PART 1

For public – contains no confidential information

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

2nd appraisal committee meeting

Technology appraisal committee B [6 August 2025]

Chair: Baljit Singh

External assessment group (EAG): BMJ Technology Assessment Group

Technical team: Anita Sangha, Alexandra Sampson, Richard Diaz

Company: Leo Pharma

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

- ✓ **Background and recap of 1st committee meeting**
- ❑ Consultation responses and key issues
- ❑ Cost-effectiveness results and other considerations
- ❑ Summary

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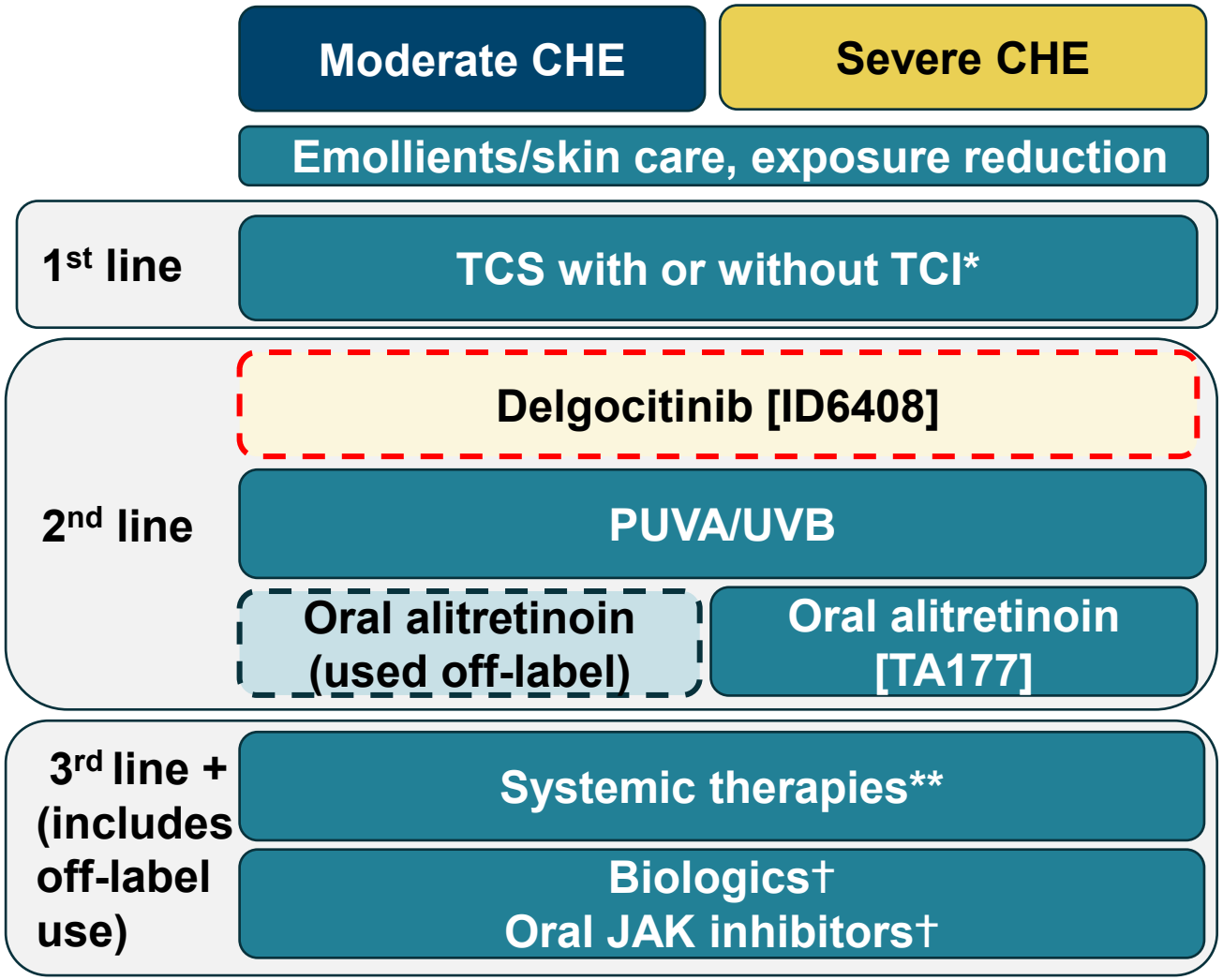
Recap

Treatment pathway

Positioning of delgocitinib: 2nd line in adults with moderate to severe CHE after TCS/TCI



