PART 1

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

For public – contains no confidential information

Technology appraisal committee B [4 June 2025]

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Company: Leo Pharma

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Chronic hand eczema (CHE)

Background: CHE is defined as HE that lasts for >3 months or relapses ≥2 times per year

- Inflammatory, non-infectious skin condition of the hands and wrists
- Most common aetiological subtypes of HE: irritant contact dermatitis, allergic contact dermatitis and atopic HE
    - a person may have more than 1 aetiological subtype

Symptoms of HE: include dryness, itching, pain, cracking, weeping and bleeding of affected skin

- Cracks in the skin may increase risk of infection, severe cases may affect mobility and use of hands
- Severity of HE symptoms are prone to fluctuation (cycles of flare-ups and remission)
- Hyperkeratotic HE includes thickening of the skin and scaling (frequently affects the palms)

Epidemiology: HE affects <10% of the population, up to 30% of people in high-risk occupational groups

- Around 33% to 50% of HE cases are classed as moderate or severe
- Eligible NHS population ~52,000 people (moderate-severe CHE where TCS inappropriate/ not working)*

*Estimate from company budget impact analysis submission
Abbreviations: HE, hand eczema; TCS, topical corticosteroids

Patient perspectives

Submissions from National Eczema Society and 1 patient expert

CHE impacts quality of life and treatment options are limited

- CHE significantly impacts physical and mental health, daily activities, work/education and social interactions
- Concerns with current treatments due to long-term safety and side effects, convenience (phototherapy requires 2-3 hospital visits/week over several months) or regular monitoring/pregnancy prevention (alitretinoin)
- Intense itching and pain from CHE can disrupt sleep, concentration and increases infection risk
- Managing eczema treatments multiple times per day and healthcare visits places a physical and emotional strain on patients and caregivers
- Managing CHE is especially challenging for:
    - women of childbearing age due to the need for treatment options without pregnancy-related precaution
    - people with darker skin tones as inflamed skin may be harder to assess visually → CHE may be underdiagnosed and undertreated

"Delgocitinib, a non-steroidal treatment targeting inflammation, provides patients with an effective option for long-term relief from CHE, particularly benefiting women of childbearing age and those without access to secondary care [for regular phototherapy/ monitoring appointments]."

Abbreviations: CHE; chronic hand eczema

Clinical perspectives

Submissions from British Association of Dermatologists and 1 clinical expert

Delgocitinib likely offers benefits to people with CHE

- Some people have CHE which fails to respond to repeated, intermittent courses of TCS and TCIs
  - second-line treatment options may carry higher risk or cost
  - delgocitinib would likely provide clinically meaningful benefit and improved HRQoL for this population
- Benefits of topical delgocitinib:
  - first topical Janus kinase (JAK) inhibitor available for CHE
  - efficacy outcomes are comparable with phototherapy and systemic therapy (such as oral alitretinoin or subcutaneous dupilumab)
  - avoids potential adverse events of TCS, such as skin thinning
  - more convenient than attending phototherapy appointments and likely less baseline investigations and blood test monitoring needed
- Delgocitinib has different administration method to alitretinoin (topical vs oral); useful to have both options

"There is a place for effective topical therapy (if conventional topical therapy such as TCS or TCI have not controlled people's hand eczema adequately), especially in those who have relative/absolute contraindications to or are unable to tolerate other systemic therapy"

Abbreviations: CHE; chronic hand eczema; HRQoL; health-related quality of life; TCI, topical calcineurin inhibitors; TCS; topical corticosteroids

Equality considerations

CHE disproportionally affects certain groups

- More common in women than men (differences in exposure patterns)
- More common in people involved in “wet work” – e.g. healthcare, service industry, or tradespeople
- Asian skin typically has thinner outer layer and more sweat glands; more sensitive to chemicals
- Diagnosis and assessment more difficult in people with darker skin tones

Existing treatments and services are not available/suitable for all people with CHE

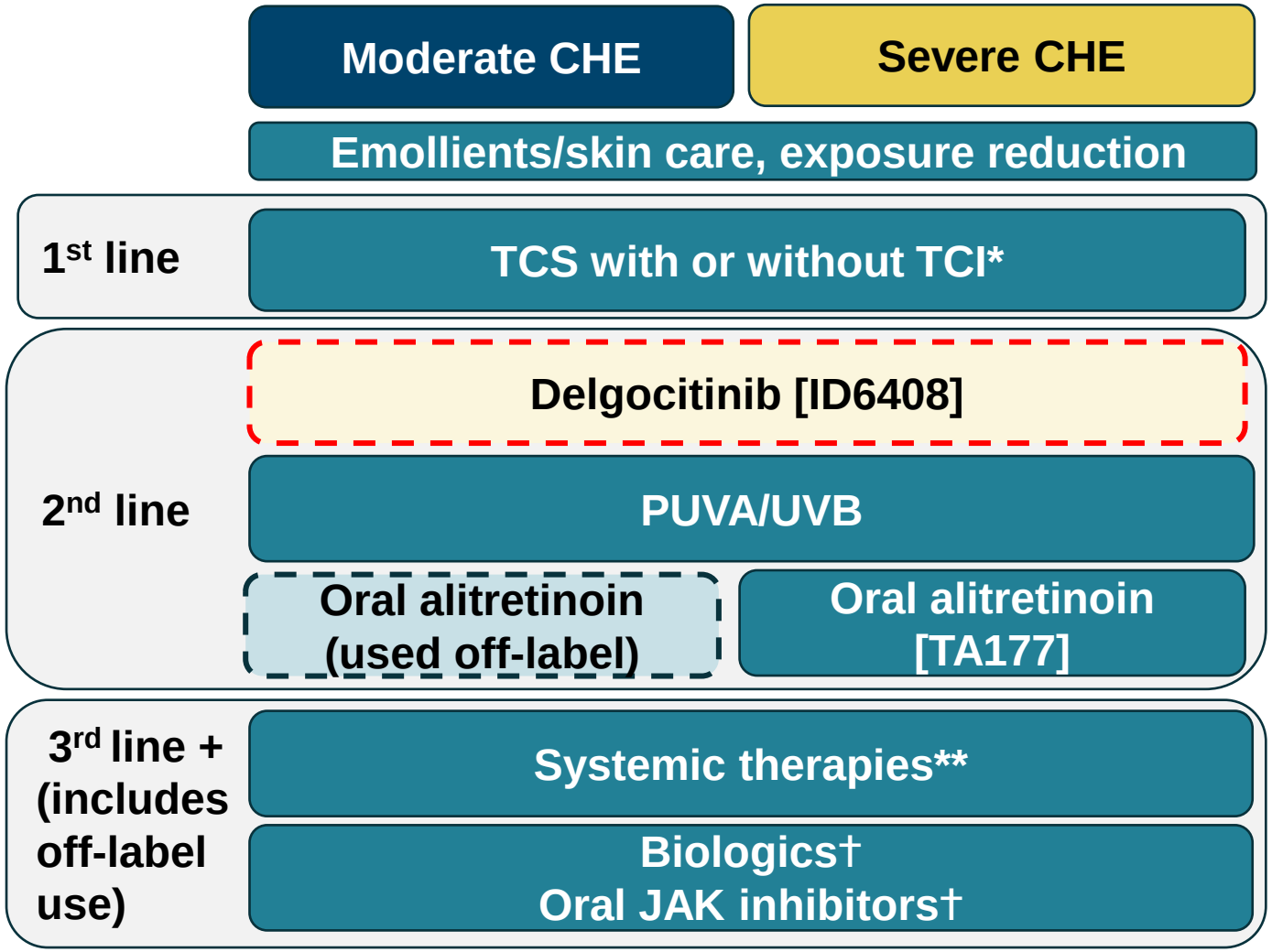
- Regional variation in diagnostic and assessment tools or specialist services within the UK
- Current immunosuppressant treatments can affect the efficacy of antivirals; disproportionate impact on people with co-morbidities requiring antivirals
- Alitretinoin:
  - is associated with a teratogenicity risk → can only be used with pregnancy prevention programme
  - is contraindicated in people with hypersensitivity to peanuts or soya
  - these contraindications cause disproportional impact of CHE to relevant groups

How should these equalities issues be considered?

