1.9
Hypertriglyceridemia	2.5	1.9
Hypercholesterolaemia	–	1
Diarrhoea	–	1
Nausea	–	3.8
Epistaxis	–	2.9
Dry eye	–	1.9
Flushing	–	1

Abbreviations: TEAEs, treatment-emergent adverse events.

Only TEAEs for which the rate was ≥1 event per 100 person years in one or more treatment arms are shown.

Rate is defined as the number of events that occurred per 100 patient years.

For the DELTA FORCE trial, the rate of severe TEAEs was greater in the alitretinoin arm (24.0) compared to the delgocitinib arm (3.3). The rates of individual severe TEAEs, for which the rate was ≥ 1 event per 100 person years in one or more treatment arms, are shown in Table 18. Overall, no severe TEAEs were reported in the delgocitinib arm, while hand dermatitis, nausea, and headaches severe TEAEs reported in the alitretinoin arms.

Table 18. Rate of severe TEAEs reported for patients in the delgocitinib and alitretinoin arms of the DELTA FORCE trial.

Severe TEAEs	Delgocitinib (Rate)	Alitretinoin (Rate)
Hand dermatitis	–	1
Nausea	–	1
Headache	–	5.8

Abbreviations: TEAEs, treatment-emergent adverse events.

Only TEAEs for which the rate was ≥1 event per 100 person years in one or more treatment arms are shown.
Rate is defined as the number of events that occurred per 100 patient years.

Based upon the information presented in the CS and clarification questions, the EAG considers that the presented results for TEAEs for the DELTA FORCE trial do not indicate any major safety concerns for delgocitinib in comparison to alitretinoin.

In the economic model, the company accounted for TEAEs associated with delgocitinib and alitretinoin in DELTA FORCE. In the trial 9.3% of delgocitinib patients experienced TEAEs, compared to 54.3% of alitretinoin patients. TEAEs were included in the model if they were associated with an incidence of at least 10% and if the difference between treatments was at least 1.5%. Based on these criteria, headache and nasopharyngitis were the only AEs considered relevant for inclusion.

As TEAEs had not been provided by grade or severity in the CS, at clarification the EAG requested for the TEAE data to be disaggregated by severity. The company provided the data as requested which outlined that an AE was recorded as severe if it resulted in death, was life-threatening, required hospitalisation, resulted in disability or incapacity, was a congenital anomaly of birth defect, a medically important condition or a malignancy. In the DELTA FORCE trial, no delgocitinib patients recorded any severe AEs. Comparatively 0.4% of alitretinoin patients recorded severe hand dermatitis and nausea and 2% recorded severe headaches.

Given the small proportion of patients which experience severe treatment related AEs, the EAG considers that AEs are not drivers of cost-effectiveness and excludes AEs in the EAG base cases.

3.4 Critique of the indirect treatment comparisons

Within the CS, the company presented the results of network meta-analyses (NMAs) for the outcomes of IGA-CHE TS, IGA-CHE TS cumulative response, HECSI-90, and discontinuation due to adverse events. For each outcome, a primary analysis (including all patients) and sensitivity analyses for moderate and severe patient subgroups were performed. Overall, the EAG has serious concerns regarding the NMAs presented by the company; as such, the focus of indirect treatment comparisons (ITCs) section centres on the additional information provided by the company in response to the EAG's clarification questions.

With regards to the NMAs provided in the CS, the EAG is concerned by the substantial clinical and methodological heterogeneity reported among the included studies. For outcomes, two different

versions of IGA-CHE were incorporated into the NMAs alongside the distinct endpoint of PGA. Additionally, the severity of patients considered by each trial differs with some trials only considering severe patient and other considering both moderate and severe patients. As such, the company has assumed that treatment effects will be consistent across patients regardless of whether they have moderate or severe CHE, although the company has accepted in the CS that this is a strong assumption and performed sensitivity analyses which only included patients with severe CHE. The EAG is concerned by this assumption as direct comparisons of the moderate and severe patients in the pooled DELTA 1 and DELTA 2 trials indicated that treatment effects may not be consistent in these groups. Furthermore, in response to a clarification question, the company noted that the different form of IGA-CHE utilised in the Worm *et al.* 2022 trial is not necessarily comparable to that implemented in the other DELTA trials as this measure underwent numerous revisions during its development. For instance, the company noted in a clarification response that some patients assigned as having mild CHE in the Worm *et al.* 2022 trial would have been considered to have moderate CHE in the other DELTA trials. As such, the EAG is concerned that the Worm *et al.* 2022 outcomes and population do not align with those of the other included trials.

The EAG also has serious concerns regarding the company's rationale for presenting the results of the fixed-effect (FE) NMAs over the random-effect (RE) NMAs. While the company assesses model fit using the deviance information criterion (DIC) they note that there is limited difference in DIC values between the FE and RE models. As such, the company would be able to select the most appropriate model based on clinical rationale which, given the heterogeneous nature of the included studies, would likely be the RE NMAs. However, the company selected the FE NMAs as, "the RE model SDs are large". In turn, the company notes that the RE NMAs have wide credible intervals compared to the FE NMAs due to these large SDs. Accordingly, the company noted that due to the sparse network and "imprecise treatment effect estimates generated by the RE model", the FE models were preferred for all outcomes. The EAG is strongly opposed to the selection of a preferred model based upon the results of such models. In the absence of a meaningful difference in the statistical fit of the FE and RE models, the EAG considers that the selection should be based on an appropriate clinical rationale (in this example, the acknowledged heterogeneity in the underlying trials) rather than a "preference" for one set of results over another.

[redacted]

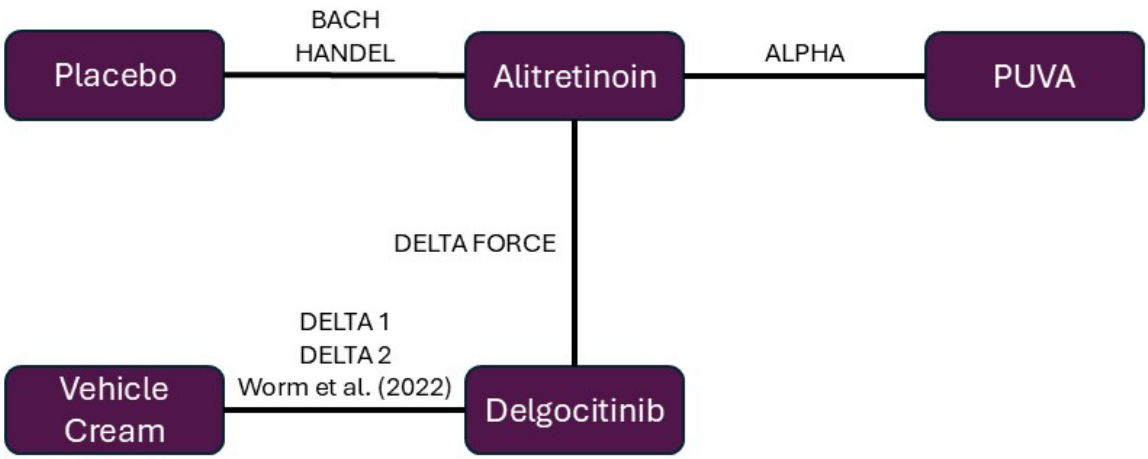
[redacted]

Overall, it is the position of the EAG that the NMAs presented in the CS are inappropriate. As such, the EAG considers that comparisons of delgocitinib to alitretinoin should be based upon the direct evidence provided by the DELTA FORCE trial. Likewise, it is the position of the EAG that comparisons of delgocitinib to PUVA should be based ITCs performed by the company in response to the EAG's clarification questions.

3.4.1 Trials informing the indirect treatment comparison

As noted above, the EAG considers that ITCs should be used to assess the relative efficacy of delgocitinib relative to PUVA, while comparisons of delgocitinib to alitretinoin should be derived from the direct evidence provided by the DELTA FORCE trial. Within the evidence network identified by the company, only the ALPHA trial considered PUVA. The evidence network, identified by the company, that comprises all trials included in one or more of the NMAs performed by the company is shown in Figure 9.

Figure 9. Network diagram of trials included in one or more NMAs performed by the company.



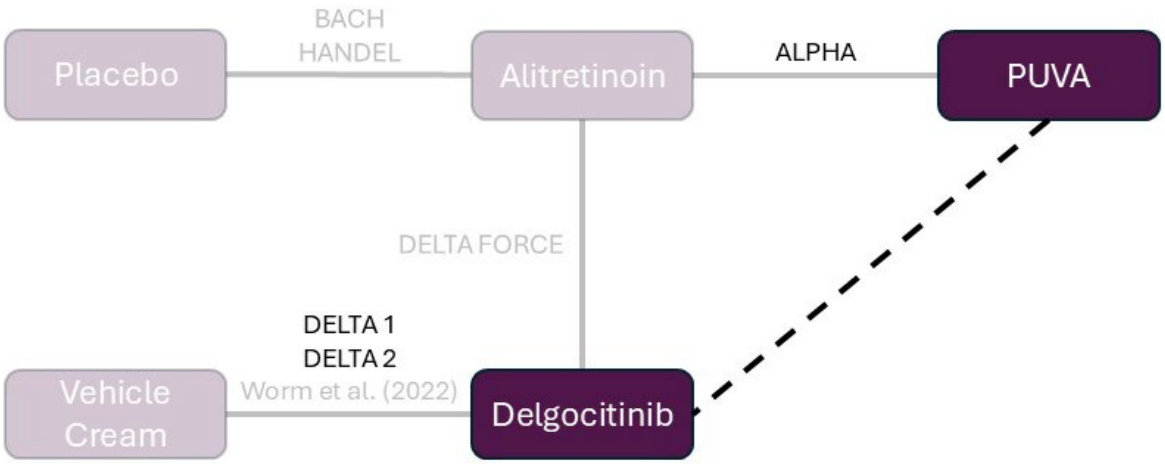
For the base case NMAs for discontinuations due to adverse events, the company combined patients who received either placebo or vehicle cream into a single group.

Abbreviations: EAG, external assessment group; NMA, network meta-analyses; PUVA, Psoralen-UV A.

As noted previously, the focus of the ITCs section centres on the additional information provided by the company in response to the EAG's clarification questions. Through clarification questions, the EAG requested that the company performed unanchored MAICs where patients who received delgocitinib in the pooled DELTA 1 and DELTA 2 trials were matched to patients who received PUVA in the ALPHA trial.

Figure 10 illustrates the network of evidence for the unanchored MAICs, including how this network compares to the NMA network considered in the CS. Across these analyses, data are utilised from the DELTA 1, DELTA 2, DELTA FORCE, and ALPHA trials. A detailed discussion of the DELTA 1, DELTA 2, and DELTA FORCE trials is provided in Section 3.2.

Figure 10. Network diagram of the trials requested by the EAG in a clarification question for inclusion in an unanchored MAIC.



The dashed line indicates the indirect treatment comparison made through a MAIC. Trial names, and treatment names, in bold indicate those trials and treatments that contributed to a MAIC.

Abbreviations: EAG, external assessment group; MAIC, matching-adjusted indirect comparison; PUVA, Psoralen-UV A.

A comparison of the baseline characteristics between the delgocitinib arms of the DELTA 1 and DELTA 2 trials and PUVA arm of the ALPHA trial is provided in Table 19. As shown by Table 19, there is broad consistency between the trials for the baseline characteristics of age, sex, and race. Likewise, the reported HECSI score at baseline reported for the PUVA arm of the ALPHA trial is broadly aligned with the baseline HECSI score reported for the DELTA 2 trial, but considerably lower than that reported for the DELTA 1 trial. Furthermore, there are substantial differences between the ALPHA and DELTA 1 and DELTA 2 trials for the prevalence of severe patients. In the ALPHA trial, the inclusion criteria stipulated that patients must have severe CHE as assessed by the physician's global assessment (PGA) scale. In contrast, the inclusion criteria for the DELTA 1 and DELTA 2 trials stipulated that the patients may have either moderate or severe CHE as assessed by the IGA-CHE scale. Accordingly, all patients in the ALPHA trial had severe CHE at baseline, while only 32.9% and 23.9% of patients had severe CHE at baseline in the DELTA 1 and DELTA 2 trials, respectively. Additionally, there is a substantial difference in the proportion of patients with hyperkeratotic CHE in the ALPHA trial compared to the DELTA 1 and DELTA 2 trials. In the ALPHA trial, 64.7% of patients had hyperkeratotic CHE, substantially higher than the 17.5% and 27.4% of patients with hyperkeratotic CHE in the DELTA 1 and DELTA 2 trials.

Table 19. Baseline characteristics of the ALPHA, DELTA 1, and DELTA 2 trials.

Baseline characteristic	DELTA 1 Delgocitinib	DELTA 2 Delgocitinib	ALPHA PUVA

Age (years); mean (SD)		44.3 (14.3)	45.3 (14.6)	45.1 (15.2)
Male (%)		37.8	35.0	34.8
White (%)		87.1	93.9	90.0
Weight (kg); mean (SD)		77.4 (17.6)	78.8 (17.9)	NR
Duration of CHE (years); median (range)		6.0 (0-63)	4.0 (0-59)	NR
Baseline IGA-CHE/PGA score	Moderate (%)	67.1	76.1	0
	Severe (%)	32.9	23.9	100
Baseline HECSI score; mean (SD)		77.6 (46.4)	64.3 (37.9)	62.2 (42.0)
Hyperkeratotic CHE (%)		17.5	27.4	64.7

Abbreviations: CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; PGA, Physician's Global Assessment; PUVA, Psoralen-UV A; SD, standard deviation.

3.4.2 Statistical methods

The company performed unanchored MAICs for the outcomes of IGA-CHE TS (at Week 12) and change from baseline HECSI score (at Week 12). Within these MAICs, the patient population of the pooled DELTA 1 and DELTA 2 trials was aligned with that of the ALPHA trial. Overall, the following six potential prognostic variables or treatment effect modifiers were sufficiently well-reported to match on:

- Age;
- Sex;
- Race (white vs non-white);
- CHE severity (moderate CHE vs severe CHE);
- HECSI score at baseline; and
- Hyperkeratosis (hyperkeratotic CHE vs non-hyperkeratotic CHE).

When requesting the additional analyses from the company, the EAG noted that the DELTA 1 and DELTA 2 trials comprised both moderate and severe CHE patients while the ALPHA trial solely comprised patients with severe CHE. Accordingly, the EAG requested that the company provide two sets of MAICs. The first set would include disease severity as a matching covariate, resulting in the comparison of delgocitinib and PUVA only comprising patients with severe CHE. In contrast, the second set would not include disease severity as a matching covariate, resulting in the delgocitinib population comprising patients with both moderate and severe CHE, while the PUVA patient population would solely comprise patients with severe CHE. Overall, the EAG deemed it most appropriate to consider the first set of MAICs that comprise patients with only severe CHE, as

disease severity has been shown to be an important prognostic factor (Section 3.3) and in doing so ensured that the pooled DELTA 1 and DELTA trial population was appropriately matched to the severe CHE only population from the ALPHA trial.

In their response to the clarification question, the company noted that there were concerns regarding the comparability of the definition of hyperkeratotic CHE between the pooled DELTA 1 and DELTA 2 trials compared to the ALPHA trial. The company noted that within the DELTA 1 and DELTA 2 trials, whether a patient was defined as having hyperkeratotic CHE was based upon the 2014 European Consensus on Skin Diseases (ECSD) guidelines.[2] In contrast, within the ALPHA trial a patient was assessed as having hyperkeratotic CHE based upon clinical morphology. As such, in their response to the clarification question, the company provided two sets of MAICs, one set where hyperkeratotic CHE was included as a matching covariate and a second set where hyperkeratotic CHE was not included as a matching covariate. As such, while the EAG acknowledges that differences in the definition of hyperkeratotic CHE exist between the trials included in the unanchored MAICs, the EAG considers it appropriate to include hyperkeratotic CHE as a matching covariate given the previously shown importance of this covariable as a treatment effect modifier (Section 3.3). Accordingly, the EAG focuses on the results of the MAICs, which included hyperkeratotic CHE as a matching covariate.

3.4.3 Clinical effectiveness results

The baseline characteristics of patients from the pooled DELTA 1 and DELTA 2 trials, after matching to the ALPHA trial were provided by the company in response to the clarification question. The baseline characteristics for the EAG's preferred MAIC that only considered severe patients and included hyperkeratotic CHE as a matching covariate are shown in Table 20. Likewise, the EAG notes that the mean HECSI score at baseline substantially decreased in the matched population compared to the unmatched population in the pooled DELTA 1 and DELTA 2 trials. Additionally, the percentage of hyperkeratotic patients substantially increased from 19.8% in the unmatched population to 64.7% in the matched population. The company did not report the values of baseline characteristics that were not matched upon. As such, the EAG was not able to assess the magnitude of the differences, in these characteristics, post-matching. Furthermore, the company did not provide a comprehensive report on the MAIC. As such, the EAG was unable to assess some aspects of the unanchored MAIC such as the application of individual patient weights. The EAG considers it important to assess the weightings given to individual patients to be able to thoroughly critique the results of the

unanchored MAIC. However, the EAG notes that the effective sample size for the pooled DELTA 1 and DELTA 2 matched population was small (n = 39). As noted in NICE technical support document 18,[21] reduced effective sample sizes may occur when there are large differences in distribution of covariates between trials, such as those reported for hyperkeratosis and baseline HECSI score in the ALPHA and pooled DELTA 1 and DELTA 2 trials (Table 20). Furthermore, a small effective sample size may be indicative that a comparison has limited ability to detect differences in treatments between matched trials.[22] As such, the small effective sample size of the matched pooled DELTA 1 and DELTA 2 population constitutes a limitation of the unanchored MAIC.

Table 20. Baseline characteristics for the ALPHA trial alongside the unmatched and matched populations for the pooled DELTA 1 and DELTA 2 trials where hyperkeratotic CHE was included as a matching covariate and only patients with severe CHE were considered.

Baseline characteristic	ALPHA trial (PUVA)	Pooled DELTA 1 and DELTA 2 trials (delgocitinib)	
		Unmatched population	Matched population
Sample size	221	182	39*
Male (%)	35.3	36.8	35.3
White (%)	90.0	87.9	90.0
Hyperkeratotic (%)	64.7	19.8	64.7
Age (mean [SD])	45.1 (15.2)	45.5 (14.1)	45.1 (13.1)
Baseline HECSI score (mean [SD])	62.2 (42.0)	102 (50.3)	62.2 (28.3)

*Corresponds to the effective sample size obtained after matching.

Abbreviations: HECSI, Hand Eczema Severity Index; PUVA, Psoralen-UV A; SD, standard deviation.

With regards to IGA-CHE TS, the EAG's preferred MAIC reported an odds ratio (OR) of

[redacted]

[redacted]. The company also provided the results of a naïve comparison between the delgocitinib arm pooled DELTA 1 and DELTA 2 trials (considering only severe patients) and the PUVA arm of the ALPHA trial. In this crude comparison, in which no weighting occurred, a [redacted] Although this crude comparison cannot be considered statistically robust, the EAG notes that the [redacted]

For change from baseline HECSI score, [redacted] Although not provided by the company, the EAG performed a naïve comparison between the delgocitinib arm pooled DELTA 1 and DELTA 2 trials (considering only severe patients) and the PUVA arm of the ALPHA trial for change from baseline HECSI score. In this crude comparison, in which no weighting occurred, [redacted]. Although this crude comparison cannot be considered statistically robust, the EAG notes [redacted].

3.5 Conclusions of the clinical effectiveness section

The EAG considers that the evidence provided by the company is appropriate to answer the decision problem, and any differences between the NICE final scope and the CS are justified (Section 2.3). The SLR was performed using appropriate methods and is likely to have identified the most relevant and current evidence (Section 3.1).

Within the CS, the company only included PUVA and alitretinoin as comparators despite the NICE final scope including other comparators such as TCIs and systemic immunosuppressive therapies. The company's assertion that PUVA and alitretinoin are the only relevant comparators for the population described in the MHRA marketing authorisation was supported by the EAG's clinical experts. However, the EAG's clinical experts noted that PUVA and alitretinoin were likely to be used in differing subgroups depending upon whether a patient with CHE had hyperkeratosis or not. The DELTA 1 and DELTA 2 trials were described by the company as being 'identical' trials that provided direct comparisons of delgocitinib to vehicle cream in patients with moderate or severe CHE. Additionally, the DELTA FORCE trial provided a direct comparison of delgocitinib to alitretinoin in patients with severe, but not moderate, CHE. The EAG considers the DELTA 1, DELTA 2, and DELTA FORCE trials to be of a low risk of bias. However, the EAG has concerns that the use of the WOCF approach to account for missing data may have biased the results of these trials in favour of delgocitinib.

Within the CS, the company noted that only the ALPHA trial included PUVA as a comparator, but that this trial did not measure IGA-CHE in contrast to the DELTA 1, DELTA 2, and DELTA FORCE trials. As the ALPHA trial measured PGA, the company has assumed that PGA is equivalent to IGA-CHE. Within the CS, the company acknowledged that the assumption of equivalence between PGA and IGA-CHE is a strong assumption. However, the company has justified the assumption by indicating that patients would be required to meet more stringent criteria to be deemed as either clear or almost clear when using IGA-CHE compared to PGA, an assertion supported by the EAG's clinical experts. As such, although no direct comparisons of IGA-CHE are available, the EAG is satisfied that PGA and IGA-CHE are approximately comparable outcomes.

Overall, the EAG considers there to be evidence that treatment with delgocitinib is associated with:

[redacted]

Furthermore, the EAG considers there to be insufficient evidence regarding the efficacy of delgocitinib relative to:

- Alitretinoin in patients with moderate CHE;
- PUVA in patients with moderate CHE; and
- PUVA in patients with hyperkeratotic, or non-hyperkeratotic, CHE regardless of severity.

[redacted]

[redacted]

[redacted] Furthermore, mild, moderate, and severe TEAEs were either consistent across patients receiving delgocitinib and alitretinoin or were reported at a greater rate in patients who received alitretinoin.