Committee conclusions at ACM1 (DG section 3.3)

- Company's original positioning reflects how delgocitinib will likely be used in practice:
  - difficult to distinguish between moderate and severe disease → small % with moderate CHE have alitretinoin off-label
  - treatment choice guided by method of administration, safety and efficacy
- PUVA and alitretinoin → relevant comparators for both moderate and severe CHE
- Delgocitinib would be prescribed in secondary care by a dermatologist, in line with SmPC

* 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]

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

Clinical evidence

No evidence for the safety or efficacy of alitretinoin or PUVA in moderate disease

Trial data

DELTA 1 and 2: RCTs → delgocitinib vs vehicle cream
Population: adults with **moderate to severe CHE*** when TCS are inadequate/unsuitable

DELTA 3: open-label extension of DELTA 1 and 2: all people had delgocitinib as needed**

DELTA FORCE: RCT → delgocitinib vs alitretinoin (inc. stratification by hyperkeratotic status)
Population: adults with **severe CHE** when TCS are inadequate/unsuitable

Committee conclusions at ACM1 (DG section 3.4-3.5)

- DELTA trials appropriate for decision making
- Delgocitinib is an effective treatment for improving CHE symptoms (based on results from DELTA trials)

Indirect comparisons → no direct evidence for delgocitinib vs PUVA

Company base case at ACM1:
NMA (fixed-effects models)
5 RCTs incl. DELTA trials, Worm 2022 and ALPHA (alitretinoin vs PUVA in adults with **severe CHE**)

EAG base case at ACM1 (severe CHE only):

- DELTA FORCE (delgocitinib vs alitretinoin)
- Company MAIC preferred → delgocitinib (pooled DELTA 1 and 2) vs PUVA (ALPHA) and matching by severity and hyperkeratosis

Committee conclusions at ACM1 (DG section 3.6)

- Company NMA preferred (preserves within-trial randomisation) over EAG approach to estimate the relative treatment effects for all treatments

*moderate = IGA-CHE score of 3, severe = IGA-CHE score of 4, **based on IGA-CHE score

Abbreviations: CHE, chronic hand eczema; DG, draft guidance; NMA, network meta-analysis; PUVA, psoralen–UV A phototherapy;

Committee's conclusions at ACM1 (1)

Section in DG	Committee conclusion
3.2 Current treatment and unmet need	People with CHE would welcome an additional treatment option (current treatments often ineffective, alitretinoin is teratogenic, phototherapy is inconvenient)
3.7 Imputation of missing data (DELTA trials)	• Impact of alternative approach to WOCF on CE results is unclear • Requested analyses using first and last observation carried forward
3.8 Company's modelling approach	• Company model acceptable for decision making • Alitretinoin should be included as a comparator for moderate CHE
3.9 Treatment effects in moderate disease	Company's assumption of equivalence in the relative treatment effects between moderate and severe CHE is reasonable
3.10 Treatment effects based on hyperkeratotic status	Treatment effects should be informed by the full population from DELTA FORCE rather than based on hyperkeratotic status
3.11 Time on treatment	• Modelled time on treatment underestimated • Requested updated CE results that reflect proportion remaining on delgocitinib, alitretinoin and PUVA in clinical practice at 1, 2 and 3 years

CE, cost-effectiveness; CHE, chronic hand eczema; PUVA, psoralen–UV A phototherapy; WOCF, worst observation carried forward

Committee's conclusions at ACM1 (2)

Section in draft guidance	Committee conclusion
3.12 Utility values	Health state-specific utilities (EAG approach) are most appropriate
3.13 Other EAG amendments to model	All amendments are appropriate except for exclusion of adverse events from DELTA FORCE
3.14 Acceptable ICER	£20,000 (~£25,000 if uncertainties are reduced by requested analyses)
3.16 Assessment of cost-effectiveness	• Most plausible ICERs for delgocitinib vs PUVA: <£20,000/QALY • Most plausible ICERs for delgocitinib vs alitretinoin: >£30,000/QALY • Delgocitinib cannot be recommended when alitretinoin is not suitable as not possible to clearly define who would be offered one treatment over the other
3.18 Equality	Issues raised cannot be addressed by technology appraisal guidance

Draft recommendation

- Delgocitinib should not be used to treat moderate to severe chronic hand eczema in adults when topical corticosteroids have not worked or are not suitable

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

- ❑ Background and recap of 1st committee meeting
- ✓ **Consultation responses and key issues**
- ❑ Cost-effectiveness results and other considerations
- ❑ Summary