Abbreviations: CHE; chronic hand eczema

Treatment pathway

Company positioning of delgocitinib in submission: 2nd line for moderate to severe CHE after TCS/TCI



Company and EAG → PUVA and alitretinoin are the only relevant comparators* (decision problem in appendix)

EAG clinical expert comments

- PUVA → topical psoralen has no MA for CHE (used off label)
  - UVB rarely used as whole-body machine
- Alitretinoin is only recommended in severe CHE [NICE TA177] in line with its MA:
  - ~50% of people with moderate CHE may receive alitretinoin off-label
- Hyperkeratotic status = treatment effect modifier:
  - delgocitinib → mostly non-hyperkeratotic but may be used in hyperkeratotic CHE
  - alitretinoin → mainly hyperkeratotic CHE
  - PUVA → mainly non-hyperkeratotic CHE

In clinical practice, would delgocitinib be primarily used for non-hyperkeratotic CHE? What would the preferred order of treatments be for people with moderate and severe CHE?

* TCI are not indicated for non-atopic subtypes of CHE ** May include ciclosporin, azathioprine, methotrexate, acitretin, mycophenolate mofetil, oral corticosteroids † May include dupilumab, lebrikizumab, baricitinib, abrocitinib, tralokinumab and upadacitinib for moderate to severe atopic dermatitis [NICE TA534, TA986, TA681, TA814]

CHE, chronic hand eczema; MA, marketing authorisation, PUVA, psoralen–UV A phototherapy; UVB, ultra-violet B; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

Delgocitinib (Anzupgo, Leo Pharma)

Marketing authorisation (MA)	• Delgocitinib is indicated for the treatment of moderate to severe CHE in adults for whom topical corticosteroids are inadequate or inappropriate • MHRA MA granted November 2024
Mechanism of action	Janus kinase (JAK) inhibitor → targets all 4 members of the JAK family of enzymes (JAK 1, JAK 2, JAK 3 and tyrosine kinase 2) involved in CHE
Administration	Recommended use of delgocitinib cream: • thin layer should be applied twice daily (at regular intervals, approximately 12 hours apart) to affected areas of the hands and wrists until the skin is clear or almost clear • if symptoms reoccur, treatment of the affected areas should be reinitiated as-needed • discontinue if no improvement after 12 weeks of continuous treatment
Price	• List price of delgocitinib cream (20 mg/g) is £595 per 60 g tube • Average modelled time on treatment during year 1 is ~24 weeks ([redacted] tubes, £[redacted]) • No confidential commercial arrangement

SmPC on delgocitinib in pregnancy: no or limited data from the use of delgocitinib in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure → preferable to avoid use during pregnancy

Abbreviations: CHE; chronic hand eczema; MHRA, Medicines & Healthcare products Regulatory Agency; SmPC, summary of product characteristics

Key issues

Issue	Resolved?	ICER impact
Inappropriate choice of indirect treatment comparisons	No – for discussion	Large (delgocitinib vs alitretinoin)
Assumption of equivalence in the relative treatment effects between moderate and severe patients	No – for discussion	Minimal to small
Use of worst observation carried forward approach	No – for discussion	Unknown
No consideration of hyperkeratotic status	No – for discussion	Large (delgocitinib vs alitretinoin)
Time on treatment	No – for discussion	Unknown

Abbreviations: ICER, incremental cost-effectiveness ratio

Additional issues with large impact on ICER

Issue	ICER impact
Delgocitinib dosing	Large (delgocitinib vs alitretinoin)
Utility values	Large (delgocitinib vs alitretinoin)

Abbreviations: ICER, incremental cost-effectiveness ratio

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Key clinical trials (1) – DELTA 1 and 2 and DELTA 3

DELTA 1 and DELTA 2 = identical trial design
16 weeks duration

Design: phase 3, randomised, double-blind
Population: adults with moderate to severe CHE (IGA-CHE score of 3 or 4) with inadequate response to TCS or TCS inappropriate

2:1 randomisation stratified by region and baseline IGA-CHE

Delgocitinib cream
(DELTA 1, n=325; DELTA 2, n=314)
20mg/g twice daily

Vehicle cream (*placebo arm*)
(DELTA 1, n=162; DELTA 2, n=159)
twice daily

Primary outcome: IGA-CHE TS at week 16
Key secondary outcomes: HECSI-90, HESCI-75, HESCI-50, HRQoL

DELTA 3
36 weeks duration

Design: phase 3, open-label extension
Population: DELTA 1 and 2 (both arms)

Delgocitinib cream (n=801)
20mg/g twice daily as needed (treatment initiated/re-initiated if IGA-CHE score ≥2 and stopped when IGA-CHE score 0 or 1 achieved)

Primary outcome: Treatment-emergent adverse events (baseline to week 38)

*see appendix treatment response

Abbreviations: CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; HRQoL, health-related quality of life; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; TCS, topical corticosteroids; TS; treatment success

Key clinical trials (2) – DELTA FORCE

DELTA FORCE
24 weeks duration

*see appendix treatment response

Design: phase 3, randomised, assessor-blinded
Population: adults with severe CHE (IGA-CHE score of 4) with inadequate response to TCS or TCS inappropriate

1:1 randomisation stratified by hyperkeratotic /non-hyperkeratotic CHE subtype and region

Delgocitinib cream (n=254)
20 mg/g twice daily for 16 weeks, then as needed [at week 16 treatment stopped if IGA-CHE score 0 or 1 (treatment re-initiated if IGA-CHE score ≥2) or 4]

Alitretinoin (n=259)
30 mg capsules daily (could be reduced to 10mg daily if experience adverse reactions) for 12 weeks, then as needed [at week 12 treatment stopped if IGA-CHE score 0 or 1 (treatment re-initiated if IGA-CHE score ≥2) or 4]

Primary outcome: Mean change in HECSI (baseline to week 12)
Key secondary outcomes (week 24): IGA-CHE TS, HECSI-90, HECSI-75, HESCI-50, time to loss of response, adverse events

- Company presented additional evidence from a phase 2b, randomised, double-blind dose-ranging trial comparing delgocitinib with vehicle cream in adults with mild to severe CHE (Worm 2022)
  - EAG do not consider trial to be pivotal because it included doses of delgocitinib that are not licensed and several outcome measures used in the trial were later adjusted prior to use in DELTA trials

Abbreviations: CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; TCS, topical corticosteroids; TS; treatment success

