Efficacy and safety of topical delgocitinib cream versus oral alitretinoin capsules in adults with severe chronic hand eczema (DELTA FORCE): a 24-week, randomised, head-to-head, phase 3 trial

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Summary

Background Chronic hand eczema is a heterogeneous, fluctuating, and long-lasting disease affecting the hands and wrists that substantially affects quality of life. For severe chronic hand eczema, topical corticosteroids are often unsatisfactory and systemic treatment can be required. The aim of the head-to-head, phase 3 DELTA FORCE trial was to evaluate the efficacy and safety of topical delgocitinib cream versus oral alitretinoin, the only currently approved systemic drug for severe chronic hand eczema.

Methods This randomised, assessor-masked, trial was conducted at 102 trial centres in Austria, Canada, France, Germany, Italy, Norway, Poland, Slovakia, Spain, and the UK. Adults (aged ≥18 years) with severe chronic hand eczema were randomly assigned (1:1) via an interactive response technology system to delgocitinib cream 20 mg/g (twice daily) or alitretinoin 30 mg (once daily) for up to 24 weeks. The primary endpoint was change in Hand Eczema Severity Index (HECSI) score from baseline to week 12. Efficacy of delgocitinib cream versus alitretinoin was assessed in all eligible randomly assigned patients who had available data at baseline, and safety was assessed in all patients exposed to trial treatment. The trial is registered with ClinicalTrials.gov (NCT05259722) and is complete.

Findings Between June 15, 2022, and Dec 5, 2023, 513 (334 [65%] female and 179 [35%] male) patients were randomly assigned to receive delgocitinib cream (n=254) or alitretinoin (n=259). Ten patients were excluded after randomisation due to not meeting eligibility criteria, so the full analysis set consisted of 250 patients in the delgocitinib group and 253 in the alitretinoin group. One patient in the delgocitinib group and three in the alitretinoin group were excluded from the primary analysis as they had missing HECSI data at baseline. A significantly greater least squares mean change in HECSI score from baseline to week 12 was observed with delgocitinib cream (–67·6 [SE 3·4]; n=249) versus alitretinoin (–51·5 [3·4]; n=250; difference –16·1 [95% CI –23·3 to –8·9], p<0·0001). Fewer patients reported adverse events in the delgocitinib group (125 [49%] of 253 patients) than in the alitretinoin group (188 [76%] of 247). The most frequent adverse events were headache (ten [4%] in the delgocitinib group *vs* 80 [32%] in the alitretinoin group), nasopharyngitis (30 [12%] *vs* 34 [14%]), and nausea (one [<1%] *vs* 14 [6%]).

Interpretation Delgocitinib cream showed superior efficacy and a more favourable safety profile versus oral alitretinoin over 24 weeks. These results support the benefit of delgocitinib cream in patients with severe chronic hand eczema.

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Introduction

Chronic hand eczema, defined as hand eczema that persists for longer than 3 months or that returns twice or more within 12 months, is one of the most common chronic inflammatory disorders that affects the hands and wrists, and is associated with pain, pruritus, and substantial occupational, non-occupational, functional, psychosocial, and socioeconomic burden.[1–3] Topical corticosteroids are currently used as the standard first-line treatment for chronic hand eczema; however, long-term or frequent use of topical corticosteroids can cause dermal atrophy, interfere with skin barrier repair, and be associated with topical corticosteroid-related cutaneous adverse events, including fissures, pain, and disease worsening.[2,4,5] Moreover, topical corticosteroids might not be sufficient for severe cases of chronic hand eczema that could require treatment with systemic therapies.[2] Alitretinoin, an oral retinoid, is currently the only systemic drug approved in some EU countries, Canada, Israel, and South Korea for the treatment of severe chronic hand eczema. This retinoic acid agonist binds to intracellular retinoic acid receptors A and X, suppresses the recruitment and activation of inflammatory cells, and inhibits cell proliferation and