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Summary of consultation responses received

National Eczema Society:

- Draft guidance does not reflect patient concerns about:
  - Long-term risk of using topical corticosteroids
  - Significant adverse effects and monitoring requirements for alitretinoin (especially for women of childbearing potential)
  - Impracticalities of phototherapy for people who work/have caring responsibilities

- Economically counter-productive to escalate patients to systemic treatments, when there is an effective topical treatment available that most patients would prefer compared to a systemic

- Need access to full range of treatment options to manage the range and mix of CHE sub-types. Treatments are not equally effective in treating all aetiologies

Company response to committee preferred assumptions

Committee's preferred assumptions at ACM1	Implemented in company base case?	For discussion?
Company's fixed-effects NMA results to inform treatment effects	Yes	No
Using health state-specific utility values	Yes	No
EAG's preferred amendments* to the model, except for adverse events	Yes	No
Including adverse events from DELTA FORCE	Yes	No
Alitretinoin is a comparator for moderate disease	Yes	No

* 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

Key issues for discussion

Key issue	ICER impact
Use of worst observation carried forward approach	Very small
Approach for increasing time on treatment	Medium
Dosing data for delgocitinib in moderate population	Medium

Company has provided range of scenarios to explore the issues listed above

Very small ICER impact

Key Issue: Use of WOCF approach (1)

Using first and last observation carried forward has little impact on CE results

Recap from ACM1 – worst observation carried forward (WOCF) approach

- Company used WOCF to impute missing data across DELTA 1, 2 and FORCE to estimate treatment effects
- EAG: WOCF generates bias against the vehicle cream + alitretinoin arms where dropout rate is highest
  - effectiveness of comparators may be underestimated in the model (may underestimate ICER)
  - suggested to use multiple imputation approach with a 'missing not missing at random' assumption
- Company: most people stopped vehicle cream or alitretinoin because of AEs or lack of efficacy → multiple imputation could introduce bias and underestimate the relative treatment effect of delgocitinib
- Committee conclusion: limitations with both approaches and unclear impact on CE results → requested analyses using first and last observation carried forward to reduce uncertainty.

Company response to DG (1)

- First observation carried forward interpreted as baseline observation carried forward (BOCF)
- New analyses conducted using both a BOCF and LOCF imputation approach, complementing WOCF
- WOCF analyses imputed data for intercurrent events (e.g. discontinuation), but LOCF and BOCF analyses only imputes for truly missing data (i.e. if patient stopped treatment their data was used as it was, without being filled in for later time points)
- Only values in NMA which couldn't explore alternative imputation methods were Worm et al. and ALPHA

AE, adverse events; BOCF, baseline observation carried forward CE, cost-effectiveness; LOCF, last observation carried forward; WOCF, worst observation carried forward

Very small ICER impact

Key Issue: Use of WOCF approach (2)

Company response to DG (2)

- Comparative efficacy results remain robust across all imputation strategies
- Regardless of imputation method (WOCF, BOCF, or LOCF), odd ratios significantly favour delgocitinib in terms of the achievement of IGA-CHE 0/1
- Modest increase in the number of alitretinoin-treated patients classified as IGA-CHE 3 when using LOCF
- Choice of imputation method has negligible impact on CE results → company base case retains WOCF

Distribution of DELTA FORCE patients across IGA-CHE severity and odds ratio of achieving IGA-CHE 0/1:

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]	

BOCF, baseline observation carried forward CE, cost-effectiveness; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LOCF, last observation carried forward; WOCF, worst observation carried forward

See appendix for NMA odds ratios

Very small ICER impact

Key Issue: Use of WOCF approach (3)

EAG comments (BOCF, LOCF, or WOCF)

- Agree that efficacy of delgocitinib relative to comparators is demonstrated, regardless of approach used
- Numerical differences in ORs across approaches (< [redacted] difference); non-trivial reduction in efficacy difference for delgocitinib vs. alitretinoin
- Company's preferred WOCF approach leads to OR for IGA-CHE TS that most favours delgocitinib
- Limitations with BOCF and LOCF; not considered robust. Would prefer multiple imputation approach
- EAG base case uses LOCF as most conservative option

Consistency of approach

- Unclear how inconsistent imputation approaches would impact results of fixed-effect NMAs. Would prefer consistent imputation approach across all studies included in NMAs,
- Also unclear how difference in accounting for intercurrent events (WOCF imputed data for intercurrent events, BOCF/LOCF didn't) impacted the results
- EAG provides scenario which uses the DELTA FORCE (WOCF) treatment effects (not NMA) to compare delgocitinib vs alitretinoin in severe CHE

Which approach should be used to impute missing data? BOCF, WOCF or LOCF?
Should DELTA FORCE (WOCF) or NMA be used to compare delgocitinib vs alitretinoin initial treatment effects in severe CHE?