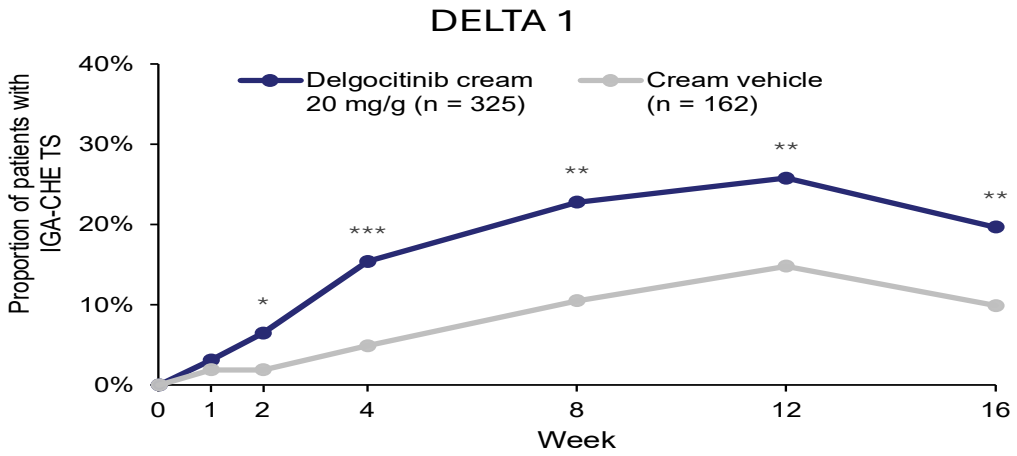
DELTA 1 and 2 – IGA-CHE treatment success (TS)

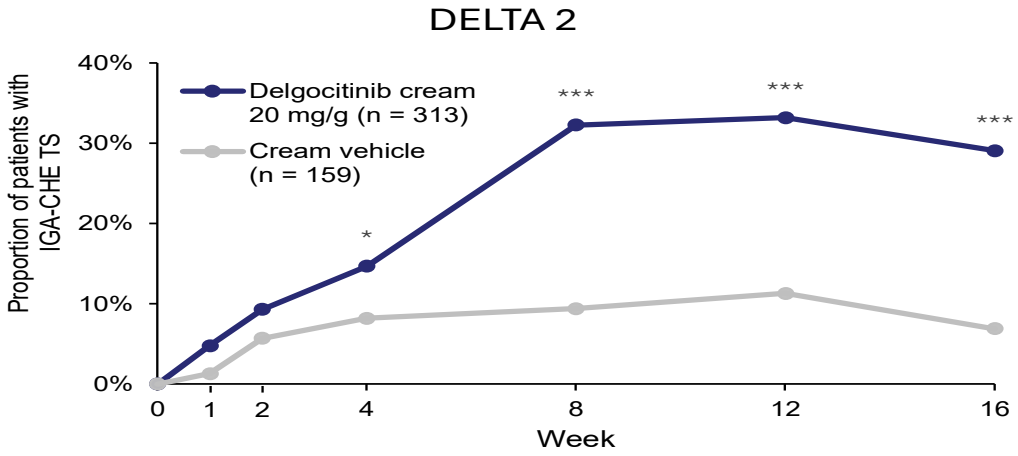
Delgocitinib is significantly more effective than vehicle cream for achieving treatment success

Proportion with IGA-CHE TS at week 16 (full analysis set)

DELTA 1		DELTA 2	
Delgocitinib (n=325)	**Vehicle cream (n=162)**	**Delgocitinib (n=313)**	**Vehicle cream (n=159)**
19.7%	9.9%	29.1%	6.9%
p=0.006		p= <0.0001	

Proportion with IGA-CHE treatment success at week 16 was significantly higher for the delgocitinib arm compared with vehicle cream arm across both trials





Key
* p <0.05
** p <0.01
*** p <0.001

- Difference in % with IGA-CHE TS was significant from week 2 in DELTA 1 and week 4 in DELTA 2
- Weeks 12-16, % with IGA-CHE TS consistently declines despite still on treatment; no explanation provided

IGA-CHE TS defined as scores of 0 (clear) or 1 (almost clear) and an improvement from baseline of ≥ 2 points (*see appendix treatment response)

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

DELTA FORCE – mean change in HECSI

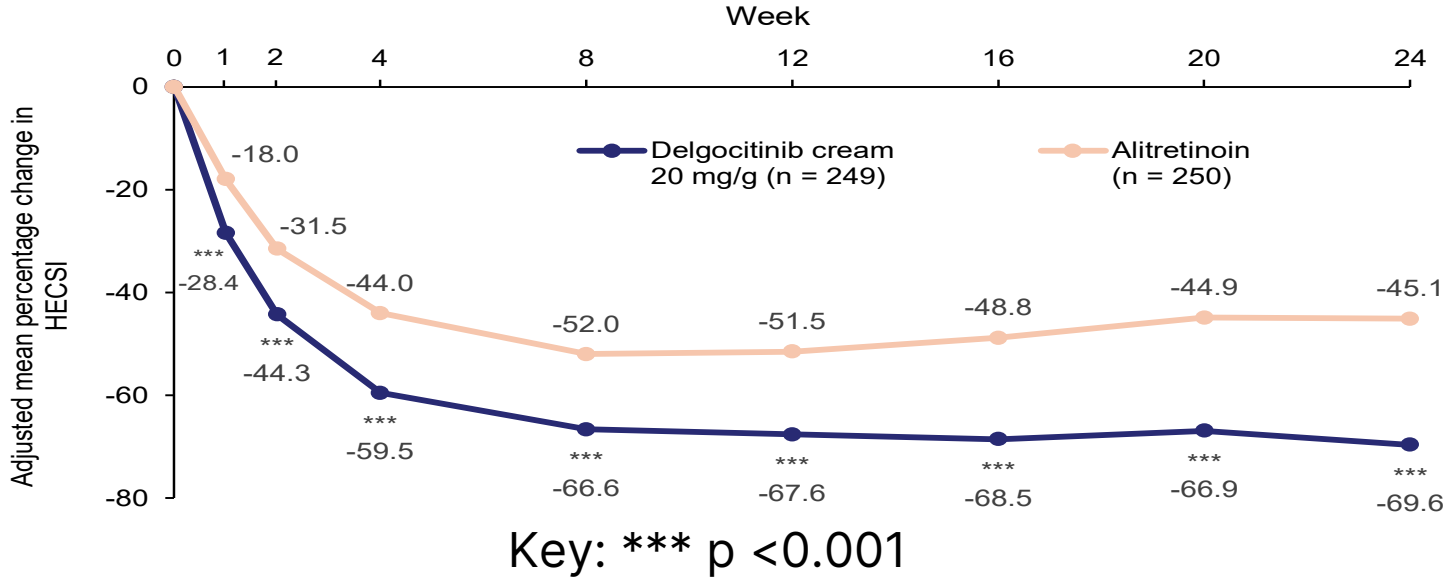
Delgocitinib is significantly more effective than alitretinoin in reducing mean HECSI score

Mean change in HECSI from baseline to week 12 (full analysis set)

	Delgocitinib (n=249)	Alitretinoin (n=250)
Mean change in HECSI	−67.6% (SE 3.37)	−51.5% (SE 3.36)
Mean difference	−16.1% (95% CI −23.28% to −8.86%)	
p value	<0.001	

Primary outcome: From baseline to week 12, the percentage reduction (improvement) in mean HECSI was significantly larger for the delgocitinib arm compared with the alitretinoin arm

Mean change in HECSI from baseline to week 24



Key: *** p <0.001

The percentage reduction (improvement) in mean HECSI was significantly larger for the delgocitinib arm compared with the alitretinoin arm from week 1 and maintained up to week 24

HECSI scores 0-360, higher scores indicate greater severity (*see appendix treatment response)

Abbreviations: CI; confidence interval; HECSI, Hand Eczema Severity Index; SE, standard error