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See Online for appendix

Research in context

Evidence before this study

A search of PubMed and ClinicalTrials.gov for comparative studies assessing the efficacy and safety of alitretinoin and other treatments in chronic hand eczema with the terms "chronic hand eczema" AND "alitretinoin" was done from database inception to July 17, 2024, with no language restrictions applied. The search identified one article of a discontinued randomised controlled trial of alitretinoin versus oral azathioprine as well as two articles of retrospective comparative studies and one terminated randomised controlled trial comparing alitretinoin versus oral ciclosporin. Alitretinoin is currently the only systemic drug specifically approved in a few countries worldwide for the treatment of severe chronic hand eczema. Delgocitinib cream is a topical pan-Janus kinase (JAK) inhibitor that affects the activation of multiple JAK-signal transducer and activator of transcription pathways involved in the skin barrier dysfunction and inflammation associated with chronic hand eczema pathogenesis. In patients with moderate to severe chronic hand eczema, delgocitinib cream showed significant improvement in all key efficacy endpoints and was well tolerated versus cream vehicle in the pivotal phase 3 DELTA 1 and DELTA 2 trials, as well as when used long-term as needed in the open-label DELTA 3 trial.

Added value of this study

To our knowledge, DELTA FORCE is the first clinical trial to assess, in a head-to-head comparison, the efficacy and safety of a topical treatment for chronic hand eczema against the only approved oral systemic therapy. The trial showed superior efficacy and a more favourable safety profile of topical delgocitinib cream compared with oral alitretinoin in patients with severe chronic hand eczema.

Implications of all the available evidence

The data from the DELTA FORCE trial support the benefits of delgocitinib cream as an efficacious and well tolerated topical treatment for this patient population with a high disease burden and unmet treatment needs. Delgocitinib cream has the potential to provide a non-steroidal topical treatment option that combines effective disease control without the safety concerns associated with long-term use of topical corticosteroids and systemic therapies.

differentiation.[6,7] Alitretinoin is specifically indicated for the treatment of patients with severe chronic hand eczema who are unresponsive to treatment with potent topical corticosteroids, but it has various safety limitations.[2,4,8,9] Treatments for moderate to severe chronic hand eczema that combine disease control with a safety profile suitable for long-term use are needed.

Delgocitinib cream is a topical pan-Janus kinase (JAK) inhibitor that affects the activation of multiple JAK-signal transducer and activator of transcription pathways involved in the skin barrier dysfunction and inflammation associated with chronic hand eczema pathogenesis.[10,11] In the phase 3 DELTA 1 (NCT04871711), DELTA 2 (NCT04872101), and open-label long-term extension DELTA 3 (NCT04949841) trials, which included adults with moderate to severe chronic hand eczema, delgocitinib cream 20 mg/g showed greater improvements in both patient-reported and clinician-reported efficacy outcomes versus cream vehicle and was well tolerated when used long-term as needed.[12,13]

The aim of the head-to-head, phase 3 DELTA FORCE trial was to evaluate the efficacy, effect on health-related quality of life (HRQoL), and safety of twice-daily topical delgocitinib cream 20 mg/g compared with once daily oral alitretinoin in patients with severe chronic hand eczema.

Methods

Trial design

DELTA FORCE was a phase 3, randomised, assessor-masked, active-controlled, parallel-group, multisite trial in which adults with severe chronic hand eczema were assigned to twice daily application of topical delgocitinib cream (20 mg/g; LEO Pharma, Dublin, Ireland) or once-daily administration of oral alitretinoin (Toctino, Almac, Kirchberg, Switzerland) for up to 24 weeks. The trial was conducted at 102 medical research centres and hospitals in Austria, Canada, France, Germany, Italy, Norway, Poland, Slovakia, Spain, and the UK (appendix pp 2–6). Alitretinoin is approved in all participating countries. The trial included 1–4 weeks of screening, up to 24 weeks of treatment, and 2-week safety follow-up periods, with an additional follow-up visit to screen for pregnancy at 5 weeks after the last dose for patients of childbearing potential who were treated with alitretinoin, which is known to be teratogenic (figure 1).