BOCF, baseline observation carried forward CE, cost-effectiveness; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; LOCF, last observation carried forward; WOCF, worst observation carried forward

Medium ICER impact

Key Issue: Time on treatment (1)

EAG agrees with overall company approach, but makes slightly different adjustments

Recap from ACM1

- Model used discontinuation rates for people who **didn't** have full response to inform discontinuation rates for people having retreatment who previously **did** have full response
- EAG clinical experts: ~25% of people on alitretinoin are still on treatment after 2 years in clinical practice
- ACM1 Clinical expert: proportion of people remaining on treatment in the model at 1, 2 and 3 years appears low for all treatments → reasonable to assume 25% would have long-term intermittent alitretinoin
- Committee conclusion: modelled ToT does not reflect clinical practice → requested analyses to include:
  - at 2 years: 25% on alitretinoin, at least 25% on delgocitinib but proportion on PUVA may be lower
  - analyses should appropriately adjust modelled time on treatment at years 1 to 3 in model

Company response to DG (1)

- Conducted structured expert elicitation; variation in estimates but upper bound aligned with Committee preference (up to 25% remain on alitretinoin at 2yrs)
- This figure differs significantly from data from RCTs
- Four sets of parameters in model affect time on treatment (discontinuation rate, re-initiation rate, threshold for retreatment and time on treatment)

RCT = randomised control trial; ToT: time on treatment;

Medium ICER impact

Key Issue: Time on treatment (2)

Company response to DG (2)

- Most appropriate method to achieving preferred ToT estimates is a combination of:
  - reducing the likelihood of discontinuation during periods of retreatment for all treatments
  - increasing severity threshold for retreatment, thus extending time to treatment reinitiation
- Once other committee preferences are included, the company base case uses following adjustments to achieve the time on treatment estimates requested by Committee in severe population:
  - people on alitretinoin reinitiate treatment at severe, and people on delgocitinib reinitiate treatment once symptoms are mild (to reflect ease of resuming topical vs oral treatment with monitoring);
  - 0% retreatment discontinuation assumption for delgocitinib during retreatment (from 2.8%) and lower odds of alitretinoin discontinuation during retreatment (from 6.83% to 3.54%; conservative assumption)
- For moderate population, following adjustments are made to achieve the time on treatment estimates requested by Committee:
  - 0% delgocitinib retreatment discontinuation
  - 50% lower odds of alitretinoin discontinuation during re-treatment

ToT: time on treatment;

Medium ICER impact

Key Issue: Time on treatment (3)

Proportion of people still on treatment in severe population

	% of patients still on delgocitinib			% of patients still on alitretinoin		
	Yr 1	Yr 2	Yr 3	Yr 1	Yr 2	Yr 3
Company preferred approach *(scenarios 4a+5 in DG response)*						
• Resume alitretinoin at severe • 0% delgocitinib retreatment discontinuation • 50% lower odds of alitretinoin discontinuation during re-treatment (from 6.83% to 3.54%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred approach						
• Resume alitretinoin at moderate • 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%).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACM1 committee preferences		≥25%			25%	

Medium ICER impact

Key Issue: Time on treatment (3)

EAG comments

- Company's assumptions around eligibility conflict with the EAG's clinical expert opinions (that alitretinoin patients would be eligible for re-treatment when symptoms relapse to a moderate severity).
- EAG considers the assumption does not reflect clinical practice and is therefore not appropriate
- EAG questions the strong assumption that there is no discontinuation during re-treatment for delgocitinib patients. Preferred assumptions are:
  - 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%).
- Proportion of patients estimated to remain on treatment after 2yrs are [redacted]% alitretinoin and [redacted]% delgocitinib; doesn't reflect committee preference but does how patients would be treated
- Company preferences are less favourable towards delgocitinib than EAG assumptions

Does committee prefer EAG or company approach for adjusting time on treatment?