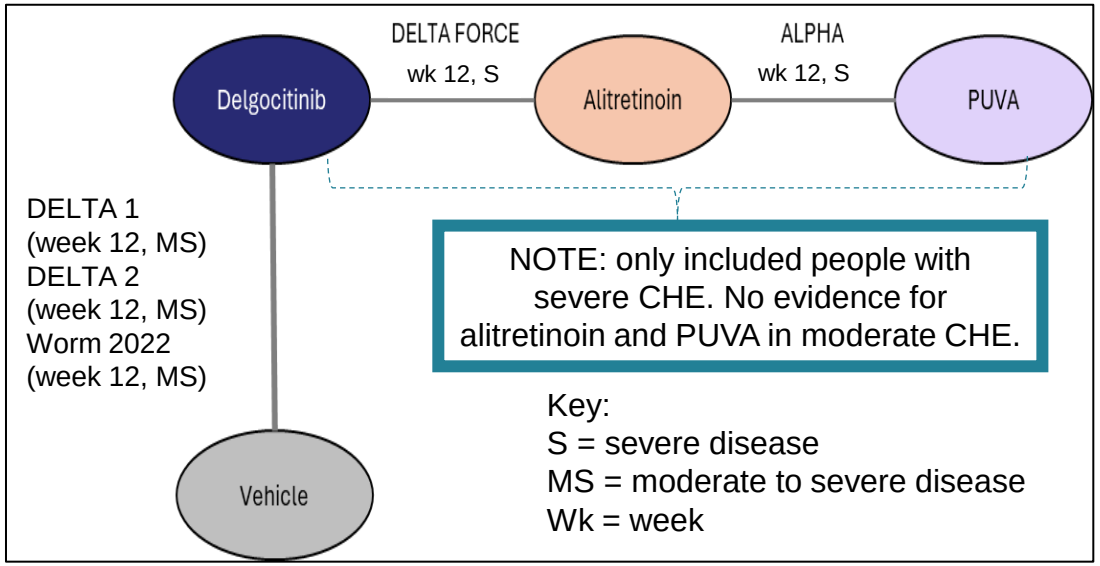
Network meta-analysis (NMA)

*see appendix treatment response

No direct evidence for delgocitinib vs PUVA; company did NMA inc. delgocitinib, alitretinoin & PUVA

- Key NMA outcomes: IGA CHE TS* (IGA-CHE used in DELTA 1 and 2, earlier version of IGA-CHE used in Worm 2022 and PGA used in alitretinoin trials), IGA-CHE TS cumulative response**, HECSI-90
- NMA results (fixed effect): [redacted]
- Random-effects NMA [redacted]
- Sensitivity analyses for moderate CHE includes people with moderate CHE from DELTA 1 & 2 and severe CHE from DELTA FORCE & ALPHA; assumes severe treatment effect = moderate treatment effect

Delgocitinib vs treatment	IGA-CHE TS: week 12 analysis (company base case, fixed effects model)		
	All people	Severe CHE	Moderate CHE
Median odds ratio (95% CI)			
Vehicle cream	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]



Analyses included: primary endpoint analysis (DELTA 1 & 2, Worm 2022 at week 16; other studies at week 12), week 12 analysis (all studies)

*proportion with IGA-CHE/PGA 0/1 response at the trial endpoint, **proportion with IGA-CHE/PGA 0/1 response by the trial endpoint

Abbreviations: CI, confidence interval; CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; IGA CHE, Investigator's Global Assessment for chronic hand eczema; PGA, Physician Global Assessment; PUVA; psoralen–UV A phototherapy; TS, treatment success

Key issue: Inappropriate choice of ITC (1)

Large impact on ICER (delgocitinib vs alitretinoin)

Company prefers NMA results, EAG prefers to use direct evidence and unanchored MAIC

EAG comments (1)

- EAG says original company NMA is inappropriate; substantial clinical and methodological heterogeneity among studies (e.g. different endpoints, different definitions, different levels of severity)
  - fixed effects models are not appropriate due to level of heterogeneity
- EAG prefers to use:
  - DELTA FORCE for delgocitinib vs alitretinoin (direct evidence, severe CHE, hyperkeratotic subgroups)
  - unanchored MAIC from clarification stage for delgocitinib vs PUVA (severe CHE)
- Unanchored MAIC:
  - matched people who took delgocitinib in pooled DELTA 1 and DELTA 2 (n=182) to people who took PUVA in the ALPHA trial (n=221)
  - effective sample size for the matched population is small (n=39) → limitation of MAIC
  - included disease severity (prognostic factor) and hyperkeratotic CHE as matching covariates
  - [redacted]

Outcome from MAIC (at week 12)	Delgocitinib vs PUVA (severe CHE)
IGA-CHE treatment success (0/1 score)	[redacted]
Change from baseline HECSI score	[redacted]

Abbreviations: CI, confidence interval; CHE, chronic hand eczema; HECSI, Hand Eczema Severity Index; ICER, incremental cost-effectiveness ratio; IGA CHE, Investigator's Global Assessment for chronic hand eczema; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA; network meta-analysis; PUVA, psoralen–UV A phototherapy; TS, treatment success

Key issue: Inappropriate choice of ITC (2)

Large impact on ICER (delgocitinib vs alitretinoin)

EAG comments (2)

- Choice of MAIC has a minimal impact on cost-effectiveness results for delgocitinib versus PUVA

Company comments (in response to clarification/factual accuracy check of the EAG report)

- NMA results
  - fixed effects model results for delgocitinib versus alitretinoin and delgocitinib versus vehicle cream are consistent with findings from included RCTs
  - delgocitinib vs PUVA → ITC results (Bucher comparison) using data from DELTA FORCE and ALPHA for IGA-CHE TS are not dissimilar from the fixed effects NMA results
- EAG preferred MAIC (delgocitinib vs PUVA) has smallest effective sample size (n=39) → substantially underpowered
- No consideration of **other MAIC** where disease severity excluded as a matching covariate (severity classifications differed between studies)
  - [redacted] (effective sample size, n=292)

Which approach does committee prefer (direct evidence and unanchored MAIC, or company NMA results)?

Abbreviations: IGA CHE, Investigator's Global Assessment for chronic hand eczema; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; MAIC; matching-adjusted indirect comparison; NMA; network meta-analysis; PUVA, psoralen–UV A phototherapy; RCT, randomised controlled trial; TS; treatment success

Minimal to small impact on ICER

Key Issue: Assumption of equivalence in the relative treatment effects between moderate and severe patients (1)

Background: DELTA FORCE (alitretinoin) and ALPHA (PUVA) include people with severe CHE

- No evidence for the safety or efficacy of alitretinoin or PUVA in people with moderate CHE
- Company has assumed that the relative effect of treatments would be consistent across people with moderate and severe CHE at baseline
  - presented subgroup analyses to support the assumption (*see appendix – slides 43 to 44)

EAG comments

- EAG clinical experts consider people with moderate CHE may receive alitretinoin (off-label) and PUVA
- Company subgroup analyses are insufficient to confirm whether the relative treatment effects between moderate and severe patients are consistent
  - effect estimates for delgocitinib are numerically different across the moderate and severe populations
- Equivalence testing (such as two one-sided tests procedure) may provide a statistically robust approach to assess whether the treatment effects between people with moderate and severe CHE are equivalent
- EAG base cases consider only delgocitinib vs alitretinoin or PUVA in severe population at baseline:
  - EAG presented scenarios around its base cases in people with moderate CHE at baseline (but consider results to be uncertain because of company's assumption) → minimal to small impact on ICER

Abbreviations: CHE, chronic hand eczema; ICER; incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy

Minimal to small impact on ICER

Key Issue: Assumption of equivalence in the relative treatment effects between moderate and severe patients (2)

Company comments (in response to factual accuracy check of the EAG report)

- Agree that the assumption of equivalence in treatment effects between people with moderate and severe CHE is strong
- Disagree that equivalence testing using subgroup data from DELTA 1 and DELTA 2 offers a solution
  - any effect modification based on disease severity is driven by differences in response to vehicle cream [similar trend observed in a study of alitretinoin versus placebo (Ruzicka 2004)]
  - if the trend is similar for any intervention studied in moderate and severe disease, then the assumption of equivalent treatment effects between directly compared active comparators is not unreasonable

Is the company's assumption of equivalence in the relative treatment effects between people with moderate and severe CHE appropriate?

