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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

New evidence submission

29th September 2025

File name	Version	Contains confidential information	Date
ID6408 Company Response to NICE draft guidance	2.0	Confidential information redacted	29/09/2025

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Abbreviations

ACM	Appraisal Committee Meeting
BOCF	Baseline observation carried forward
CHE	Chronic hand eczema
CI	Confidence interval
DLQI	Dermatology Life Quality Index
EAG	External Assessment Group
ICER	Incremental cost-effectiveness ratio
IGA-CHE	The Investigator Global Assessment of Chronic Hand Eczema
LOCF	Last observation carried forward
LYG	Life years gained
NHS	National Health Service
NMA	Network meta-analysis
PAS	Patient Access Scheme
PUVA	Psoralen plus ultraviolet A
QALY	Quality-adjusted life years
WOCF	Worst observation carried forward

Provision of new information for consideration: ID6408 Delgocitinib for treating moderate to severe chronic hand eczema

Summary of additional evidence

Further to the first Appraisal Committee Meeting (ACM) regarding delgocitinib for the treatment of moderate to severe chronic hand eczema (CHE) held on 4th June 2025 and the subsequent publication of draft guidance, some key areas of uncertainty have been identified.

The Company has provided further analyses to explore and reduce this residual uncertainty, summarised below under the following headings:

1. Method for imputing missing data
2. Time on treatment for delgocitinib, alitretinoin, and psoralen plus ultraviolet A (PUVA)
3. Delgocitinib dosing data in moderate and severe CHE

To supplement these analyses, the Company conducted a structured expert elicitation exercise with five UK dermatologists, a sample that was geographically representative of NHS practice across the country. Reports of this work are provided as an appendix **(Appendix A)** and referenced throughout this response.

Revised economic analyses, which take into account the new evidence and the Committee preferences noted in the draft guidance, are presented in this document with full details.

The Company propose a new base case, detailed on page 15, to inform committee decision making.

Summarising committee requests and additional analyses

The Committee requested the following additional analyses after the first Appraisal Committee Meeting:

- Use of the first and last observation carried forward method to impute missing data in DELTA trials
- Updated cost-effectiveness estimates that reflect the proportion of people remaining on delgocitinib, alitretinoin and PUVA in clinical practice at 1, 2 and 3 years

The Committee recognised that delgocitinib offers benefits over current second-line CHE treatments due to its topical administration and manageable safety profile. It agreed that, if the company provides analyses that reduce these uncertainties, it will accept an incremental cost-effectiveness ratio (ICER) of £25,000 per QALY gained in its decision making.

NICE Committee preferred assumptions:

- Use the company's fixed-effects network meta-analysis (NMA) results to inform treatment effects
- Use health state-specific utility values
- Including adverse events from DELTA FORCE
- Comparing delgocitinib with alitretinoin and PUVA in both moderate and severe populations
- Include the EAG's preferred amendments to the model, except for adverse events (see below)

EAG suggested amendments to the model:

- Using delgocitinib dosing data from DELTA FORCE to inform the comparison versus alitretinoin
- Using the weighted average of week 12 and week 24 delgocitinib dosing data from DELTA 1, DELTA 2 and DELTA FORCE to inform the comparison between delgocitinib and PUVA
- Proportion of people who discontinue to next-line treatment/best supportive care based on ALPHA
- Remove alitretinoin from the next-line treatment basket and reduce the basket efficacy to 25.6%
- Adjust dermatologist visit frequencies in each health state to align with EAG's clinical expert opinion
- Not including adverse events from DELTA FORCE

Executive summary

This submission addresses the Committee's key discussion areas and outlines the Company's position in response to the draft guidance.

1. **Imputation of missing data** – While noting the Committee's preference for using the fixed-effects NMA model, the Company has provided the requested analyses relating to imputation of missing data. Specifically, these explore both baseline and last observation carried forward approaches. Through conducting these analyses, the Company has demonstrated the negligible impact on relative cost effectiveness of delgocitinib versus alitretinoin and consistent significantly improved efficacy in the achievement of The Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE) 0/1.

   On this basis, the company maintains that the worst observation carried forward method initially used is robust and appropriate.

2. **Time on treatment** – Further analysis was requested for the proportion of patients remaining on delgocitinib, alitretinoin, and PUVA treatment at 2 years. The Company has implemented structured expert elicitation, reviewed clinical data and updated the model accordingly. The resulting economic analyses now incorporate this feedback through necessary adjustments to treatment rules in the model. The Company recognises the Committee's preferred time-on-treatment estimates, achieving these in its revised base case analysis. However, this required the implementation of some unrealistic assumptions compared to trial data with regards to discontinuation and retreatment and these have been outlined transparently.

3. **Delgocitinib dosing data for moderate CHE** – The Committee recommended that delgocitinib dosing in the model be derived from DELTA FORCE, which only included severe patients. The Company considers this approach to be methodologically disproportionate for moderate CHE and instead proposes using data from the subgroup of moderate patients at baseline included in DELTA 1 and DELTA 2 to inform delgocitinib consumption in the moderate population. These data were submitted as part of the Company's response to clarification questions. Clinical expert elicitation further supports lower topical consumption in moderate CHE, which should be reflected in cost and dosing assumptions. This approach ensures a robust and generalisable estimation of delgocitinib resource use which reflects UK clinical practice.

4. **Alitretinoin as a comparator in moderate CHE** – Although the final scope identified alitretinoin as a comparator for severe CHE only, in line with its NICE recommendation, the Company recognises its off-label use in moderate CHE in UK practice. The Company has therefore provided analyses to explore alitretinoin as comparator in moderate CHE but reaffirms that analyses in the moderate population are informed by patient characteristics and outcome data from the most relevant data source, to ensure clinical and methodological appropriateness.

5. **Alitretinoin cost** – A confidential NHS tender price exists for alitretinoin, which is not known to the Company. Consequently, the base-case analysis uses published list prices for alitretinoin and the model flexibility allows the EAG to explore this appropriately in review.

6. **Key results** – The updated base-case and scenario analyses have been developed in line with the Committee's preferred assumptions. The base case analysis below, inclusive of a patient access scheme (PAS) for delgocitinib and focusing on severe CHE, demonstrates that delgocitinib is a cost-effective treatment option compared to current treatments (alitretinoin and PUVA), used in second-line practice.

Base case model results (delgocitinib at PAS price, alitretinoin and PUVA both at list price)

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; PUVA, Psoralen plus ultraviolet A; QALY, Quality-adjusted life years

1. Method for imputing missing data

The Company recognises the Committee's preference for using the fixed-effects NMA to estimate relative treatment effects between delgocitinib and PUVA. Direct evidence is available from DELTA FORCE for the comparison between delgocitinib and alitretinoin, though this study included severe patients only.

We appreciate the committee's feedback regarding preferred analytic methods for estimating relative treatment effects in the assessment of delgocitinib compared with alitretinoin and PUVA. The request for first observation carried forward has been interpreted to mean baseline observation carried forward (BOCF). In response, additional analyses have been conducted using both a BOCF and last observation carried forward (LOCF) imputation approach, complementing the original analyses which used the worst observation carried forward (WOCF) method. It is worth noting that the WOCF method used in the originally submitted analyses imputed data for intercurrent events including discontinuation. In the additional analyses submitted using BOCF and LOCF imputation methodology, data are taken as observed regardless of intercurrent events and only imputed where missing.

The impact of using alternative methods of imputing missing data from DELTA FORCE has been illustrated through a series of scenario analyses that start with the base case using the composite estimand, which applies the WOCF in the event of permanent treatment discontinuation or missing data (see **Table 1**). Across all imputation strategies, the comparative efficacy results remain robust. Delgocitinib consistently demonstrates significantly greater efficacy than alitretinoin in the achievement of IGA-CHE 0/1 response. Notably, regardless of the choice of imputation method used (WOCF, BOCF, or LOCF), the relative superiority of delgocitinib is observed in terms of the achievement of IGA-CHE 0/1. Amongst patients who do not achieve IGA-CHE 0/1, the distribution across IGA-CHE 2, 3 and 4 is consistent across methods of data imputation. The only exception is a modest increase in the number of alitretinoin-treated patients classified as IGA-CHE 3 when using LOCF, this shift does not appreciably influence the overall interpretation of comparative effectiveness.

Table 1. Distribution of DELTA FORCE patients across IGA-CHE severity and odds ratio of achieving IGA-CHE 0/1 using worst, baseline and last observation carried forward to impute missing data

Treatment arm	IGA-CHE 0/1	Not IGA-CHE 0/1			n	Odds ratio (95% CI) IGA-CHE 0/1
		IGA-CHE 2, n (%)	IGA-CHE 3, n (%)	IGA-CHE 4, n (%)		Delgocitinib vs Alitretinoin
WOCF, composite estimate						
Delgocitinib	68 (27.2)	[redacted]	[redacted]	[redacted]	250	***1.88 (1.22, 2.89)***
Alitretinoin	42 (16.6)	[redacted]	[redacted]	[redacted]	253	
BOCF						
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
LOCF						
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BOCF, Baseline observation carried forward; CI, Confidence interval; IGA-CHE, The Investigator Global Assessment of Chronic Hand Eczema; LOCF, Last observation carried forward; WOCF, Worst estimate carried forward.

In addition, when exploring the impact of the different imputation methods on the results for the fixed-effects NMA, all results remain statistically significant in favour of delgocitinib. These results are presented in **Table 2** below and are stratified based on disease severity.