The institutional review board or independent ethics committee at each investigational centre (appendix pp 2–6) approved the DELTA FORCE protocol. The trial was conducted in accordance with the consensus ethical principles of the Declaration of Helsinki,[14] the Council for Internal Organization of Medical Sciences International Ethical Guidelines,[15] applicable International Council of Harmonisation good clinical practice guidelines,[16] and other applicable laws and regulations. An independent data monitoring committee was not instituted (with institutional review board or independent ethics committee approval) as the trial included an adult patient population that was not vulnerable, the investigator assessing safety was unmasked, and the comparator was a medicine used for its licensed indication. No potential safety or toxicity concerns were identified for delgocitinib cream 20 mg/g that required close monitoring by an unmasked data monitoring committee. The trial is registered with ClinicalTrials.gov (NCT05259722).

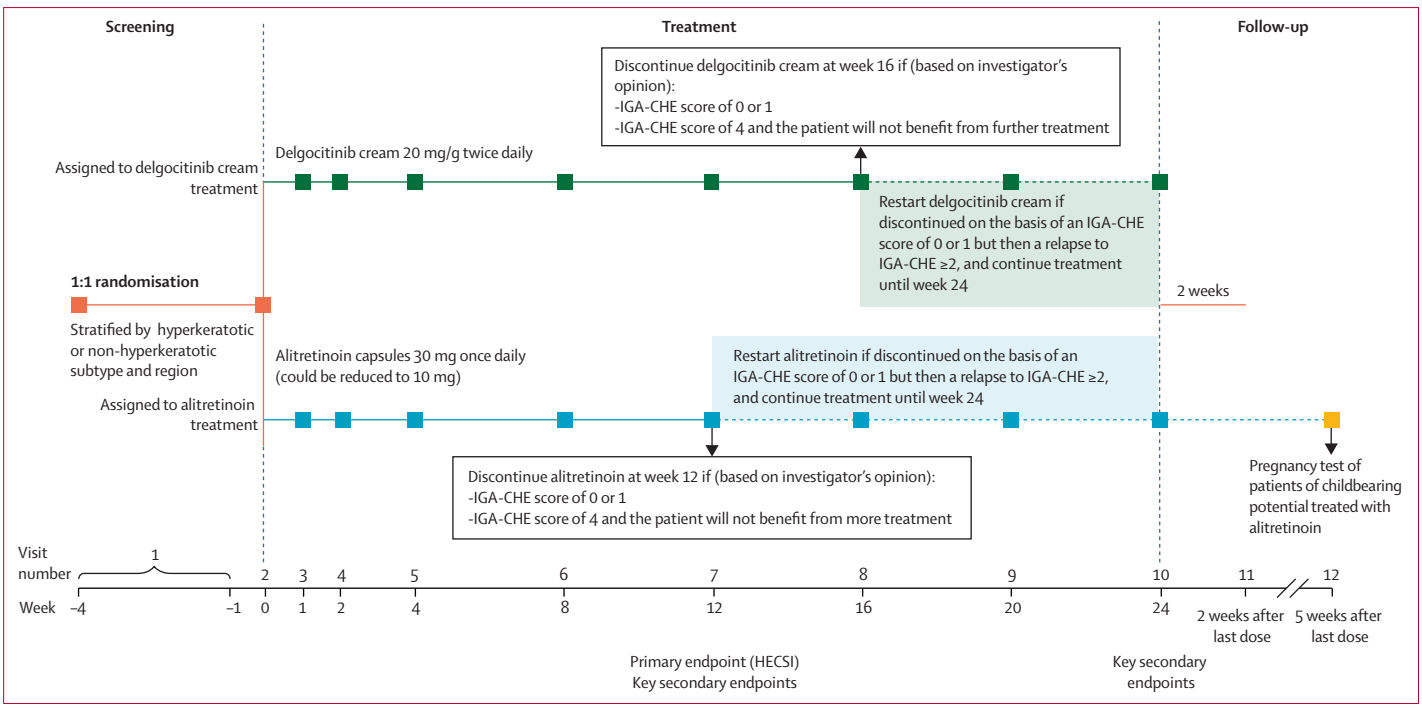


Figure 1: **Trial design for DELTA FORCE**

For patients treated with medications requiring a 28-day washout period before baseline, the duration of the screening period was extended to up to 31 days to ensure appropriate washout. For patients of childbearing potential, the duration of the screening period was extended to up to 42 days to ensure compliance with contraceptive and pregnancy prevention programme requirements. IGA-CHE scores relate to severity, with a score of 0 indicating clear, 1 indicating almost clear, 2 indicating mild, 3 indicating moderate, and 4 indicating severe. HECSI=Hand Eczema Severity Index. IGA-CHE=Investigator's Global Assessment for Chronic Hand Eczema.

Participants

Patients in the DELTA FORCE trial were adults (aged ≥18 years) with severe chronic hand eczema as defined by an Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) score of 4 within a five-point scale with the following scores: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). An IGA-CHE score of 4 was defined as having at least one sign from each of the following two subsets: marked erythema (deep or bright red), marked and thick scaling, or marked hyperkeratosis or lichenification; and high density of vesicles with erosions, marked oedema, or one or more deep fissures.[17] Patients also had either a documented inadequate response to topical corticosteroid treatment or documentation that topical corticosteroids were otherwise medically inadvisable. Patients were recruited primarily from the trial centres. Patients were excluded if they had concurrent skin diseases on the hands, had previously received treatment with systemic or topical JAK inhibitors, or had a contraindication for alitretinoin use according to the product label. A full list of inclusion and exclusion criteria is provided in the appendix (pp 7–11). Demographics including patient sex were collected at screening as determined by the unmasked investigator. Written informed consent was obtained from all patients.