While the above results indicate a consistent benefit of delgocitinib over alitretinoin in the overall population, these results do not consider a patient's hyperkeratotic status, which the EAG's clinical experts considers to be a treatment effect modifier. As the DELTA FORCE trial included a patient's hyperkeratotic status as a stratification variable, the results of subgroup analyses for patients with hyperkeratotic and non-hyperkeratotic CHE are unlikely to be of a high risk of bias.

[redacted]

[redacted]

As no direct evidence exists for the comparison of delgocitinib to PUVA, indirect evidence for this comparison was obtained from MAICs comprising patients who received PUVA in the ALPHA trial and patients who received delgocitinib in the pooled DELTA 1 and DELTA 2 trials.

[redacted] Additionally, the ALPHA trial did not report the results of subgroup analyses for patients with hyperkeratotic or non-hyperkeratotic CHE. As such, there is no clinical evidence for the comparison of delgocitinib to PUVA in patients with hyperkeratotic or non-hyperkeratotic CHE. However, the EAG's clinical experts indicated that the treatment effect of both delgocitinib and PUVA would be expected to be greater in patients with non-hyperkeratotic CHE than patients with hyperkeratotic CHE. Despite this, there is uncertainty with regards to the direction, and magnitude, of the relative treatment effect observed between delgocitinib and PUVA in these subgroups.

Within the NICE final scope, aetiology (i.e., atopic or contact CHE) was listed as a subgroup of interest.

[redacted] Accordingly, with regards to aetiological or morphological subtypes, it is the opinion of the EAG that hyperkeratotic status is the key subgroup to consider based upon the results of subgroup analyses and assertions from the EAG's clinical experts that a patient's treatment is likely to be dependent upon their hyperkeratotic status.

As the DELTA FORCE and ALPHA trials only comprised patients with severe CHE, there is no clinical evidence for the comparison of delgocitinib to alitretinoin or PUVA in patients with moderate CHE. Although alitretinoin has only received marketing authorisation for patients with severe CHE, the EAG's clinical experts have indicated that up to 50% of patients with moderate CHE may receive alitretinoin on an off-label basis. Likewise, the EAG's clinical experts considers that both moderate and severe patients may receive PUVA. In response to a clarification question, the company outlined that they have assumed that the relative treatment effect of delgocitinib versus alitretinoin and PUVA is consistent across patients with moderate and severe CHE. This assumption is based upon results provided by the company in response to a clarification question, [redacted] Instead, this hypothesis may be explored with equivalency testing.[20] Additionally, the EAG is concerned by the assumption that relative treatment effects would be consistent for comparisons of delgocitinib to alitretinoin and delgocitinib to PUVA between the moderate and severe subgroups, given the paucity of clinical evidence to support this assumption.

4 Cost effectiveness

Table 21 and Table 22 presents the company's updated (i.e., post clarification) base case results for the severe and moderate chronic hand eczema (CHE) subgroups. Bases case and scenario analyse results which include the PAS discounts for alitretinoin, ciclosporin and dupilumab are provided in the confidential appendix.

Table 21. Company's base case results post clarification – severe CHE subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Pairwise ICER (£/QALY)
Deterministic results							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,526
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Probabilistic results							
Delgocitinib	[redacted]	-	[redacted]		-		
Alitretinoin	[redacted]	-	[redacted]	[redacted]	-	[redacted]	9,744
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	Dominated

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; LY, life year; PUVA, psoralen–UVA phototherapy; QALY, quality-adjusted life-year

Table 22. Company's base case results post clarification – moderate CHE subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Pairwise ICER (£/QALY)
Deterministic results							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Probabilistic results							
Delgocitinib	[redacted]	-	[redacted]	-	-	-	-
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	Dominated

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; LY, life year; PUVA, psoralen–UVA phototherapy; QALY, quality-adjusted life-year

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

The company conducted three separate systematic literature reviews (SLRs) to identify published cost-effectiveness, health-related quality of life (HRQoL) and cost and resource use studies relevant

to the appraisal. The cost-effectiveness SLR was originally conducted in November 2022 and updated in July 2024. The HRQoL SLR was conducted in July 2024 and was an update of a previous SLR that was originally run in 2020 and updated in 2023. The costs and resource use SLR was originally conducted in 2018 and was updated several times, with the most recent update conducted in August 2024.

The company searched an appropriate selection of data sources, including the following electronic literature databases: Embase, MEDLINE, MEDLINE In-Process, Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, The University of York Centre for Reviews and Dissemination (CRD), the National Health Service Electronic Evaluations Database (NHS EED), Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cost-Effectiveness Analysis (CEA) Registry and the International Network of Agencies for Health Technology Assessment (INAHTA) database. Grey literature searches of health technology assessment (HTA) bodies and hand-searching was also conducted of conference proceedings and reference lists of included publications.

A summary of the External Assessment Group's (EAG's) critique of the company's methods to identify relevant evidence is presented in Table 23.

Table 23. EAG critique of company SLR methods

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E.1.1.	Appendix F.1.1.	Appendix G.1.1.	Appropriate
Inclusion/ exclusion criteria	Appendix E.1.2.1.	Appendix F.2.1.	Appendix G.2.1.	Appropriate
Screening	Appendix E.1.2.1.	Appendix F.2.1.	Appendix G.2.1.	Appropriate
Data extraction	Appendix E.1.2.2.	Appendix G.2.2.	Appendix G.2.2.	Appropriate
Quality assessment of included studies	Appendix E.1.2.3.	Appendix G.2.2.	Appendix G.2.3.	Appropriate

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

The cost-effectiveness SLR identified 267 records, the HRQoL SLR identified 1,235 records and 667 records were identified by the costs and resource use SLR. Of these, 7, 68 and 84 records reached full-text screening following the removal of duplicates and exclusions at the tile/abstract stage for the economic evaluation, HRQoL and, resource use and cost SLRs, respectively.

From the full-text screening, five economic evaluations, 15 HRQoL studies and 4 cost and resource use studies were deemed potentially relevant by the company to the decision problem with a list of these studies provided in Appendix E.3, F.3 and G.3 of the company submission (CS).

Of the economic evaluations identified, none provided a previous model for the evaluation of delgocitinib, thus the company developed a *de novo* Markov model. However, the included economic evaluations were used to inform the company's approach to the *de novo* model.

Similarly the company considered that none of the HRQoL studies identified provided utility values more appropriate or relevant to the decision problem than the utility data captured in the DELTA trials; the values of which have been applied in the company's base case (see Section 4.2.7).

Finally, the company considered that none of the resource use and cost studies provided appropriate data for use in the model and instead used data from the DELTA trials as well as assumptions to inform the model.

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

4.2.1 NICE reference case checklist

Table 24 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.

Table 24. 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	All relevant health outcomes for CHE have been included in the economic model.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company with a fully incremental analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A non-lifetime horizon is appropriate given all patients have progressed from the intervention after and comparators after five years and the treatments do not impact mortality.

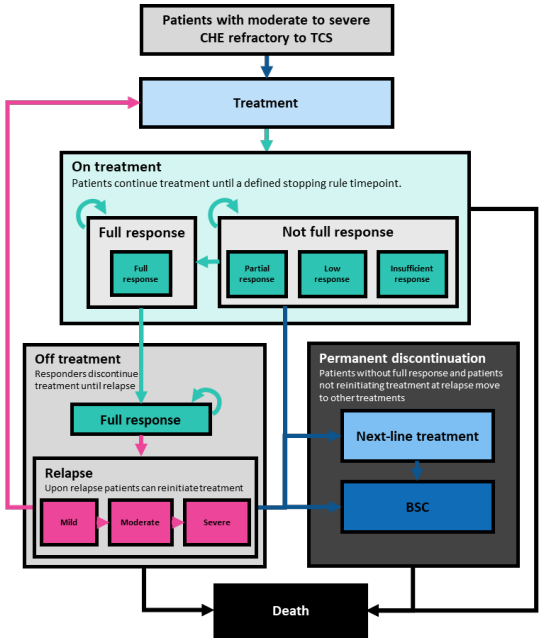
Synthesis of evidence on health effects	Based on systematic review	The company has performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health outcomes have been expressed in terms of QALYs, with health state utility values being informed by EQ-5D values.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D values were obtained from CHE patients from the DELTA trials. Treatment outcomes from these trials similarly informed treatment effects directly or in-directly (NMA).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The source considered for HRQoL can be considered relevant to the UK.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The economic evaluation matches the reference case.
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	All relevant costs are included appropriately.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: CHE, chronic hand eczema; EAG, External Assessment Group; NMA, network meta-analysis; NHS, national health service; PSS, personal social services; QALY, quality-adjusted life year

4.2.2 *Modelling approach and model structure*

The company developed a *de novo* Markov model that allowed patients to be on-treatment, off-treatment, experience a relapse of symptoms, be re-treated, and discontinue to next-line treatments or best supporting care (BSC) with death as an absorbing health state Figure 11.

Figure 11. Model schematic (reproduced from Figure 29 in the CS)



After initial treatment (12 weeks), patients who have achieved a full response weeks transition to the off-treatment health state, while partial and low responders continue treatment for another 12 weeks and insufficient responders move on to next line treatments or best supportive care (BSC). After a maximum additional 12 weeks of treatment, patients who achieve a full response progress to the off-treatment health state with all other patients discontinuing to either next-line treatments or BSC. Treatment response was defined in terms of IGA-CHE with a scenario conducted by the company using the Hand Eczema Severity Index (HECSI). Table 25 presents the treatment response for each IGA-CHE category.

Table 25. Response definitions (reproduced from Table 54 in the CS)

Health state	IGA-CHE (base case)	HEC SI (scenario analysis)
Full response	IGA-CHE 0 (clear) or 1 (almost clear)	HECSI 90
Partial response	IGA-CHE 2 (mild)	HECSI 75 to 89
Low response	IGA-CHE 3 with 1-point improvement from baseline (moderate)	HECSI 50 to 74
Insufficient response	IGA-CHE 3 without improvement from baseline or IGA-CHE 4 (severe)	< HECSI 50

Abbreviations: HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema.

Patients who achieved a full response from initial treatment (by week 12) or continued treatment (up to week 24) remain off-treatment until relapse, when patients can become eligible for retreatment. Patients can initiate retreatment on an as-needed basis, with the maximum duration of retreatment being 24 weeks and no limit to the number of rounds a patient can be retreated following relapse.

4.2.2.1 EAG critique

The EAG considers that the model developed by the company is appropriate but is concerned with how patients who have responded by 12 weeks and by 24 weeks transition to the same off-treatment health state. The EAG's clinical experts stated that there may be differences in prognostic factors between 12-week and 24-week responders, with those that responded faster to treatment potentially experiencing more time to relapse and a higher probability of full response to retreatment compared to 24-week full responders. At clarification the EAG requested the company to conduct a subgroup analysis comparing the rate of relapse, retreatment response and discontinuation between 12- and 24-week responders and if outcomes were substantially different, to conduct a scenario analysis assessing the separate subgroups.

In the company's response, they stated that during the development of the model, they had investigated if future outcomes among 12-week and beyond 12-week full responders might differ, concluding that the evidence suggested that future outcomes were broadly similar.

On investigation into the potential difference in the rate of relapse between 12 and 24-week responders, the company presented Figures 8 and 9 in the company's response to clarification. The Figures present the time to symptom relapse between patients who achieved a full response in DELTA 1 and 2 and relapsed and those who achieved a full response in DELTA 3 and relapsed. The company stated that there is a consistent overlap in rate of relapse between the 12 and 24-week responders and the rate of relapse following initial and retreatment, which the EAG considers reasonable.

To evaluate the difference in the probability of achieving a full response on retreatment between 12 week and 24 week responders, the company highlighted an analysis of DELTA provided in the company submission which outlined that of the [redacted] patients that achieved a full response in DELTA 1 and 2, before entering DELTA 3, [redacted] relapsed and were retreated with an estimated median time to regaining full response of 8 weeks. Comparatively, of the [redacted] patients who had not achieved full

response by DELTA 3, [redacted] achieved a full response but later relapsed and restarted treatment with a median time to regaining full response of 12 weeks. The EAG considers this analysis suggests that earlier responders to treatment will respond to treatment faster compared to later responders and that this difference between patients is not accounted for in the model.

To investigate the difference in the proportion of patients opting not to be retreated with delgocitinib following relapse, the company used the number of censored patients at week 0 for the outcome of time to response following the first retreatment in DELTA 3. The data indicated that [redacted] of patients who entered DELTA 3 with a full response were censored at week 0 compared to [redacted] of patients who achieved a full response during DELTA 3. Using these data in proxy, the company considered that patients who experience a response by week 12 may be more likely to re-initiate treatment than patients who experienced a response later than week 12, which the EAG considers reasonable.

Having provided the data requested by the EAG, the company noted that although the model was not built to allow any differentiation by responders at week 12 and after week 12, they tried to approximate the impact of the difference. To conduct the scenario, the company calculated a weighted mean probability of not restarting treatment ([redacted]) based on the previously estimated treatment discontinuation rates ([redacted]) and the proportions of patients that achieved a full response by 12 and 24 weeks in the model. Applying these values to the delgocitinib arm led to a small increase in the ICER from £8,221 (submitted base case) to £8,992.

The EAG considers that the analyses provided by the company have highlighted the similarities in rates of relapse between 12- and 24-week responders and that the ICER is relatively robust to the differences in discontinuation between the patient's subgroups. While the differences in response to re-treatment was not explored by the company in scenario analyses, the EAG considers that accounting for the difference in treatment effects between 12- and 24-week response would be unlikely to overly impact the ICERs given the difference in treatment effects between these patients applies to both delgocitinib and its comparators, mitigating the potential bias to an extent. As such, while the outcomes of the model are more uncertain by not accounting for the differences in treatment effects between 12- and 24-week responders, the EAG considers that adapting the model to include the difference in treatment effects would not provide an overly dissimilar ICER or impact the decision of cost-effectiveness between treatments.

4.2.3 Population and comparators

As moderate CHE patients are ineligible for alitretinoin within its marketing licence, psoralen with ultraviolet (PUVA) was considered the only relevant comparator to delgocitinib for the treatment of moderate CHE. For severe CHE patients, alitretinoin and PUVA were considered appropriate comparators to delgocitinib.

To investigate the difference in cost-effectiveness between delgocitinib and PUVA in treating moderate CHE, all patients in the model were assumed to have moderate symptoms (IGA-CHE 3) at baseline. Similarly, all patients were assumed to have severe symptoms (IGA-CHE 4) at baseline when comparing delgocitinib to PUVA and alitretinoin.

In the CS, the company noted that in contrast to the current market authorisation, alitretinoin may be used off-label in clinical practice to treat patients with moderate CHE.

4.2.3.1 EAG critique

The EAG agrees with company that, based on its marketing authorisation, patients with moderate CHE are ineligible for treatment with alitretinoin; However, given its use off-label was supported by the EAG's clinical experts, the EAG considers that alitretinoin is an appropriate comparator for moderate CHE patients.

At clarification the EAG requested the company to conduct a scenario comparing the treatment of delgocitinib to alitretinoin in moderate patients. The EAG suggested using the relative delgocitinib treatment effects between severe and moderate patients in DELTA 1 and 2 and the comparative treatment effects between delgocitinib and alitretinoin in DELTA FORCE to estimate an alitretinoin treatment effect in moderate patients. The company conducted the scenario using the odds ratio between severe and moderate patients in DELTA 1 and 2, applying the rates of response to DELTA FORCE, leading to a per-week probability of response of [redacted]% and [redacted]% for delgocitinib and alitretinoin respectively, resulting in an ICER of £12,721.

To assess the cost-effectiveness of delgocitinib compared to alitretinoin in patients with moderate symptoms at baseline, the EAG has provided a scenario around the EAG base case using the moderate treatment effects estimated in the company's scenario. The EAG notes scenario relies on

the uncertain assumption of equivalence of relative treatment effects between severe and moderate symptom patient at baseline for delgocitinib and alitretinoin.

The EAG's clinical experts also indicated that in clinical practice the choice between treatments is less dictated by the severity of symptoms (moderate vs severe) but by the type of symptoms. Specifically, that alitretinoin is used to treat hyperkeratotic patients, while PUVA is used to treat non-hyperkeratotic patients. When asked which type of patients the clinician expected to treat with delgocitinib, the clinician considered delgocitinib would be used to treat non-hyperkeratotic patients.

The company was therefore requested to explore the hyperkeratotic and non-hyperkeratotic treatment effects of delgocitinib compared to the most appropriate comparator, namely, the hyperkeratotic treatment effects compared to alitretinoin using DELTA FORCE and non-hyperkeratotic treatment effects compared to PUVA using ALPHA and the DELTA studies.

The company conducted the scenarios as requested, with the modelling assumptions used for delgocitinib compared to alitretinoin in hyperkeratotic patients presented in Table 26. From the subgroup analysis of DELTA FORCE, the EAG notes that only [redacted]% of hyperkeratotic delgocitinib patients achieved a full response by week 12, compared to [redacted]% of alitretinoin patients. The company additionally highlighted that the probability of relapse following full response in the hyperkeratotic subgroup was estimated to be [redacted] times higher compared to the overall DELTA FORCE population.

Table 26. Parameters for patients with severe hyperkeratotic CHE from DELTA FORCE (reproduced from Table 39 in the clarification response)

Parameter	Delgocitinib	Alitretinoin	Notes
Probability of IGA-CHE 0/1 at week 12	[redacted]%	[redacted]%	DELTA FORCE; Hyperkeratotic subgroup specific [23]
Distribution across non full response states at week 12	PR: [redacted]% LR: [redacted]% InR: [redacted]%	PR: [redacted]% LR: [redacted]% InR: [redacted]%	DELTA FORCE; Hyperkeratotic subgroup specific [23]
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	DELTA FORCE; Hyperkeratotic subgroup specific [23]

Discontinuation	[redacted]% (based on 12-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)	DELTA FORCE; Hyperkeratotic subgroup specific [23]
Loss of IGA-CHE 0/1 response	[redacted]% (calculated by applying risk ratio of [redacted] to base case risk)	[redacted]% (based on median time to relapse of [redacted] weeks)	DELTA 3 [13]
Response to re-treatment	Base case	Base case	DELTA 3 [13]

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

While DELTA FORCE was used to inform the majority of the modelling assumptions in the scenario, the company considered there to be too few data to inform retreatment effects. In these instances, DELTA 3 was used to inform the retreatment effects, as in the company base case assumptions. The company considered this a reasonable approach given that CHE morphology can change over time and that a patient presenting with hyperkeratosis may not have the same predominate clinical subtype going forward. While the EAG agrees with this statement, the EAG notes that its clinical expert stated that a patient's current subtype of symptoms would affect the decision about which treatment to prescribe.

The company added that as delgocitinib patients will be retreated when symptoms relapse to mild, if patients are hyperkeratotic, they may respond better to retreatment compared to initial treatment as symptoms are mild as opposed to severe. The company added that there are a number of reasons why alitretinoin may not be acceptable for some patients and the full clinical picture needs to be considered when treating patients with CHE. In the scenario, delgocitinib resulted in fewer QALYs and greater costs compared to alitretinoin, reflecting an ICER in the northwest quadrant and delgocitinib being dominated by alitretinoin.

The company similarly conducted a scenario exploring the non-hyperkeratotic delgocitinib treatment effects compared to alitretinoin using the modelling assumptions presented in Table 27. As with the hyperkeratotic scenario, DELTA 3 was used to inform loss of response and response to re-treatment. The scenario found delgocitinib to be cost-effective compared to alitretinoin, resulting in an ICER of £11,193.

In the EAG's base case, delgocitinib and alitretinoin treatment effects have been informed using the complete DELTA FORCE population and not the hyperkeratotic subgroup treatment effects. The DELTA FORCE treatment effect was considered more appropriate as not all hyperkeratotic patients will be eligible for alitretinoin or would choose to be treated with alitretinoin given the pregnancy

prevention programme required concurrently. However, scenario analyses around the EAG's base case have been provided using the hyperkeratotic subgroup treatment effects.

Table 27. Parameters for patients with severe non-hyperkeratotic CHE from DELTA FORCE (reproduced from Table 40 in the clarification response)

Parameter	Delgocitinib	Alitretinoin	Notes
Probability of IGA-CHE 0/1 at week 12	[redacted]%	[redacted]%	DELTA FORCE; Non-hyperkeratotic subgroup specific [23]
Distribution across non full response states at week 12	PR: [redacted]% LR: [redacted]% InR: [redacted]%	PR: [redacted]% LR: [redacted]% InR: [redacted]%	DELTA FORCE; Non-hyperkeratotic subgroup specific [23]
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	From PR: [redacted]% (based on 12-week probability of [redacted]%) From LR: [redacted]% (based on 12-wk probability of [redacted]%)	DELTA FORCE; Non-hyperkeratotic subgroup specific [23]
Discontinuation	[redacted]% (based on 12-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)	DELTA FORCE; Non-hyperkeratotic subgroup specific [23]
Loss of IGA-CHE 0/1 response	Base case	Base case	DELTA 3 [13]
Response to re-treatment	Base case	Base case	DELTA 3 [13]

Abbreviations: IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

To compare non-hyperkeratotic delgocitinib and PUVA patients, the EAG requested the company to conduct an indirect treatment comparison using DELTA FORCE and ALPHA. In response the company stated that due to a lack of hyperkeratotic and non-hyperkeratotic subgroup data being presented in the ALPHA trial, the indirect comparison could not be provided as requested. The company was also requested to conduct an indirect treatment comparison between ALPHA and pooled DELTA 1 and 2 patients which was conducted as requested. As described in detail in Section 3.4, four MAICs were conducted by the company, matching separately by disease severity (severe symptom matching or no symptom matching) and hyperkeratosis status at baseline (hyperkeratotic status matching vs no hyperkeratotic status matching). The company stated that hyperkeratosis was not previously included due to a lack of comparability in how hyperkeratosis was captured in the ALPA and DELTA 1 and DELTA 2 trials. Across all MAIC treatment effects, delgocitinib was found to dominate PUVA.