Table 2. Fixed-effects NMA odds ratios for delgocitinib versus comparators (week 12 IGA-CHE 0/1 endpoint response outcome)

Delgocitinib vs treatment	Median odds ratios (95% credible intervals)					
	Severe CHE			Moderate CHE		
	WOCF (submitted)	BOCF	LOCF	WOCF (submitted)	BOCF	LOCF
Cream vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOCF, Baseline observation carried forward; CHE, Chronic hand eczema; CI, Confidence interval; IGA-CHE, The Investigator Global Assessment of Chronic Hand Eczema; LOCF, Last observation carried forward; PUVA, Psoralen plus ultraviolet A; WOCF, Worst estimate carried forward.

For further details of the input parameters informing week 12 efficacy in the cost-effectiveness analysis based on both the results of the NMA for IGA-CHE 0/1 and the distribution of patients across non-responder states using different methods for imputing missing data, please see Appendix B.

Overall, the impact of the imputation method on the relative cost effectiveness of delgocitinib versus alitretinoin appears to be negligible. The revised base case ICERs for delgocitinib at PAS price compared to alitretinoin at list price go from [redacted] using WOCF to [redacted] using BOCF and [redacted] using LOCF. We trust that these additional analyses address the Committee's request and support confidence in the generalisability and consistency of the clinical and cost-effectiveness findings for delgocitinib regardless of the imputation method selected.

2. <u>Time on treatment for delgocitinib, alitretinoin and PUVA</u>

The committee has expressed that it would like to see analyses that include 25% of people on alitretinoin remaining on treatment at 2 years in the model. The committee thought the proportion of people remaining on delgocitinib at 2 years in the model should be at least 25%, but the proportion on PUVA may be lower than 25%. It discussed that the analyses should appropriately adjust the modelled time on treatment at years 1 and 3 in the model and that the ICER was likely to be sensitive to the difference in proportions of people remaining on treatment.

The structured expert elicitation exercise conducted by the Company attempted to quantify the proportion of patients remaining on alitretinoin and PUVA at 24 months and the level of uncertainty associated with the estimates provided by experts. Quantitative responses, estimating the proportion of patients experiencing a positive response to treatment in 24 weeks, found the range was 20-75% of alitretinoin patients and 20-50% of PUVA patients. The structured expert elicitation responses estimated that 32% of alitretinoin responders and 11% of PUVA responders are expected to still be on treatment at year 2, suggesting that 7-25% of all alitretinoin patients and 2-6% of all PUVA patients would be expected to still be on treatment at year 2. The results demonstrated that there is variation of time on treatment with alitretinoin across clinicians' patient cohorts, but the upper bound of results aligned with the Committee considerations i.e. the maximum proportion of all people starting alitretinoin that remain on treatment at 2 years is 25%.

To note, data for time on treatment with alitretinoin from randomised controlled trials differs significantly from the Committee's preferred time on treatment. So, adjusting the model to ensure that 25% of all patients who have alitretinoin remain on treatment at 2 years is a deviation from the available evidence. This is important to understand in the context of the updated economic analyses, which attempt to align with the Committee preferred time on treatment estimates.

Modifying model parameters and assumptions to increase the modelled time on treatment for alitretinoin also results in the proportion of people remaining on delgocitinib at 2 years in the model being higher than 25%, in line with Committee expectations. There are four sets of parameters and assumptions that affect the expected time cycling on and off a given treatment, so the following changes can extend the proportion still "on treatment":

- Turn off discontinuation from treatment
- Increase proportion re-initiating treatment at the point of a relapse
- Extend time to treatment re-initiation by increasing the severity threshold for re-treatment eligibility
- Extend the time on treatment for partial responders to treatment at week 24

In order to meet the Committee's preferred time on treatment estimates, some modelled scenarios involved the implementation of potentially unrealistic assumptions with regards to discontinuation and retreatment, compared to trial data and the marketing authorisation. For example, extending the time on treatment for partial responders to treatment at week 24 would require alitretinoin treatment to run beyond 24 weeks, which is potentially regarded as the maximum recommended duration for a single course of alitretinoin treatment in CHE according to its marketing authorisation and the current NICE recommendation. The Company believes that the most appropriate method to achieving the preferred time on treatment estimates is a combination of reducing the likelihood of discontinuation during periods of retreatment for all treatments and increasing the severity threshold for retreatment to extend the time to treatment reinitiation.

3. <u>Delgocitinib dosing data</u>

The Committee's suggestion to derive delgocitinib dosing data for the model exclusively from DELTA FORCE presents significant methodological concerns given the trial's exclusive recruitment of severe CHE patients. DELTA FORCE was carefully designed as a head-to-head, phase 3 study comparing delgocitinib to alitretinoin in adults with severe CHE, and as such, the published data on dosing and treatment patterns only reflect usage in a population with the greatest disease burden and associated need for medication. Applying this dosing data directly to moderate patients risks systematically overestimating resource use and costs in the economic model for the moderate subpopulation.

In contrast, the DELTA 1 and DELTA 2 trials jointly recruited adults with moderate to severe CHE and captured consumption and usage patterns for the full spectrum of disease severity in the target population. Utilising data from the patients with moderate CHE at baseline from DELTA 1 and DELTA 2 allows for a robust and proportionate synthesis of dosing and consumption in moderate patients. These data were submitted, along with data for patients with severe CHE at baseline from DELTA FORCE, DELTA 1 and DELTA 2, as part of the Company's response to clarification question B25 and are presented again here for ease of reference.

The descriptive statistics from DELTA 1, DELTA 2 and DELTA FORCE at week 12 suggest that weekly usage of both delgocitinib and its comparator cream vehicle is higher on average among patients with severe CHE at baseline than patients with moderate CHE at baseline. There is an exception in the case of moderate patients who experienced worsening disease severity to IGA-CHE 4 during the trial (see

Table 3). **Table 4** presents the mean dosing values after estimating a weighted average across the clear and nearly clear IGA-CHE scores.

Table 3. Delgocitinib and cream vehicle consumption data at 12 weeks from DELTA 1, DELTA 2 and DELTA FORCE based on IGA-CHE score, stratified by treatment and disease severity

IGA-CHE category	Severe CHE		Moderate CHE (DELTA 1 & 2)	
	Delgocitinib (D1, D2 and DFORCE)	Cream vehicle (D1 and D2 only)	Delgocitinib	Cream vehicle
0	[redacted]	-	[redacted]	[redacted]
1		[redacted]		
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 4. Delgocitinib mean consumption from DELTA 1, DELTA 2 and DELTA FORCE across IGA-CHE category

IGA-CHE category	Severe CHE	Moderate CHE
	Descriptive statistics (D1, D2 and DFORCE)	Descriptive statistics (D1 and D2)
0/1	[redacted]	[redacted]
2		
3		
4		

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.

Furthermore, clinical expert insight from the expert elicitation (Appendix A) highlighted that the consumption of topical treatments differs substantially between moderate CHE and severe CHE, with greater use of topical treatment by patients with severe CHE at baseline. This is reflective of both clinical practice and patient experience, where the extent and intensity of inflammation, as well as skin surface area involved, directly modulates consumption. Thus, any approach that extrapolates severe patient dosing to moderate cases without appropriate adjustment undermines the accuracy and credibility of the health economic analysis.

Unlike delgocitinib, alitretinoin's formulation is an oral tablet. The approved dosing of 30mg indicated for severe CHE is standardised regardless of severity, and there is no licensed dose for moderate CHE as alitretinoin is used off-label in the moderate patient subpopulation. This means that dosing is the same whether patients' symptoms are at the lower or higher end of the severity spectrum, as dose adjustment is made according to patient tolerability rather than disease severity. A lower dose of 10mg is reserved for those who experience unacceptable adverse effects (such as headache), as confirmed by clinical expert feedback. Also, the alitretinoin list price is the same for the 10mg and 30mg of dose, so alitretinoin dose is assumed to have no impact on acquisition cost.

Therefore, it is suggested that the most reasonable and evidence-aligned approach for calculating delgocitinib dosage in the moderate CHE population is to use an estimate informed by moderate patients included in DELTA 1 and DELTA 2. This method aligns with real-world clinical behaviour as

confirmed by both trial and expert evidence. Such an approach ensures that modelled treatment costs and outcomes for moderate disease are neither over- nor underestimated, supporting a fair, clinically relevant and methodologically sound evaluation. The Company accepts that delgocitinib dosing for the severe patient population can be derived from DELTA FORCE data.

4. Inclusion of alitretinoin as a comparator for moderate CHE

While the final NICE scope specified alitretinoin as a comparator only for the severe CHE population, the Company recognises that in current UK clinical practice alitretinoin is also prescribed off-licence in some moderate CHE cases, especially when patients have failed or are intolerant to other available therapies. In this context, the Company is willing to accept the Committee's preference for including alitretinoin as a comparator in the moderate CHE population.

However, to ensure methodological robustness and clinical relevance, it is essential that the patient characteristics informing the moderate delgocitinib population are derived from studies representative of this group. The DELTA 1 and DELTA 2 trials included both moderate and severe CHE patients, providing a robust evidence base for scenarios modelling moderate disease. The Company therefore suggests that patient baseline characteristics and dosing for moderate patients within the delgocitinib arm should be informed by the moderate patient population directly observed in DELTA 1 and DELTA 2, maintaining the integrity and generalisability of the clinical and economic analysis.

5. Cost of alitretinoin

There is a confidential NHS tender price for alitretinoin that is not available to the Company. Therefore, all base case cost-effectiveness analyses in this submission will use the published list price for alitretinoin to ensure transparency and reproducibility.