Medium ICER impact

Key Issue: Dosing data for delgocitinib in moderate CHE

Company says delgocitinib dosing will be less for people with moderate CHE at baseline

Recap from ACM1

- Committee preferred EAG amendments to model includes using dosing data from DELTA FORCE

Company response to DG

- Accept appropriateness of using DELTA FORCE dosing data for 'severe at baseline' population
- However, applying this to 'moderate at baseline' population risks overestimating resource use and costs
- While alitretinoin is oral treatment (where dose/cost is the same, regardless of severity), delgocitinib is topical:
  - people with moderate disease will consume less (so will cost less) than people with severe disease
  - Clinical expert elicitation supports lower dosing in moderate CHE; intensity of inflammation, as well as skin surface area involved, modulates consumption
- Propose using data from moderate patients in DELTA 1 & 2 to inform dosing in moderate population

Delgocitinib mean consumption from DELTA 1, DELTA 2 and DELTA FORCE across IGA-CHE category

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

- Delgocitinib usage generally higher among patients with severe CHE at baseline than moderate CHE
- Exception for moderate patients who experienced worsening severity to IGA-CHE 4

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

Key Issue: Dosing data for delgocitinib in moderate CHE

EAG comments

- Question assumption that people with same IGA-CHE score will use different dosage across populations
- If no fundamental difference between people 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 DELTA FORCE is robust source for dosing data
- If subgroups are fundamentally different, then EAG considers DELTA 1 and 2 studies are appropriate
- In EAG base case, use dosing from DELTA FORCE for moderate CHE population; scenario provided using DELTA 1 and 2

Should delgocitinib dosing data for people with moderate CHE at baseline come from DELTA FORCE, or DELTA 1 & 2?

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

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

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Summary of base case assumptions at ACM2

Assumption	Committee preference at ACM1	Company base case at ACM2	EAG base case at ACM2
Time on treatment approach	ToT should be longer for all treatments. At 2yrs: • 25% of people still on alitretinoin • ≥25% of people still on delgocitinib • PUVA may be lower than 25%	Committee target met by: • Alitretinoin and PUVA patients eligible for re-treatment when **severe** • **Zero** discontinuation during re-treatment for delgocitinib patients	Adjustment made, lower than committee preference: • Alitretinoin patients eligible for re-treatment when **moderate** • **Half** discontinuation during re-treatment for delgocitinib patients
Imputation approach	Also consider BOCF and LOCF	WOCF	LOCF
Efficacy parameters < wk12	Fixed effect NMA	Fixed effect NMA	Fixed effect NMA Scenario provided using DELTA FORCE
Delgocitinib dosing; moderate CHE	DELTA FORCE	DELTA FORCE (Scenario provided using DELTA 1 and DELTA 2)	DELTA FORCE (Scenario provided using DELTA 1 and DELTA 2)

BOCF, baseline observation carried forward; LOCF, last observation carried forward; NMA, network meta-analysis; WOCF, worst observation carried forward

Cost-effectiveness results

As confidential discounts are available for treatments in the pathway,

ICERs will be presented in Part 2 slides

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Key issues for discussion

- Which approach should be used to impute missing data? BOCF, WOCF or LOCF? Should DELTA FORCE (WOCF) or NMA be used to compare delgocitinib vs alitretinoin initial treatment effects in severe CHE?
- Does committee prefer EAG or company approach for adjusting time on treatment?
- Should delgocitinib dosing data for people with moderate CHE at baseline come from DELTA FORCE, or DELTA 1 & 2?

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

Supplementary appendix

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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

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

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

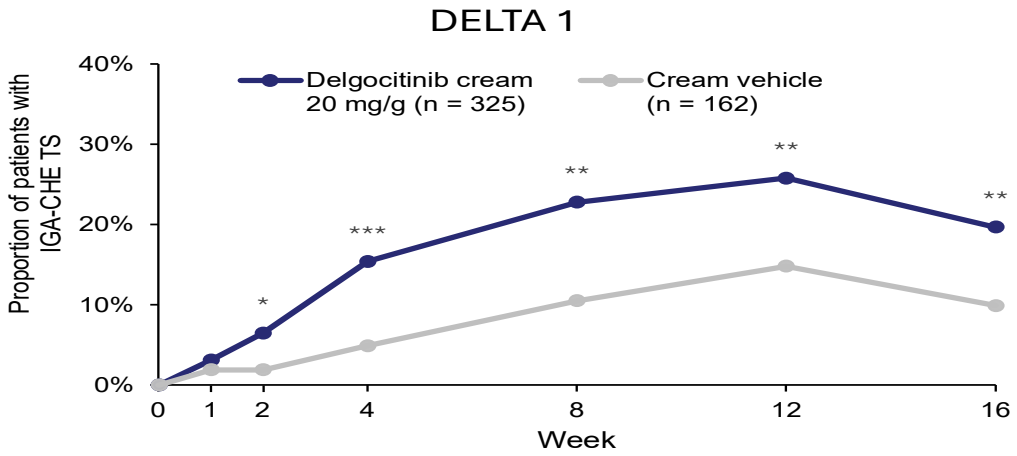
DELTA 1 and 2 – IGA-CHE treatment success (TS)