The EAG considers that the MAIC results matching patients by severe symptoms and hyperkeratotic status at baseline provides the most robust treatment effects given matching by hyperkeratosis status at baseline is inclusive of both hyperkeratotic and non-hyperkeratotic patients. The EAG notes that the MAIC estimated mean odds ratio is [redacted], indicating that there is little to no difference in the proportion of patients who achieved a full response by 12 weeks. The outcomes of this MAIC are therefore assumed in the EAG base case comparing delgocitinib to PUVA.

As with the comparison to alitretinoin, a scenario around the EAG base case comparing delgocitinib to PUVA has been provided for patients with moderate symptoms at baseline. The scenario informs treatments effects using the relative treatment effect between severe and moderate patients in DELTA 1 and 2 and applying the odds ratio from the MAIC to the relative treatment effect in order to estimate a PUVA treatment effect in patients with moderate symptoms at baseline.

4.2.4 Perspective, time horizon and discounting

The cycle length of the model was four weeks with a half-cycle correction applied. A 10-year time horizon was assumed, as by this time all patients have progressed to next-line treatments or BSC and treatments do not impact mortality. As scenario analyses, time horizons of 3, 5 and 30 years were explored by the company with the 3 and 50-year time horizons resulting in ICERs of £5,324 and £8,550 respectively.

The perspective of the analysis was based on the UK NHS and PSS, with future costs and benefits discounted using an annual rate of 3.5%, as per the NICE reference case.[24]

4.2.4.1 EAG critique

The EAG considers the model cycle length to be appropriate given the time patients are expected to respond to treatment, continue treatment and relapse. The EAG highlights that in the model delgocitinib patients experience the longest time on treatment, with all delgocitinib patients estimated to be off treatment by just less than five years, compared to three years for alitretinoin patients and two years for PUVA patients.

4.2.5 Treatment effectiveness

4.2.5.1 Primary treatments

4.2.5.1.1 Initial treatment

Initial treatment effects (12 weeks) in the company base case were informed using the Network Meta Analysis (NMA). The company noted that from the studies included in the NMA, delgocitinib is the only treatment for which moderate patient (DELTA 1 and 2) and severe patient (DELTA 1, 2 and FORCE) treatment effects were available. Clinical data for the effectiveness of alitretinoin and PUVA are only available for severe patients, as only severe patients were included in the DELTA FORCE and ALPHA studies. Therefore, the NMA treatment effects for patient with moderate symptoms at baseline synthesised evidence from the moderate patient subgroup from DELTA 1 and 2, with severe treatment effects from DELTA FORCE and ALPHA. The treatment effects in patients with moderate symptoms therefore assume that the relative treatment effects of delgocitinib and alitretinoin in DELTA FORCE and of alitretinoin and PUVA in ALPHA would be similar if evaluated among patients with moderate symptoms. The company notes that this assumption allows comparisons to be modelled between delgocitinib and PUVA using the best available RCT data.

Using the 12-week probability of achieving a full response from the NMA, a per cycle probability of full response was estimated, assuming that the underlying rate of response was constant. As the 16-week outcomes were the primary end point of the DELTA trials, a scenario analysis using the per cycle probability of full response derived from the 16-week outcomes was explored. Table 28 presents the probabilities of achieving a full response in the first 12 weeks of treatment using the 12-week and 16-week per cycle probabilities.

Table 28. Probabilities of and treatment effects for full response (IGA-CHE 0/1) in first 12 weeks of treatment (reproduced from Table 57 in the CS)

Treatment	12-week risk	Odds ratio	4-week risk	Source
Week 12 analysis (base case)				
Severe CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
Alitretinoin	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC	[redacted]	[redacted]	-	NMA
Moderate CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA

BSC	[redacted]	[redacted]	-	NMA
Primary endpoint analysis (scenario analysis)				
Severe CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
Alitretinoin	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC	[redacted]	[redacted]	-	NMA
Moderate CHE				
Delgocitinib	[redacted]	[redacted]	[redacted]	NMA
PUVA	[redacted]	[redacted]	[redacted]	NMA
BSC	[redacted]	[redacted]	-	NMA

Abbreviations: HECSI, Hand Eczema Severity Index; IGA-CHE, investigator global assessment for chronic hand eczema; NA, not applicable; PUVA, psoralen–UV A phototherapy.

After 12 weeks (three model cycles), patients who had achieved a full response transitioned to the off-treatment health state while patients who had not achieved a full response were assumed to continue treatment for up to another 12 weeks.

4.2.5.1.2 Continued treatment

After 12-weeks in the model patients continuing treatment were distributed across the non-response health states (mild, moderate and severe). The distribution of patients was informed by the 12-week subgroup analysis of the DELTA 1, 2 and FORCE trials for delgocitinib patients and DELTA FORCE for alitretinoin patients. Where data were missing in the subgroup analyses, the company used a worst observation carried forward approach (WOCF) to impute the data. For PUVA patients, the distribution of patients across the non-responder's health states was assumed to be the same as alitretinoin from DELTA FORCE. The company noted that this may underestimate the number of insufficient responders from ALPHA; therefore, the ALPHA distributions were explored as a scenario analysis, using only the observed data and assuming missing data were due to an insufficient response. In the absence of available data to inform the moderate baseline PUVA patients, the distribution of patients across non-response health states was assumed to be the same as for delgocitinib. The company noted that based on trends observed in the severe CHE group, this may again overestimate the 12-week PUVA response.

Using the distributions of patients across the non-response health states, patients were then mapped to response health states (partial, low and insufficient response) based on the improvement from baseline at 12 weeks. For severe patients at baseline, the severity health states were mapped

directly to the response states (partial response = mild severity [IGA-CHE 2], low response = moderate severity [IGA-CHE 3] and insufficient response = severe severity [IGA-CHE 4]). However, for patients with moderate symptoms at baseline (IGA-CHE 3) the same mapping could not be used, as low responders would be considered IGA-CHE 3, which would reflect a low treatment response as opposed to symptoms unchanged from baseline. A such, moderate baseline patients with IGA-CHE 3 by week 12 were considered non-responders. Table 29 presents the proportions of patients assumed in each response and severity state by baseline severity.

Table 29. Proportion of patients in each non-full response state at week 12 (reproduced from Table 58 in the CS)

Comparator	IGA-CHE severity states			IGA-CHE response states			Source/notes
				PR	LR	InR	
	IGA-CHE 2	IGA-CHE 3	IGA-CHE 4	IGA-CHE 2	IGA-CHE 3 with 1-pt Δ	No Δ	
Moderate CHE							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate subgroup analysis of DELTA 1 and DELTA 2[13]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to delgocitinib.
BSC [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Moderate subgroup analysis of DELTA 1 and DELTA 2 vehicle arm[13]
Severe CHE (base case)							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Severe subgroup analysis of DELTA 1 and DELTA 2 and DELTA FORCE, pooled[13]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	DELTA FORCE
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to alitretinoin
BSC [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Severe subgroup analysis of DELTA 1 and DELTA 2 vehicle arm[13]
Severe CHE (sensitivity analysis using ALPHA data for alitretinoin and PUVA, assuming NRI for missing data)							
Alitretinoin	21.4%	35.8%	42.8%	21.4%	35.8%	42.8%	ALPHA[25]
PUVA	15.6%	28.0%	56.5%	15.6%	28.0%	56.5%	
Severe CHE (sensitivity analysis using ALPHA data for alitretinoin and PUVA, observed cases)							
Alitretinoin	30.1%	50.4%	19.5%	30.1%	50.4%	19.5%	ALPHA[25]
PUVA	25.7%	46.0%	28.3%	25.7%	46.0%	28.3%	

Abbreviations: IGA-CHE, investigator global assessment for chronic hand eczema; InR, insufficient response; LR, low response; NRI, non-responder imputation; PR, partial response; PUVA, psoralen–UV A phototherapy; Δ, change/improvement

To inform the treatment effects for patients continuing treatment from week 12 to 24 in the model, the company used a *post hoc* analysis of DELTA 3 to inform the probabilities of full response from each response state for delgocitinib patients. For alitretinoin patients, the continued treatment effects were assumed to be the same as delgocitinib patients, given that a *post hoc* analysis of DELTA FORCE indicated that the proportions of patients that achieved a full response at week 24 was similar between the treatment arms (from IGA-CHE 2, [redacted]% vs [redacted]%, from IGA-CHE 3, [redacted]% vs [redacted]%, for delgocitinib and alitretinoin patients, respectively).

Although the ALPHA trial allowed patients with a partial response to continue treatment, no data were available from the trial that could be used to inform treatment effects for PUVA or alitretinoin patients between weeks 12 and 24. Therefore, in the absence of available data, the delgocitinib and alitretinoin continued treatment effects were similarly applied to PUVA patients. The company noted that, given the difference in treatment effects between delgocitinib and PUVA at 12 weeks, assuming that the 24-week PUVA treatment effects are equal to those of delgocitinib, likely overestimates the PUVA treatment effects.

As with initial treatment effects, the per cycle probability of achieving a full response was estimated using the 24-week treatment effects, assuming a constant rate of full response over time. Table 30 presents the probabilities of achieving a full response for each treatment given a patient's symptom severity at baseline.

Table 30. Per-cycle probability of full response with continued treatment by non-responder health state (reproduced from Table 59 in the CS)

Strategy	Per-cycle probability of achieving full response			Source/notes
	From partial response		From low response	
	Moderate at baseline	Severe at baseline		
Delgocitinib	[redacted]	[redacted]	[redacted]	*Post hoc* analysis of DELTA 3.
Alitretinoin	[redacted]	[redacted]	[redacted]	Assumed to be the same as delgocitinib based on *post hoc* analysis of DELTA FORCE.
PUVA	[redacted]	[redacted]	[redacted]	Assumed equivalent to alitretinoin in absence of evidence.

Abbreviations: IGA-CHE, investigator global assessment for chronic hand eczema; NA, not applicable; PUVA, psoralen–UV A phototherapy

4.2.5.1.3 Relapse

After achieving a full response to treatment, patients progress to the off-treatment health state until symptom relapse. To estimate the rate of relapse a *post hoc* analysis of the DELTA 3 trial was conducted which estimated a mean time to symptom progression to the mild symptom state (IGA-CHE ≥ 2) of [redacted]. The median time to the development of moderate or severe symptoms (IGA-CHE 3 and 4) could not be estimated as patients-initiated treatment as soon as symptoms had become mild (IGA-CHE ≥ 2).

In DELTA FORCE, median time to symptom progression was longer than measured in DELTA 3, with delgocitinib patients experiencing symptom progression after [redacted]. Comparatively, mean time till symptom relapse for alitretinoin patients was [redacted]. The company noted that although the sample size for relapsed patients in DELTA FORCE was small ([redacted] and [redacted] delgocitinib and alitretinoin patients, respectively) and follow-up limited (8 weeks and 12 weeks for delgocitinib and alitretinoin patients, respectively) the alitretinoin results are not dissimilar to those measured in the BACH and HANDEL studies, which reported a time until relapse of 8 and 8.3 weeks for delgocitinib and alitretinoin patients, respectively. As in the DELTA 3 trial, the median time to moderate or severe symptoms could not be estimated as patients initiated treatment as soon as symptoms had become mild.

In the 52 weeks of the ALPHA trial, 90.7% of alitretinoin and 70.2% of PUVA patients experienced symptom relapse. While mean time to relapse was not reported, KM curves were presented, which infer no evidence of a difference in the rate of relapse between treatment groups.

In the model, the company has made the simplifying assumption of using DELTA FORCE to inform the probability of relapse to mild symptoms for delgocitinib and alitretinoin patients, with the alitretinoin probability being also applied to PUVA patients, given no evidence of a difference between PUVA and alitretinoin patients in ALPHA. The probability of relapse to moderate and severe symptoms for all treatments was informed by the ALPHA trial using the transition matrices reported by Wittmann *et al.*, which defined transition between week 24 to 36, and week 36 to 52.[25]

Table 31 presents a summary of the per cycle probabilities of relapse assumed in the model and their respective sources.

Table 31.Probability of relapse (reproduced from Table 60 in the CS)

Strategy	Mild relapse (pMild)	Moderate relapse (pMod)	Severe relapse (pSev)	Source
Delgocitinib	[redacted]	20.9%	2.2%	Probability of mild relapse calculated from DELTA FORCE; probability of moderate and severe relapse based on data from ALPHA.
Alitretinoin	[redacted]	20.9%	2.2%	
PUVA	[redacted]	20.9%	2.2%	Assumed equal to alitretinoin based on conclusions of no difference from ALPHA

Abbreviations: PUVA, psoralen–UV A phototherapy.

4.2.5.1.4 Re-treatment

After relapsing and starting retreatment, patients can go on to achieve a full response once again. If a patient does not achieve a full response within 24 weeks of retreatment in the model, they progress to next-line therapy or BSC. It is assumed that patients can continue to relapse and be retreated without limit if a full response is achieved within 24 weeks of the start of retreatment.

In the model the company has assumed that the severity threshold at which patients are eligible to restart treatment varies by the comparator. It was assumed that delgocitinib may be restarted as soon as symptoms become mild, reflecting the clinical trial and it's expected use in clinical practice; While alitretinoin and PUVA are restarted at the point of moderate or severe relapse to reflect their current use in clinical practice. To test the impact of these assumptions the company explored scenario analyses in which all treatments were resumed at the same point.

With respect to retreatment effects, for delgocitinib patients, it was measured that after 32 weeks of follow-up in the DELTA 3 trial, [redacted]% of patients achieved a full response. Comparatively in DELTA FORCE, median time to full response was [redacted] for delgocitinib treated patients, with [redacted]% of patients responding during [redacted]. For alitretinoin patients in DELTA FORCE, the median time to achieve full response was [redacted], with [redacted] having responded within [redacted] of retreatment.

The company stated that in the absence of reliable comparative delgocitinib and alitretinoin patient data, a simplifying assumption was preferred, that assumed the retreatment effects for delgocitinib and alitretinoin treatments were the same. The company noted that given the difference in treatments in DELTA FORCE, this assumption may underestimate the potential advantages of delgocitinib over alitretinoin; however, the company considered this underestimation may be

mitigated to a certain extent, given the difference in severity thresholds for when patients become eligible for re-treatment. In the absence of data to inform PUVA re-treatment effects, it was also assumed that the delgocitinib and alitretinoin retreatment effects similarly applied to PUVA patients being retreated.

A such, a per-cycle probability of achieving a full response of [redacted]% was assumed in the model for all treatments, based on [redacted]% of delgocitinib patients achieving full response within 32 weeks of follow-up in DELTA 3. Given the strong assumption of equal retreatment efficacy across all treatments, this assumption was tested by the company in a sensitivity analysis.

4.2.5.2 EAG critique

The EAG considers that the methodologies employed by the company to apply treatment effects in the model are robust but is concerned with the appropriateness of using the NMA to inform initial treatment effects. As described in detail in Section 3.4, the EAG considers that the NMA is methodologically flawed, with the calculated treated effects being inappropriate to inform treatment effects in the model.

As such, the EAG considers it more appropriate to inform treatment effects in the model using direct treatment comparisons were possible. Therefore, at clarification the company was requested to assess cost-effectiveness of delgocitinib, relative to alitretinoin, using the outcomes measured in DELTA FORCE. Specifically, the company was requested to conduct a scenario analysis comparing delgocitinib to alitretinoin using the treatment effects, time to relapse, discontinuation, utilities and treatment use from DELTA FORCE trial for severe patients, and a separate scenario using only DELTA FORCE to inform the initial treatment effects. The company conducted the scenarios as requested, using the model parameters as described in Table 32. The former scenario led to an increase in the ICER from £8,526 to £16,039; only using the DELTA FORCE initial treatment effects led an increase in the ICER to £10,720.

The EAG considers that the DELTA FORCE treatment effects provide the most robust modelling assumptions when comparing delgocitinib to alitretinoin, therefore, the DELTA FORCE treatment effects have been assumed in the EAG base case.

Table 32. Treatment response, relapse, and discontinuation probabilities for delgocitinib and alitretinoin using data from DELTA FORCE only (reproduced from Table 37 in the CQ response)

Parameter	Delgocitinib	Alitretinoin

Probability of IGA-CHE 0/1 at week 12	[redacted]	[redacted]
Distribution across non full response states at week 12	[redacted]	[redacted]
Per-cycle probability of full response for continued treatment	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)	From PR: [redacted]% (based on 12-wk probability of [redacted]%) From LR: [redacted]% (based on 12-week probability of [redacted]%)
Per-cycle probability of relapse (to mild CHE)	[redacted]% (as per base case)	[redacted]% (as per base case)
Per-cycle probability of full response with re-treatment	[redacted]% (based on 8-week probability of [redacted]%)	[redacted]% (based on 12-week probability of [redacted]%)
Per-cycle probability of permanent discontinuation from continued initial treatment and retreatment	[redacted]% (as per base case)	[redacted]% (as per base case)
Proportion of patients opting not to re-initiate initial treatment following relapse	[redacted]%	[redacted]%
Utilities	Baseline: 0.674 FR: [redacted] PR: [redacted] LR: [redacted] InR: [redacted]	Same as delgo due to the structural assumption that all active treatments are associated with the same utilities.
Delgocitinib dose (g/week)	FR: [redacted] g PR: [redacted] g LR: [redacted] g InR: [redacted] g	NA

Abbreviations: FR, full response; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; InR, insufficient response; LR, low response; PR, partial response.

To investigate the cost effectiveness of delgocitinib relative to PUVA, the company was requested to conduct an indirect treatment comparison between delgocitinib and PUVA. As described in Section 3.4.3, the company conducted a series of MAICs between ALPHA and pooled DELTA 1 and 2. Four MAICs were provided based on the matching of patient severity (severe symptom matching or no matching) and baseline hyperkeratosis status (hyperkeratotic status matching or no matching). When matching severe patients and hyperkeratotic status, the 12-week treatment effect odds ratio was measured at [redacted]; However, delgocitinib was found to dominate PUVA when using the results from all MAICs in the cost-effectiveness analysis.

As described in Section 4.2.3, the EAG considers that the MAIC results matching patients by severe symptoms and hyperkeratotic status at baseline provides the most robust treatment effects given matching by hyperkeratosis status at baseline is inclusive of both hyperkeratotic and non-hyperkeratotic patients. The MAIC is therefore assumed in the EAG base case comparing delgocitinib to PUVA.

Lastly, as described in detail in Section 3.2, the EAG considers the company's use of worst observation carried forward (WOCF) to impute missing data for the estimation of treatment effects is inappropriate, given the comparators of delgocitinib had relatively more in-trial missing data, introducing bias towards the delgocitinib treatment effect. As such, the treatment effectiveness of the comparators of delgocitinib may be underestimated in the model, leading to an underestimation of the ICER. As alternative methods were not used by the company in scenario analyses, the EAG is uncertain to what extent different imputation methods would influence the decision of cost-effectiveness. However, as the EAG considers that the ICER may be sensitive to the underestimation of the delgocitinib comparator treatment effects, this is considered a key issue.

4.2.5.3 Next-line treatments and BSC

Patients who discontinue treatment go on to receive next-line treatments or BSC. Next-line treatments were modelled as a basket of treatments based while BSC was assumed to include topical corticosteroid (TCS), topical calcineurin inhibitors (TCIs) and emollients only.

To inform the proportions of patients that go on to receive each treatment, the company used data from the RWEAL study which identified that 76.8% of patients with moderate CHE and 59.1% of patients with severe CHE reported TCS use without additional oral, biological or phototherapy treatments.[6] It was therefore assumed that 23.2% of moderate and 40.9% of severe patients move on to next-line therapies before BSC. In a sensitivity analysis, the company used the ALPHA trial to inform the rate of next-line treatment uptake in which 80.3% of patients moved on to next-line treatments before BSC.

Next-line treatments were assumed to be used intermittently or as a course of treatment based on a duration from the RWEAL study. Table 33 presents the basket of next-line treatments and the percentage of patients on each treatment, with the same basket being assumed for each treatment arm.

Table 33. Basket of next-line treatments and assumed proportions of severe patients on treatment

Treatments	Proportions of patients on treatment	Source
Acitretin	0.0%	RWEAL study[6]
Azathioprine	4.8%	
Methotrexate	17.5%	
Ciclosporin	11.1%	
Oral steroids	14.3%	
Alitretinoin	23.8%	
PUVA	6.3%	
UVB	11.1%	
Dupilumab	11.1%	
TCS	99.4%	

Abbreviations: PUVA, psoralen–UV A phototherapy; TCS, topical corticosteroid; UVB, Ultraviolet B.

The company noted that the treatment effects of the basket of next-line treatment effects relied on the simplifying assumption that the basket was as effective as alitretinoin in the RWEAL study. This assumption was based on an assessment by physicians in the RWEAL study who judged 40.6% of alitretinoin patients to be in a low disease health state. While a low disease health state was not described in terms of IGA-CHE, the company has assumed it would reflect a state of being IGA-CHE ≤2. Therefore, the alitretinoin response rate was considered a reasonable proxy for all the therapies in the next-line treatment basket.

BSC treatment effects were informed using the vehicle arm in DELTA 1 and DELTA 2. As a scenario, BSC was assumed to have no independent effect, and patients would revert to their baseline severity of symptoms.

4.2.5.4 EAG critique

The EAG agrees with how the company has applied next-line treatment and BSC treatment effects but disagrees with the basket of treatments and the assumed treatment effects.

While the RWEAL study has been used to inform the inclusion of alitretinoin in the basket of next-line treatments, the EAG notes that alitretinoin patients would have already failed on alitretinoin and so would be unlikely to receive alitretinoin as a next line treatment. Similarly, if patients previously treated with delgocitinib and PUVA progress, they may not be treated with alitretinoin given its use primarily in hyperkeratotic patients. Therefore, the EAG considers that the inclusion of

alitretinoin as a next-line treatment may be inappropriate and the treatment effects of the basket overestimated.

At clarification, the company was requested to conduct a scenario removing alitretinoin from the basket of next-line therapies and to estimate a revised treatment effect for the remaining treatments in the basket. In their response, the company noted that CHE is a complex disease in which clinical presentation can change over time. Therefore, alitretinoin and PUVA were included in the next-line basket to capture the range of options which may be used. The company considered that no reliable data were available to inform the efficacy of next-line treatments therefore alitretinoin was used in proxy.