6. Base-case and scenario analyses

In response to the discussion at the first ACM and the outputs of the draft guidance, the economic analyses have been updated to align with the Committee's stated preferences and recommendations. Recognising that there remains uncertainty related to some key parameters—including dosing assumptions, imputation of missing data and time on treatment—we have systematically explored and presented a range of plausible values and scenarios. For example, the Committee expressed its preference for deriving delgocitinib dosing from DELTA FORCE, specifically in comparisons with alitretinoin. The Company maintains that dosing in the moderate population can only be appropriately informed by delgocitinib consumption directly observed among patients with moderate CHE at baseline in DELTA 1 and DELTA 2. Therefore, a scenario has been presented where delgocitinib dosing for moderate patients in the model is derived from DELTA 1 and DELTA 2.

By thoroughly investigating the impact of these uncertainties, we aim to present the Committee with the most credible and evidence-based assessment of delgocitinib's cost-effectiveness compared with alitretinoin. This approach will ensure that the base-case results are as robust, transparent, and representative of real-world clinical practice as possible. In **Table 5** below, an ICER is presented for each scenario analysis of delgocitinib versus alitretinoin, where the PAS price of delgocitinib and list price of alitretinoin is used and the proportion of patients starting delgocitinib or alitretinoin who are still "on treatment" after 1, 2 and 3 years is presented. Base case cost-effectiveness results versus PUVA and alitretinoin are provided in **Table 8**.

All scenarios are aligned with the Committee's preferred assumptions for the economic analysis, applying the following parameters and assumptions:

- Health state-specific utilities
- Next-line treatment basket informed by ALPHA, efficacy of next-line treatment basket is 25.6%

- Removal of alitretinoin from next-line treatment basket
- Healthcare resource utilisation according to EAG expert opinion (e.g. dermatologist visits)
- Include adverse events from DELTA FORCE
- Use the fixed-effects NMA

Given the Committee's preference for the fixed-effects NMA and to utilise delgocitinib dosing from DELTA FORCE to inform the economic model, the Company suggests that the starting point for all scenarios presented includes the use of the fixed-effects NMA to inform relative treatment efficacy up to week 12 and then relevant parameters from DELTA FORCE thereafter (Scenario 1). This ensures that efficacy and other inputs into the model are aligned with the dosing applied in the model, rather than detachment of data sources which reduces the reliability and robustness of modelling results.

Scenario 0 is provided for reference, to demonstrate the impact on ICER results and time on treatment when the Committee's preferred assumptions are applied to the original base case model submitted by the Company. However, this scenario is deemed to be implausible as it detaches the source of clinical efficacy and dosing. The Committee prefers to use DELTA FORCE data to inform delgocitinib dosing, so it is only appropriate to maintain the same data source for delgocitinib patient outcomes, rather than DELTA 3 which is a separate study. Moreover, implementation of the Committee's preferred assumptions does not achieve the time on treatment estimates requested. Therefore, subsequent scenarios build upon Scenario 1 to increase delgocitinib and alitretinoin time on treatment in the model.

Table 5. Results of scenario analyses (delgocitinib PAS price [redacted] and alitretinoin list price)

	Parameter change	**ICER**	**% of patients still on delgocitinib**			**% of patients still on alitretinoin**		
			Yr 1	**Yr 2**	**Yr 3**	**Yr 1**	**Yr 2**	**Yr 3**
0	Committee preferences applied to original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe population								
1	Committee preferences with DFORCE outcomes post-12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual scenarios to increase time on treatment								
2	0% discontinuation and 100% re-uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Partial responders to delgocitinib and alitretinoin at week 12 can continue treatment to week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4a	Alitretinoin resume at severe (not moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4b	Alitretinoin resume at severe (not moderate) and delgocitinib resume at moderate (not mild)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined scenarios to increase time on treatment								
2+3	0% discontinuation and 100% re-uptake, and partial responders to delgocitinib and alitretinoin at week 12 can continue treatment to week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4a+5	Alitretinoin resume at severe, 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4b+5	Alitretinoin resume at severe and delgocitinib resume at moderate, 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate population								
0	Committee preferences applied to original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Committee preferences with DFORCE outcomes post-12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Committee preferred scenarios with moderate dosing								

0a	Committee preferences with moderate dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6a	Committee preferences with DFORCE outcomes post-12 weeks and moderate dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined scenarios to increase time on treatment								
5+6	Committee preferences with DFORCE outcomes post-12 weeks and 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+6a	Committee preferences with DFORCE outcomes post 12 weeks, moderate dosing, 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DFORCE, DELTA FORCE trial; ICER, Incremental cost-effectiveness ratio; PAS, Patient Access Scheme.

In **Table 5**, the base case ICER and time on treatment results from the original submission are provided for reference. Scenario 1 outlines the results when all Committee preferred assumptions have been applied to the original base case and DELTA FORCE parameters are applied post-week 12 to align with the Committee's preferred dosing data source. Since this scenario does not achieve the target time on treatment estimates requested by the Committee, subsequent scenarios adjust the following modelling parameters to increase the time that patients remain on treatment with both delgocitinib and alitretinoin: treatment discontinuation, treatment re-initiation at the point of a relapse, severity threshold for re-treatment eligibility and time on treatment for partial responders to treatment at week 24.

Scenario 2 assumes that there is no discontinuation for patients during retreatment and that all patients resume treatment following relapse. This scenario lacks face validity because it leads to patients on PUVA having higher on-treatment probability than alitretinoin at years 1, 2 and 3 (see results in Appendix C). Scenario 3 introduces an updated stopping rule such that partial responders (i.e. patients achieving an IGA-CHE 2) to delgocitinib and alitretinoin at week 12 can continue treatment up to week 52, instead of week 24 as applied in the original base case. A combination of these two scenarios (Scenario 2+3) is provided in the list of analyses above, which produces time on treatment outcomes aligned with the Committee's preference. However, the Company believes that this scenario is less realistic given that it assumes no patients discontinue treatment, with continued treatment beyond week 12 or with re-treatment, and that they all opt to resume treatment with the same intervention following relapse. This is not consistent with data from DELTA FORCE, nor with data from the ALPHA trial.

Scenario 4 adjusts the severity at which patients reinitiate treatment upon relapse of symptoms, so patients having alitretinoin and PUVA reinitiate treatment at severe and patients having delgocitinib reinitiate treatment once their symptoms are mild (4a) or moderate (4b). This reflects the practical ease of resuming use of a topical treatment for patients, as opposed to treatments which require attendance in a secondary care setting. Scenario 5 applies a 0% retreatment discontinuation assumption for delgocitinib during retreatment and 50% lower odds of alitretinoin discontinuation during retreatment. This discontinuation assumption for alitretinoin is more realistic than assuming no patients discontinue during retreatment, while the assumption of zero discontinuation during delgocitinib retreatment is conservative as there is a disproportionate increase in costs relative to clinical efficacy in the delgocitinib arm of the model. The Company considers that a combination of these two scenarios (Scenario 4a+5) is the most robust clinically plausible scenario that achieves the time on treatment estimates requested by the NICE Committee.

The moderate population has been considered separately in Scenario 6 (which replicates Scenario 1 but for the moderate population only) and Scenario 6a, which applies delgocitinib dosing data from moderate patients in DELTA 1 and DELTA 2. To increase the proportion of patients remaining on treatment at 2 years, two subsequent combined scenarios (Scenario 5+6 and Scenario 5+6a) are presented. These combined scenarios incorporate the most plausible method for increasing time on treatment, which adjusts odds of treatment discontinuation during retreatment to 0 for delgocitinib and 50% lower for alitretinoin.

Following consideration of each of the scenario analyses presented and clinical expert opinion received by the Company, Scenario 4a+5 was determined to be the most plausible analysis and selected as the base case analysis for evaluation. The final model results are presented in **Table 6**, including a confidential PAS discount for delgocitinib.

Table 6. Base case results for comparison of delgocitinib with alitretinoin in severe CHE (inclusive of delgocitinib PAS discount)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]				

Abbreviations: CHE, Chronic hand eczema; ICER, Incremental cost-effectiveness ratio; LYG, Life years gained; QALY, Quality-adjusted life years.

To further highlight the negligible impact of method of imputing missing data (WOCF, BOCF, LOCF) on the economic analyses results, **Table 7** below outlines how the ICER is affected by varying method of imputation for each relevant scenario. Given this negligible impact, final analyses utilise the WOCF method.

Table 7. Results of relevant scenario analyses stratified by method of imputing missing data (using delgocitinib price inclusive of PAS and alitretinoin list price)

	Parameter change	Method of imputation	ICER vs alitretinoin
Severe population			
1	Committee preferences with DFORCE outcomes post-12 weeks	WOCF	[redacted]
		BOCF	
		LOCF	
2+3	0% discontinuation and 100% re-uptake, and partial responders to delgocitinib and alitretinoin at week 12 can continue treatment to week 52	WOCF	
		BOCF	
		LOCF	
4a+5	Alitretinoin resume at severe, and 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	WOCF	
		BOCF	
		LOCF	
Moderate population			
6	Committee preferences with DFORCE outcomes post-12 weeks	WOCF	
		BOCF	
		LOCF	
5+6	Committee preferences with DFORCE outcomes post-12 weeks and 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	WOCF	
		BOCF	
		LOCF	
6a	Committee preferences with DFORCE outcomes post-12 weeks and moderate dosing	WOCF	
		BOCF	
		LOCF	
5+6a	Committee preferences with DFORCE outcomes post 12 weeks, moderate dosing and 0% delgocitinib retreatment discontinuation and 50% lower odds of alitretinoin discontinuation during re-treatment	WOCF	
		BOCF	
		LOCF	

Abbreviations: BOCF, Baseline observation carried forward; DFORCE, DELTA FORCE trial; ICER, Incremental cost-effectiveness ratio; LOCF, Last observation carried forward; WOCF, Worst estimate carried forward.