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive delgocitinib cream 20 mg/g or alitretinoin 30 mg (figure 1). Randomisation was performed via an interactive response technology system and stratified by chronic hand eczema subtype (hyperkeratotic or non-hyperkeratotic) and region (North America or Europe). Due to the different administration routes for the two trial drugs, patients were not masked to the treatment assignment. To ensure unbiased clinical efficacy assessments, each trial site was required to have at least one masked assessor, who was not involved in the screening of patients, and an unmasked investigator. Additional details are provided in the appendix (p 12).

Procedures

In the delgocitinib group, delgocitinib cream 20 mg/g was applied twice daily (approximately 12 h apart) in a thin layer to the areas affected by chronic hand eczema until week 16, regardless of clearance status (ie, whether the eczema improved or resolved during the treatment period according to the IGA-CHE score). In the alitretinoin group, one oral capsule of alitretinoin 30 mg was taken once daily, preferably at the same time each day, until week 12, regardless of clearance status. In the event of an unacceptable adverse event, the alitretinoin dose could be reduced to 10 mg in alignment with the

product label.[6] The first application or dose of trial drug was administered by the patient at the trial site under the supervision of the unmasked investigator or delegate, and subsequent applications or doses were administered by the patient at home. Trial visits were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24. From weeks 16–24 (for the delgocitinib cream group) or from weeks 12–24 (for the alitretinoin group), patients continued their treatment if the IGA-CHE score was 2 or higher as assessed by the masked assessor, and, in the opinion of the unmasked investigator, the patient could benefit from continued treatment. In both treatment groups, the protocol recommended that patients stop treatment at week 16 (delgocitinib) or week 12 (alitretinoin) if they reached IGA-CHE treatment success (defined as an IGA-CHE score of 0 [clear] or 1 [almost clear, meaning barely perceptible erythema only] with at least a two-step improvement from baseline). Treatment decisions were made by the unmasked investigator following the IGA-CHE score assessed by the masked assessor. Patients who stopped their treatment due to an IGA-CHE score of 0 or 1 reinitiated their treatment if they had a relapse to an IGA-CHE score of 2 or higher and remained on continuous treatment until week 24.