In order to conduct a scenario for the EAG, alitretinoin was removed from the basket while increasing the assumed proportions of ciclosporin, methotrexate and dupilumab, and the effectiveness of the basket increased to assume 80% of patients on next-line treatments achieved a low disease state. While the EAG agrees with the removal of alitretinoin, the EAG considers that its removal would lead to a decrease in next-line treatment efficacy compared to the increase to 80% from 46.1%.

In the CS, the company stated that the next-line treatment effectiveness was estimated using the ongoing and stopped use of alitretinoin in the RWEAL study. On review of the study outcomes, the EAG was unable to calculate how the next-line treatment effectiveness had been estimated. At the clarification stage, the company was asked to detail how treatment effects had been calculated with the company responding that the RWEAL data used to inform the model had been accidently omitted and therefore shared in the clarification response (Table 34). The table highlights the proportions of patients in the RWEAL that achieved low disease activity across different treatments included in the next-line of treatments basket, which the company used to estimate a weighted average across the ongoing and stopped populations based on sample size.

Table 34. Judgment on the current alitretinoin or TCS treatments outcome, overall and by treatment family (adapted from Table 44 in the CQ response)

Alitretinoin or TCS treatments that are ongoing	Overall, N = 1552	Treatment					
		Alitretinoin, N = [redacted]	TCS, N = [redacted]	uhTCS, N = [redacted]	hTCS, N = [redacted]	mTCS, N = [redacted]	ITCS, N = [redacted]

Achieved low disease activity state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Failure to maintain a low disease activity state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: hTCS: high potency topical corticosteroids, ITCS: low potency topical corticosteroids, mTCS: moderate potency topical corticosteroids, N: number of subjects, TCS: topical corticosteroids, uhTCS: ultra-high potency topical corticosteroids.

The EAG notes only the ongoing and not the stopped populations have been provided, therefore the EAG was unable to validate how the company has calculated next-line of treatment effects. However, the EAG notes that in Table 34 the proportion of alitretinoin patients in the low disease health state are approximately 15-20% higher than those of the next-line basket. As such, while the company has previously stated that it would not be possible to calculate the next-line treatment effects without alitretinoin, the EAG considers that the company could have used the same weighting methodology of patients in the low disease activity states to calculate a treatment effect using the basket of treatments in Table 34, excluding alitretinoin.

Given the approximate 15% difference between alitretinoin and the other basket treatments, the EAG conducted a scenario assuming a next-line treatment effectiveness of 25.6% given the previous assumption of 40.6% and a 15% difference. The scenario led to a small decrease in the ICER, from £8,526.11 to £8,238.68. This assumption is included in the EAG base case.

The EAG also aimed to validate the expected proportions of patients who would discontinue to next-line treatments and BSC with their clinical expert. Compared to the company base case which assumes that 49.1% of patient would move on to next-line treatments, as was measured in the RWEAL study, the EAG's clinical experts' opinion was more aligned with the ALPHA study in which approximately 80% of patients moved on to next-line treatments before BSC. Therefore, in the EAG base case, the ALPHA study has been used to inform the proportions of patients who move on next-line treatments and BSC after discontinuation from delgocitinib or comparators.

4.2.6 Time on treatment

In addition to discontinuing treatment due to a patient's response to initial, continued or retreatment, patients in the model were able to discontinue while on treatment (after the initial 12

weeks of treatment) or opt not to be re-treated after relapse, instead progressing to next-line treatments or BSC.

In the company base case, on-treatment discontinuation for delgocitinib and alitretinoin was informed using the rate of patient discontinuation between weeks 12 and 24 of DELTA FORCE, resulting in rates of [redacted]% and [redacted]% per cycle for delgocitinib and alitretinoin patients respectively. Using a Bucher indirect comparison between DELTA FORCE and ALPHA, an on-treatment discontinuation rate of [redacted]% was estimated for PUVA patients. The company noted that no discontinuation data for patients undergoing retreatment was available; therefore, the discontinuation rates measured during initial treatment (between weeks 12 to 24) were applied to patients on treatment during re-treatment.

With respect to patients opting not be re-treated, DELTA 3 was used to inform delgocitinib off-treatment discontinuation, and ALPHA for alitretinoin and PUVA patients. Providing discontinuation rates of [redacted]%, [redacted]% and [redacted]% for delgocitinib, alitretinoin and PUVA patients, respectively.

Table 35 below provides a summary of the per-cycle discontinuation probabilities.

Table 35. Per-cycle probability of discontinuation (reproduced from Table 61 in the CS)

Strategy	Odds ratio vs delgocitinib	Probability	Source
Discontinuation from continued initial treatment and re-treatment			
Delgocitinib	-	[redacted]	DELTA FORCE *post hoc* analysis
Alitretinoin	[redacted]	[redacted]	DELTA FORCE *post hoc* analysis
PUVA	[redacted]	[redacted]	Simple ITC comparing PUVA vs delgocitinib using odds ratio of PUVA vs alitretinoin from ALPHA and odds ratio of alitretinoin vs delgocitinib from DELTA FORCE.
Proportion of patients electing not to re-initiate initial treatment following loss of response			
Delgocitinib	NA	[redacted]	D3, *post hoc* analysis
Alitretinoin	NA	52.1%	ALPHA[25]
PUVA	NA	95.6%	ALPHA[25]

Abbreviations: NA, not applicable; ITC, in-direct treatment comparison; PUVA, psoralen–UV A phototherapy.

4.2.6.1 EAG critique

The EAG is concerned with the company's approach to treatment discontinuation, specifically with the on-treatment discontinuation for patients being re-treated. The company notes that no

discontinuation data for patients undergoing retreatment were available, therefore, discontinuation rates measured from week 12 to 24 in DELTA FORCE were applied as a proxy. Therefore, on-treatment discontinuation for patients being retreated is exclusively informed by patients that failed to achieve a full response by week 12 (partial and low responders). The EAG considers this to be inappropriate as on-treatment discontinuation is likely overestimated for patients being retreated, leading to patients progressing to next-line treatments and BSC more quickly.

Table 36 presents the proportion of patients estimated to remain on treatment in the model. The Table shows that PUVA patients progress fastest to next-line treatments and BSC followed by alitretinoin and delgocitinib patients. After two years in the model, all PUVA patients have progressed with just under [redacted] of delgocitinib patients and [redacted] of alitretinoin patients remaining on treatment. When validating these proportions with the EAG's clinical experts, the expert stated that in their clinical practice, approximately 25% of their alitretinoin patients are still on treatment (continuing to relapse and be retreated) after two years.

Table 36. Model time on treatment

Years	Proportion of patients on treatment in the model.		
	Delgocitinib	Alitretinoin	PUVA
0.5	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
1.5	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
2.5	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]

Abbreviations: PUVA, psoralen–UV A phototherapy.

At clarification, the company was asked what they considered contributed to the difference between patients estimated to be on treatment in the model and the EAG's clinical experts' expectation based on their clinical practice, as well as the implications of this difference in terms of cost effectiveness. In response, the company considered that according to DELTA FORCE only [redacted] of alitretinoin patients achieved a full response within 24 weeks of treatment (or 25.6% according to the company's NMA). The company noted that additional factors contributing to the portion of patients continuing to be treated over time include the probability of achieving a full response on retreatment, discontinuation while on treatment and after relapse. If in clinical practice alitretinoin patients are less likely to discontinue treatment and more likely to respond to retreatment then the time on treatment for alitretinoin would increase. As such, the company considered that acquisition

costs of alitretinoin would increase at a rate higher than that of QALYs gained, which is likely to decrease the ICER.

The EAG considers that the company has only considered the consequences of time on treatment for alitretinoin being underestimated in the model when the same logic may also apply to delgocitinib patients. If the proportion of alitretinoin patients cycling between full response and relapse is being underestimated in the model, given that delgocitinib is more effective than alitretinoin, it is likely that the proportion of delgocitinib patients continuing to cycle from full response to relapse may be higher than that of alitretinoin patients.

The treatment durations estimated in the model are uncertain due to immature data, with the EAG's clinical experts suggested that the actual time patients spend on treatment is likely to be longer than currently estimated. As delgocitinib is more costly than its comparators, a longer time on treatment would lead to an increase in the ICER. However, the extent of the underestimation and the actual differences in treatment times are unknown. As such, the impact of more accurate time on treatment data on the cost-effectiveness results is uncertain. The EAG, therefore, considers this a key modelling uncertainty.

4.2.7 Health-related quality of life

Health state utility values (HSUVs) included in the model for both the moderate and severe CHE subgroups were derived from pooled EQ-5D-5L data collected in DELTA 1 and DELTA 2. During DELTA 1 and 2, all patients in the ITT population completed the EQ-5D-5L questionnaire at all trial visits except for week 2 (weeks 0, 1, 4, 8, 12 and 16). As per the NICE reference case, the company mapped the EQ-5D-5L data to EQ-5D-3L using the mapping algorithm by Hernández Alava *et al.* 2020.

A mixed model for repeated measures (MMRM) was used to analyse the pooled utility data from DELTA 1 and DELTA 2. The company used backward selection to select variables included in the final specification of the regression model. The final utility regression modelled the change in EQ-5D-3L from baseline to week 16 as a function of age, baseline EQ-5D-3L score, HECSI. HECSI pain score and treatment received for each health state (see equation below).

$$\text{EQ-5D}=\alpha+\beta_1\text{Age}+\beta_2\text{EQ5D baseline}+\beta_3(\text{HECSI})+\beta_4(\text{HESDpain})+\beta_5\text{Treatment}$$

The definition of response for the utility values was based on IGA-CHE. However, the company also performed the MMRM regression using HECSI response definitions. Utility values for active treatment informing the health states in the model are presented in Table 37. For the company's base case, active treatment utility values were used for delgocitinib, alitretinoin and PUVA.

Table 37. Active treatment health state utility values used in the economic model (reproduced from Table 63 of the CS)

Health state	Moderate CHE subgroup	Severe CHE subgroup
Baseline	0.665	0.617
Full response	[redacted]	[redacted]
Partial response and mild CHE states	[redacted]	[redacted]
Low response and moderate CHE states	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema.

Utility values for next-line treatment and BSC are presented in Table 38 and Table 39. It was assumed by the company that utility values for next-line treatment and BSC were the same for both delgocitinib and comparator arms of the economic model.

To calculate the utility values for next-line treatment, based on the RWEAL study the company assumed that 40.6% of patients on next-line treatment would be evenly distributed across IGA-CHE 0/1 and 2 and the remaining 59.4% would be evenly distributed across IGA-CHE 3 and 4. These proportions were used to estimate a weighted utility value based on the average of the active treatment utility values for full and partial response and the average active treatment utility values for low and insufficient response (see Table 38).

Table 38. Next-line treatment utility value by severity

Response	Proportion (RWEAL)	Average utility	
		Moderate CHE subgroup	Severe CHE subgroup
Full response/ Partial response and mild CHE states	40.6%	[redacted]	[redacted]
Low response and moderate CHE states/ Insufficient response and severe CHE states	59.4%	[redacted]	[redacted]
Weighted utility value	-	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema

Note: Average utility value is based on the average of the active treatment utility values (Table 37) for the response categories outlined in the table.

For the BSC utility value, vehicle treatment utility values by response obtained from the MMRM regression were weighted by week 12 vehicle treatment response data from DELTA 1 and DELTA 2 (see Table 39).

Table 39. Best supportive care utility value by severity

Health state	Moderate		Severe	
	Utility	Proportion	Utility	Proportion
Full response	[redacted]	[redacted]	[redacted]	[redacted]
Partial response and mild CHE states	[redacted]	[redacted]	[redacted]	[redacted]
Low response and moderate CHE states	[redacted]	[redacted]	[redacted]	[redacted]
Insufficient response and severe CHE states	[redacted]	[redacted]	[redacted]	[redacted]
Weighted utility value	-	[redacted]	-	[redacted]

Abbreviations: CHE, chronic hand eczema.

Utilities in the model were adjusted for age, as per the NICE technology evaluation manual.[26] General population utility values adjusted for age and sex were obtained from the HSE 2014 dataset, as recommended by the DSU.

4.2.7.1 EAG critique

The EAG considers that compared to the company's preferred approach, which assumes that health state utilities are dependent on health state, treatment and baseline symptom severity, it is more appropriate to assumed utilities are only dependent on health state, given that there is no strong evidence for a treatment or baseline severity specific benefit has been provided.

At the clarification stage the company was requested to provide the mean EQ-5D utilities from DELTA 1, 2 and FORCE for each health state and the 95% confidence intervals of the utilities calculated from the MRMM model. In response, the company provided Table 40; however, no confidence intervals for the utilities estimated from the regression were provided.

Table 40. Mean EQ-5D-3L utilities from DELTA trials (reproduced from Table 48 in the CS)

Health state	Severe CHE (DELTA 1, 2 & FORCE)				Moderate CHE (DELTA 1 & 2)			Overall (no split by baseline severity)			
	delgocitinib n=409	Alitretinoin (DELTA FORCE only) n=236	Vehicle treatment (D1&D2 only) n=90	Overall n=735	Delgocitinib n=452	Vehicle treatment n=227	Overall n=679	delgocitinib (D1, D2 & DFORCE) n=861	Alitretinoin (DELTA FORCE only) n=236	Vehicle (D1 & D2) n=317	Overall n=1414
Baseline	0.617 (n=735)				0.665 (n=679)			0.640 (n=1414)			
IGA-CHE 0/1	[redacted]										
IGA-CHE 2	[redacted]										
IGA-CHE 3	[redacted]										
IGA-CHE 4	[redacted]										

Abbreviations: CHE, Chronic hand eczema; D1, DELTA 1 trial; D2, DELTA 2 trial; DFORCE, DELTA FORCE trial; IGA-CHE, Investigator's Global Assessment for Chronic Hand Eczema; n = number of patients

At the EAG's request the company conducted a scenario utilising the overall utilities for each health state, not split by baseline severity or treatment, which led to a small increased in the ICER in the severe population to £10,667, with delgocitinib continuing to dominate PUVA in the moderate patient population.

For both delgocitinib comparisons, the EAG considers that using the pooled utility data across all DELTA trials provides the most robust health state utility values, given it makes best use of the available data, thereby providing the most certain outcomes. As patients in the EAG base cases are assumed to have severe symptoms at baseline, given DELTA FORCE and ALPHA are used to inform treatment effects and neither study included patients with moderate symptoms at baseline, the utility values derived from patients with severe symptoms at baseline have been used to inform health state utility values in the EAG base cases. Similarly, in contrast to the company approach, the same health state utility values are assumed for patients on primary treatments, next-line treatments and BSC.

4.2.8 Resource use and costs

The following costs were included in the company's model:

- Treatment acquisition costs (primary, next-line and BSC treatments);
- Monitoring costs for alitretinoin;
- Health-state resource use and costs;
- Cost of adverse events (AEs).

Drug costs were sourced from the British National Formulary (BNF). Unit costs for PUVA and health-state resource use were sourced from the NHS Tariff 2023/25, NHS Schedule of Reference Costs 2022/2023 and PSSRU 2023.

A confidential PAS discount/CMU price is available for alitretinoin, ciclosporin and dupilumab. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.1 for details on the source of the confidential price for each treatment.

4.2.8.1 *Primary treatment acquisition costs*

The list price of delgocitinib is [redacted] per 60g tube. The dosing regimen for delgocitinib is a thin layer of cream to be applied twice daily to the affected skin of the hands and wrists until the skin is clear or almost clear. The SmPC for delgocitinib also states that in the event of recurrence of the signs and symptoms of CHE (flares), twice-daily treatment of the affected areas should be re-initiated as needed, and treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment. The company noted that the amount of delgocitinib used may vary between patients and also by severity of CHE. As such, the company estimated the weekly usage of delgocitinib by response category using a MMRM regression informed by weekly consumption data (12 weeks) from DELTA 1, DELTA 2 (moderate and severe CHE) and DELTA FORCE (severe CHE only). Weekly mean usage was then estimated by taking an average of delgocitinib usage over 12 weeks (Table 41)

In scenario analyses, the company explored using an overall weekly mean usage across response categories ([redacted] g/week), obtained from the MMRM regression, applied to all health states, and weekly mean usage from the DELTA trials with the lowest and highest reported usage ([redacted] g/ week from DELTA 2 and [redacted] g/ week from DELTA FORCE). The company's scenario analyses identify weekly delgocitinib usage as a key driver of cost-effectiveness.

The acquisition costs for the comparators, alitretinoin and PUVA are presented in Table 42.

Table 41. Weekly usage of delgocitinib (in grams) by severity and response based on MMRM regression

Week	Weekly usage (grams)							
	Moderate CHE subgroup (DELTA 1 & 2)				Severe CHE subgroup (DELTA 1, 2 & FORCE)			
	Full response 0/1	Partial response 2	Low response 3	Insufficient response 4	Full response 0/1	Partial response 2	Low response 3	Insufficient response 4
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weekly mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema; IGA-CHE, Investigator's Global Assessment of Chronic Hand Eczema; MMRM, mixed model with repeated measures

Table 42. Comparator acquisition costs

Comparator	Pack size/ no. of sessions	Unit cost	Treatment regimen	Assumptions/ Source
Alitretinoin	30 x 10 mg capsules	£493.72	Single capsule taken daily.	Based on data from DELTA FORCE, 21.1% of patients on alitretinoin have a dose reduction to 10 mg once daily. Unit cost obtained from the BNF[27]
	30 x 30 mg capsules	£493.72		
PUVA	One session	£145.03	2 sessions per week.	Cost taken from NHS tariff 2022/23 (JC47Z – outpatient procedure)

Abbreviations: PUVA, psoralen-UVA phototherapy

4.2.8.2 Next line and best supportive care costs

Table 43 presents the unit costs and dosing assumptions for next-line treatments and BSC. Next line treatment were costed as weighted costs, calculated using the annual costs and time spent on treatment.

Table 43. Acquisition costs for next-line therapy and BSC

Treatment	Pack description	Unit cost	Source Dosing/consumption
Additional treatments included in next-line therapy basket			
Ciclosporin	30 caps (50 mg)	£35.97	200 mg median daily dose according to data from RWEAL (consistent with 2.5-3 mg/kg/day based on SmPC)
Methotrexate	100 tablets (2.5 mg)	£5.29	15 mg per week Based on SPC
Acitretin	60 capsules (25 mg)	£55.24	25 mg median daily dose according to data from RWEAL
Azathioprine	56 tablets (50 mg)	£1.31	50 mg median daily dose according to data from RWEAL
Oral steroids	56 tablets (25 mg)	£50.00	25 mg median daily dose according to data from RWEAL
UVB	One session	£94.00	2 sessions per week
Dupilumab	2 pre-filled disposable injection	£1,264.89	300 mg every other week based on SmPC for AD
Components of BSC			
Emollients	One tub (500 g)	£4.95	8.6 g per week based on average vehicle consumption from DELTA 1 and 2
TCIs	One tube (60 g)	£39.74	2 g applied twice daily; 28 g per week
TCS (cost per g calculated as weighted average across different potencies; weights from RWEAL)			
Mild potency	One tube (15 g)	£2.48	1 g applied once or twice daily; 11 g per week
Moderate potency	One tube (100 g)	£6.49	
High potency	One tube (100 g)	£6.12	
Ultra-high potency	One tube (100 g)	£7.90	

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; g, gram; mg, milligram; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PUVA, psoralen–UV A phototherapy; SmPC, summary of product characteristics; TCI, Topical calcineurin inhibitors; TCS, Topical corticosteroids; UVB, ultraviolet B.

4.2.8.3 Monitoring costs

As patients treated with alitretinoin require concurrent monitoring, the following monitoring resources and costs were assumed in the model for alitretinoin patients (Table 44).

Table 44. Per cycle monitoring resource use associated with alitretinoin (reproduced from Table 67 in the CS)

Parameter	Usage	Price	Notes	Source
Proportion of women who are of childbearing potential	15%	NA	NA	NICE TA177[28]
Contraceptives	0.3	£2.82 per 63-tablet pack	Contraception required for duration of alitretinoin treatment and two additional months (in line with TA177)	Microgynon 30 (one 3-month box)
Pregnancy test kit	1.3	£1.00 per kit	In line with TA177, pregnancy consultation one month prior to and at start of treatment, then every 28 days for duration of alitretinoin treatment and at 5 weeks following end of treatment	ALPHA trial[25]
Ward nurse time	1.3	£8.83 for 10 minutes	Same frequency as pregnancy test kit	Nurse time based on band 5 ward nurse hourly salary of £53 10 minutes per test
Lipid monitoring	1.0	£6.63 per test	Every four weeks	DAPS08 – Phlebotomy

Abbreviations: NHS, National Health Service; NICE, National Institute of Health and Care Excellence; TA, technology appraisal.

4.2.8.4 Health-state resource use and costs

While the health care resource use SLR conducted by the company identified a number of studies relevant to the indication, the samples of the studies identified were not deemed representative of the UK CHE population and none reported estimates by disease severity. Therefore, healthcare resource use was informed using the company's assumptions, with the company considering that

patients with partial, low or insufficient response would visit their dermatologist more frequently than full response patients given their symptoms are not well managed and that all CHE patients would visit their GP once a year (Table 45). Using these frequencies, annual health state costs were calculated as described in Table 46.

The company noted that a study was identified that did report inpatient and outpatient costs by disease severity, which was used in a scenario analysis. Augustin *et al.* 2011 described a cross-sectional study conducted in 25 outpatient practices and clinics across Germany. The company noted that although eczema management differs in Germany compared to the UK, the studies provided evidence that could be adapted and used in the model.

Table 45. Health state resource use (reproduced from Table 68 in the CS)

Type of resource use	Unit cost	Source	Annual number of visits by health state			
			FR	PR	LR	InR
Dermatologist visit	£90.00	WF01A-Dermatology follow-up attendance – single professional[29]	1	4	4	4
GP visit (10 minutes)	£49.00	Jones 2023[30]	1	1	1	1

Abbreviations: BSC, best supportive care; FR, full response; GP, general practitioner; InR, insufficient response; LR, low response; NHS, National Health Service; PR, partial response.