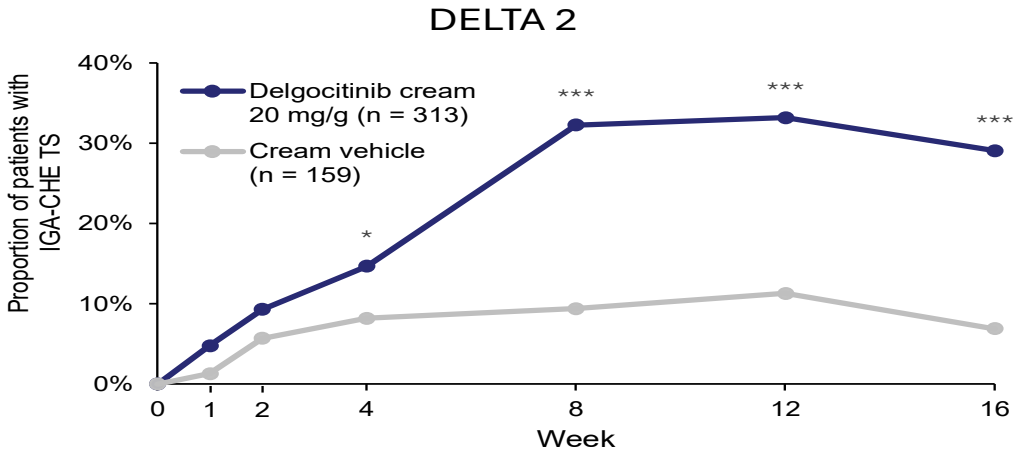
Delgocitinib is significantly more effective than vehicle cream for achieving treatment success

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

DELTA FORCE – mean change in HECSI

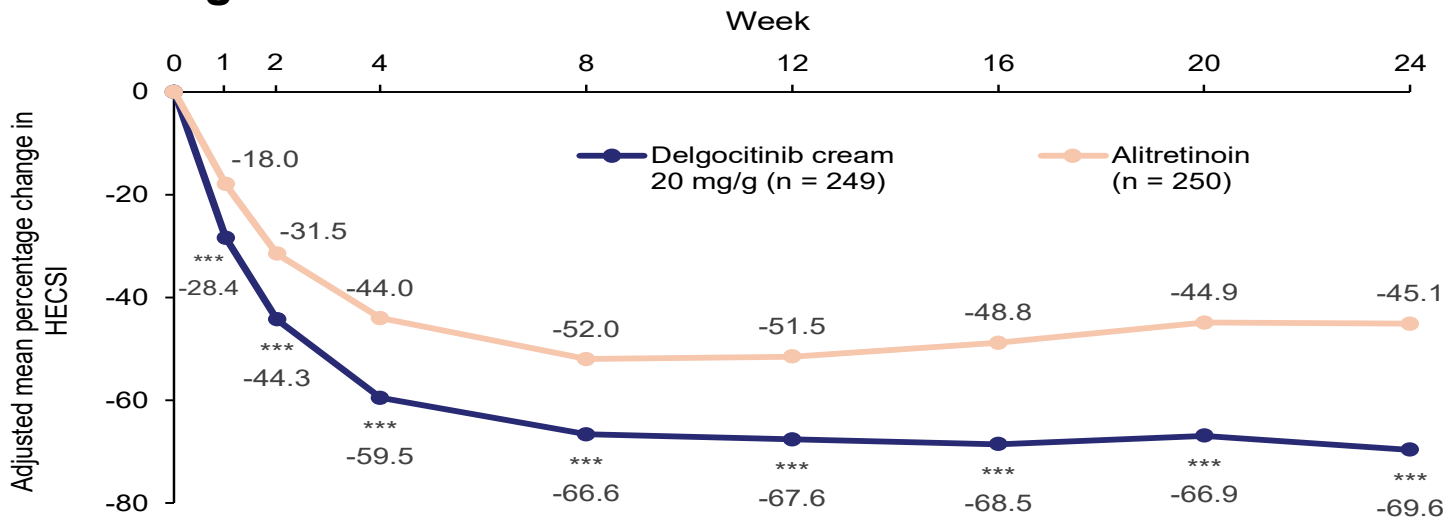
Delgocitinib is significantly more effective than alitretinoin in reducing mean HECSI score