Base-case cost-effectiveness results for patients with severe CHE and with moderate CHE are shown in **Table 8** for the PAS price of delgocitinib versus the list prices of alitretinoin and PUVA. Delgocitinib was less costly and more effective than PUVA in both the moderate and severe CHE populations. The ICER for delgocitinib compared with alitretinoin was [redacted] per QALY in the severe CHE population and delgocitinib dominates alitretinoin in the moderate population. Where we assume a case-mix of 60% moderate CHE patients and 40% severe patients, delgocitinib dominates both alitretinoin and PUVA.

Using the distribution of second-line CHE treatments estimated in the budget impact model (52% alitretinoin and 48% PUVA), the ICER remains cost effective. This exploratory analysis provides an insight into the impact expected if delgocitinib is adopted as a second-line treatment in NHS clinical practice.

Table 8. Base-case analysis results in the moderate and severe CHE population for delgocitinib at PAS price, alitretinoin and PUVA at list price and scenario analysis assuming a mix of moderate and severe CHE

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	Pairwise ICER (£/QALY)
Severe CHE							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid comparator (52% alitretinoin /48% PUVA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate CHE (sensitivity analysis)							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid comparator (52% alitretinoin /48% PUVA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate to severe CHE (sensitivity analysis assuming 60% moderate and 40% severe)							
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hybrid comparator (52% alitretinoin /48% PUVA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; LY, life year; PUVA, psoralen–UVA phototherapy; QALY, quality-adjusted life-year

In terms of the results of the probabilistic analysis, which are presented in , the ICER for delgocitinib versus alitretinoin among severe patients was [redacted] and was more cost effective than alitretinoin in [redacted] of iterations at a willingness to pay threshold of £20,000 per QALY gained, and in [redacted] of iterations at a threshold of £30,000. Delgocitinib dominated PUVA and was more cost effective than PUVA in [redacted] of iterations at thresholds of £20,000 and £30,000 per QALY. Among moderate patients, delgocitinib dominated both alitretinoin and PUVA in [redacted] of iterations.

Table 9. Probabilistic sensitivity analysis for revised base-case with delgocitinib at PAS price, alitretinoin and PUVA at list price

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Pairwise ICER (£/QALY)
Severe CHE					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate CHE					
Delgocitinib	[redacted]	[redacted]	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conclusion

Recognising the complexity of cost-effectiveness decision making for novel treatments, the Company has provided the additional analyses requested by the Committee. In addition, through expert elicitation the Company has made every effort to narrow uncertainty and seek clinical validation on key areas that were discussed during and after the first ACM. Finally, the Company has included a PAS discount to meet the cost effectiveness threshold of £25,000 per QALY proposed by the committee, even when considering that a commercially confidential price exists for alitretinoin. This commercial arrangement results in delgocitinib continuing to be dominant versus PUVA and being within the cost-effectiveness threshold versus alitretinoin.

The updated base-case analysis aligns closely with the Committee's preferred assumptions across all key parameters, and we have transparently outlined the rationale for each modelling choice and explored the impact of alternative approaches. The Company believes that the revised base case represents the most appropriate and robust scenario for decision-making and provides a sound foundation for the Committee to reach a positive and informed conclusion at the second ACM.

The additional information and context provided in this submission addresses the outstanding questions relating to clinical practice and provide the basis for appropriate access for moderate to severe CHE patients, for whom existing topical treatments are insufficient and the burden of disease remains high. The Company remains willing to fully cooperate with future requests to support a robust evaluation and ultimately enable access to a novel, efficacious topical treatment for patients with CHE.

Appendices

Appendix A. Expert elicitation summary report

To address some of the uncertainties related to treatment of CHE in clinical practice, expert elicitation was conducted with five dermatologists who have specialist clinical experience of treating CHE in NHS practice. The expert elicitation consisted of expert interviews as well as a structured elicitation exercise. The interviews were conducted virtually with each of the five clinical experts individually in July 2025.

The objectives of the expert interviews can be summarised as follows:

1. To understand if clinicians face difficulty in obtaining approval for using alitretinoin in patients with moderate CHE that have a DLQI score of less than 15
2. To understand if there is a difference in the amount of topical treatment used by patients with moderate CHE compared to patients with severe CHE
3. To understand the proportion of patients who experience a positive response to alitretinoin or PUVA by week 24, and whether those who do not achieve a positive response at 24 weeks are eligible to receive alitretinoin or PUVA again
4. To understand the level of severity that clinicians would consider restarting treatment with alitretinoin or PUVA in patients who previously experienced a positive response, following a loss of response/relapse

For the structured elicitation exercise, experts received 1:1 training to introduce the concept of structured elicitation and common forms of cognitive bias that may impact the results. Experts were first asked to quantify their individual lower and upper bounds probabilities to express the level of uncertainty associated with the parameter of interest. The elicitation tool then constructed resulting intervals divided into equally sized ‘bins’, into which experts allocated ‘chips’ to indicate their perceived likelihood of the probability lying within each interval. Experts were also asked to provide a rationale for their answers and given an opportunity to revise their results at the end of the exercise, as well as after seeing the aggregated results once all interviews had been completed.

The aim of the structured expert elicitation exercise was to achieve consensus on the time patients spend receiving second-line treatments in UK clinical practice to treat moderate and severe CHE, specifically:

- To understand the proportion of patients still receiving treatment, through periods of relapse and re-treatment, with alitretinoin at 24 months
- To understand the proportion of patients still receiving treatment, through periods of relapse and re-treatment, with PUVA at 24 months

The qualitative responses to the interview questions are summarised below:

1. Use of alitretinoin in moderate CHE patients

Clinicians reported differences in their ability to obtain approval for prescribing alitretinoin moderate CHE patients with a DLQI score of less than 15. While some clinicians were able to navigate prescribing barriers easily, others highlighted that auditing processes and pharmacy protocol often make it difficult to access alitretinoin for these patients. Some patients are aware of the DLQI threshold associated with prescribing alitretinoin and may intentionally emphasise symptoms to reach the qualifying score of 15 to access treatment. Nonetheless, clinician judgement remains central to treatment choice alongside patient preference, especially when disease burden is significant.

2. Dosing of topical treatment in patients with moderate and severe CHE

All clinicians agreed that the consumption of topical treatments differs substantially between moderate CHE and severe CHE, with greater use of topical treatment in severe patients.

3. Response to treatment and retreatment with alitretinoin

The proportion of moderate to severe patients who experience a positive response to alitretinoin was reported to vary widely, ranging from 20% to 75%, with CHE subtype being an important influencing factor.

Among patients who do not respond to alitretinoin by week 24, most clinicians indicated that retreatment could still be considered, primarily driven by patient preference and the limited availability of alternative treatment options. Even in cases where patients did not achieve clear or almost clear skin, some clinicians would still prescribe alitretinoin again if it previously led to an improvement in DLQI score. Importantly, a patient's response in a subsequent treatment cycle does not necessarily correlate with their response during initial treatment. However, if significant side effects were experienced during initial treatment, clinicians agreed it was unlikely that the patient would choose to undergo treatment again.

When considering patients who had previously responded positively to alitretinoin, clinicians differed in how they determined the threshold for restarting treatment following a relapse. Some were comfortable restarting treatment even at mild severity, particularly when prompted by the patient. Overall, decisions are highly guided by patient choice, especially in cases where alitretinoin had been effective previously. The timing of relapse also plays a key role and influences retreatment decisions.

4. Response to treatment with PUVA

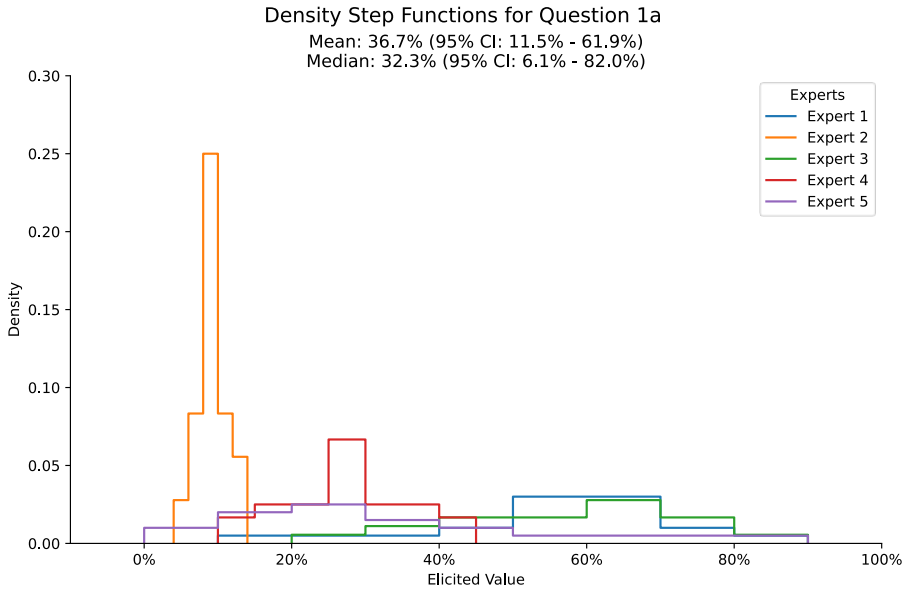
For PUVA, clinicians reported response rates for moderate to severe CHE patients ranging from 20 to 50%.