Table 46. Health state costs (reproduced from Table 69 in the CS)

Health state	Total cost		Source/notes
	Base case	Scenario analysis	
Full response	£197	£197	Scenario analysis: Augustin 2011[31]
Partial response	£641	£385.10	
Low response	£641	£949.41	
Insufficient response	£641	£1,093.03	
Next-line treatment	£550.89	£724.84	Weighted average by efficacy of next-line basket.
BSC (moderate)	£585.52	£772.05	Weighted average based on the effectiveness of BSC.
BSC (severe)	£599.95	£822.95	

Abbreviation: BSC, best supportive care.

4.2.8.5 EAG critique

The EAG considers that methods and costs used to model monitoring, next-line and BSC costs are appropriate but questions the usage data assumed for delgocitinib and the frequency of dermatologist visits for each heath state.

At clarification, the company was requested to present the mean usage data from the DELTA trials with 95% confidence intervals, the company presented the data as requested (Tables 49, 50 and 51 in the CQ response), in addition to presenting Table 47 which provides a summary of the mean values from the DELTA trials and the MMRM values.

Table 47. IGA-CHE category: treatment outcomes across trials (reproduced from Table 54 in the CQ response)

IGA-CHE category	Severe CHE			Moderate CHE	
	Descriptive statistics (DELTA 1, DELTA 2 and DELTA FORCE)	MMRM (all timepoints)	MMRM (up to week 12 only)	Descriptive statistics (DELTA 1 and DELTA 2)	MMRM (up to week 12 only)
0/1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema; IGA, investigator global assessment; MMRM, mixed model for repeated measures.

From the table provided, the company noted that among patients with severe CHE at baseline, usage of delgocitinib at week 12 was greater from the descriptive statistics than those estimated by the MMRM model; with the only exception being for patients in the severe symptom health state where the MMRM model usage was greater. The company noted that for patients with moderate symptoms at baseline, mean consumption between the pooled DELTA trials and the MRMM model was more comparable, with the MRMM model providing higher consumption estimates for all health states except severe symptoms.

Between the usage sources, the company considered that the most appropriate source was dependent on what was considered to be the most relevant drivers of treatment usage. The descriptive statistics are a function of the total usage for achieving a particular response at week 12, while the MMRM estimates more closely reflect consumption for a given CHE severity over time.

The EAG notes that while 12-week usage data by treatment and severity have been provided separately to the 24-week data. Given the company's concerns that the 12-week data only provide a snapshot of usage, the EAG considers that 12-week and 24-week consumption could be combined to provide a more holistic estimate of consumption over time for delgocitinib patients. The EAG

therefore calculated a weighted average using the 12- and 24-week delgocitinib usage across the DELTA trials for severe patients and explored this usage in a scenario. Table 48 presents the usage assumed in the scenario compared to the MMRM values preferred in the company base case and in DELTA FORCE.

Table 48. Modelled delgocitinib usage

IGA-CHE category	MMRM (all timepoints)	12 week (DELTA 1, DELTA 2 and DELTA FORCE)	Weighted 12 and 24 week (DELTA 1, DELTA 2 and DELTA FORCE)	DELTA FORCE overall
0/1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema; g, gram; IGA, investigator global assessment; MMRM, mixed model for repeated measures.

The EAG considers that assuming the 12- and 24-week weighted average usage in severe patients is appropriate when comparing delgocitinib to PUVA as it makes the best use of the available data over a longer duration of time. With respect to comparing delgocitinib to alitretinoin, the EAG considers that the amount of delgocitinib used may be directly related to effectiveness, therefore usage from the DELTA FORCE trial should be assumed. As such, in the EAG base cases, the weighted DELTA 1,2 and DELTA FORCE severe patient 12- and 24-week data have been used to inform delgocitinib usage when compared to PUVA, and DELTA FORCE is used to inform delgocitinib usage compared to alitretinoin.

With respect to health state resource use, the EAG validated the company-assumed GP and dermatologist annual frequencies with its clinical expert; the clinician stated that they wouldn't expect to see full responder patients for follow-up, that partial responders would most likely receive two dermatologist visits and low responders six dermatologist visits. The expert noted that BSC patients would only be seen every two to three months as these patients will need psychological assistance. The EAG conducted a scenario assuming these frequencies, which led to a small change in the ICER. These frequencies are included in the EAG base case.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

Table 49 and Table 50 presents the company's base case deterministic and probabilistic cost-effectiveness results analyses for the severe and moderate chronic hand eczema (CHE) subgroups. A probabilistic sensitivity analysis (PSA) was conducted to assess the joint parameter uncertainty around base case results using a Monte Carlo simulation that derived probabilistic results from 1,000 generated simulations.

Table 49. Company's base case results post clarification – severe CHE subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Pairwise ICER (£/QALY)
Deterministic results							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8,526
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Probabilistic results							
Delgocitinib	[redacted]	-	[redacted]		-		
Alitretinoin	[redacted]	-	[redacted]	[redacted]	-	[redacted]	9,744
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	PUVA dominated

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; LY, life year; PUVA, psoralen–UVA phototherapy; QALY, quality-adjusted life-year

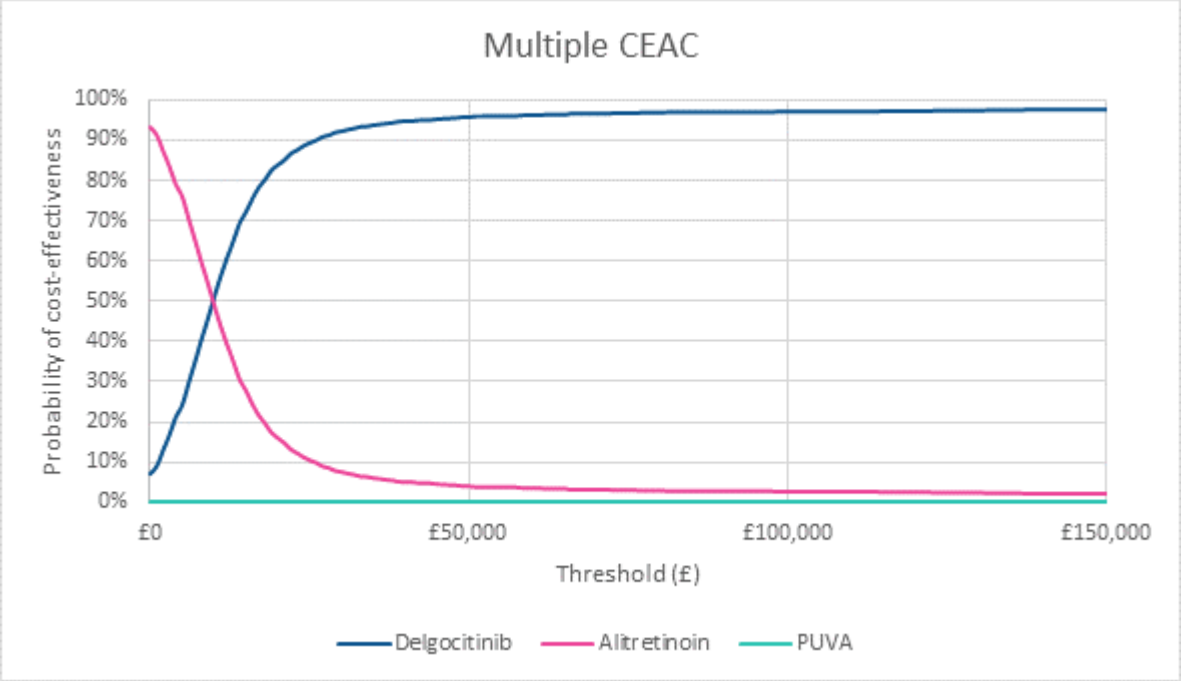
Table 50. Company's base case results post clarification – moderate CHE subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Pairwise ICER (£/QALY)
Deterministic results							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Probabilistic results							
Delgocitinib	[redacted]	-	[redacted]	-	-	-	-
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	PUVA dominated

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; LY, life year; PUVA, psoralen–UVA phototherapy; QALY, quality-adjusted life-year

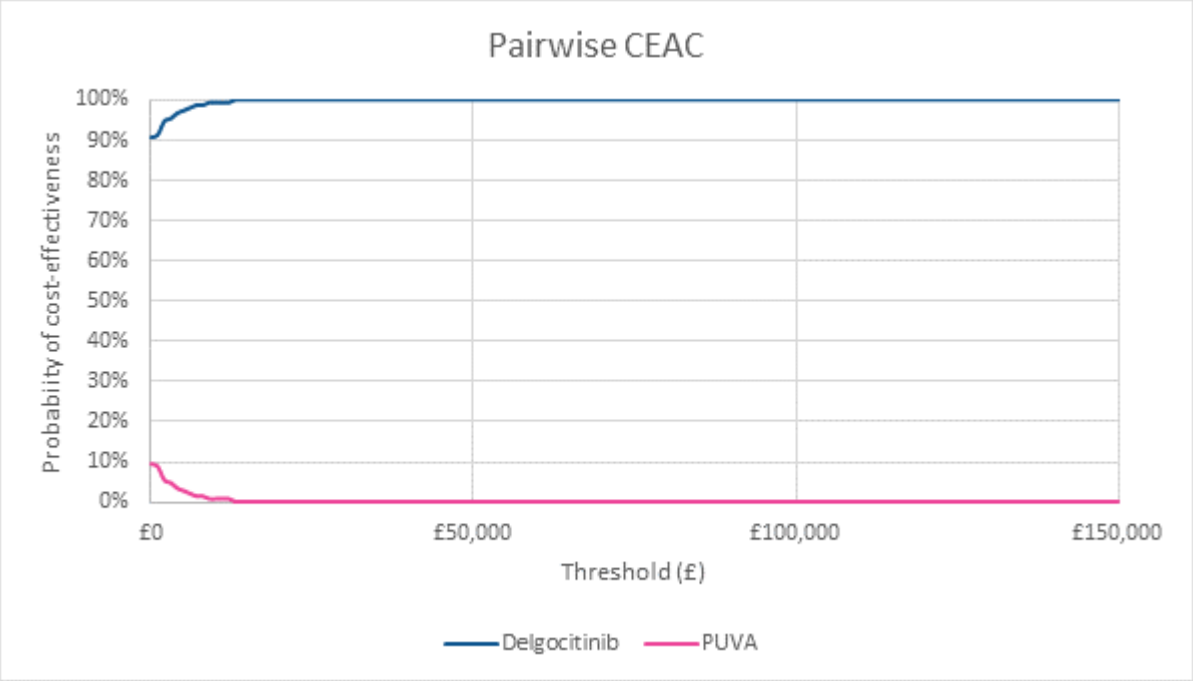
The company's cost-effectiveness acceptability curves are shown in Figure 12 and Figure 13, presenting that in patients with severe symptoms at baseline delgocitinib had the highest likelihood of being cost-effective followed by alitretinoin. At a £20,000 and £30,000 willingness to pay threshold. delgocitinib was found to have a probability of 83.8% and 92.2% of being cost-effective, respectively. For patients with moderate symptoms as baseline, delgocitinib was found to dominate PUVA in 89.9% of the Monte Carlo iterations.

Figure 12. PSA cost-effectiveness acceptability curve of all comparators for severe CHE (reproduced from Figure 12 in the CS)



Abbreviations: CHE, chronic hand eczema; CS, company submission; PUVA, psoralen plus ultraviolet-A

Figure 13. PSA cost-effectiveness acceptability curve for moderate CHE (reproduced from Figure 13 in the CS)



Abbreviations: CHE, chronic hand eczema; CS, company submission; PUVA, psoralen plus ultraviolet-A

5.2 Company's sensitivity analysis

The company conducted one-way sensitivity analyses (OWSA) to assess the sensitivity of the model to individual parameter uncertainty. The company provided a tornado diagram displaying the most influential parameters on the incremental net monetary benefit given a £20,000 willingness to pay threshold.

Figure 14. Tornado plot of delgocitinib vs alitretinoin for severe CHE (reproduced from Figure 14 in the CQ response)

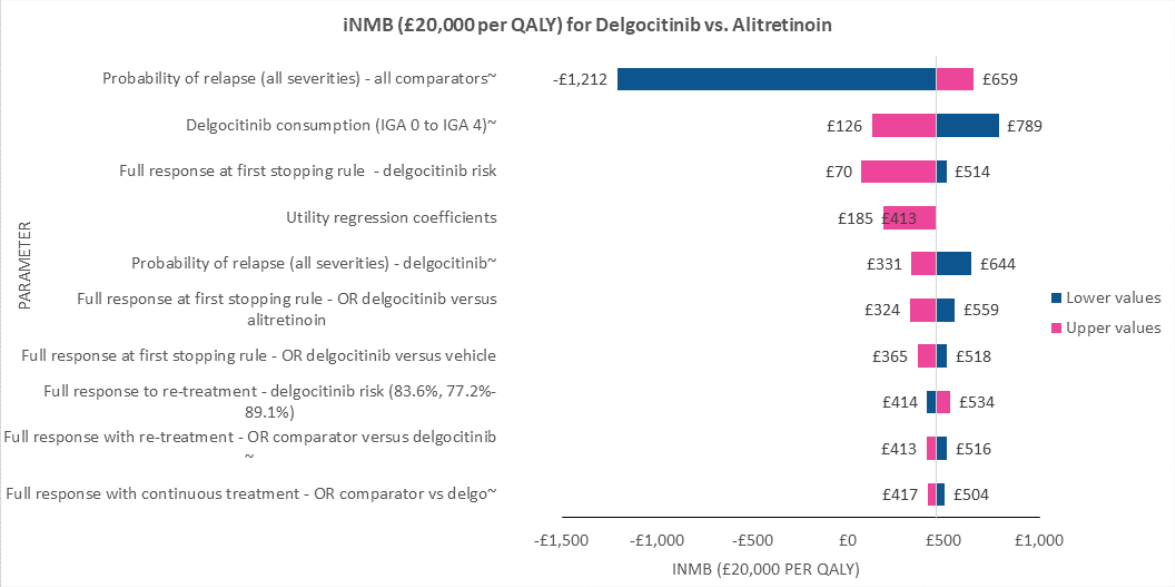
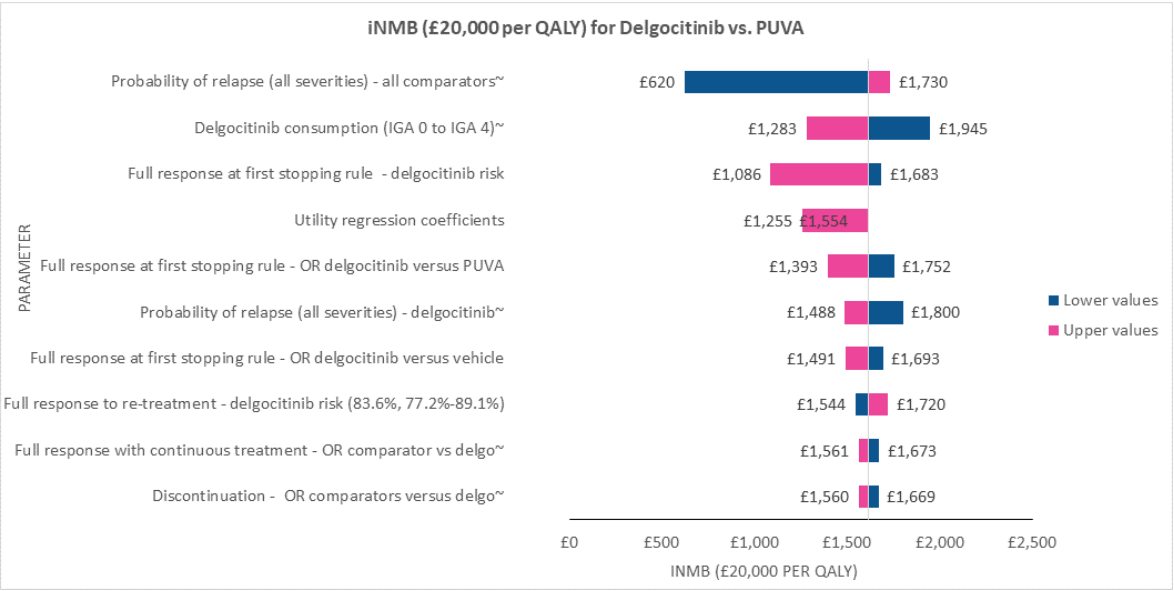


Figure 15. Tornado plot of delgocitinib vs PUVA for severe CHE (reproduced from Figure 15 in the CQ response)



5.3 Company's scenario analysis

The company undertook a range of scenario analyses to explore the impact of alternative assumptions for key model parameters. Results of the scenarios are presented below in Table 69. The results are based on the deterministic version of the model which the EAG considers is reasonable given the similarity in the company's deterministic and probabilistic base case results.

Table 51. Scenario analyses for severe CHE and moderate CHE (reproduced from Table 60 in the CQ response)

Scenario	Severe CHE		Moderate CHE
	Delgocitinib vs alitretinoin ICER	Delgocitinib vs PUVA ICER	Delgocitinib vs PUVA ICER
Base case	£8,526	Dominated	Dominated
Time horizon			
1 year	Dominates	Dominated	Dominated
3 years	£5,324	Dominated	Dominated
5 years	£7,780	Dominated	Dominated
30 years	£8,550	Dominated	Dominated
Stopping rules			
Scenario 1	£15,378	£1,956	£2,395
Scenario 2	£19,965	£7,258	£2,395
Scenario 3	£21,938	£14,314	£12,045
Delgocitinib usage (g/week)			
Overall average ([redacted])	£7,030	Dominated	Dominated
DELTA 2 ([redacted])	£402	Dominated	Dominated
DELTA FORCE ([redacted])	£17,750	Dominated	Dominated
As-needed initial treatment	£8,256	Dominated	Dominated
Health state definition			
HECSI responses (< 50, 50, 75, 90)	£9,377	Dominated	Dominated
NMA results			
Primary endpoint NMA	£6,583	Dominated	Dominated
Cumulative response NMA	£9,766	Dominated	Dominated
Distribution of non-responders at week 12			
Equal for all treatments based on delgocitinib	£4,289	Dominated	NA
ALPHA for alitretinoin and PUVA (severe only) – NRI	£9,714	Dominated	NA
ALPHA for alitretinoin and PUVA (severe only) - OC	£4,529	Dominated	NA
Relapse			
Delgocitinib informed by D3	£10,657	Dominated	Dominated
Risk of relapse with alitretinoin and PUVA assumed to be 50% of risk with delgocitinib	£18,500	Dominated	Dominated
Alternative re-initiation assumptions			

All reinitiate at IGA-CHE ≥ 2	£7,919	Dominated	Dominated
All reinitiate at IGA-CHE ≥ 3	£6,463	Dominated	Dominated
Alitretinoin non-reinitiation: 12%	Dominates	Dominated	Dominated
Response and discontinuation from retreatment			
Differential probabilities of response by treatment	£7,496	Dominated	Dominated
Retreatment discontinuation 50% of initial continued treatment discontinuation	£9,790	Dominated	Dominated
Utilities			
Response-dependent and treatment-independent utilities from DELTA 1, 2 and FORCE	£10,412	Dominated	Dominated
Health state costs			
Health state costs increase with IGA-CHE severity based on data from Augustin 2011	£6,992	Dominated	Dominated
Adverse effects			
No utility decrement	£8,668	Dominated	Dominated
No cost impact	£8,801	Dominated	Dominated
No cost nor utility decrement	£8,948	Dominated	Dominated
Dermatologist visit for AEs	£7,970	Dominated	Dominated
Next-line and BSC assumptions			
Next-line progression and basket composition from ALPHA	£7,951	Dominated	Dominated
Next-line efficacy: 75% in LDA	£8,666	Dominated	Dominated
Percent move to next-line treatment: 75%	£8,264	Dominated	Dominated
LDA defined as full response	£8,626	Dominated	Dominated
Patients on BSC revert to baseline CHE severity	£5,302	Dominated	Dominated

Abbreviations: BSC, best supportive care; CHE, chronic hand eczema, g, gram; HECSI; hand eczema severity index; ICER, incremental cost-effectiveness ratio; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; NMA, network meta-analysis; NRI, non-responder imputation; OC, observed case; PUVA, psoralen–UV A phototherapy

5.4 Model validation and face validity check

The face validity of the model concept was checked during an advisory board made up of the company's clinical and health economic experts. The company undertook several quality control measures to validate the model findings. Developers of the model were tasked with internal quality control. A second modeler, not involved in the programming, reviewed the model code and

formulae, and conducted extreme value analysis to verify the model results. The lead modeler scrutinised the programming and references.

6 Additional economic analysis undertaken by the EAG

6.1 EAG scenario analysis

Table 52 presents the results of the EAG's exploratory scenario analyses. Confidential PAS discounts or confidential medicine unit (CMU) prices are available for subsequent lines of alitretinoin, ciclosporin and dupilumab and are included in the scenario and results provided in the confidential appendix.

Table 52. Results of the EAG's scenario analyses

	Results per patient	Delgocitinib (1)	Alitretinoin (2)	PUVA (3)	Incremental 1-2	Incremental 1-3
0	Company base case					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	£8,526	PUVA dominated
1	Informing next line treatment basket composition using ALPHA and removing alitretinoin from the basket of next-line treatments and assuming 25.6% of patients on next-line treatments are in the low-activity disease state					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	7,139	PUVA dominated
2	Using the 12 and 24-week weighted delgocitinib treatment usage to inform the comparison to PUVA					
	Total costs (£)	[redacted]	-	[redacted]	-	[redacted]
	QALYs	[redacted]	-	[redacted]	-	[redacted]
	ICER (£/QALY)	-	-	-	-	PUVA dominated
3	Assuming the HCRU frequencies provided by the EAG's clinical experts					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	-	7,441	PUVA dominated

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.2 EAG preferred assumptions

The EAG presents in Table 53, the EAG's preferred modelling assumptions for evaluating the cost-effectiveness of delgocitinib CHE compared to alitretinoin and PUVA for the treatment of chronic hand eczema (CHE). As the EAG does not consider the NMA treatment effects are appropriate, and instead relies on alternative treatment effectiveness sources, the EAG base case cost-effectiveness results have been provided by comparator and not within a fully incremental analysis. The EAG base case comparing delgocitinib to alitretinoin is presented in Table 56, with the EAG base case comparing delgocitinib to PUVA presented in Table 57.