Abbreviations: CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio

Unknown impact on ICER

Key Issue: Use of WOCF approach (1)

Company prefers WOCF, EAG would prefer multiple imputation to impute missing data

Background – worst observation carried forward (WOCF) approach

- Company has used WOCF approach to impute missing data for the estimation of treatment effects
  - DELTA 1 and 2 → WOCF estimates data at week 16 for 6.6% (delgocitinib) and 18.4% (vehicle cream)
  - DELTA FORCE → WOCF estimates data at week 24 for 12.4% (delgocitinib) and 39.5% (alitretinoin)
- Company performed multiple imputation, with a missing at random assumption, to account for missing data in a sensitivity analyses
  - company noted that this approach led to overly optimistic treatment effects at Week 12 for the DELTA FORCE trial. No results were presented for other timepoints or trials.

EAG comments

- EAG is concerned that the use of the WOCF approach has the potential to bias comparisons of delgocitinib to vehicle cream or alitretinoin in favour of delgocitinib
  - WOCF approach generates bias against the treatment arm in which the dropout rate is highest
  - dropout rates are greater in the vehicle cream and alitretinoin arms compared to the delgocitinib arms → effectiveness of comparators may be underestimated in the model (which may underestimate ICER)
- EAG suggests that multiple imputation, with a missing not at random assumption, should be used over WOCF to impute missing data as it is likely to be associated with a lower risk of bias
  - there may still be limitations with this approach as high dropout rate in the latter stages of some trials

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Abbreviations: ICER; incremental cost-effectiveness ratio

Unknown impact on ICER

Key Issue: Use of WOCF approach (2)

Company comments (in response to factual accuracy check of the EAG report)

- At clarification, company presented evidence which breaks down the timing and reason for discontinuations across the DELTA trials → company considers this provides context to the choice of imputation method
    - multiple imputation may introduce bias as most discontinuations were driven by a lack of effect or adverse events resulting in the potential underestimation of the relative effects for delgocitinib

Is company's WOCF approach appropriate to account for missing data across the DELTA trials, or should multiple imputation, with a missing not at random assumption, be explored?

Abbreviations: ICER, incremental cost-effectiveness ratio; WOCF; worst observation carried forward

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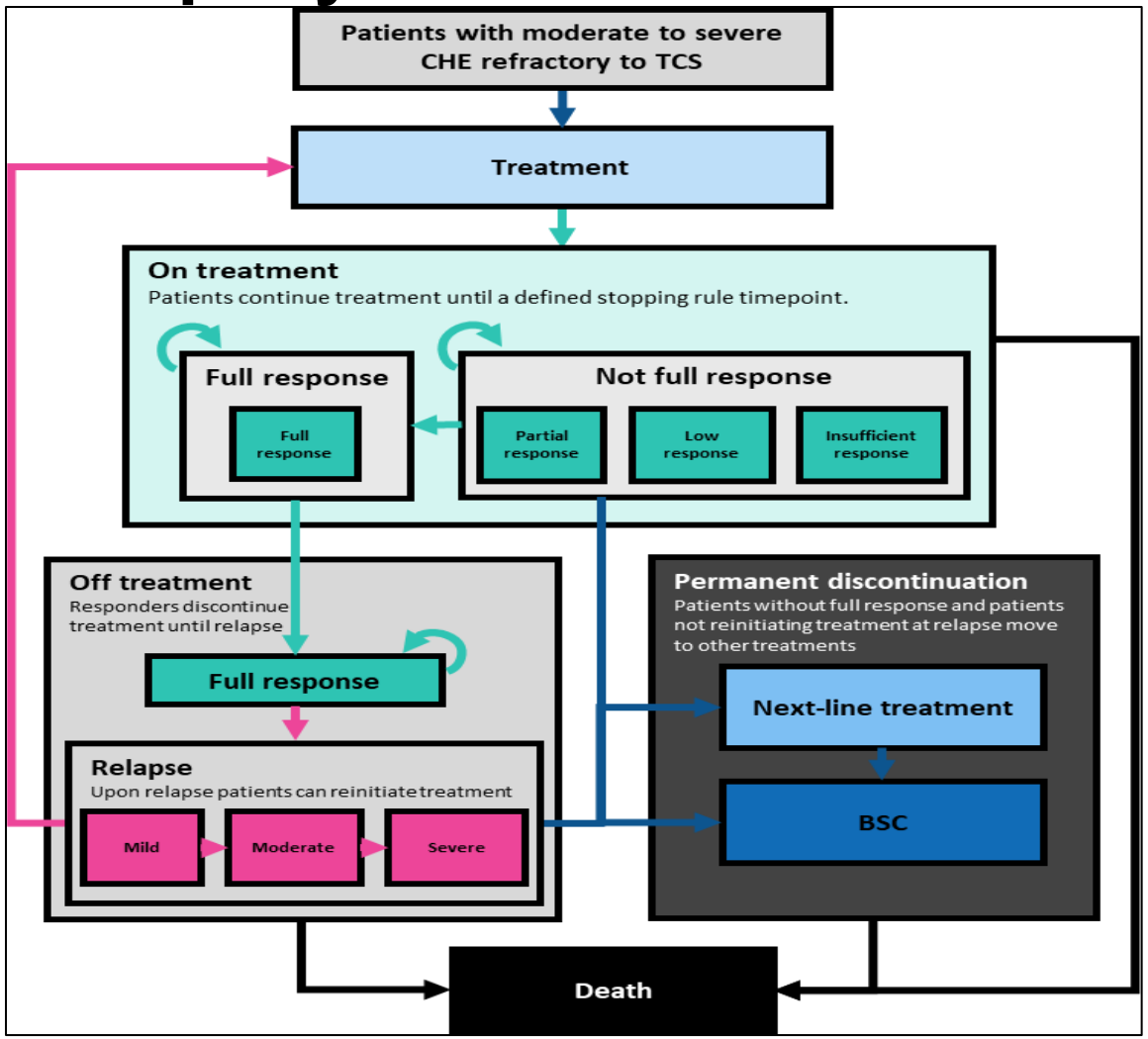
Company's model overview



EAG considers the model structure appropriate for addressing the decision problem

Comparators:

- Moderate: PUVA
- Severe: PUVA & alitretinoin

Markov cohort model, time horizon = 10 years

- 12-week initial treatment (all people on treatment)
  - full response → off treatment
  - partial/low response → treatment is continued up to week 24 (if full response → off-treatment, if no full response → next-line treatment/BSC)
  - insufficient response → next line-treatment/BSC
- Relapse (off-treatment) → maximum re-treatment is 24 weeks, but no limits to rounds of re-treatment
- 4-weekly cycle with half-cycle correction

Health state	IGA-CHE (base case)
Full response	IGA-CHE 0 (clear) or 1 (almost clear)
Partial response	IGA-CHE 2 (mild)
Low response	IGA-CHE 3 with 1-point improvement from baseline (moderate)
Insufficient response	IGA-CHE 3 without improvement from baseline or IGA-CHE 4 (severe)