If a patient's alitretinoin dose was decreased from 30 mg to 10 mg due to unacceptable adverse events, the dose was not permitted to be increased at a later point during the trial. Local safety requirements for alitretinoin use were followed, and educational material about alitretinoin was discussed with and provided to patients at inclusion. Patients receiving alitretinoin were monitored and stopped treatment if they developed depression, mood disturbance, psychosis, or aggression as assessed by the unmasked assessor and were referred to a mental health-care professional for further assessment.

In both treatment groups, the use of emollients was permitted during the trial, and patients were instructed to not change their usual skincare routine. However, patients were instructed to not use emollients on the affected areas within 2 h before trial visits and 2 h after delgocitinib cream application. If medically necessary (ie, to control intolerable chronic hand eczema symptoms during the treatment and follow-up periods), rescue treatment was prescribed to patients if recommended by the masked assessor following efficacy assessments (IGA-CHE and Hand Eczema Severity Index [HECSI]). The unmasked investigator selected and initiated the rescue medication. Alitretinoin was not allowed to be used as rescue treatment. If rescue treatment was initiated, patients had to stop the trial drug immediately and were not allowed to restart it.

Outcomes

The primary endpoint of the DELTA FORCE trial was the change in HECSI score from baseline to week 12. HECSI, assessed by the masked assessor, scores the intensity of six clinical signs of chronic hand eczema (erythema, infiltration or papulation, vesicles, fissures, scaling, and oedema) using a four-point scale, from 0 (none or absent) to 3 (severe), and the extent of the lesions on each of the five areas (fingertips, fingers [except fingertips], palms, backs of hands, and wrists) using a five-point scale; the total HECSI score, calculated by multiplying the area score for each location by the total sum of the intensity of each clinical feature, ranges from 0 to 360.[18]

Key secondary endpoints were a 90% or greater improvement in HECSI score from baseline (ie, HECSI-90) at week 12, IGA-CHE treatment success at week 12, change in Hand Eczema Symptom Diary (HESD) itch and pain scores (weekly average) from baseline to week 12, area under the curve (AUC) of HECSI-90 from baseline up to week 24, AUC of reduction from baseline in Dermatology Life Quality Index (DLQI) score up to week 24, and change in HECSI score from baseline to week 24. A list of exploratory endpoints is presented in the appendix (pp 13–14). Other secondary endpoints were numbers of treatment-emergent adverse events and treatment-emergent serious adverse events from baseline up to week 26, and number of adverse events leading to trial drug discontinuation up to week 24.

IGA-CHE was assessed by the masked assessor.[17] HESD scores were used to assess the severity of six signs or symptoms of chronic hand eczema (itch, pain, cracking, redness, dryness, and flaking) in the previous 24 h using an 11-point scale, with 0 indicating no symptoms and 10 indicating severe symptoms; patients assessed the severity of these symptoms daily in an electronic diary and a weekly average was derived from daily scores.[19] The DLQI questionnaire was completed by patients during trial visits to score the effect of their condition on ten items related to their quality of life during the previous week on a four-point Likert scale (0=not at all/not relevant, 1=a little, 2=a lot, and 3=very much).[20] The AUC of HECSI-90 from baseline up to week 24 represents the number of days with a 90% reduction in HECSI score until week 24. The AUC of reduction from baseline in DLQI score up to week 24 represents the cumulative improvement in DLQI score until week 24.

Safety was assessed by the unmasked investigator and included evaluating adverse events and monitoring vital signs, electrocardiograms, and clinical laboratory parameters. Adverse events were graded as mild, moderate, or severe.