As described in Section 4.2.3, the EAG has additionally provided scenarios around the EAG base cases (Table 58). Delgocitinib has been compared to alitretinoin, using the hyperkeratotic and non-hyperkeratotic subgroup treatment effects from DELTA FORCE, with outcomes explored in patients with moderate symptoms at baseline line using the relative treatment effects measured in DELTA 1 and 2. A scenario has also been conducted assessing cost-effectiveness of delgocitinib against PUVA in patients with moderate symptoms at baseline using the delgocitinib moderate treatment effect from DELTA 1 and 2 and the MAIC results between DELTA 1 and 2 and ALPHA. The EAG highlights that the scenarios exploring treatment effects in the moderate symptom population rely on the strong and uncertain assumption that the delgocitinib relative treatment effect between moderate and severe patients measured in DELTA 1 and 2 similarly applies to alitretinoin and PUVA.

Table 53. EAG preferred modelling assumptions

Delgocitinib vs alitretinoin EAG preferred assumptions	Delgocitinib vs PUVA EAG preferred assumptions
Population	
Severe	Severe
Delgocitinib dosing	
DELTA FORCE overall	Weighted average of 12- and 24-week DELTA 1,2 and FORCE usage data
Next line treatment discontinuation pathway	
ALPHA	ALPHA
Next line treatment basket and reduce next-line treatment efficacy	
Remove alitretinoin and decreasing the proportion of patients assumed to be in the low disease health state to 25.6%	Remove alitretinoin and decreasing the proportion of patients assumed to be in the low disease health state to 25.6%
Probability of full response at 12 weeks	
DELTA FORCE	MAIC matching by severe symptoms and HK status
Per-cycle probability of full response for continued treatment	

DELTA FORCE	DELTA 3
Per-cycle probability of full response for retreatment	
DELTA FORCE	DELTA 3
Per-cycle probability of relapse	
DELTA FORCE	DELTA 3
Per-cycle probability of permanent discontinuation from continued initial treatment	
DELTA FORCE	DELTA FORCE
Proportion of patients opting not to re-initiate initial treatment following relapse	
DELTA FORCE	DELTA 3
AEs	
Not included	Not included
HSUVs	
Derived from severe population across DELTA trials	Derived from severe population across DELTA trials
HCRU	
EAG clinical expert opinion	EAG clinical expert opinion

Abbreviations: AE, adverse events; HCRU, health care resource use; HSUV, health state utility value; MAIC, matching-adjusted indirect comparison.

Table 54. EAG's preferred model assumptions, delgocitinib vs alitretinoin

Preferred assumption	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	-	8,526
Delgocitinib dosing (DELTA FORCE)	22,419	22,419
Next line treatment discontinuation pathway (ALPHA)	7,951	21,985
Next line treatment basket and reduce next-line treatment efficacy (No alitretinoin, efficacy assumed at 25.6%) *	7,986	20,999
Probability of full response at 12 weeks (DELTA FORCE)	9,627	21,372
Per-cycle probability of full response for continued treatment (DELTA FORCE)	9,719	21,831
Per-cycle probability of full response for retreatment (DELTA FORCE)	8,823	16,549
Proportion of patients opting not to re-initiate initial treatment following relapse (DELTA FORCE)	2,327	15,240
Not including AEs	8,948	15,498
HSUVs derived from pooled DELTA trials	11,551	20,260

HCRU according to EAG's clinical experts	7,441	18,541

*Includes previous assumption

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 55. EAG's preferred model assumptions, delgocitinib vs PUVA

Preferred assumption	Incremental ICER	Cumulative ICER (£/QALY)
Company base case	-	PUVA dominated
Delgocitinib dosing (12- and 24-week weighted dosing from DELTA 1,2 and FORCE)	PUVA dominated	PUVA dominated
Next line treatment discontinuation pathway (ALPHA)	PUVA dominated	PUVA dominated
Next line treatment basket and reduce next-line treatment efficacy (No alitretinoin, efficacy assumed at 25.6%) *	PUVA dominated	PUVA dominated
Probability of full response at 12 weeks (MAIC matching by severe symptoms and HK status)	PUVA dominated	PUVA dominated
Per-cycle probability of relapse (DELTA 3)	PUVA dominated	PUVA dominated
Not including AEs	PUVA dominated	PUVA dominated
HSUVs using pooled DELTA trials	PUVA dominated	PUVA dominated
HCRU according to EAG clinical expert	PUVA dominated	PUVA dominated

*Includes previous assumption

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 56. EAG base case, delgocitinib vs alitretinoin, severe symptoms at baseline

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	18,541
Probabilistic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	19,017

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 57. EAG base case, delgocitinib vs PUVA, severe symptoms at baseline

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Probabilistic outcomes					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 58. EAG base case scenario analyses

Intervention	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Delgocitinib vs alitretinoin in patients with moderate symptoms at baseline					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	20,425
Delgocitinib vs PUVA in patients with moderate symptoms at baseline					
Delgocitinib	[redacted]	[redacted]	-	-	-
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	PUVA dominated
Delgocitinib vs alitretinoin in patients with hyperkeratosis					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	Delgocitinib dominated
Delgocitinib vs alitretinoin in patients with non-hyperkeratosis					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	8,165

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

6.2.1 EAG sensitivity analysis

In the EAG's sensitivity analysis using the EAG's preferred assumptions, delgocitinib compared to alitretinoin was found to have a 55.5% probability of being cost-effective given a willingness to pay threshold of £20,000 per QALY, and an 87.8% probability of being cost-effective at a £30,000 per QALY threshold (Figure 16 and Figure 17).

Comparatively, delgocitinib compared to PUVA was found to have a 98.5% and 98.7% probability of cost effectiveness given a willingness to pay threshold of £20,000 and £30,000, respectively (Figure 18 and Figure 19).

Figure 16. Delgocitinib vs alitretinoin cost-effectiveness acceptability curve.

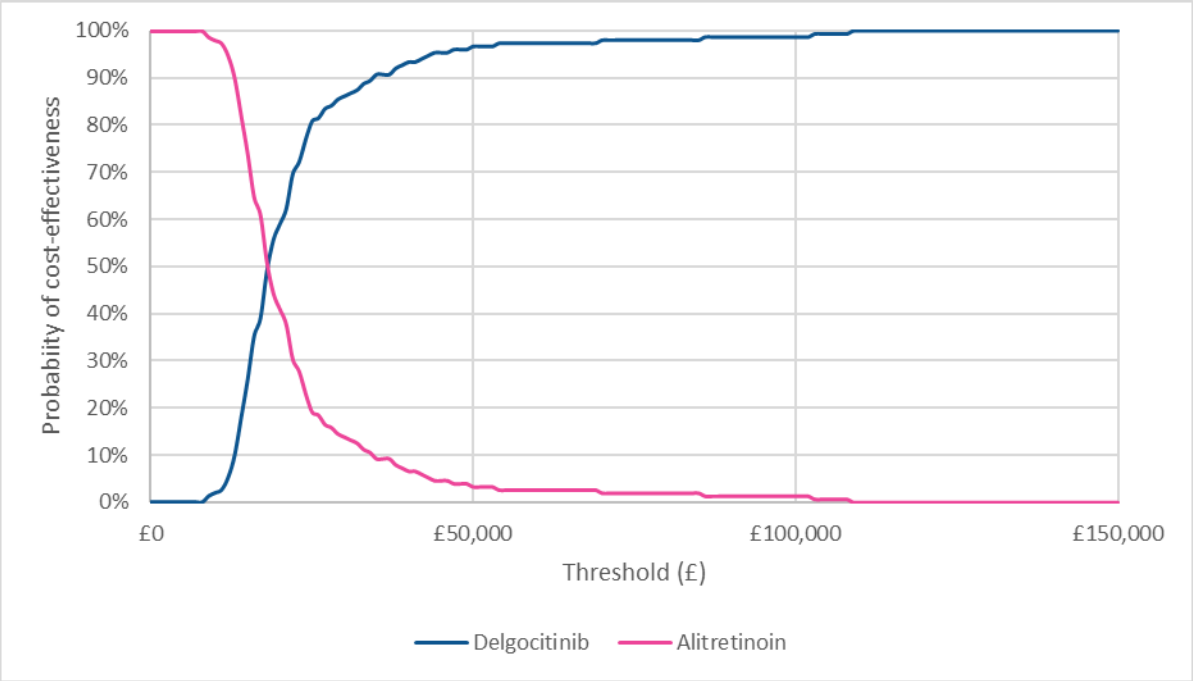


Figure 17. Delgocitinib vs alitretinoin, cost-effectiveness scatter plot, £20,000/QALY WTP threshold

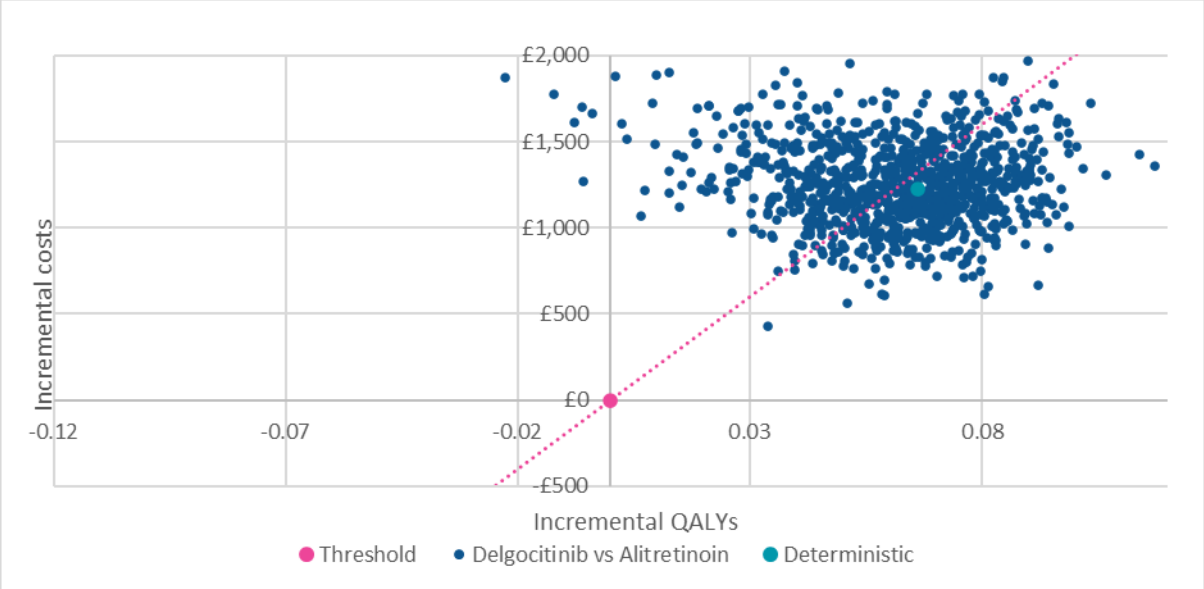


Figure 18. Delgocitinib vs PUVA cost-effectiveness acceptability curve

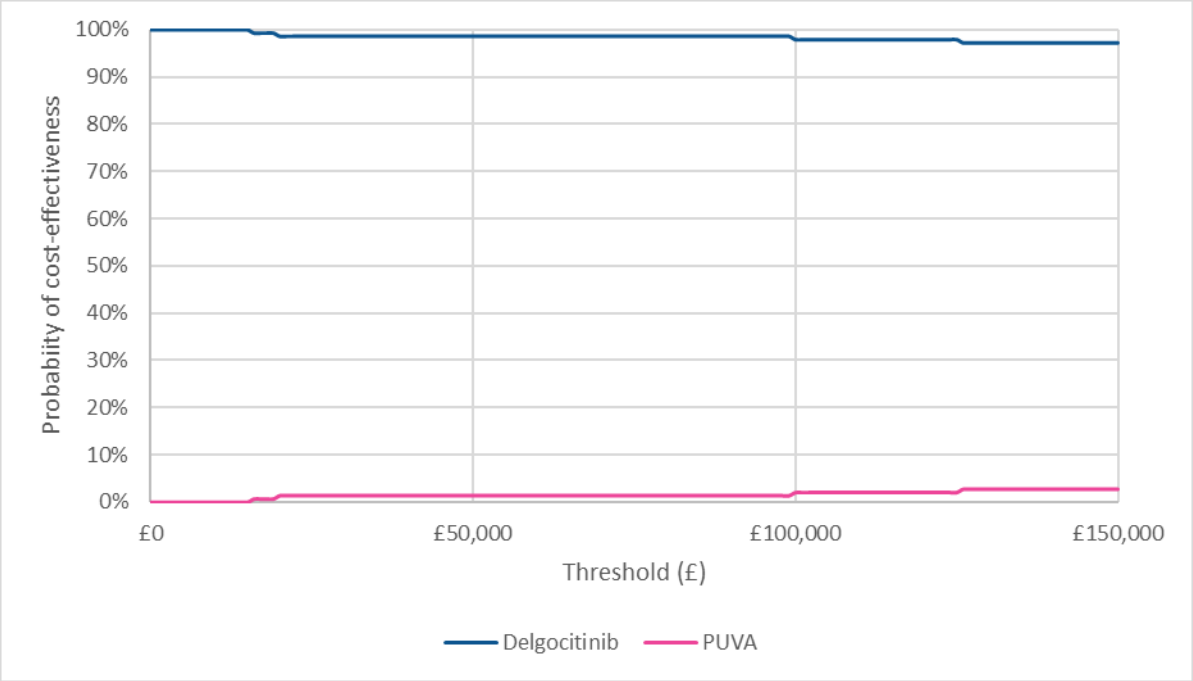
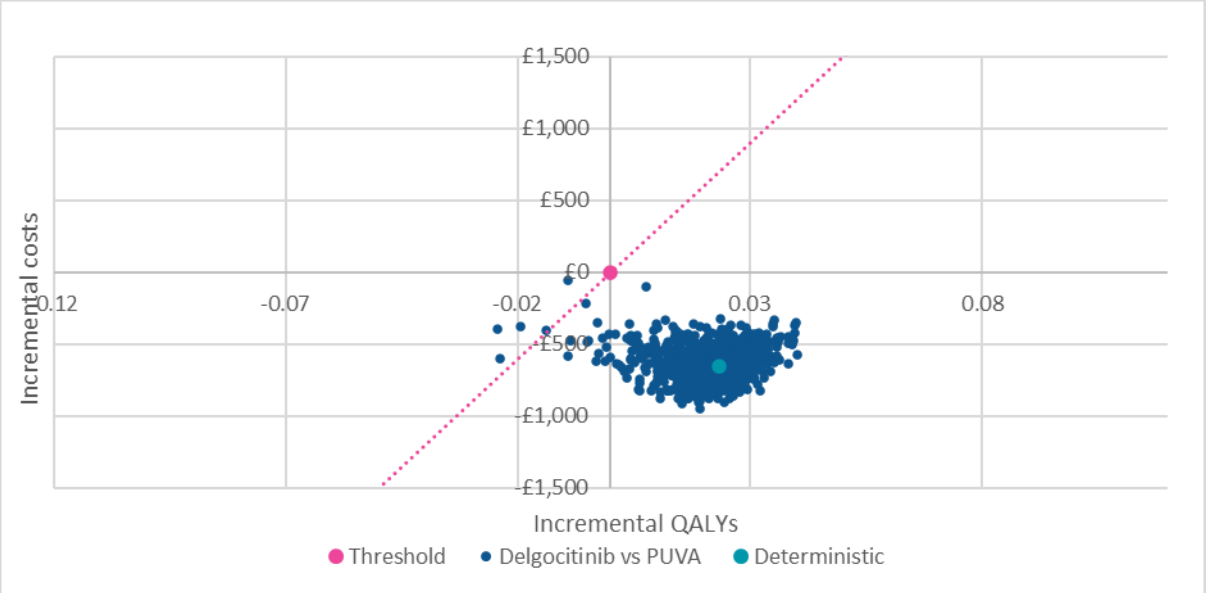


Figure 19. Delgocitinib vs PUVA, cost-effectiveness scatter plot, £20,000/QALY WTP threshold



6.3 Conclusions of the cost effectiveness sections

The EAG considers that the model developed by the company accounts for the key stages of CHE treatment and adequately captures the patient journey.

While the EAG noted that it may be inappropriate that both 12-week and 24-week responders transition to the same health state on achieving a full response to treatment, with the EAG's clinical experts suggesting that there may be differences in prognostic factors between these patients, the EAG considers that the company has shown that the rates of relapse are sufficiently similar between the 12- and 24-week responders, and that exploring the differences in discontinuation led to relatively minor changes in the ICER. Therefore, the EAG considers that adapting the model to account for the difference in treatment effects between 12- and 24-week responders would be unlikely to overly impact the ICERs given not accounting for the differences impacts delgocitinib and its comparators alike.

The EAG's clinical experts also noted that contrary to the company's assumed comparators, alitretinoin is used to treat patients with moderate symptoms, adding critically that the decisions between treatments is less driven by the severity of symptoms but instead symptom morphology. In clinical practice, alitretinoin is used to treat hyperkeratotic patients and PUVA non-hyperkeratotic patients, with delgocitinib also expected to be used to treat non-hyperkeratotic patients. The EAG considers that these opinions were confirmed by the company's subgroup analysis of DELTA FORCE by hyperkeratotic status, which resulted in delgocitinib being potentially cost-effective in non-hyperkeratotic patients compared to alitretinoin — and having no treatment benefit in hyperkeratotic patients, leading to delgocitinib being dominated compared to alitretinoin. While the EAG considers hyperkeratotic status to have a strong treatment effect modifier, in the EAG base cases treatment effects are inclusive of both non- and hyperkeratotic patients, given that not all patients will be eligible or willing to be treated with alitretinoin, given required concurrent pregnancy prevention programmes. Therefore, overall, the EAG considers that delgocitinib is likely to be cost-effective compared to alitretinoin in non-hyperkeratotic CHE patients and the preferred option in hyperkeratotic patients who are unwilling to receive alitretinoin (as delgocitinib dominates PUVA). However, in hyperkeratotic patients suitable for alitretinoin, delgocitinib is unlikely to be considered cost-effective.

The EAG considers that one of the prominent flaws of the model is the lack of mature data to inform long term treatment effects and patient behaviours. While in clinical practice a patient's response to treatment may change over time, in addition to their rates of relapse and rates of discontinuation; due to the limited lengths of the DELTA studies these potential changes are unable to be modelled. The EAG notes that the company has used the most appropriate available data where possible, but when considering that discontinuation rates from patients yet to respond to treatment are assumed

to apply to patients that have previously achieved a full response from treatment, there are implications to the generalisability of the time on treatments estimated by the model. Given the difference between the time on treatment estimated in the model (2% of alitretinoin patients still on treatment by two years) and the EAG's clinical experts' opinion (approximately 25% of alitretinoin patients by two year), the EAG is concerned with the implications of time on treatment in the model not being generalisable to clinical practice and the impact to the decision of cost-effectiveness. The EAG raises this as a key issue.

Another key issue is the company's use of worst observation carried forward to impute missing data in the estimation of treatment effects. Given that alitretinoin and PUVA were associated with more missing data in the relevant trials, the EAG considers that the comparator treatment effects may be underestimated in the model, leading to an underestimation of the ICER. As the EAG considers that the ICER would be sensitive to these underestimations, the EAG raises this as a key issue in the model.

In terms of health-related quality of life, the EAG strongly disagrees with the company's approach which assumes a health state, symptom severity at baseline and a treatment-specific utility effect. The EAG notes that in the company approach, patients achieving a full response on primary treatments or BSC experience difference health related qualities of life although their symptoms have resolved. The EAG has, therefore, preferred to assume the mean utilities from the DELTA trials, applying these utilities for all treatments in the same health states.

The EAG notes that the ICER is most sensitive to the usage of delgocitinib assumed in the model. In the company base case, a mixed model for repeating measures was used to estimate delgocitinib usage, however, the EAG notes that compared to usage from the trial, the company's model led to an overall underestimation. The EAG therefore preferred to assume the delgocitinib usage from the trial, with DELTA FORCE informing usage in the comparison to alitretinoin and DELTA 1, 2 and FORCE informing the comparison to PUVA.

Overall, aside for the potential inappropriate modelling of time on treatment and underestimation of the comparator treatment effects, the EAG considers that with the EAG preferred modelling assumptions provide robust cost-effectiveness outcomes that are suitable to inform decision-making.