Abbreviations: BSC, best supportive care; CHE, chronic hand eczema; IGA CHE, Investigator's Global Assessment for chronic hand eczema; PUVA, psoralen–UV A phototherapy; TCS, topical corticosteroids

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	Pooled DELTA 1 and 2: moderate (IGA-CHE 3) and severe (IGA-CHE 4) subgroups
Delgocitinib and comparators efficacy	• Week 12: probability of initial full response based on NMA ○ proportions in non-full response states (informed by subgroup analyses of DELTA trials) mapped to partial, low and insufficient response states* • Week 12 to 24: probability of full response for continued treatment (from partial and low response states) based on post hoc analysis of DELTA 3 • Probability of relapse (off-treatment) to mild symptoms from DELTA FORCE and moderate/severe symptoms from ALPHA • Probability of full response after relapse (re-treatment) based on DELTA 3
Costs and resource use	Drug costs, monitoring costs (alitretinoin), health-state resource use and costs, AEs
Subsequent treatments (% based on RWEAL and by disease severity)**	• Next-line treatment basket (before BSC): acitretin, azathioprine, methotrexate, ciclosporin, oral steroids, alitretinoin, PUVA, UVB, dupilumab and TCS • BSC: TCS, TCIs and emollients (efficacy = vehicle cream from DELTA 1 and 2)
AEs (DELTA FORCE) and drug wastage	• AEs included if incidence ≥10% and difference between treatments was ≥1.5% • No wastage costs are assumed for delgocitinib

*Based on improvement from baseline at 12 weeks

** RWEAL: chart review study (inc. UK patients) in adults with moderate to severe CHE who have had TCS or for whom TCS were inappropriate

Abbreviations: AEs, adverse events; BSC, best supportive care; IGA CHE, Investigator's Global Assessment for chronic hand eczema; NMA, network meta-analysis; c; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UVB, ultra-violet B

Utility values

Utilities are dependent on health state, treatment and baseline severity in company base case

- Pooled EQ-5D-5L data from DELTA 1 and 2 were mapped to EQ-5D-3L for moderate and severe subgroups
- Mixed model for repeated measures (MMRM) was used to analyse the pooled utility data in terms of health state, treatment and symptoms at baseline
  - modelled the change in EQ-5D-3L from baseline to week 16, definition of response based on IGA-CHE
- Utilities for next-line treatment and BSC (same for both delgocitinib and comparator arms)
  - next-line treatment → proportions from RWEAL used to estimate weighted utility values
  - BSC → vehicle cream utilities from MMRM were weighted based on response data from DELTA 1 and 2

Health state	Company base case utilities for active treatments (delgocitinib, alitretinoin, PUVA)		EAG base case utilities (all treatments)
	Moderate CHE	Severe CHE	
Baseline	0.665	0.617	0.617
Full response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Low response	[redacted]	[redacted]	[redacted]
Insufficient response	[redacted]	[redacted]	[redacted]

EAG comments

- No evidence for treatment-specific or severity-specific utility difference
- Prefer to use health-state-specific utilities, using pooled utility data for delgocitinib across all DELTA trials
- People in the same health state have the same HRQoL irrespective of treatment

Does committee prefer company approach or EAG approach?

Abbreviations: BSC, best supportive care; CHE, chronic hand eczema; EQ-5D, EuroQol-5 dimensions; HRQoL, health-related quality of life; IGA CHE, Investigator's Global Assessment for chronic hand eczema; PUVA, psoralen–UV A phototherapy

Large impact on ICER (delgocitinib vs alitretinoin)

Key Issue: No consideration of hyperkeratotic status (1)

Treatment effect for delgocitinib vs alitretinoin differs by hyperkeratotic status; impacts CE

Background

- Clinical experts say hyperkeratosis is a treatment effect modifier and guides treatment decisions
- People with hyperkeratotic CHE likely to take alitretinoin, non-hyperkeratotic CHE likely to take PUVA
- DELTA 1 and DELTA 2 trials not stratified for hyperkeratotic status; DELTA FORCE trial was
- Delgocitinib vs alitretinoin: direct comparison by hyperkeratotic status possible (DELTA FORCE)
  - [redacted]% delgocitinib patients achieved full response* by week 12, vs. [redacted]% for alitretinoin)
  - [redacted]% of delgocitinib patients achieved full response* by week 12, vs. [redacted]% of alitretinoin patients). *See appendix for full results – slides 45 to 46)

EAG comments

- Despite differences in the definition of hyperkeratosis in unanchored MAICs studies, hyperkeratotic CHE should be included as matching covariate given that it is a treatment effect modifier
- Using overall DELTA FORCE treatment effects (includes people with non-hyperkeratotic and hyperkeratotic CHE) vs hyperkeratotic status treatment effects has significant impact on CE results for delgocitinib vs alitretinoin
- EAG uses overall DELTA FORCE treatment effects in its base case (rather than hyperkeratotic subgroup treatment effects) as not all people with hyperkeratotic CHE will be eligible/willing to take alitretinoin (e.g. pregnancy prevention programme)

*IGA-CHE score of 0 or 1 with a ≥ 2-step improvement from baseline. Abbreviations: CE, cost-effectiveness; CHE, chronic hand eczema; ICER, incremental cost-effectiveness ratio; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; MAIC, matching-adjusted indirect comparison; PUVA, psoralen–UV A phototherapy; TS, treatment success

Key Issue: No consideration of hyperkeratotic status (2)

Company comments (in response to clarification)

- Delgocitinib vs PUVA:
  - Indirect comparison cannot be provided due to a lack of hyperkeratotic and non-hyperkeratotic subgroup data in the ALPHA trial for outcomes of interest
  - Lack of comparability in how hyperkeratosis was captured in the ALPHA and DELTA 1 & DELTA 2 trials
- Delgocitinib vs alitretinoin:
  - For people with hyperkeratotic CHE who cannot take alitretinoin, delgocitinib is more convenient and cost-effective than PUVA
  - While differences on HECSI endpoints were less definitive in the hyperkeratotic subgroup, people on delgocitinib appear to experience meaningful improvements in patient-relevant measures of itch, pain and quality of life regardless of subgroup.

Does committee prefer to consider the overall CHE population, regardless of hyperkeratotic status, or to consider subgroups?

Abbreviations: CHE, chronic hand eczema, HECSI, Hand Eczema Severity Index; ICER, incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy

Unknown impact on ICER

Key Issue: Time on treatment (1)

EAG considers modelled time on treatment may not reflect clinical practice

Background

- Discontinuation rates from week 12 to 24 in DELTA FORCE were used to estimate on-treatment discontinuation for people undergoing re-treatment (informed by people whose CHE did not achieve a full response by week 12)

Years	Proportion of people on treatment in the model		
	Delgocitinib	Alitretinoin	PUVA
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]

EAG comments (1)

- On-treatment discontinuation is likely overestimated for people being retreated (as the model uses discontinuation rates informed by people who **didn't** have full response, to inform discontinuation rates for people who previously **did** have full response) → so people are progressing to next-line treatments and BSC in the model too quickly
- EAG's clinical experts consider that ~25% of people on alitretinoin are still on treatment (continuing to relapse and be retreated) after 2 years in clinical practice
- Company discussed the consequences of time on treatment being underestimated for alitretinoin in the model, without considering that delgocitinib may also be underestimated
- Delgocitinib ToT may be more underestimated than alitretinoin, given that delgocitinib is more effective than alitretinoin in specific patient populations.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PUVA, psoralen–UV A phototherapy; ToT, time on treatment

Unknown impact on ICER

Key Issue: Time on treatment (2)

EAG comments (2)

- ICER likely to be highly sensitive to the difference in the proportions of people remaining on treatment
- Clinical expert opinion on the expected time on treatment for people that achieve a full response on treatment and scenario analyses exploring these opinions would likely resolve this issue

Company comments (in response to clarification)

- If in clinical practice, more people on alitretinoin are likely to require treatment beyond week 12, or the rates of discontinuation are lower, or more people re-initiate treatment at the point of relapse, then:
  - modelled time on treatment with alitretinoin will increase
  - acquisition costs of alitretinoin will increase at a higher rate than the QALYs gained from staying on treatment → decrease ICER of delgocitinib versus alitretinoin
- Model includes some alitretinoin use in the next-line treatment basket to indirectly account for use beyond initial discontinuation

What proportion of people would likely remain on delgocitinib and alitretinoin at 1, 2 and 3 years if their CHE has responded to treatment?