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

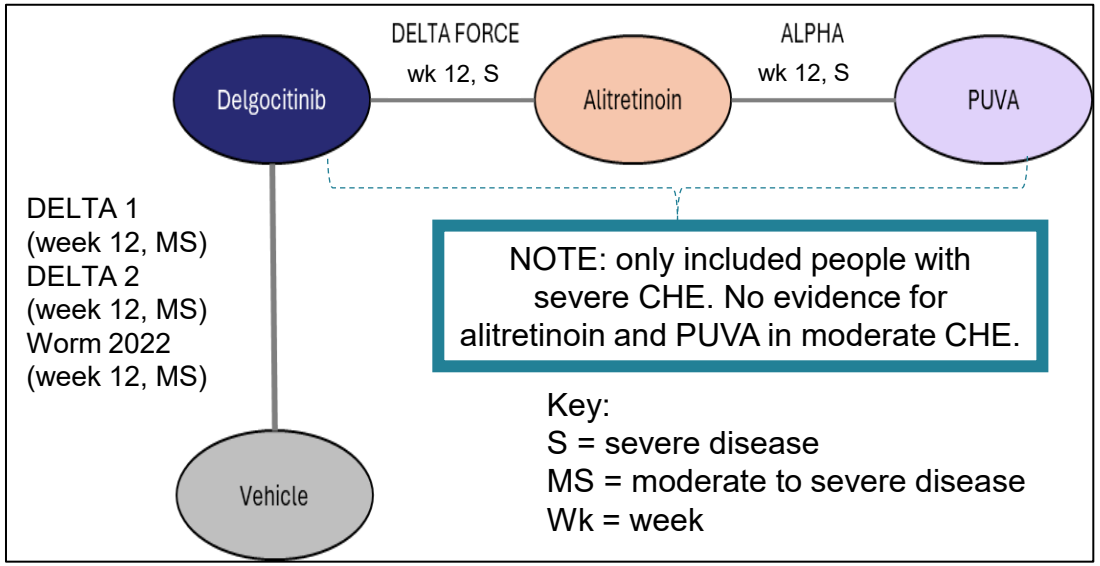
Abbreviations: CI; confidence interval; HECSI, Hand Eczema Severity Index; SE, standard error

Network meta-analysis (NMA)