Statistical analysis

The trial sample size of 510 patients was chosen to provide 80% power to establish superiority of delgocitinib cream 20 mg/g with regard to change from baseline to week 12 in HECSI score, based on a one-sided hypothesis test at a 2·5% significance level (appendix p 36). A difference in the mean change from baseline to week 12 in HECSI score of 7·5 (SD 30)

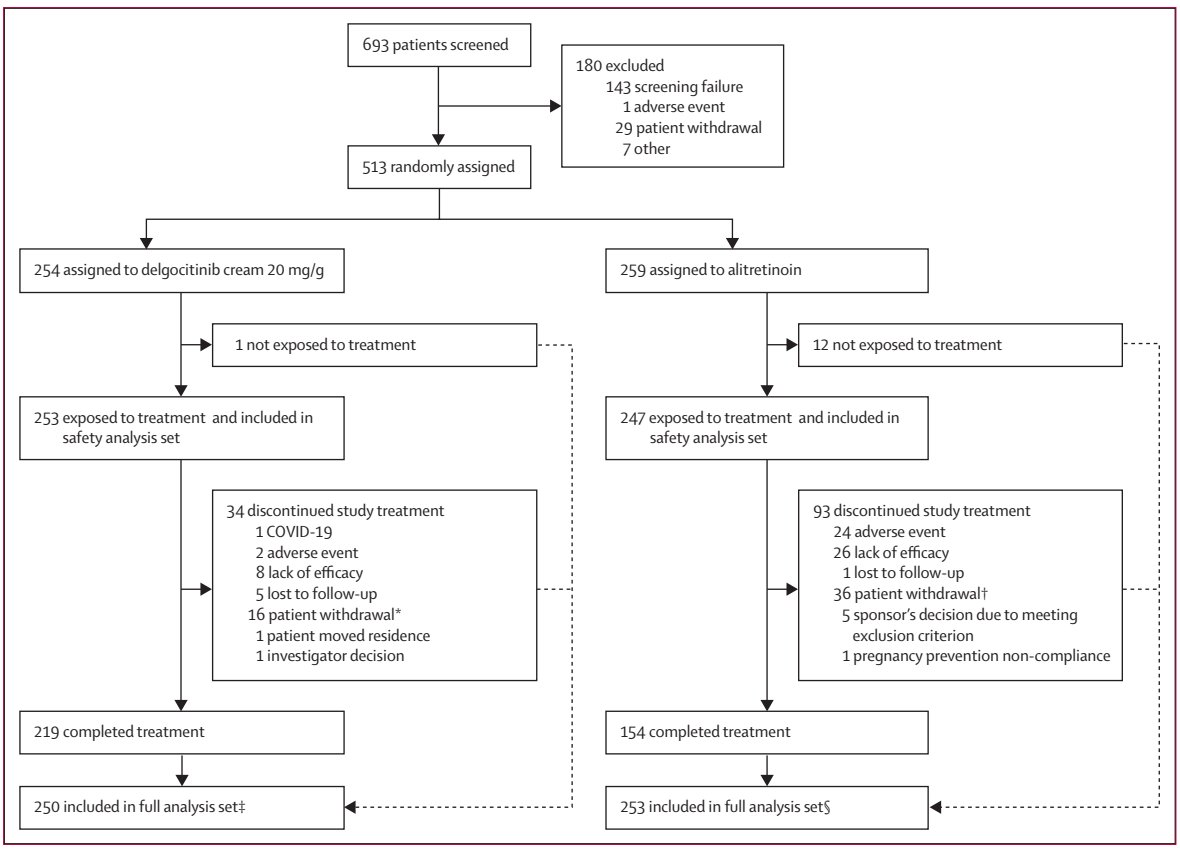


***Figure 2*: DELTA FORCE trial profile**

*Including 1 patient whose primary reason was recorded as Other: patient decision. †Including 2 patients whose primary reasons were recorded as Other: patient decision, and 1 patient whose primary reason was recorded as Other: personal issues. ‡Four patients were excluded from the full analysis set due to inclusion criteria not being met (n=1) or exclusion criteria being met (n=3). §Six patients were excluded from the full analysis set due to inclusion criteria not being met (n=1) or exclusion criteria being met (n=5).

between the delgocitinib cream and alitretinoin treatment groups was targeted because of the results from the delgocitinib cream phase 2b trial (NCT03683719). We used IGA-CHE score as a surrogate endpoint because published HECSI data for alitretinoin are scarce.[9,11]