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

EAG preferred amendments to model

1) **Treatment effects**
   - EAG considers company NMA is methodologically flawed → prefers direct evidence from DELTA FORCE (delgocitinib vs alitretinoin) and MAIC (delgocitinib vs PUVA) to inform treatment effects
2) **Health state utility values**
   - Company utilities (informed by DELTA 1 and 2) depend on health state, treatment and baseline severity
   - EAG prefers to use mean utilities from all DELTA trials, applied for all treatments in the same health states
3) **Delgocitinib dosing**
   - Company used MMRM regression to estimate weekly mean usage of delgocitinib from all DELTA trials (by severity and response) and applied this to both comparisons (alitretinoin and PUVA)
   - EAG considers that MMRM underestimates usage compared to trials → prefers to use delgocitinib dosing from the DELTA trials which are specific to each comparison (alitretinoin and PUVA)
4) **Proportion discontinuing to NLT/BSC (EAG clinical opinion aligned more with ALPHA than RWEAL*)**
5) **NLT basket and efficacy (alitretinoin inappropriate, treatment effects of NLT basket overestimated)**
6) **Healthcare resource use (adjusted frequencies of dermatologist visits to align with clinical opinion)**
7) **No inclusion of adverse events (not a driver of cost-effectiveness results)**

EAG amendments 1 to 3 have a large impact on the ICER for delgocitinib vs alitretinoin
EAG amendments have minimal impact on cost-effectiveness results for delgocitinib vs PUVA

Does committee accept EAG amendments 3-7? ***(Amendments 1-2 already discussed)***

*see appendix – slide 47. Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MAIC, matching-adjusted indirect comparison; MMRM, mixed model for repeated measures; NLT, next-line treatment; NMA, network meta-analysis; PUVA, psoralen–UV A phototherapy

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case (delgocitinib vs alitretinoin)	EAG base case (delgocitinib vs PUVA)
Population	Moderate (vs PUVA) and severe CHE	Severe CHE	
Treatment effects	NMA* (also DELTA FORCE, DELTA 3 and ALPHA)	All from DELTA FORCE	MAIC* (matching by severity and hyperkeratosis), DELTA 3**
Utility values	Derived from DELTA 1, 2. Different utilities for NLT and BSC	Derived from pooled DELTA trials	
Delgocitinib dosing	MMRM regression (all DELTA trials) to estimate mean usage	DELTA FORCE	Weighted average of 12- and 24-week DELTA 1, 2 and FORCE usage data
Proportion on NLT and BSC	Based on RWEAL	Based on ALPHA	
NLT basket	Includes alitretinoin, efficacy assumed at 40.6%	No alitretinoin, efficacy assumed at 25.6%	
Health care resource use	FR: 1 derm visit, PR/LR/InR: 4 derm visits	FR: 0 derm visits; PR: 2 derm visits, LR: 6 derm visits, InR: 5 derm visits	
AEs	Included from DELTA FORCE	Not included	

*informs probability of full response at week 12 **informs per-cycle probability to mild relapse for delgocitinib (DELTA FORCE in company base case)

Abbreviations: BSC; best supportive care; CHE; chronic hand eczema; derm, dermatologist; FR/PR/LR/InR, full, partial, low and insufficient response; MAIC, matching-adjusted indirect comparison; MMRM, mixed model for repeated measures; NLT; next-line treatment; NMA; network meta-analysis; PUVA, psoralen–UV A phototherapy

Cost-effectiveness results

As confidential discounts are available for treatments in the pathway, ICERs will be presented in Part 2 slides

ICER ranges (including confidential discounts) presented below to aid transparency

Summary - company consider that no additional QALY weighting for severity should be applied

- Company base case probabilistic results:
  - delgocitinib vs alitretinoin (severe CHE subgroup): ICER above £30,000 per QALY gained
  - delgocitinib vs PUVA (moderate and severe CHE subgroups): ICER below £30,000 per QALY gained
- EAG base case probabilistic results:
  - delgocitinib vs alitretinoin (severe CHE at baseline): ICER above £30,000 per QALY gained
  - delgocitinib vs PUVA (severe CHE at baseline): ICER below £30,000 per QALY gained

Summary of EAG scenarios presented in part 2:	**Impact on CE results**
1) Delgocitinib vs PUVA in people with moderate CHE at baseline	**Scenarios 1-2: minimal to small**
2) Delgocitinib vs alitretinoin in people with moderate CHE at baseline	
3) Delgocitinib vs alitretinoin in people with hyperkeratotic CHE	**Scenarios 3-4: large**
4) Delgocitinib vs alitretinoin in people with non-hyperkeratotic CHE	

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

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Other considerations

Benefits of delgocitinib not captured in the QALY calculation: company considerations

- **Favourable safety profile vs systemic therapies**
  - risk of serious AEs with systemic therapies → not seen for delgocitinib across DELTA trials
- **No pregnancy prevention programme is needed for delgocitinib**
- **Delgocitinib is more accessible compared to phototherapy (requires specific facilities)**
  - people may live far from hospital and phototherapy can be inconvenient and costly to access
- **Delgocitinib has fewer barriers to timely re-initiation of treatment compared with alitretinoin**
  - people whose CHE relapses after achieving a treatment response on alitretinoin (and have discontinued treatment) may need a specialist appointment and monitoring to re-initiate treatment
  - re-initiation of delgocitinib may only require a GP appointment and people may have leftover cream from previous treatment
- **Delgocitinib is expected to have additional benefits to people with CHE and society**
  - effective CHE treatment prevents disruption to work/education

Abbreviations: AEs, adverse events; CHE, chronic hand eczema

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company submission does not include a managed access proposal for delgocitinib

- Company consider that there are no ongoing studies that will provide additional relevant evidence in the next 12 months

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Key issue	ICER impact	Slides
Inappropriate choice of indirect treatment comparison	Large (delgocitinib vs alitretinoin)	17-18
Assumption of equivalence in the relative treatment effects between moderate and severe patients	Minimal to small	19-20
Use of worst observation carried forward approach	Unknown	21-22
No consideration of hyperkeratotic status	Large (delgocitinib vs alitretinoin)	27-28
Time on treatment	Unknown	29-30

Abbreviations: ICER, incremental cost-effectiveness ratio

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

Supplementary appendix

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Summary of decision problem (1)

	Final scope	Company	EAG comments
Population	Adults with moderate to severe CHE that has not responded to treatment with TCS or for whom TCS are inadequate or inappropriate	As per final scope	• DELTA 1 and 2, and Worm 2022 trials match the population in final scope and SmPC for delgocitinib • DELTA FORCE and ALPHA only consider people with severe CHE ○ comparisons of delgocitinib to alitretinoin and PUVA (direct or indirect) are in a narrower population than in the final scope and SmPC
Intervention	Delgocitinib cream	As per final scope	As per final scope and SmPC
Outcomes	• Measures of disease severity • Measures of symptom control including improvement in itch • Time to relapse/prevention of relapse • Adverse effects of treatment • Health-related quality of life	As per final scope	• Outcomes listed in the final scope are covered in the DELTA trials • EAG's clinical experts noted that the endpoints of IGA-CHE, HECSI, HESD, and HEIS, are not routinely assessed in clinical practice