7 References

1. MHRA. Summary of Product Characteristics: Anzupgo 20 mg/g cream. 2024. Available from: https://mhraproducts4853.blob.core.windows.net/docs/69f6d1d0fd9df92404c45454660c57b5017e1d34. Date accessed: 07 March 2025.
2. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J, et al. Guidelines for diagnosis, prevention and treatment of hand eczema--short version. *J Dtsch Dermatol Ges* 2015; **13**: 77–85.
3. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM, et al. Guidelines for diagnosis, prevention, and treatment of hand eczema. *Contact Dermatitis* 2022; **86**: 357–78.
4. Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population - A systematic review and meta-analysis. *Contact Dermatitis* 2021; **84**: 361–74.
5. Grant L, Seiding Larsen L, Burrows K, Belsito DV, Weisshaar E, Diepgen T, et al. Development of a Conceptual Model of Chronic Hand Eczema (CHE) Based on Qualitative Interviews with Patients and Expert Dermatologists. *Adv Ther* 2020; **37**: 692–706.
6. Giménez-Arnau AM, Bewley A, Molin S, Apfelbacher C, Brignoli L, Corriveau J, et al., editors. Patient characteristics and comorbidities in moderate to severe CHE: Results from the RWEAL study. European Academy of Dermatology and Venereology; 2024; Amsterdam.
7. National Institute for H, Clinical E. SINGLE TECHNOLOGY APPRAISAL (STA): TA177 SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE. 2008. Available from: https://www.nice.org.uk/guidance/ta177/resources/eczema-chronic-alitretinoin-basilea-medical-submission2. Date accessed: 07 March 2025.
8. NICE. Delgocitinib for treating moderate to severe chronic hand eczema: Final scope, 2025. Date accessed.
9. Pharma LEO. DELTA 1 clinical study report. 2023.
10. Pharma LEO. DELTA 2 clinical study report. 2023.
11. Pharma LEO. DELTA 3 clinical study report. 2023.
12. Pharma LEO. DELTA FORCE clinical study report. 2023.
13. Bissonnette R, Warren RB, Pinter A, Agner T, Gooderham M, Schuttelaar MLA, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema (DELTA 1 and DELTA 2): results from multicentre, randomised, controlled, double-blind, phase 3 trials. *Lancet* 2024; **404**: 461–73.
14. Worm M, Thyssen JP, Schliemann S, Bauer A, Shi VY, Ehst B, et al. The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial. *Br J Dermatol* 2022; **187**: 42–51.
15. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *Pharmacoeconomics* 2023; **41**: 199-207.
16. Weisshaar E, Yüksel YT, Agner T, Larsen LS, Grant L, Arbuckle R, et al. Development and Validation of a Patient-Reported Outcome Measure of the Impact of Chronic Hand Eczema on Health-Related Quality of Life: the Hand Eczema Impact Scale (HEIS). *Dermatology and therapy* 2024: 1-24.
17. Pharma LEO. Data on file, CHECK study results. 2024.
18. Pharma LEO. Data on file, RWEAL study results. 2024.
19. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**.
20. Lakens D. Equivalence Tests: A Practical Primer for t Tests, Correlations, and Meta-Analyses. *Soc Psychol Personal Sci* 2017; **8**: 355-62.

21. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
22. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Kantor E, Bao Y, et al. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010; **28**: 935-45.
23. Giménez-Arnau AM, Pinter A, Sondermann W, Reguiai Z, Woolf R, Lynde C, et al., editors. DELTA FORCE trial: A 24-week head-to-head Phase 3 trial comparing the efficacy and safety of topical delgocitinib cream with oral alitretinoin capsules in adults with severe Chronic Hand Eczema. European Academy of Dermatology and Venerology; 2024; Amsterdam.
24. Brazier J, Longworth L. NICE DSU Technical Support Document 8: an introduction to the measurement and valuation of health for NICE submissions. 2011.
25. Wittmann M, Smith IL, Brown ST, Berekmeri A, Vargas-Palacios A, Sunderland L, et al. Alitretinoin versus phototherapy as the first-line treatment in adults with severe chronic hand eczema: the ALPHA RCT. *Health Technol Assess* 2024; **28**: 1–123.
26. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [PMG36], 2022. Available from: https://www.nice.org.uk/process/pmg36. Date accessed: November 2024.
27. National Institue for Health and Care Excellence. British National Formulary. 2025. Available from: https://bnf.nice.org.uk/. Date accessed: March 2025.
28. National Institute for H, Care E. TA177: Alitretinoin for the treatment of severe chronic hand eczema. 2009. Available from: https://www.nice.org.uk/guidance/ta177/resources/alitretinoin-for-the-treatment-of-severe-chronic-hand-eczema-pdf-82598440714693. Date accessed: 16 February 2024.
29. England NHS. Non-mandatory guide prices. 2023. Available from: https://www.england.nhs.uk/wp-content/uploads/2020/11/22-23NT_Non-mandatory-guide-prices.xlsx. Date accessed: 31 October 2024.
30. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022 Manual. Technical report. 2023. Available from: https://kar.kent.ac.uk/100519/. Date accessed: 31 October 2024.
31. Augustin M, Kuessner D, Purwins S, Hieke K, Posthumus J, Diepgen TL. Cost-of-illness of patients with chronic hand eczema in routine care: Results from a multicentre study in Germany. *Br J Dermatol* 2011; **165(4)**: 845–51.

8 Appendices

8.1 Price sources for treatments included in the confidential appendix

Table 59. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Alitretinoin	MPSC agreement
Ciclosportin	MPSC agreement
Dupilumab	Simple PAS

Abbreviations: MPSC, Medicines procurement and supply chain; PAS, patient access scheme.

Single Technology Appraisal

Delgocitinib for treating moderate to severe chronic hand eczema [ID6408]

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 **5pm on 25 March 2025** 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 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 List price of delgocitinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 32, the text reads: *"The base cases reported reflect the list price of treatments, not delgocitinib which reflects the PAS price, , with the discounts for relevant treatments included in the confidential appendix."*	The text should be re-written: *The base cases reported reflect the list price of treatments, with the discounts for relevant treatments included in the confidential appendix.*	First, the price submitted in the CS is the NHS list price for delgocitinib. Second, the Company believes there are typos in this sentence.	The EAG thanks the company for identifying these factual inaccuracies and has updated the text accordingly.
On page 94, the text reads: *"Costs are inclusive of a delgocitinib patient access scheme (PAS) discount. "*	This sentence should be removed.	Costs are not inclusive of a PAS discount. The price submitted in the CS is the NHS list price.	
On page 140, the text reads: *"These results reflect the company's proposed patient access scheme (PAS) discount on the list price of delgocitinib."*	This sentence should be removed.	Costs are not inclusive of a PAS discount. The price submitted in the CS is the NHS list price.	

Issue 2 Description of marketing authorisation for comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 38, the text reads: *"However, the EAG's clinical experts asserted that an estimated 50% of patients with moderate CHE would be prescribed alitretinoin as second-line treatment on an off-label basis. In contrast to alitretinoin, PUVA holds marketing authorisation for use in patients with either moderate or severe CHE"*	The text should be revised: *In contrast to alitretinoin, PUVA medication **does not** hold marketing authorisation in the UK, though European guidance suggests the technology's use in patients with either moderate or severe CHE.*	PUVA medication does not hold marketing authorisation for the treatment of CHE in the UK and its use is off label among both moderate and severe patients.	The EAG thanks the company for identifying this inaccuracy and has updated the text accordingly.

Issue 3 Description of endpoints in DELTA 1, DELTA 2 and DELTA FORCE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 57, in Table 14, under the DELTA 3 study, the text reads: *" HECSI-50 (post-hoc analysis; not predefined in DELTA FORCE trial)."*	The reference to *DELTA FORCE* should be changed to *DELTA 3*.	The section describes outcomes from the DELTA 3 trial not the DELTA FORCE trial.	The EAG thanks the company for identifying this inaccuracy and has updated the text accordingly.

On page 57, in Table 14, under the DELTA 3 study, the text reads: "*HECSI-75 (post-hoc analysis; not predefined in DELTA FORCE trial)"*	The words "*(post-hoc analysis; not predefined in DELTA FORCE trial)"* should be removed.	HECSI 75 was a secondary endpoint in the DELTA 3 study.	
On page 57, in Table 14, under the DELTA 3 study, the text reads: "*Time to loss of response (post-hoc analysis; not predefined in DELTA FORCE trial).*"	The words "*(post-hoc analysis; not predefined in DELTA FORCE trial)"* should be removed.	The analysis of loss of response in DELTA 3 was predefined as an exploratory endpoint in the trial protocol.	
On page 57, the text reads: "Additionally, the EAG noted that several outcomes were not pre-specified and as such only considered post-hoc. "	The word *several* should be amended.	After correcting the above statements, only HECSI 50 remains as an outcome measured through post-hoc analysis; therefore, "several" overstates the magnitude of the issue.	
On page 62, the text reads: *"(post-hoc analysis; not predefined in DELTA FORCE trial)"*	The words "*(post-hoc analysis; not predefined in DELTA FORCE trial)"* should be removed.	HECSI 75 at week 12 and week 24 was predefined in the DELTA FORCE trial protocol as an exploratory endpoint.	
On page 63, the text reads: "*Across the DELTA 1, DELTA 2, and DELTA FORCE trials, the primary outcome was the Investigator Global Assessment of Chronic Hand*	The text should be revised to state that IGA-CHE TS was the primary outcome in DELTA 1 and DELTA 2 and a secondary outcome in DELTA FORCE.	IGA-CHE TS was a primary endpoint in the DELTA 1 and DELTA 2 trials, but a key secondary endpoint in the DELTA FORCE trial.	

Eczema treatment success (IGA-CHE TS).”			
On page 74, the text reads: *"For the DELTA FORCE trial, HECSI-75 was assessed post-hoc. "*	We suggest revising the text to For the DELTA FORCE trial, HECSI-75 was assessed as a pre-defined exploratory endpoint.	HECSI 75 was predefined in the DELTA FORCE trial protocol as an exploratory endpoint.	

Issue 4 Terminology around aetiologic and morphologic subtypes

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 37, the text reads: *"the EAG’s clinical experts indicated that CHE aetiology is likely to be a treatment effect modifier. Firstly, the EAG’s clinical experts indicated that alitretinoin is more likely to be effective in patients with hyperkeratotic CHE compared to either vesicular or atopic hand eczema. In contrast, PUVA is thought to be effective in patients with vesicular or hyperkeratotic subtypes of CHE."*	The text should be revised *: the EAG’s clinical experts indicated that CHE* ***morphology*** *is likely to be a treatment effect modifier. Firstly, the EAG’s clinical experts indicated that alitretinoin is more likely to be effective in patients with hyperkeratotic CHE compared to either vesicular or atopic hand eczema. In contrast, PUVA is thought to be effective in patients with vesicular or atopic hand eczema of CHE.*	The CHE subtypes described are clinical types, not aetiological types. If aetiology is the effect modifier, it should be split between atopic, irritant contact and allergic contact dermatitis, noting that the Company does not have data in protein contact dermatitis. Hyperkeratotic and vesicular hand eczema are not restricted to a single aetiology, e.g. hyperkeratotic phases can occur in atopic hand eczema. We also suspect that the reference to the hyperkeratotic subtype in the final sentence is	The EAG thanks the company for identifying this inaccuracy and has updated the text accordingly.

		a typo and should refer to atopic hand eczema.	

Issue 5 Quality assessment of data extraction methods in Company SLRs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 47, the EAG state that they have “some concerns” regarding data extraction. They state: "Data extraction was performed by a single reviewer, while a quality assessment was performed by a second independent reviewer. Any discrepancies were resolved by consensus across both reviewers. No information is provided in the CS regarding the quality assessment of the extracted data. For instance, it is unclear whether the quality assessment comprised a review of the entire dataset or a check of 10% of the extracted data. In conjunction with the data extraction being performed by a single	We suggest that this section is revised following the provision of further information regarding the quality assessment process undertaken across the entire dataset by a second reviewer.	We can confirm that the quality assessment of the extracted data comprised a review of the entire extracted dataset by a second reviewer. We appreciate that this was somewhat ambiguous from the write up in Appendix B 1.1.4 and we would have welcomed the opportunity to provide further information during the clarification stage.	The EAG thanks the company for providing additional information regarding the assessment of the extracted data. Following this additional information, the EAG has updated Table 13 (page 47) accordingly.

reviewer, the EAG has some concerns that data extraction may potentially comprise some errors."			

Issue 6 Use of worst observation carried forward for estimation of treatment effects

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 20, Table 5, the text reads: "*Accordingly, the EAG suggests that the multiple imputation should be used, over WOCF, to impute missing data as it is likely to be associated with a lower risk of bias.*" "*The EAG suggests that it would be preferable, due to the high risk of bias resulting from the use of the WOCF approach, to impute missing data using multiple imputation. However, the EAG notes that due to the high dropout rate in the latter stages of some trials, there may still be limitations with using a multiple imputation approach.*"	We request that the EAG provide additional context to the discussion and critique of the WOCF versus multiple imputation methods for accounting for missing data in the DELTA trials, by referring to the additional data submitted by the company during clarification and the potential risk and direction of bias related to the use of both methods.	The EAG suggests the use of multiple imputation as a way to address the missing data due to high drop out rates in the comparator arms of the DELTA trials. Although they briefly mention in the Executive Summary that there may still be some limitations with using this approach, they do not discuss this further in the rest of the report. The EAG also does not discuss, in any detail, the evidence presented by the company during clarification, which breaks down the timing and reason for discontinuations across the	The EAG notes that the company's request does not relate to a factual inaccuracy. However, the EAG notes that reasons for discontinuation within the DELTA trials were previously detailed in Table 14 (page 54) and Table 15 (page 61). Additionally, the EAG has adjusted the wording in Table 5 (page 20) to clarify that multiple imputation with a missing not at random assumption may be used, while also referencing the results of the sensitivity analyses

		DELTA trials and would provide relevant context to the choice of imputation method. Specifically, the EAG makes no mention of how multiple imputation may introduce bias given that most discontinuations were driven by a lack of effect or adverse events resulting in the potential underestimation of delgocitinib's relative effects.	provided by the company in response to a clarification question.

Issue 7 Assumption of equivalence in the relative treatment effects between moderate and severe patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 18, Table 3 describes the EAG's concerns regarding the assumption of equivalence in the relative treatment effects between moderate and severe patients. The description of the issue and the evidence to	We request that the EAG provide more context to the argument that equivalence testing of subgroup data from the vehicle cream-controlled DELTA 1 and DELTA 2 studies will reduce the uncertainty related to assumptions of equivalence between the active comparators for CHE.	The company agrees that the assumption of equivalence in treatment effects across moderate and severe CHE is strong but disagrees that equivalence testing using subgroup data from DELTA 1 and DELTA 2 offers a solution. Our assertion is that	Not a factual inaccuracy. No change required.

contextualise it has not been presented it its entirety in the Executive Summary or in the corresponding sections of the report.	Alternatively, we request that the EAG present, or at least refer to, the supporting evidence shared as part of the company's response to clarification, namely the availability of data to show a similar difference between moderate and severe treatment effects for a placebo comparison of alitretinoin, albeit noting the limitations of borrowing from such evidence. This evidence lends support to the assertion that the effect modification is observed for comparisons with vehicle and placebo but not as applicable to comparisons between active treatments.	any effect modification based on disease severity that has been observed is driven by differences in response to vehicle. This was supported by evidence presented in our response to clarification where we presented evidence showing a similar trend in a placebo-controlled phase 2 dose-finding study of alitretinoin (Ruzicka et al. 2004). If the trend is similar for any intervention studied in moderate and severe patients, then the assumption of equivalent treatment effects between directly compared active comparators is not unreasonable.	

Issue 8 Discussion around choice of fixed versus random effects NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 84, the text reads: "[redacted] [redacted]	The noteworthiness of the preferred model results should be revisited in light of a fair comparison of the directly observed results, the FE NMA results and the RE NMA results. Any corresponding changes to the text included in Table 2 should also be considered.	The company accepts that the EAG disagrees with the choice of model given the potential for clinical heterogeneity and agrees that the choice of FE or RE NMAs has implications for the interpretation of the comparisons; however, the commentary in this paragraph is misleading. First, there is little that is noteworthy about the statistical significance of the FE model results for the comparison between delgocitinib and alitretinoin and between delgocitinib and vehicle cream, given that these are consistent with the findings from the included RCTs. Each of the vehicle cream-controlled studies showed a statistically significant result for delgocitinib as did all the pairwise meta-analyses presented in the clarification responses. Similarly, the results	Not a factual inaccuracy. No change required.

[redacted]		generated by the FE model for delgocitinib versus alitretinoin are nearly identical to the directly observed results from DELTA FORCE. The odds ratio of delgocitinib versus alitretinoin from the trial was 1.88 (95% CI: 1.22 to 2.89) and from the FE NMA was [redacted]. In terms of differences, the odds ratio from the RE NMA is more noteworthy in its uncertainty relative to the directly observed data: [redacted]. Secondly, the comparison between delgocitinib and PUVA was limited to IGA-CHE TS as there was no data from ALPHA to enable a comparison on IGA-CHE cumulative response or HECSI 90. Even for the outcome of IGA-CHE TS, a simple Bucher comparison using data from DELTA FORCE and ALPHA gives a statistically significant odds ratio of 2.71 (95% 1.42 to 5.19) which is not dissimilar from the FE NMA results.	

Issue 9 Matching-adjusted indirect comparison of delgocitinib versus PUVA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 88, the text reads: *"Overall, the EAG deemed it most appropriate to consider the first set of MAICs that comprise patients with only severe CHE, as disease severity has been shown to be an important prognostic factor (Section 3.3) and in doing so ensured that the pooled DELTA 1 and DELTA trial population was appropriately matched to the severe CHE only population from the ALPHA trial."*	The text should make explicit mention of the effective sample size in this comparison and the corresponding limitations of any analysis based on a sample this small. Results of the final MAIC submitted as part of the clarification responses should also be considered in a sensitivity analysis.	The EAG have selected the MAIC presented in the clarification response with the smallest effective sample size and make no mention of the limitations associated with comparing a matched population of 39 delgocitinib-treated patients with 221 PUVA-treated patients. They also do not present any of the sensitivity analyses where IGA-CHE / PGA severity was excluded as a matching covariate, reflecting what appears to be discrepancies between the studies in terms of IGA-CHE and PGA severity classifications despite similarities in baseline HECSI scores, another indicator of disease severity.	The EAG has included additional text (Section 3.4.3, page 89) that details the small effective sample size for the matched population from the pooled DELTA 1 and DELTA 2 trials. The EAG notes that the company's request to describe the results of the sensitivity analysis in which IGA-CHE / PGA severity was excluded as a matching covariate is not a factual inaccuracy. As noted in Section 3.4.2 (page 88), disease severity has been shown to be an important prognostic factor. As such, the EAG considers it important that unanchored MAICs capture all prognostic variables in line with DSU guidelines (TSD 18).

On page 92, the text reads: *"As no direct evidence exists for the comparison of delgocitinib to PUVA, indirect evidence for this comparison was obtained from MAICs comprising patients who received PUVA in the ALPHA trial and patients who received delgocitinib in the pooled DELTA 1 and DELTA 2 trials.* [redacted] *. "* On page 105, the text reads "*The EAG considers that the MAIC results matching patients by severe symptoms and hyperkeratotic status at baseline provides the most robust treatment effects given matching by hyperkeratosis status at baseline is inclusive of both hyperkeratotic and non-hyperkeratotic patients. The EAG notes that the MAIC estimated mean odds ratio is* [redacted]*, indicating that there is little to no difference in the proportion of patients who*	The second sentence of this paragraph should be revised: [redacted] *, but it is worth noting that the effective sample size from the DELTA trials informing this comparison was very small (n=39).* The statement should also be updated to reflect results of the sensitivity analysis in which IGA-CHE / PGA severity was excluded as a matching covariate. Discussion of the choice of MAIC, results and use in the EAG preferred base case of the economic model should be revised to reflect any changes to the above sections.	First, the indirect comparisons are available for HECSI score change from baseline not HECSI-90. Secondly, there is no acknowledgement of the small effective sample size for the EAG preferred MAIC, though this is a notable limitation of the analysis. Finally, there is insufficient exploration of the uncertainty in this comparison or acknowledgement of the other MAIC presented, namely one where IGA-CHE / PGA severity was excluded as a matching covariate.	The EAG thanks the company for identifying that HECSI-90 was referred to instead of change from baseline HECSI score. This has been updated on page 93. The EAG has included additional text (Section 3.4.3, page 89) that details the small effective sample size for the matched population from the pooled DELTA 1 and DELTA 2 trials. The EAG notes that the company's request to describe the results of the sensitivity analysis in which IGA-CHE / PGA severity was excluded as a matching covariate is not a factual inaccuracy. As noted in Section 3.4.2 (page 88), disease severity has been shown to be an important prognostic factor. As such, the EAG considers it important that unanchored MAICs capture all prognostic variables in line with DSU guidelines (TSD 18). Likewise, given that comparisons controlling for all appropriate covariates, such as IGA-CHE and PGA severity, provide the most accurate treatment effects,

achieved a full response by 12 weeks. The outcomes of this MAIC are therefore assumed in the EAG base case comparing delgocitinib to PUVA." On page 115, the text reads: "*As described in Section 4.2.3, the EAG considers that the MAIC results matching patients by severe symptoms and hyperkeratotic status at baseline provides the most robust treatment effects given matching by hyperkeratosis status at baseline is inclusive of both hyperkeratotic and non-hyperkeratotic patients. The MAIC is therefore assumed in the EAG base case comparing delgocitinib to PUVA.*"			independent of certainty due to sample sizes, the EAG considers that only the MAICs which control for these parameters provide robust treatment effects that can be used to inform the model. As such MAICs not controlling for these parameters have not been explored by the EAG.

Issue 10 Efficacy of next-line basket

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 116, the EAG state that "Similarly, if patients previously treated with delgocitinib and PUVA progress [to next-line treatment], they may not be treated with alitretinoin given its use primarily in hyperkeratotic patients. Therefore, the EAG considers that the inclusion of alitretinoin as a next-line treatment may be inappropriate and the treatment effects of the basket overestimated."	The limitation of this assumption should be stated: *Therefore, the EAG considers that the inclusion of alitretinoin as a next-line treatment may be inappropriate and the treatment effects of the basket overestimated. However, the exclusion of alitretinoin from the next-line basket may underestimate its use as CHE morphology is known to change over time.*	This presumes that there is no change or evolution to the morphological subtype of CHE over time which is incorrect.	This is not a factual inaccuracy. While the EAG agrees that symptom morphology can change over time, specifically between relapses. If a patient presents with a specific morphology and is unresponsive to treatments and therefore progresses, the EAG considers that the symptoms being treated are those which did not respond to treatment and therefore have not changed between the primary or next-line treatments being administered.
On page 118, the text reads: *"As such, while the company has previously stated that it would not be possible to calculate the next-line treatment effects without alitretinoin, the EAG considers that the company could have*	If the EAG believe the company should have used TCS efficacy alone to estimate response to the NL basket, then the latter half of the sentence should be revised to be more specific: *…the EAG considers that the company could have used the same weighting*	The EAG have suggested that the company revise the NL basket efficacy to be based on the treatments in Table 34, excluding alitretinoin. After excluding alitretinoin, the only data reported in Table 34 are for TCS patients. Low disease	Table 34 reflects a basket of treatments from the RWEAL study, as such this is not a factual inaccuracy.

used the same weighting methodology of patients in the low disease activity states to calculate a treatment effect using the basket of treatments in Table 34, excluding alitretinoin."	*methodology of patients in the low disease activity states to calculate a treatment effect using the basket of low, mid, high and ultra-high potency TCS in Table 34, excluding alitretinoin.*	activity estimated for TCS was not considered generalisable to the broader treatments included in the next line basket.	
In Table 7, Table 8, Table 54 and Table 55, the assumed efficacy of the next-line treatment basket is stated to be 26.5%.	The value of 26.5% should be amended to 25.6% throughout.	The company suspects that this is a typo as the percentage described on page 118 and used in the model was 25.6%.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.