Among patients who did not respond by week 24, clinicians agreed that they would generally not consider repeating the treatment once the full course had been completed. The exception was for patients who either experienced partial benefit or were unable to complete the initial treatment course, in which case retreatment with PUVA would be considered.

In patients who previously experienced a positive response to PUVA, clinicians would consider restarting treatment in patients with moderate or severe CHE, but this would be guided by the speed of relapse. A rapid relapse is viewed as an indication of limited treatment response. However, clinicians are cautious in offering repeat courses of PUVA due to the associated risk of skin cancer, extended wait times and strain on hospital resources. As a result, PUVA would typically not be offered again within 12 months of stopping treatment, with patient preference being a key factor in decision making.

Structured expert elicitation results

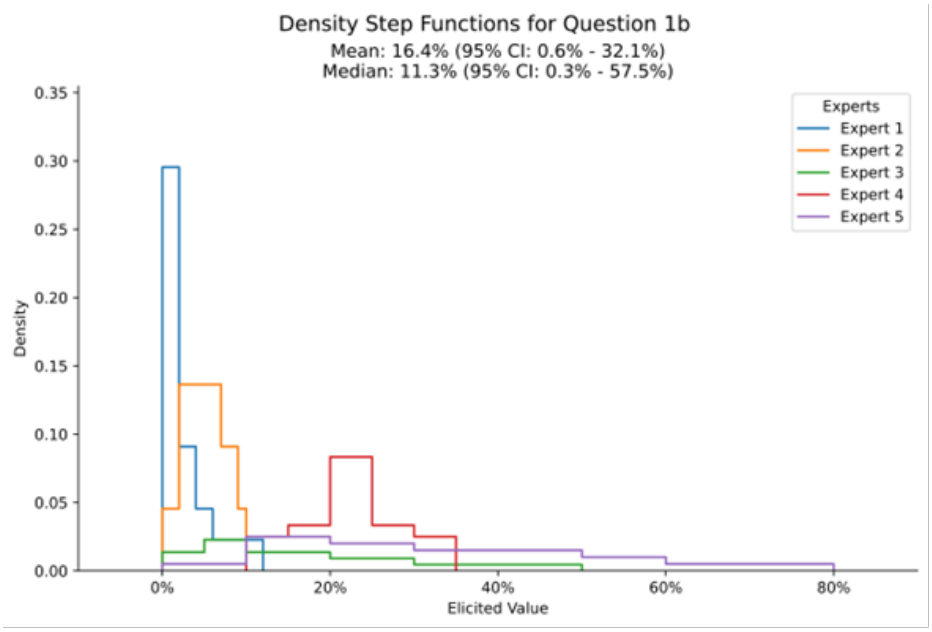
Figure 1: Probability distributions of the proportion of patients still receiving alitretinoin at 24 months after initiation, considering those patients that experienced a positive response to treatment with alitretinoin at 24 weeks.



Abbreviations: CI: Confidence interval.

The median estimated proportion of patients still receiving alitretinoin at 24 months is 32.3% (95% CI: 6.1% - 82.0%). Individual responses varied, as illustrated by the probability distributions.

Figure 2: Probability distributions of the proportion of patients still receiving PUVA at 24 months after initiation, considering those patients that experienced a positive response to treatment with PUVA at 24 weeks.



Abbreviations: CI: Confidence interval.

The median proportion of patients remain on PUVA at 24 months is 11.3% (95% CI: 0.3% - 57.5 %). Experts indicated different levels of certainty, reflected by the variation in the initial ranges selected.

Expert elicitation conclusion

The outputs of the qualitative interviews highlight the complex landscape of treatment decision-making for moderate to severe CHE patients. Prescribing alitretinoin can be challenging for some clinicians due to external restrictions, particularly for patients with lower DLQI scores, though clinicians often prioritise patient preference. Observed response rates to alitretinoin and PUVA vary amongst clinicians, and clinicians take a nuanced approach to retreatment. Alitretinoin is more readily restarted due to limited treatment options, while PUVA is limited by safety concerns and logistical constraints. For both PUVA and alitretinoin, relapse timing and patient preference are key considerations for retreatment.

Based on the results of the structured expert elicitation exercise, clinicians estimated that alitretinoin (median: 32.3%) is more likely to be used at 24 months in patients who had previously achieved a positive response at 24 weeks than PUVA (median: 11.3%). These results were driven by the high treatment burden for both alitretinoin and PUVA and the lack of treatment alternatives. Alitretinoin patients who achieve a positive response and do not experience side effects are likely to request the same treatment again when they relapse. However, there is a large cohort of alitretinoin patients who do not tolerate the treatment or have poor compliance with blood tests, and they will not receive alitretinoin again. As PUVA treatment is time consuming and can be difficult to access, patients may be reluctant to receive an additional round of treatment 24 months after treatment initiation. Due to the associated risk of skin cancer, PUVA is not a long-term option and would only be considered if the patient achieved a good response from the initial treatment (e.g. clearance for 6 months to 1 year). The large confidence intervals demonstrate the variation of clinical practice for treating CHE in a real-world setting as well as the variation in each clinician's individual patient cohort.

Appendix B. Parameters for response and non-response using alternative imputation methods

Table 1. Week 12 response rates and distributions of non-responders across partial, low and insufficient response rates using worst observation carried forward imputation (composite estimand)

Comparator	IGA-CHE 0/1	Not IGA-CHE 0/1 severity states			IGA-CHE non-response states			Source/notes
					PR	LR	InR	
	12-week risk [a]	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]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to delgocitinib in the absence of moderate evidence.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2 vehicle arm
Severe CHE (base case)								
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 and DELTA FORCE, pooled.
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from DELTA FORCE.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to alitretinoin
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 vehicle arm

[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] Values are based on the vehicle / placebo comparator in the NMA and define the probability of full response in the BSC health state.

Table 2. Week 12 response rates and distributions of non-responders across partial, low and insufficient response rates using baseline observation carried forward imputation

Comparator	IGA-CHE 0/1	Not IGA-CHE 0/1 severity states			IGA-CHE non-response states			Source/notes
					PR	LR	InR	
	12-week risk [a]	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]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to delgocitinib in the absence of moderate evidence.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to delgocitinib.
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2 vehicle arm
Severe CHE (base case)								
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 and DELTA FORCE, pooled.
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from DELTA FORCE.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to alitretinoin
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 vehicle arm

[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] Values are based on the vehicle / placebo comparator in the NMA and define the probability of full response in the BSC health state.

Table 3. Week 12 response rates and distributions of non-responders across partial, low and insufficient response rates using last observation carried forward imputation

Comparator	IGA-CHE 0/1	Not IGA-CHE 0/1 severity states	IGA-CHE non-response states	Source/notes

					PR	LR	InR	
	12-week risk [a]	**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]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to delgocitinib in the absence of moderate evidence.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumed equivalent to delgocitinib.
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from moderate subgroup analysis of DELTA 1 and DELTA 2 vehicle arm
Severe CHE (base case)								
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 and DELTA FORCE, pooled.
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from DELTA FORCE.
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states assumed equivalent to alitretinoin
BSC [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Probability of response from NMA. Distribution across non-responder states from severe subgroup analysis of DELTA 1 and DELTA 2 vehicle arm

[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] Values are based on the vehicle / placebo comparator in the NMA and define the probability of full response in the BSC health state.

Appendix C. Results of scenario analyses versus PUVA using delgocitinib PAS price

Table 1 presents the results of scenario analyses comparing delgocitinib to PUVA in severe and moderate CHE patients. With the application of the PAS to delgocitinib's price, delgocitinib dominates PUVA across all scenarios, and this holds whether dosing is based on the Committee's preference of using the weighted average of week 12 and week 24 delgocitinib dosing data from DELTA 1, DELTA 2 and DELTA FORCE or on the dosing data used from DELTA FORCE (as presented in the revised base case analyses in Table 8 of the main submission). Delgocitinib's dominance holds regardless of whether input values applied subsequent to week 12 in the model are based on the originally submitted base case (scenario 0) or on data derived directly from DELTA FORCE (scenario 1).

The same parameters explored to increase the time on treatment in the comparison with alitretinoin were tested here in the comparison with PUVA. Scenario 4a+5 in the severe CHE subpopulation and scenario 5+6a in the moderate CHE subpopulation were considered the best calibrated to achieve the levels of time on treatment sought by the Committee and were therefore taken into the revised base case presented in Table 8 of the main submission.