For the primary and key secondary endpoints, except for the key secondary endpoint of change in HECSI score from baseline to week 24, confirmatory one-sided (superiority) hypotheses were tested for delgocitinib cream versus alitretinoin based on the composite estimand. Change in HECSI score from baseline to week 24 was initially evaluated for non-inferiority using a non-inferiority margin of 10 (ie, M=10).[21] If non-inferiority was found to be statistically significant, superiority was evaluated. With the composite estimand, data collected after initiation of rescue treatment or after permanent discontinuation of trial drug, as well as any other missing data, were imputed with worst observation carried forward (including baseline value, for continuous endpoints) or non-response (for binary endpoints). A closed testing procedure with hierarchical tests was used to control the overall type I error at a nominal one-sided 2·5% level (appendix p 36). Two-sided p values are reported. The one-sided (superiority) hypotheses were rejected if the two-sided p-value was smaller than $2\times\alpha=5\%$ and if the point estimate was in favour of the alternative hypothesis.

For continuous endpoints, an ANCOVA model with effects of treatment group, hyperkeratotic or non-hyperkeratotic subtype, and baseline value was used. For binary endpoints, the Cochran–Mantel–Haenszel test stratified by hyperkeratotic or non-hyperkeratotic subtype was used to calculate the difference in response rates between the treatment groups with 95% CI. For the AUC endpoints, a robust ANCOVA model with the AUC as dependent variable, and treatment, hyperkeratotic or non-hyperkeratotic subtype, and baseline value as covariates was used. The AUC of HECSI-90 was derived from the function of HECSI-90 response, where 1 was assigned when response was observed and 0 otherwise. The AUC of reduction from baseline in DLQI score up to week 24 was based on all changes of DLQI score values until week 24; the AUC unit was days×DLQI score reduction. Prespecified sensitivity analyses were conducted for the primary and key secondary endpoints to assess the robustness of the

	Total (n=513)	Delgocitinib cream (n=254)	Alitretinoin (n=259)
Age, years	45·0 (33·0–56·0)	46·0 (34·0–56·0)	44·0 (31·0–56·0)
Sex*			
Male	179 (35%)	87 (34%)	92 (36%)
Female	334 (65%)	167 (66%)	167 (64%)
Race			
White	477 (93%)	237 (93%)	240 (93%)
Asian	14 (3%)	9 (4%)	5 (2%)
Black or African American	4 (1%)	1 (<1%)	3 (1%)
Multiple	2 (<1%)	2 (1%)	0
Other or not reported	16 (3%)	5 (2%)	11 (4%)
Region†			
Europe	459 (89%)	229 (90%)	230 (89%)
North America	54 (11%)	25 (10%)	29 (11%)
Country†			
Austria	5 (1%)	2 (1%)	3 (1%)
Canada	54 (11%)	25 (10%)	29 (11%)
France	30 (6%)	14 (6%)	16 (6%)
Germany	136 (27%)	63 (25%)	73 (28%)
Italy	22 (4%)	13 (5%)	9 (3%)
Norway	2 (<1%)	1 (<1%)	1 (<1%)
Poland	180 (35%)	89 (35%)	91 (35%)
Slovakia	14 (3%)	9 (4%)	5 (2%)
Spain	64 (12%)	36 (14%)	28 (11%)
UK	6 (1%)	2 (1%)	4 (2%)
Age at onset of chronic hand eczema, years	37·0 (22·0–50·0)	37·5 (22·0–51·0)	36·0 (22·0–49·0)
Duration of chronic hand eczema, years	4·0 (2·0–10·0)	4·0 (2·0–13·0)	4·0 (2·0–10·0)
Chronic hand eczema subtype‡			
Irritant contact dermatitis	151 (29%)	75 (30%)	76 (29%)
Atopic hand eczema	123 (24%)	66 (26%)	57 (22%)
Allergic contact dermatitis	112 (22%)	58 (23%)	54 (21%)
Hyperkeratotic eczema	63 (12%)	31 (12%)	32 (12%)
Vesicular hand eczema (pompholyx)	58 (11%)	22 (9%)	36 (14%)
Not reported	6 (1%)	2 (1%)	4 (2%)
IGA-CHE			
Severe	512 (100%)	254 (100%)	258 (>99%)
Mild	1 (<1%)§	0	1 (<1%)§
HECSI			
n	508	252	256
Mean (SD)	91·8 (54·7)	90·9 (54·7)	92·7 (54·9)
Median (IQR)	80·0 (52·0–117·0)	79·5 (52·5–114·5)	80·0 (52·0–119·0)
DLQI			
n	475	233	242
Mean (SD)	12·8 (6·2)	12·7 (6·3)	13·0 (6·1)
Median (IQR)	12·0 (8·0–17·0)	12·0 (8·0–17·0)	12·0 (8·0–17·0)
≥4	457/475 (96%)	222/233 (95%)	235/242 (97%)
HESD itch (weekly average)¶			
n	484	240	244
Mean (SD)	5·9 (2·7)	5·8 (2·8)	6·0 (2·7)
Median (IQR)	6·2 (3·9–8·0)	6·1 (3·8–8·0)	6·4 (4·1–8·0)
≥4	362/484 (75%)	177/240 (74%)	185/244 (76%)