Issue 11 Conclusions regarding cost-effectiveness of delgocitinib in hyperkeratotic and non-hyperkeratotic CHE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 147-148, the text reads: *" The EAG considers that these opinions were confirmed by the company's subgroup analysis of DELTA FORCE by hyperkeratotic status, which resulted in delgocitinib being potentially cost-effective in non-hyperkeratotic patients compared to alitretinoin — and having no treatment benefit in*	We suggest the following revision to the text: *The EAG considers that these opinions were confirmed by the company's subgroup analysis of DELTA FORCE by hyperkeratotic status, which resulted in delgocitinib being potentially cost-effective in non-hyperkeratotic patients and being dominated compared to alitretinoin in hyperkeratotic patients.*	Stating that there is no treatment benefit in hyperkeratotic patients is misleading on its own and fails to consider the outcomes not captured in the model (e.g. HESD itch, DLQI) where the difference is not statistically significant. It is more accurate to describe the modelled	Not a factual inaccuracy. No change required..

hyperkeratotic patients,, leading to delgocitinib being dominated compared to alitretinoin. "		benefits for delgocitinib relative to alitretinoin.	

Issue 12 Corrections of data and typographical errors in the text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 76, the text reads: "[redacted]"	[redacted]	The result at Week 24 shows a non-statistically significant difference in favour of delgocitinib.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 77, the text reads: "[redacted]	[redacted]	The data reported here for HESD pain score corresponds to data presented in the clarification question for HESD itch score.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.

[redacted]"	[redacted]		
On page 79, the text reads: "[redacted]"	The text should be amended: *Similarly*, [redacted]."	The EQ-5D-3L index change results favour delgocitinib in HK patients, though differences are not statistically significant.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 92, the text reads: "[redacted]	Both references to Week 16 should be revised to Week 24.	Outcomes from DELTA FORCE that were presented in the clarification responses related to Week 12 and Week 24, so we presume that this is a typo.	The EAG thanks the company for identifying this typographical error and has updated the text accordingly.

[redacted]"			
On page 98, the text reads: *" After an additional 12 weeks of treatment, patients who achieve a full response progress to the off-treatment health state with all other patients discontinuing to either next-line treatments or BSC."*	The text should be revised to *"After a maximum additional 12 weeks of treatment, patients who achieve a full response progress to the off-treatment health state with all other patients discontinuing to either next-line treatments or BSC."*	Patients who continue treatment beyond week 12 discontinue in the cycle after they respond. The way that the EAG has written it leads one to believe that all patients continue for a full 12 additional weeks of treatment.	While this is not a factual inaccuracy the EAG has updated the text to avoid confusion.
On page 107, the text reads: *"After 12 weeks (three model cycles), patients who had achieved a full response transitioned to the off-treatment health state while patients who had not achieved a full response were assumed to continue treatment for another 12 weeks"*	The text should be revised to "*"After 12 weeks (three model cycles), patients who had achieved a full response transitioned to the off-treatment health state while patients who had not achieved a full response were assumed to continue treatment for up to another 12 weeks"*	Patients who continue treatment beyond week 12 discontinue in the cycle after they respond. The way that the EAG has written it leads one to believe that all patients continue for a full 12 additional weeks of treatment.	While this is not a factual inaccuracy the EAG has updated the text to avoid confusion.
On page 105, the text reads: *"As scenario analyses, time horizons of 3, 5 and 30 years*	The text should be revised: *As scenario analyses, time horizons of 1, 3, 5 and 30 years were explored by the company with*	The company submitted scenario analysis using 1, 3, 5 and 30- year time horizons.	Not a factual inaccuracy. No change required.

were explored by the company with the 3 and 50-year time horizons resulting in ICERs of £5,324 and £8,550 respectively."	*the 3 and 30-year time horizons resulting in ICERs of £5,324 and £8,550 respectively. In addition, a scenario analysis using a 1-year time horizon showed delgocitinib to dominate alitretinoin.*		
On page 116, Table 33 the heading of column 2 reads: *"Proportions of patients on treatment"*	The table heading should be revised to *Proportion of severe patients on treatment*	The values presented are for severe patients in the RWEAL study.	While this is not a factual inaccuracy the EAG has updated the text to avoid confusion.
On page 128, Table 42, the reference for one session of PUVA is listed as the *NHS tariff 2023/25 "*	The reference should be revised to the NHS Reference Costs 2022/23 It should also be made clear that this was not the unit cost used in the company base case. The company base case used a unit cost of £94.00 from the NHS tariff 2023/25, which aligns with the cost of UVB listed later in Table 43.	As per the company's response to question B28 in the clarification response, the cost cited is from the NHS reference costs 2022/23, not the NHS tariff 2023/25.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 143, Table 55, the EAG's preferred model assumptions are listed out and include two scenarios that are already part of the company base case: Per-cycle probability of permanent discontinuation	These scenarios should be removed from the list as they are already part of the Company base case on row 1.	The assumptions listed in the EAG's preferred base case were already used in the company base-case, which is presented in row 1 of the table.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.

from continued initial treatment (DELTA FORCE) Proportion of patients opting not to re-initiate initial treatment following relapse (DELTA 3)			
On page 35, the text reads: *"vehicle cream arm of the DELTA FORCE trial"*	The word *vehicle cream* should be replaced with *alitretinoin*	There was no vehicle arm in DELTA FORCE. DELTA FORCE included delgocitinib and alitretinoin.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 40, the text reads: *"One RCT (JADE DARE) that compared dupilumab to placebo in patients with atopic dermatitis and was included in the SLR"*	The word *placebo* should be replaced with *abrocitinib.*	The JADE DARE study did not include a placebo arm. JADE DARE included dupilumab and abrocitinib.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 44, the text reads: *"Furthermore, in response to clarification questions, the company provided the results of subgroup analyses, for the DELTA FORCE trial, comparing patients who received delgocitinib or alitretinoin in either the moderate or severe CHE subgroups"*	This sentence should be removed.	The company did not provide subgroup evidence by CHE severity from the DELTA FORCE trial as there were no moderate patients in DELTA FORCE.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.

On page 56, the text reads: "*Accordingly, the EAG is concerned that, given the imbalance in discontinuation rates between the rates, the use of worst observation carried forward as an imputation method for missing data has the potential to underestimate the treatment effect in the vehicle cream arms"*	The second use of *rates* in the sentence should be replaced with *arms.*	We suspect that this is a typo.	The EAG thanks the company for identifying this typographical error and has updated the text accordingly.
On page 62, the text reads: *"Accordingly, the EAG is concerned that, given the imbalance in discontinuation rates between the rates, the use of worst observation carried forward as an imputation method for missing data has the potential to underestimate the treatment effect in the vehicle cream arms"*	The second use of *rates* in the sentence should be replaced with *arms.* The reference to *the vehicle cream arms* should be replaced with *the alitretinoin arm.*	We suspect that these are typos.	The EAG thanks the company for identifying this typographical error and has updated the text accordingly.
On page 69, the text reads: "[redacted]	The 95% CI for the IGA-CHE TS outcome at Week 12 and Week 24 should be re-written as [redacted] and [redacted]	The lower and upper bounds of the 95% CI are reversed.	The EAG thanks the company for identifying this typographical error and has updated the text accordingly.

[redacted]"			
On page 71, the text reads: *"At Week 16, there was a non-statistically significant difference, in favour of moderate patients, in the number of patients who achieved HECSI-90 regardless of whether they received delgocitinib (OR 0.87, 95% CI: 0.6 to 1.26) or vehicle cream (OR 1.96; 95% CI: 0.78 to 4.91). Likewise, at Week 12… "*	*At Week 16, there was a non-statistically significant difference in the number of patients who achieved HECSI-90, in favour of severe patients if they received delgocitinib (OR 0.87, 95% CI: 0.6 to 1.26) and in favour of moderate patients if they received vehicle cream (OR 1.96; 95% CI: 0.78 to 4.91).* The word *likewise* in the subsequent sentence should be removed.	At week 16, there was a non-statistically significant difference in favour of severe patients in if they received delgocitinib and in favour of moderate patients if they received vehicle cream.	The EAG thanks the company for identifying this factual inaccuracy and has updated the text accordingly.
On page 73, the text reads: "[redacted]"	The 95% CI for the HECSI-90 MD at week 12 should be re-written as [redacted]	The lower and upper bounds of the 95% CI are reversed.	The EAG thanks the company for identifying this typographical error and has updated the text accordingly.

On page 116, the EAG incorrectly refer to the RWEAL study as WREAL.	The text should be amended to “While the RWEAL study…”	Correction of a typo.	The EAG thanks the company for identifying these typographical errors and has updated the text accordingly.
On page 53, the text reads: *"expertss"*	We suggest that *expertss* be revised to *experts*	We suspect that this is a typo.	
On page 74, the text reads: *"is defined proportion of patients"*	Text should be revised to *defined as the proportion of patients*	We suspect that this is a typo.	
On page 101, the text reads: *"As moderate CHE patients are illegible for alitretinoin within its marketing licence, psoralen with ultraviolet (PUVA) was considered the only relevant comparator to delgocitinib for the treatment of moderate CHE."*	*Illegible* should be changed to *ineligible*	We suspect that this is a typo.	
On page 126, the text reads: *"([redacted] g/week)"*	This should read *([redacted] g/week)*	Table 51 indicates that the overall average was [redacted] g per week.	The EAG thanks the company for identifying these factual inaccuracies and has updated the text accordingly.
On page 94 and 133, Table 21 and Table 49, the probabilistic total QALY value for PUVA is incorrectly listed as *5.25.* The probabilistic incremental	5.25 should be changed to 5.740. 0.54 should be changed to 0.047. 0.039 should be changed to 0.035.	Table 59 of the clarification responses shows that it should be 5.740 total QALYs. It also shows that the incremental QALYs for delgocitinib versus alitretinoin are 0.035.	

QALYs versus delgocitinib are also incorrectly listed as 0.54. The probabilistic incremental QALYs versus alitretinoin are also incorrectly listed as 0.039.			
On page 113, the text reads: "*The former scenario led to an increase in the ICER from £8,526 to £16,744; only using the DELTA FORCE initial treatment effects led an increase in the ICER to £11,023.*"	The ICER values should be corrected to what was presented in the clarification responses: £16,744 should change to £16,039 "11,023 should change to £10,720	The ICERs do not align with the ICERs presented in the clarification responses to questions B3 and B4.	

Issue 13 Modelling issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Page 101, the text reads: "*The company conducted the scenario using the odds ratio between severe and*	We suggest that the text is revised for clarity: *The company conducted the scenario using the odds ratio between severe and moderate patients in DELTA 1 and 2 applied to the rates of response*	As it is written, it gives the impression that the odds ratio applied in this scenario is derived from a comparison of severe and moderate patients	The EAG thanks the company for identifying the factual inaccuracy and has updated the text accordingly.

moderate patients in DELTA FORCE, leading to a per-week probability of response of [redacted]% and [redacted]% for delgocitinib and alitretinoin respectively."	*in DELTA FORCE, leading to a per-week probability of response of [redacted]% and [redacted]% for delgocitinib and alitretinoin respectively*	in DELTA FORCE, though there were no moderate patients included in DELTA FORCE.	
On page 102, the text reads: "*From the subgroup analysis of DELTA FORCE, the EAG notes that only [redacted]% of hyperkeratotic delgocitinib patients achieved a full response, compared to [redacted]% of alitretinoin patients.*"	We suggest that the text is revised for clarity: *From the subgroup analysis of DELTA FORCE, the EAG notes that by week 12 only [redacted]% of hyperkeratotic delgocitinib patients achieved a full response, compared to [redacted]% of alitretinoin patients.*	The EAG have not reported the timepoint for the response rates, which is important given the fact that some patients not achieving full response at week 12 will continue with treatment and achieve a full response later.	While this is not a factual inaccuracy the EAG has updated the text to avoid confusion.
On page 107, the text reads: "*The distribution of patients was informed by the 12-week subgroup analysis of the DELTA 1 and 2 trials for delgocitinib patients and DELTA FORCE for alitretinoin patients.*"	We suggest that the text is revised: The distribution of patients was informed by a 12-week subgroup analysis of the DELTA 1, DELTA 2 and DELTA FORCE trials for delgocitinib patients and DELTA FORCE for alitretinoin patients.	The distribution of patients across the health states for delgocitinib was informed by data from all three DELTA trials. For moderate patients, the only subgroup data was from DELTA 1 and 2, but for severe patients, the data came from all three trials.	The EAG thanks the company for identifying these factual inaccuracies and has updated the text accordingly.
On page 122, the text reads: "*The definition of response for the utility*	We suggest that the text is revised: *The definition of response for the utility values was based on IGA-CHE score in*	The definition of response for the utility values was based on IGA-CHE scores, not	

values was based on HECSI. However, the company also performed the MMRM regression using IGA-CHE response definitions."	*the base case and based on HECSI response in a scenario analysis.*	HECSI. HECSI score was included in the regression as a covariate.	
The utility values presented in Table 37 are based on the updated model utilities following clarification response, but the utility values presented in Table 38 and Table 39 are based on the original submission.	We suggest that the EAG updates the utility values in Table 38 and Table 39 to be consistent with the values in Table 37.	The weighted utility values presented in Table 38 and Table 39 have not been updated to reflect the revised utility values presented in the clarification responses and used in the EAG preferred base case.	
On page 123, the text reads: "*At the clarification stage the company was requested to provide the mean EQ-5D utilities from DELTA 1, 2 and FORCE for each health state and the 95% confidence intervals of the utilities calculated from the MRMM model. In response, the company provided Table 40; however, no confidence intervals for the utilities*	We request that the EAG provides the additional context that sufficient data was presented in the clarification request to properly capture parameter uncertainty in the economic model. That is, even though 95% Cis around the utility values were not provided, the company did provide full details, including imprecision, of the regression output and covariance matrices.	The statement as written is strictly accurate in that the company did not provide the 95% confidence intervals of the utility values requested; however, the way that it is written is misleading. All parameters to enable proper incorporation of the utility regression into the model and to explore uncertainty probabilistically were provided by the company.	Not a factual inaccuracy. No change required..

<table>
<tr><td>estimated from the regression were provided.”</td><td></td><td></td><td></td></tr>
<tr><td>On page 131, the text reads: “Between the usage sources, the company considered that the most appropriate source was dependent on what was considered to be the most relevant drivers of treatment usage. The descriptive statistics are a function of the total usage at week 12, while the MMRM estimates more closely reflect consumption for a given CHE severity over time.”</td><td>We request that the EAG revised the text:

Between the usage sources, the company considered that the most appropriate source was dependent on what was considered to be the most relevant drivers of treatment usage. The descriptive statistics are a function of the total usage to achieve a particular response at week 12, while the MMRM estimates more closely reflect consumption for a given CHE severity over time.</td><td>The statement as written does not capture the interpretation that the company asserted in the response to clarification, so we would request that the EAG consider changing the wording for clarity.</td><td>While this is not a factual inaccuracy the EAG has updated the text to avoid confusion.</td></tr>
<tr><td>On pages 131-132, the text reads: “The EAG notes that while 12-week usage data by treatment and severity has been provided separately to the 24-week data. Given the company’s concerns that the 12-week data only provides a snapshot of usage, the</td><td>We suggest that the EAG use the following values derived from Table 52 of the clarification response:

<table><tr><th>IGA-CHE category</th><th>Up to Week 24 (DELTA 1, DELTA 2, DELTA FORCE</th></tr><tr><td>0/1</td><td>[redacted]</td></tr></table></td><td>We believe that there has been a misinterpretation of the delgocitinib consumption data presented in the clarification response, which has led to an inappropriate averaging across time points in the EAG’s preferred base case.</td><td>Not a factual inaccuracy. No change required.

The EAG notes that consumption is greater at 12 weeks compared to up to 24 weeks. Therefore, using the up</td></tr>
</table>

EAG considers that 12-week and 24-week consumption could be combined to provide a more holistic estimate of consumption over time for delgocitinib patients. The EAG therefore calculated a weighted average using the 12- and 24-week delgocitinib usage across the DELTA trials for severe patients and explored this usage in a scenario. Table 48 presents the usage assumed in the scenario compared to the MMRM values preferred in the company base case and in DELTA FORCE."	2	[redacted]	Table 52 of the clarification response (24-week delgocitinib consumption data on IGA-CHE categories by treatment and severity) presents the mean weekly usage of delgocitinib based on the IGA-CHE severity category at the last time point up to week 24 in the DELTA trials. This includes data up to week 16 in DELTA 1 and 2 and up to week 24 in DELTA FORCE. The weighted average across 12 and 24 weeks usage values calculated by the EAG are therefore inappropriate because they double count the data up to week 12. The more appropriate source based on their description would be the descriptive statistics from Table 52 of the clarification response. The values were estimated by dividing the total usage over	to 24 week consumption data to inform consumption for patients that achieve a full response by 12 weeks and stop treatment is inappropriate, as it leads to an underestimation of consumption. As the model does not allow for separate consumption values to be applied to patients being treated to 12 weeks and beyond 12 weeks, the weighted average is preferred in the EAG base case.
	3	[redacted]		
	4	[redacted]		

		the period by the duration of the period structured For DELTA FORCE, this means that total usage over 24 weeks was quantified among patients in each IGA-CHE category at week 24 and then used to derive the mean weekly consumption assuming it was evenly distributed across all 24 weeks. For DELTA 1 and DELTA 2, the total usage over 16 weeks was quantified among patients in each IGA-CHE category at week 16 and then used to derive an estimate of weekly consumption.	
Page 145, Section 6.2.1 of the EAG report, which presents the probabilistic sensitivity analysis results reports probabilities of cost-	We are not sure what the correct values should be, but a run of the model where alitretinoin is the comparator produced probabilities of delgocitinib being most cost-effective of 68.9% and 91.4% at	We cannot reproduce similar probabilities of delgocitinib's cost-effectiveness versus alitretinoin at the £20,000 and £30,000 per QALY thresholds	Not a factual inaccuracy. No change required.

effectiveness for delgocitinib versus alitretinoin and versus PUVA. We have re-run the PSA in the model provided by the EAG to the company but cannot reproduce similar values.	£20,000 and £30,000 thresholds, respectively. These are quite different from the 55.5% and 87.8% reported in the EAG report.	using the EAG's model and a refresh of the probabilistic sensitivity analysis. This may not be an error, but we would expect the values to be more similar than what we have observed and request that the EAG double check the values presented.	The EAG has rerun the PSA and achieved similar outcomes to those in the EAG report, specifically, a 57.4% and 86.2% probability of cost effectiveness at a WTP threshold of £20,000 and £30,000, relative to the 55.5% and 87.8% in the EAG report.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
On page 71, the text reads: "[redacted] *The results of the RE model were not associated with any heterogeneity (I2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model.*	These results were not marked as CIC in the clarification responses.	*"At Week 12, the RE meta-analysis indicated that there was a statistically significant difference in the proportion of patients who achieved HECSI-90 (OR 4.28; 95% CI: 2.95 to 6.22). The results of the RE model were not associated with any heterogeneity (I2 = 0.0%), indicating that the results of the RE model are likely to be the same as those from the FE model. At Week 16, the RE meta-analysis indicated that there was a statistically significant difference in the*	The EAG thanks the company for identifying these inaccuracies and has updated the text accordingly.

[redacted]		*proportion of patients who achieved HECSI-90 (OR 3.51; 95% CI: 2.42 to 5.10)."*	
On page 74, the text reads: *"For the DELTA FORCE trial, HECSI-75 was assessed post-hoc. At Week 12, a statistically significant difference in the proportion of patients who achieved an HECSI-75 response between the delgocitinib (55.4%) and alitretinoin (46.0%) arms was reported (p = 0.0357)."*	These data are marked as CIC in the submission (Table 158 of Appendix B)	[redacted]	
On page 77, the text reads: [redacted]	These data are not marked as CIC in the CS.	The text can be unredacted: *there was a statistically significant difference, at Week 12, between the mean change in HESD pain score from baseline in the delgocitinib (−2.9) and alitretinoin (−2.3) arms (p = 0.018). Likewise,*	
On page 78-79, the text reads: *"For the DELTA FORCE trial, there was a not statistically significant difference, between patients who received delgocitinib and alitretinoin, in mean change in EQ-5D-3L index from baseline*	These values are redacted in Table 35 of the CS.	This sentence should be redacted: [redacted]	

at Week 12 (MD 0.034; 95% CI: −0.001 to 0.069; p = 0.056) and a statistically significant difference at Week 24 (MD 0.066; 95% CI: 0.027 to 0.104; p < 0.001)."		[redacted]	
On page 103, Table 26, the data for alitretinoin discontinuation, "*7.2% (based on 12-week probability of 20.0%)*"	These values are redacted in Table 39 of the clarification responses.	These data should be redacted: [redacted]% and [redacted]%	
On page 114, the text reads: "When matching severe patients and hyperkeratotic status, the 12-week treatment effect odds ratio was measured at 1.01"	The odds ratio from the MAIC was redacted in the clarification responses and is redacted elsewhere in the EAG report	The odds ratio of [redacted] should be redacted.	