Table 1. Results of scenario analyses (using delgocitinib PAS price [redacted] versus PUVA, including time on treatment variables

	Parameter change	ICER	% of patients still on delgocitinib			% of patients still on PUVA[a]		
			Yr 1	Yr 2	Yr 3	Yr 1	Yr 2	Yr 3
0	Original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe population								
1	Committee preferences with DFORCE outcomes post-12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual scenarios to increase time on treatment								
2	O% discontinuation and 100% re-uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Partial responders to delgocitinib at week 12 can continue treatment to week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4a	PUVA resume at severe (not moderate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4b	PUVA resume at severe (not moderate) and delgocitinib resume at moderate (not mild)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	0% delgocitinib retreatment discontinuation and 50% lower odds of PUVA discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined scenarios to increase time on treatment								
2+3	0% discontinuation and 100% re-uptake, and partial responders to delgocitinib at week 12 can continue treatment to week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4a+5	PUVA resume at severe, 0% delgocitinib retreatment discontinuation and 50% lower odds of PUVA discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4b+5	PUVA resume at severe, delgocitinib resumes at moderate (not mild), 0% delgocitinib retreatment discontinuation and 50% lower odds of PUVA discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate population								
6	Committee preferences with DFORCE outcomes post-12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+6	Committee preferences with DFORCE outcomes post-12 weeks and 0% delgocitinib retreatment discontinuation and 50% lower odds of PUVA discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6a	Committee preferences with moderate dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5+6a	Committee preferences with DFORCE outcomes post-12 weeks, moderate dosing, 0% delgocitinib retreatment discontinuation and 50% lower odds of PUVA discontinuation during re-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Note that the percent still on treatment with PUVA includes both patients still on initial PUVA as well as those receiving PUVA as part of the NL treatment basket.

NICE National Institute for Health and Care Excellence

Delgocitinib for treating moderate to severe chronic hand eczema

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 28 July 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National Eczema Society

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	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 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. AbbVie is a corporate member of National Eczema Society and pays an annual fee for this of £20,000 plus VAT.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned this recommendation does not reflect patient concerns about the long-term risk of using topical corticosteroids (TCS) to manage chronic hand eczema, including concerns of topical steroid withdrawal (TSW). This is the reality for many patients, who are not currently offered anything other than TCS. For many patients, topical corticosteroids are not an effective treatment

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	anyway. The availability of an effective topical treatment for chronic hand eczema will hugely improve the quality of life for the many thousands of people who suffer from the debilitating condition. It seems economically counter-productive to suggest patients should be escalated to systemic treatments, when there is an effective topical treatment available that most patients would prefer compared to a systemic.
2	We are concerned this recommendation does not sufficiently take into account patient concerns about the significant adverse effects of alitretinoin, when there is a treatment like delgocitinib that has a much better safety profile and is more effective. The furore around alitretinoin for treating acne is indicative of patient worries. To suggest alitretinoin and delgocitinib are compatible is dismissive of patient concerns and preferences. Phototherapy, requiring multiple hospital visits over months, is simply not a practical option for many working people and those with family responsibilities.
3	We are concerned this recommendation does not take into account the importance of providing convenient and effective treatments for CHE for women of childbearing age. Using alitretinoin necessitates medical and laboratory monitoring and a pregnancy prevention programme. Women, who are disproportionately affected by CHE, need safer and better treatments for CHE.
4	We are concerned this recommendation does not take into account the needs for a range of treatment options to manage CHE. This is really important to access an effective treatment to manage the range and mix of sub-types including irritant contact dermatitis and atopic eczema. To imply current treatments are somehow equally effective in treating all aetiologies in misleading.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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Delgocitinib for treating moderate to severe chronic hand eczema

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

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

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

EAG response to company draft guidance comments

July 2025

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 174560.

1 Introduction

This report contains the External Assessment Group's (EAG's) critique of the additional analysis and assumptions informing the Single Technology Appraisal (STA) of delgocitinib (brand name: Anzupgo®; Leo Pharma, Ballerup, Denmark) for treating severe chronic hand eczema [ID6408] following the draft guidance published post Appraisal Committee Meeting (ACM) 1.

Table 1 presents a brief overview of the key issues identified by the EAG as being potentially important for decision making. Table 2 presents EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 2 of this report details the EAG critique of the additional analysis requested by the Committee post ACM-1, provided by the company.

The EAG notes that the company has proposed an update to the Patient Access Scheme (PAS) discount for delgocitinib. As the updated PAS is yet to be approved, the EAG has been advised by the National Institute for Health and Care Excellence (NICE) to use the PAS from the company's original submission in their analyses and base cases.

All issues identified represent the EAG's view, not the opinion of NICE.

Table 1. Summary of key issues

#	Summary of issue	Report sections
1	Imputation of missing data	2.1
2	Delgocitinib dosing assumptions for patients with moderate symptoms at baseline	2.3

Table 2. EAG's preferred model assumptions

Scenario	Delgocitinib vs alitretinoin		Delgocitinib vs PUVA	
	ICER (£)	Change from company base case (£)	ICER (£)	Change from company base case (£)
Patients with severe symptoms at baseline				
Company base case	£22,472	-	£12,745	-
Last observation carried forward	£22,213	-£259	£13,365	£620
Moderate alitretinoin and PUVA patients eligible for re-treatment	£18,507	-£3,965	£12,020	-£725
Half per cycle re-treatment discontinuation	£22,981	£509	£10,800	-£1,945

Patients with moderate symptoms at baseline				
Company base case	£11,827	-	£3,678	-
Last observation carried forward	£11,849	£22	£4,183	£505
Moderate alitretinoin and PUVA patients eligible for re-treatment	£5,845	-£5,982	£3,357	-£321
Half per cycle re-treatment discontinuation	£11,216	-£611	£949	-£2,729
DELTA FORCE delgocitinib dosing	£22,129	£10,302	£13,047	£9,369

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TTD, time to treatment discontinuation.

2 EAG response

2.1 Imputation of missing data

Following Appraisal Committee Meeting 1 (ACM), the Committee requested that the company provide additional analyses to evaluate the choice of imputation approach to account for missing data in the company's DELTA trials. Within the DELTA 1, DELTA 2, and DELTA FORCE trials, the company had previously used a worst observation carried forward (WOCF) approach to impute missing data. However, the Committee requested that the company use the alternate imputation approaches of baseline observation carried forward (BOCF) and last observation carried forward (LOCF). Accordingly, within the resubmission, the company has presented the results of analyses for the DELTA FORCE trial, and indirect treatment comparisons (ITCs) using the BOCF, LOCF, and submitted WOCF approaches. However, from the company's resubmission, it is unclear whether the company only compared the BOCF, LOCF, and WOCF imputation approaches in the DELTA FORCE trial (comparing delgocitinib to alitretinoin in severe patients) and not the DELTA 1 or DELTA 2 trials (comparing delgocitinib to vehicle cream in moderate and severe patients). Additionally, the company noted that WOCF used within the company's original submission imputed data for intercurrent events including discontinuation. However, when implementing the BOCF and LOCF imputation approaches, the company took data as observed, regardless of intercurrent events, and only imputed data where it was missing. As such, it is unclear how this difference in accounting for intercurrent events between imputation approaches would impact the results of such approaches.

While the company has performed additional analyses in line with the Committee's request to consider the BOCF and LOCF imputation approaches, the EAG notes that these approaches are associated with limitations and, despite being widely implemented, are not considered to be robust

imputation approaches.[1, 2] The WOCF imputation approach introduces bias against the comparator arm with the higher dropout rate. As such, the WOCF approach would be expected to bias results in favour of delgocitinib for the DELTA 1, DELTA 2, and DELTA FORCE trials. Likewise, the only situation in which the LOCF approach is unbiased is when missing data occurs solely by chance and the known data has exactly the same distribution as the unknown missing data.[2] Accordingly, the EAG considers that it would have been preferable to implement a multiple imputation approach, given that this approach is widely considered to be a robust method to impute missing data.[3]

2.1.1 DELTA trials

2.1.1.1 DELTA 1 and DELTA 2

Within the company's resubmission, the company did not present results to demonstrate how the choice of imputation approach affected the results of the DELTA 1 and DELTA 2 trials. Accordingly, based upon the company's resubmission, it is unclear whether additional analyses where the BOCF and LOCF imputation approaches were applied to the DELTA 1 and DELTA 2 trials were performed.

2.1.1.2 DELTA FORCE

For the DELTA FORCE trial, the company presented the results of the comparison of the WOCF, BOCF, and LOCF imputation approaches in Table 3. However, the company did not specify which timepoint these results correspond to (e.g., Week 12 or Week 16). For the DELTA FORCE trial, the company presented, for each imputation approach, the number of patients who had an Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE) score of 0 or 1 (i.e., those patients achieving IGA-CHE treatment success [IGA-CHE TS]), 2, 3, and 4. Additionally, the company provided odds ratios (ORs) for the comparison of delgocitinib to alitretinoin.

Table 3. Distribution of DELTA FORCE patients across IGA-CHE severity and odds ratio of achieving IGA-CHE 0/1 using worst, baseline and last observation carried forward to impute missing data. Reproduced from Table 1 in the company's resubmission.

Treatment arm	IGA-CHE 0/1	Not IGA-CHE 0/1			n	Odds ratio (95% CI) IGA-CHE 0/1
		IGA-CHE 2, n (%)	IGA-CHE 3, n (%)	IGA-CHE 4, n (%)		Delgocitinib vs Alitretinoin
WOCF, composite estimate						
Delgocitinib	68 (27.2)	[redacted]	[redacted]	[redacted]	250	1.88 (1.22 to 2.89)
Alitretinoin	42 (16.6)	[redacted]	[redacted]	[redacted]	253	
BOCF						
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

LOCF						
Delgocitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BOCF, Baseline observation carried forward; CI, Confidence interval; IGA-CHE, The Investigator Global Assessment of Chronic Hand Eczema; LOCF, Last observation carried forward; WOCF, Worst estimate carried forward.