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

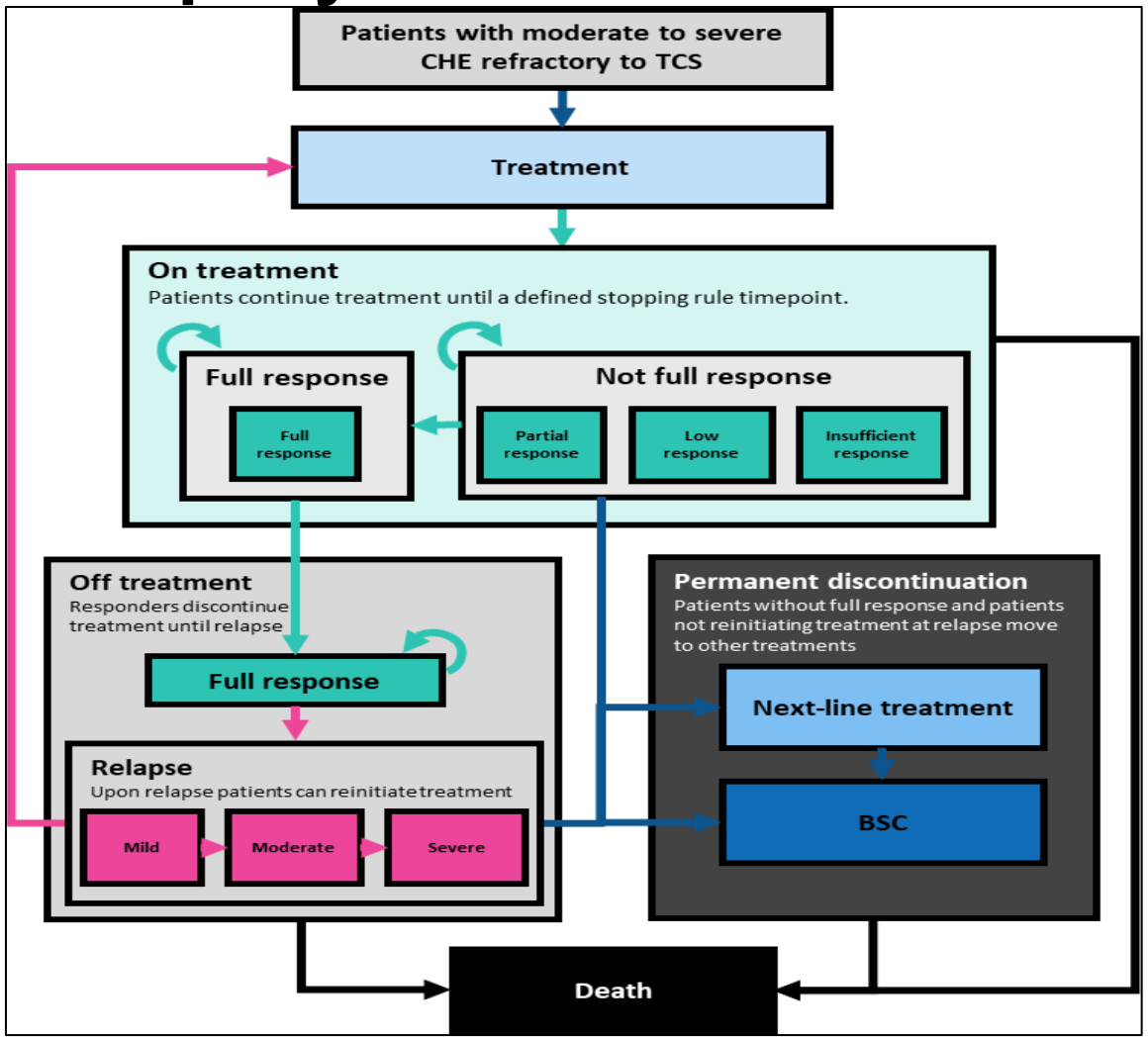
Delgocitinib vs treatment	IGA-CHE TS: week 12 analysis (company base case, fixed effects model)		
	All people	Severe CHE	Moderate CHE
Median odds ratio (95% CI)			
Vehicle cream	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]



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

Company's model overview



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)

EAG considers the model structure appropriate for addressing the decision problem

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

Comparators for moderate disease

Company consider alitretinoin is only a relevant comparator for people with severe CHE

Recap from ACM1

- Alitretinoin MA and NICE TA177 restricts its use for people with severe CHE only (as modelled by company)
- Clinical experts explained:
  - severity is subjective → often difficult to distinguish between moderate and severe disease
  - in moderate disease → PUVA typically used, but small proportion have alitretinoin off-label
  - treatment choice guided by method of administration, safety and efficacy → some people may prefer convenience of topical cream even if means slower or less complete therapeutic response
- Committee conclusion: PUVA and alitretinoin are both relevant comparators for moderate and severe CHE

Company response to DG

- Accept Committee's preference for including alitretinoin as a comparator in moderate CHE population
- To ensure methodological robustness and clinical relevance, baseline characteristics and dosing for delgocitinib arm should be informed by the moderate patient population observed in DELTA 1 and DELTA 2

EAG comments

- No comment provided

Very small ICER impact

Key Issue: Use of WOCF approach

Company response to DG

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	BOCF	LOCF	WOCF	BOCF	LOCF
Cream vehicle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PUVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alitretinoin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Link back to main slides on key issue

Efficacy parameters from week 12

Company uses DELTA FORCE efficacy parameters from week 12 to align with dosing data

Recap from ACM1

- Committee preferred company's fixed-effects NMA to inform treatment effects in the model, (rather than EAG preference of DELTA FORCE for delgocitinib vs alitretinoin)

Company response to DG

- Clear conclusion on preferred source for treatment effects <12wks, but unclear if company (DELTA 3) or EAG efficacy parameters (DELTA FORCE) should be used for 12wks+
- For consistency with source of dosing data (DELTA FORCE), updated company base case uses DELTA FORCE parameters from week 12 for comparison with alitretinoin (as per original EAG base case) rather than DELTA 3 (as per original company base case)
- This ensures efficacy and other inputs are aligned with the dosing data source; supports the reliability and robustness of modelling results
- Scenario is provided using original company base case parameters, but company deems this implausible as it detaches the source of clinical efficacy and dosing

EAG

- No comment provided