Abbreviations: CHE; chronic hand eczema; HECSI, Hand Eczema Severity Index; HEIS, Hand Eczema Impact Scale; HESD, Hand Eczema Symptoms Diary; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; PUVA, psoralen–UV A phototherapy; SmPC, summary of product characteristics; TCS, topical corticosteroids;

Summary of decision problem (2)

	Final scope	Company	EAG comments
Comparators	• Alitretinoin (in severe CHE) • Topical calcineurin inhibitors (TCIs) • Ultraviolet light therapy (PUVA, narrowband UVB) • Systemic immunosuppressive therapies (azathioprine, ciclosporin, methotrexate and mycophenolate mofetil)	Relevant comparators to delgocitinib are alitretinoin and PUVA: • TCIs are used 1st line alongside TCS for CHE → not as a monotherapy for target population • Immunosuppressants are for CHE refractory or contraindicated to 1st and 2nd line options and are positioned at a different point in the treatment pathway (3rd line+) • PUVA was assumed as a proxy for narrowband UVB (unit costs are the same)	• Agree relevant comparators are alitretinoin and PUVA • Data are only available for these comparators in people with severe CHE ○ EAG's clinical experts consider that people with moderate CHE would still be expected to receive alitretinoin (~50%, used off-label) and PUVA

Link back to treatment pathway slide

Abbreviations: CHE; chronic hand eczema; PUVA, psoralen–UV A phototherapy; TCS, topical corticosteroids; UVB, ultra-violet B

Measurement of treatment response

CHE severity may be classified as mild, moderate or severe according to:

- **Physician's Global Assessment (PGA) scale:** 5 levels (0 = clear to 4 = severe)
- **Investigator's Global Assessment (IGA) scale:** 5 levels (0 = clear to 4 = severe)
- **IGA-CHE scale:** 5 levels (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, or 4 = severe)
  - developed by the company for specific use in people with CHE (in contrast to IGA and PGA which are broad-use dermatological assessment tools)
- **Hand Eczema Severity Index (HECSI)**: rates the severity of 6 clinical signs of HE (erythema, infiltration/papulation, vesicles, fissures, scaling and oedema) at the time of evaluation
  - HECSI total ranges from 0 to 360 with higher scores indicating greater severity
  - treatment responses in trials are often defined as HECSI-50, HECSI-75 or HECSI-90, representing ≥50%, ≥75% and ≥90% reductions in HECSI from baseline, respectively

EAG and clinical expert comments

- EAG's clinical experts considered:
  - IGA-CHE is not routinely used to measure clinical response with PGA more commonly used
  - HECSI is a measure of clinical response that is more widely used in Europe
- Clinical expert: clinically meaningful response → reduce IGA severity for CHE to clear or almost clear

Link back to main slides on clinical trials

Abbreviations; CHE, chronic hand eczema; HE, hand eczema

Key Issue: Assumption of equivalence in the relative treatment effects between moderate and severe patients (1)

Background – DELTA 1 and 2 severity subgroup analyses (full analysis set)

IGA-CHE TS* at week 12 and 16 by disease severity at baseline

Outcome and timepoint	Pooled DELTA 1 and 2 Moderate subgroup (IGA-CHE = 3)		Pooled DELTA 1 and 2 Severe subgroup (IGA-CHE = 4)	
	Delgocitinib (n = 456)	Vehicle cream (n=230)	Delgocitinib (n=182)	Vehicle cream (n=91)
Week 12				
Proportion with response, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in %	[redacted]		[redacted]	
p value	[redacted]		[redacted]	
Week 16				
Proportion with response, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference in %	[redacted]		[redacted]	
p value	[redacted]		[redacted]	

*IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline

Link back to main slides on key issue

Abbreviations: CI, confidence interval; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; TS, treatment success

Key Issue: Assumption of equivalence in the relative treatment effects between moderate and severe patients (2)

Background – DELTA 1 and 2 severity subgroup analyses (full analysis set)

Comparison of IGA-CHE TS* between moderate and severe subgroups for each treatment arm

Timepoint	Moderate vs severe	Pooled DELTA 1 and DELTA 2 Delgocitinib arms		Pooled DELTA 1 and 2 Vehicle cream arms	
		Moderate (n=456)	Severe (n=182)	Moderate (n=230)	Severe (n=91)
Week 12	Responders, n	[redacted]	[redacted]	[redacted]	[redacted]
	Odds ratio	[redacted]		[redacted]	
Week 16	Responders, n	[redacted]	[redacted]	[redacted]	[redacted]
	Odds ratio	[redacted]		[redacted]	

Odds ratios comparing IGA-CHE TS* between treatments in moderate and severe subgroups

Pooled DELTA 1 and 2	Severity subgroup	Odds ratio, delgocitinib vs vehicle cream	
		Week 12	Week 16
	Moderate	[redacted]	[redacted]
	Severe	[redacted]	[redacted]

*IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline

Link back to main slides on key issue

Abbreviations: CI, confidence interval; IGA-CHE; Investigator's Global Assessment for chronic hand eczema; TS, treatment success

Key Issue: No consideration of hyperkeratotic status (1)

Background – DELTA FORCE hyperkeratotic status subgroup analyses (full analysis set)

Week 12 results

Endpoint	Delgocitinib		Alitretinoin		p-value
Hyperkeratotic					
HECSI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA-CHE-TS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HECSI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L Index change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-hyperkeratotic					
HECSI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA-CHE-TS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HECSI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L Index change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline

Link back to main slides on key issue

Abbreviations: EQ-5D, EuroQol-5 dimensions; HECSI, Hand Eczema Severity Index; IGA-CHE TS; Investigator's Global Assessment for Chronic Hand Eczema treatment success; SE, standard error

Key Issue: No consideration of hyperkeratotic status (2)

Background – DELTA FORCE hyperkeratotic status subgroup analyses (full analysis set)

Week 24 results

Endpoint	Delgocitinib		Alitretinoin		p-value
Hyperkeratotic					
HECSI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA-CHE-TS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HECSI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L Index change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-hyperkeratotic					
HECSI 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IGA-CHE-TS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HECSI 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L Index change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥ 2-step improvement from baseline

Link back to main slides on key issue

Abbreviations: EQ-5D, EuroQol-5 dimensions; HECSI, Hand Eczema Severity Index; IGA-CHE TS; Investigator's Global Assessment for Chronic Hand Eczema treatment success; SE, standard error

Proportion on next-line treatment and BSC

EAG comments

- EAG clinical expert validated the expected proportions who would discontinue to next-line treatments and BSC
- Compared to the company base case (assumes proportions as measured in the RWEAL study), EAG clinical expert considered that the proportion of people who would move on to next line treatments was more aligned with the ALPHA study

Modelled utilisation of next-line treatments and BSC (after discontinuation of initial treatment)

	Company base case (based on RWEAL)		EAG base case (based on ALPHA)
	Moderate CHE	Severe CHE	Severe CHE
Next-line treatment	23.2%	40.9%	80.3%
BSC	76.8%	59.1%	19.7%

Link back to EAG preferred amendments to model slide

Abbreviations: BSC, best supportive care; CHE, chronic hand eczema