When discussing the results of the additional analyses for the DELTA FORCE trial, the company asserts that the comparative efficacy results, of delgocitinib relative to alitretinoin, remain robust. As such, the company notes that, across all imputation approaches, delgocitinib consistently demonstrates a significantly greater efficacy compared to alitretinoin for the outcome of IGA-CHE TS. Additionally, the company noted that the percentage of patients in each group of IGA-CHE score was relatively consistent. However, the single exception of this was that there was an increased percentage of patients with an IGA-CHE score of 3, and a decreased percentage of patients with an IGA-CHE score of 4, when the LOCF imputation approach was used.

The EAG is in broad agreement with the conclusions of the company. However, the EAG notes that there are numerical differences in the ORs, comparing delgocitinib to alitretinoin, for IGA-CHE TS across the imputation approaches. For instance, the OR [redacted] when using the WOCF imputation approach to [redacted] when using the LOCF imputation approach. Accordingly, there is up to a [redacted] difference in ORs depending on the implemented imputation approach, which represents a non-trivial reduction in the difference in efficacy of delgocitinib relative to alitretinoin. Additionally, the EAG notes that the company's preferred WOCF imputation approach leads to an OR for IGA-CHE TS that is the most in favour of delgocitinib. Finally, the EAG notes that it is unclear whether these results would change if intercurrent events were consistently accounted for across all of the considered imputation approaches.

2.1.2 Fixed-effect network meta-analyses

Following ACM1, the Committee's preference for the ITCs was to use the fixed-effect network meta-analyses (NMAs) presented by the company. Accordingly, the company presented the results of fixed-effect NMAs, stratified by disease severity, where different imputation approaches (i.e., BOCF, LOCF, and the submitted WOCF) were implemented (Table 4). However, as noted above, it is unclear whether the company considered the impact of using BOCF and LOCF in all DELTA trials or solely the

DELTA FORCE trial. As such, it is unclear whether the results of the NMAs provided by the company (Table 4) were performed using updated results for all DELTA trials or solely the DELTA FORCE trial.

Table 4. Fixed-effects NMA odds ratios for delgocitinib versus comparators (week 12 IGA-CHE 0/1 endpoint response outcome). Reproduced from Table 2 in the company's resubmission.

Delgocitinib vs treatment	Median odds ratios (95% credible intervals)					
	Severe CHE			Moderate CHE		
	WOCF (company base case)	BOCF	LOCF	WOCF (company base case)	BOCF	LOCF
Cream vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOCF, Baseline observation carried forward; CHE, Chronic hand eczema; CI, Confidence interval; IGA-CHE, The Investigator Global Assessment of Chronic Hand Eczema; LOCF, Last observation carried forward; PUVA, Psoralen plus ultraviolet A; WOCF, Worst estimate carried forward.

When discussing the results of the fixed-effect NMAs, the company noted that all results remain statistically significant in favour of delgocitinib. While the EAG agrees with the company regarding the statistical significance of the fixed-effect NMAs, the EAG notes that there are some considerable differences in the ORs, for each comparison and subgroup, depending on which imputation approach was implemented. For instance, for the comparison of delgocitinib to PUVA in the moderate CHE subgroup, the reported OR was [redacted] when using the WOCF imputation approach compared to [redacted] when using the LOCF imputation approach. Accordingly, there is up to a [redacted] difference in ORs depending on the implemented imputation approach, which represents a non-trivial reduction in the efficacy of delgocitinib relative to PUVA or other comparators. Likewise, the EAG notes that the company's preferred WOCF imputation approach leads to ORs for IGA-CHE TS that is the most in favour of delgocitinib for all combinations of comparators and disease severity subgroups.

The EAG notes that the results of the relative comparisons of delgocitinib to alitretinoin, and delgocitinib to PUVA, are consistent across both the moderate CHE and severe CHE subgroups for each imputation approach. The EAG anticipates that this is likely to have occurred due to data for these comparisons only being available from the DELTA FORCE and ALPHA trials that solely considered patients with severe CHE. Furthermore, the EAG notes that it is unclear whether the

results of the fixed-effect NMAs would change if intercurrent events were consistently accounted for across all of the considered imputation approaches. Finally, the EAG notes that it is unclear whether the different imputation approaches were applied solely to the DELTA FORCE trial or to all DELTA trials. If the BOCF and LOCF imputation approaches were only applied to the DELTA FORCE trial then the trials included in the fixed-effect NMA would have comprised trials with different imputation approaches (i.e., WOCF for the DELTA 1 and DELTA 2 trials and BOCF/LOCF for the DELTA FORCE trial). Accordingly, the EAG considers it preferable to implement a consistent imputation approach across all studies included in the NMAs. As such, it is unclear what effect the inconsistent use of imputation approaches across the DELTA trials would have upon the results of the fixed-effect NMAs.

2.1.3 Summary

Considering the results presented in the company's resubmission, the EAG agrees with the company that the significant comparative efficacy of delgocitinib relative to all other comparators is demonstrated regardless of whether the BOCF, LOCF, or WOCF imputation approaches were implemented. However, the EAG has identified the following issues regarding the additional analyses presented by the company:

- The EAG would have preferred a multiple imputation approach to have been considered given known limitations with BOCF, LOCF, and WOCF imputation approaches.
- The company's resubmission is unclear as to whether BOCF and LOCF imputation approaches were implemented solely for the DELTA FORCE trial or all DELTA trials.
    - If the BOCF and LOCF imputation approaches were only implemented for the DELTA FORCE trial, it is unclear how the mixed imputation approaches implemented would impact the results of the fixed-effect NMAs.
- There were non-trivial differences in the efficacy of delgocitinib relative to other comparators, based on DELTA FORCE and NMA results, depending upon the imputation approach.
    - For all analyses, the company's preferred WOCF imputation approach led to ORs that were most in favour of delgocitinib relative to all other comparators.
- Intercurrent events were accounted for differently for the company's preferred WOCF imputation approach compared to the BOCF and LOCF imputation approaches.

- It is unclear whether the difference in accounting for intercurrent events, between the imputation approaches, would affect the results of the additional analyses performed by the company.

While acknowledging the divergence from the Committee's stated preference, the EAG's preferred approach would be to use direct evidence from the DELTA FORCE trial for the comparison of delgocitinib to alitretinoin, as opposed to the fixed-effect NMAs. Furthermore, the uncertainty surrounding the potentially inconsistent imputation approaches across the DELTA trials further supports the EAG's position.

Given that the LOCF approach is the most conservative, and is therefore associated with the lowest decision risk, it has been included in the EAG's preferred assumptions. The EAG additionally provides an alternative base case, which uses the DELTA FORCE (WOCF) treatment effects to compare delgocitinib to alitretinoin in patients with severe symptoms at baseline, given that in the company and EAG base case assumptions, all other treatment effects are informed using DELTA FORCE

2.2 Time on treatment for delgocitinib, alitretinoin and PUVA

At ACM 1 the clinical experts agreed with the opinions of the EAG clinical expert that in contrast to the five percent estimated in the model, "around 25% of people on alitretinoin would still being having treatment after two years in clinical practice", specifically stating that "they thought it was reasonable to assume that 25% of people would have long term intermittent courses of alitretinoin to manage their chronic hand eczema". In the published draft guidance, the Committee concluded that "…modelled time on treatment did not reflect clinical practice" and "[the Committee] would like to see analyses that include 25% of people on alitretinoin remaining on treatment at two years in the model".

In order to achieve the scenario as requested by the Committee, the company considered that the most appropriate method to achieving the preferred time on treatment estimates was a combination of reducing the likelihood of discontinuation during periods of re-treatment and increasing the severity threshold for re-treatment eligibility, thus extending the time to treatment re-initiation. In the company's updated base case assumptions, it was assumed that;

- Alitretinoin and PUVA patients would be eligible for re-treatment when patient symptoms relapse to severe (IGA-4) (previously eligible when symptoms relapsed to moderate [IGA-3]);

- Alitretinoin per cycle discontinuation during re-treatment was half that previously assumed (from 6.83% to 3.54%);
- Delgocitinib per cycle discontinuation during re-treatment was 0% (from 2.8%).

Under these assumptions the proportion of alitretinoin patients estimated to remain on treatment after two years of treatment increased from [redacted] to [redacted].

The EAG agrees with the company that per cycle re-treatment discontinuation and re-treatment eligibility can greatly influence the proportions of patients on treatment estimated in the model. However, the EAG notes that the company's assumptions around eligibility conflict with the EAG's clinical expert opinions, which reflected that alitretinoin patients would be eligible for re-treatment when symptoms relapse to a moderate severity. As such the EAG considers the assumption does not reflect clinical practice and is therefore not appropriate.

With respect to the company's assumptions around per-cycle re-treatment discontinuation, the EAG considers that adjusting this parameter is appropriate given the parameter is not informed by patients who discontinued during re-treatment in the DELTA FORCE trial. The EAG notes that in the original submission, the per-cycle discontinuation during re-treatment was assumed to be the same as the per cycle discontinuation during continued treatment in DELTA FORCE (the additional 12 weeks of treatment provided to patients who failed to achieve a full response after the initial 12 weeks of treatment). The EAG was critical of this assumption as patients who had failed to achieve a full response during initial treatment were used to inform the discontinuation of patients who had achieved a full response during re-treatment.

The EAG considers that the company's assumption that alitretinoin patient per cycle discontinuation during re-treatment is half that previously assumed is appropriate but questions the strong assumption that there is no discontinuation during re-treatment for delgocitinib patients. Given the suitability of assuming half the discontinuation rate for alitretinoin patients, the EAG considers that the assumption is equally suitable for delgocitinib patients. Therefore, the EAG's base case assumptions include:

- Alitretinoin per cycle discontinuation during re-treatment was half that of continued treatment in DELTA FORCE (from 6.83% to 3.54%);
- Delgocitinib per cycle discontinuation during re-treatment was half that of continued treatment in DELTA FORCE (from 2.84% to 1.42%).

The EAG notes that under these assumptions, the proportions of alitretinoin and delgocitinib patients estimated to remain on treatment after two years are [redacted] and [redacted], respectively. As such, the EAG base case assumptions fail to replicate the proportion of patients who would remain on treatment in clinical practice but reflects how patients would be treated in clinical practice, which the EAG considers to be of more critical importance.

The EAG notes that there are limited differences in the incremental cost and QALYs when assuming the different sets of company and EAG eligibility and discontinuation assumptions; however, in terms of costs effectiveness the company's preferred assumptions are less favourable towards delgocitinib than the EAG assumptions. Changing the eligibility of re-treatment for alitretinoin patients to requiring severe symptoms leads to decreased costs and QALYs for alitretinoin patients as they spend more time off treatment (but not discontinued to next line care) and in more severe health states. Overall, the differences in incremental cost and QALYs between the company and EAG preferred assumptions are £[redacted] and [redacted] QALYs.

2.3 Delgocitinib dosing

In the published draft guidance following ACM 1, the Committee considered that the EAG's modelling assumptions were appropriate, aside from the exclusion of adverse events from the model, specially stating that "[the Committee] concluded that all the EAG's other amendments [aside the exclusion of adverse events] to the model were appropriate". With respect to dosing, in the EAG listed assumptions DELTA FORCE consumption data was used to inform dosing in the comparison between delgocitinib and alitretinoin, with DELTA 1,2 and FORCE used to inform the delgocitinib and PUVA comparison.

In the company's response to the draft guidance, the company considered that deriving dosing data exclusively from DELTA FORCE for both patients with severe and moderate symptoms at baseline in the model presented significant methodological concerns given the trial's exclusive inclusion of patients with severe symptoms. As such, the company considered that applying dosing data directly to moderate patients risks systematically overestimates resource use and costs in the model for patients with moderate symptoms. The company notes that the DELTA 1 and 2 trials recruited both patients with moderate symptoms at baseline, and as such, would be a more appropriate source from which to inform dosing for patients with moderate symptoms at baseline as it allows for a robust and proportion synthesis of dosing and consumption in moderate patients.

While the EAG agrees with the company that informing the dosing of patients with moderate symptoms at baseline based on trial data from patients with moderate symptoms at baseline has face validity; however, the EAG is concerned around the implicit assumptions included within this assumption, namely, that patients with the same symptom severity will use different dosages of treatment. If there is no fundamental difference between patients with moderate and severe symptoms at baseline, and patients with moderate symptoms at baseline are simply those that are yet to progress to severe symptoms, then the EAG considers that DELTA FORCE is a robust source from which to derive dosing data, as after initial treatment, dosing is dependent on the severity of symptoms on relapse, which is the same for moderate and severe patients at baseline alike.

If patients with moderate and severe symptoms at baseline are fundamentally different, meaning they can be considered as separate groups (moderate patients and severe patients), then the EAG considers that the DELTA 1 and 2 studies are an appropriate source for informing treatment dosing. This is because these studies are directly relevant to patients who start with moderate symptoms.

This distinction is important *if* the moderate symptoms experienced by patients who begin with moderate symptoms are different from the moderate symptoms experienced by patients who begin with severe symptoms and then relapse to moderate symptoms.

The EAG notes the different recorded dosages of delgocitinib for severe patients at baseline in DELTA FORCE and moderate symptoms at baseline in DELTA 1 and 2 (Table 5). In the EAG base case, the delgocitinib dosage per symptom severity category has been informed using DELTA FORCE, however, an alternative base case has also been provided which assumes the moderate patient at baseline DELTA 1 and 2 dosing. The alternative base case highlights the sensitivity of the ICER to the dosing of delgocitinib.

Table 5. Delgocitinib consumption per symptom severity state. Reproduced from Table 4 in the company's resubmission.

IGA-CHE category	Severe symptoms at baseline	Moderate symptoms at baseline
	DELTA FORCE	DELTA 1 and DELTA 2
0/1 (clear / almost clear)	[redacted]	[redacted]
2 (mild)	[redacted]	[redacted]
3 (moderate)	[redacted]	[redacted]
4 (severe)	[redacted]	[redacted]

Abbreviations: IGA-CHE, Investigator's Global Assessment for chronic hand eczema

3 EAG base case assumptions and results

Table 6 outlines the EAG's preferred base case modelling assumptions, used to inform the EAG's base case results as presented in Table 7.

Table 8 provides the alternative EAG base cases which additionally include the assumptions outlined in Sections 2.1.3 and 2.3, namely;

- Using DELTA FORCE to inform the 12-week treatment effects instead of the Network Meta-Analysis (NMA) when comparing delgocitinib to alitretinoin;
- Using DELTA 1 and 2 to inform the dosing of delgocitinib for patients with moderate symptoms at baseline.

Table 6. EAG preferred modelling assumptions

Preferred assumption	Delgocitinib vs alitretinoin		Delgocitinib vs PUVA	
	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)	Independent ICER (£/QALY)	Cumulative ICER (£/QALY)
Patients with severe symptoms at baseline				
Company base case	£22,472	-	£12,745	-
Last observation carried forward	£22,213	£22,213	£13,365	£13,365
Moderate alitretinoin and PUVA patients eligible for re-treatment	£18,507	£20,622	£12,020	£13,492
Half per cycle re-treatment discontinuation	£22,981	£19,660	£10,800	£10,926
Patients with moderate symptoms at baseline				
Company base case	£11,827	-	£3,678	-
Last observation carried forward	£11,849	£11,849	£4,183	£4,183
Moderate alitretinoin and PUVA patients eligible for re-treatment	£5,845	£6,209	£3,357	£4,039
Half per cycle re-treatment discontinuation	£11,216	£3,017	£949	£1,186
DELTA FORCE dosing	£22,129	£17,854	£13,047	£11,799

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy; QALY, quality-adjusted life year.

Table 7. EAG base case outcomes

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Patients with severe symptoms at baseline							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,660
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,926
Patients with moderate symptoms at baseline							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,854
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,799
Probabilistic results							
Patients with severe symptoms at baseline							
Delgocitinib	[redacted]	-	[redacted]	-	-	-	-
Alitretinoin	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£22,170
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£11,084
Patients with moderate symptoms at baseline							
Delgocitinib	[redacted]	-	[redacted]	-	-	-	-
Alitretinoin	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£20,065
PUVA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	£11,872

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy; QALY, quality-adjusted life year.

Table 8. Alternative base case

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Patients with severe symptoms at baseline – DELTA FORCE initial treatment effects (WOCF)							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,241
Patients with moderate symptoms at baseline – DELTA 1 and 2 dosing from patients with moderate symptoms at baseline							
Delgocitinib	[redacted]	[redacted]	[redacted]	-	-	-	-

Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,017
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,186

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy; QALY, quality-adjusted life year.

4 Conclusion

Overall, the External Assessment Group (EAG) considers that the company has provided the analyses as requested by the Committee in the draft guidance. However, in the EAG's opinion, the analyses have provided only limited additional insight into the cost-effectiveness of delgocitinib relative to its comparators.

While the company has conducted scenario analyses using a baseline observation carried forward (BOCF) and last observation carried forward (LOCF) approach to account for the missing data in DELTA FORCE. It is unclear if the same methods were used to account for missing data in the DELTA 1 and DELTA 2 trials in the network meta-analysis (NMA), undermining confidence in the accuracy of the results from the presented NMAs. Similarly, the EAG remains of the opinion that multiple imputation would have been a more robust and appropriate imputation approach to account for the missing data. The EAG is uncertain to what extent using multiple imputation would have provided similar or different treatment effectiveness estimates compared to those used in the scenario analyses and assumed in base cases.

Similarly, the company conducted scenario analysis exploring proportions of patients remaining on treatment as expected in clinical practice; however, in order to emulate these proportions, assumptions around the eligibility for re-treatment were made, which conflicted with how patients would be treated in clinical practice according to the EAG's clinical experts. As such, these assumptions have not been included in the EAG base case.

With respect to dosing, the company has raised the potential inappropriateness of using the DELTA FORCE dosing data to inform the usage of patients with moderate symptoms at baseline, given DELTA FORCE exclusively recruited patients with severe symptoms at baseline. The EAG notes the dosage data is informed using data from patients at baseline, but also during retreatment which should be similar between patients with moderate and severe symptoms at baseline unless these patients are fundamentally different. The EAG notes than the dosages are not dissimilar between DELTA FORCE (severe patients) and DELTA 1 and DELTA 2 (moderate patients), however, the ICER is highly sensitive to dosing. The EAG has therefore provided base cases using both the DELTA FORCE and DELTA 1 and DELTA 2 dosages.

Lastly, while the company have submitted an updated Patient Access Scheme (PAS) discount for delgocitinib, it has yet to be approved and so has not been included in this report. The EAG notes that due to the previously agreed list price of delgocitinib being assumed in the model, and the limited differences in the new evidence provided, the EAG cost-effectiveness estimates are reflective of those provided in their original report.

5 References

1. National Research Council. The prevention and treatment of missing data in clinical trials. 2011.
2. Lachin JM. Fallacies of last observation carried forward analyses. *Clinical Trials* 2016; **13**: 161-8.
3. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. *Jama* 2015; **314**: 1966-7.