(Table 1 continues on next page)

efficacy results with respect to the handling of missing data.

Efficacy endpoints were assessed in the full analysis set, which comprised all eligible randomly assigned patients. Patients who did not have an IGA-CHE score of 4 at screening and baseline, or who met the exclusion criterion of having psychiatric disorders within the year before randomisation, were excluded from the full analysis set; this decision was made on the basis of masked data. For each endpoint, patients with missing baseline data for that outcome were excluded from the analysis. Safety endpoints were assessed in the safety analysis set, which comprised all patients who were exposed to the trial drugs. Adverse events were presented in terms of the number and percentages of patients, number of events, and event rate per 100 patient-years. The statistical analyses were performed using SAS software version 9.4.

Role of the funding source

The funder of the trial had roles in trial design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between June 15, 2022, and Dec 5, 2023, 693 patients from ten countries were screened and 513 patients were randomly assigned to delgocitinib cream (254 [50%]) or alitretinoin (259 [50%]; figure 2). Overall, 503 (98%) of the 513 patients were included in the full analysis set and 500 (97%) were included in the safety analysis set. Ten patients were excluded from the full analysis set due to inclusion criteria not being met (n=2) or exclusion criteria being met (n=8). 373 (73%) patients completed the 24-week treatment period. Permanent discontinuations of the trial drug were more frequent in the alitretinoin group (93 [36%] of 259 patients) than in the delgocitinib group (34 [13%] of 254; figure 2; appendix p 37). The primary reasons for permanent discontinuations of trial drug included lack of efficacy (26 [10%] patients in the alitretinoin group *vs* eight [3%] in the delgocitinib group), adverse events (24 [9%] *vs* two [1%]), and withdrawal by the patient (36 [14%] *vs* 16 [6%]).

The mean duration of exposure was 149·7 days (SD 34·4), or approximately 21 weeks, for the delgocitinib group and 119·8 days (55·0), or approximately 17 weeks, for the alitretinoin group. Of the 247 patients in the alitretinoin group, 42 (17%) reduced their dose from 30 mg to 10 mg due to unacceptable adverse events, and ten (4%) reduced their dose due to other non-adverse event-related reasons; dose reductions were the most frequent at week 8, occurring in 15 (6%) patients. 70 (28%) of the 254 patients in the delgocitinib group stopped treatment due to an IGA-CHE score of 0 or 1 at week 16 or later, and 51 (20%) of the 259 patients in the alitretinoin group stopped treatment for the same reason at week 12 or later. Of these, 39 (56%) of the 70 patients in the delgocitinib group and 31 (61%) of

the 51 patients in the alitretinoin group restarted treatment due to relapse (an IGA-CHE score ≥2). Rescue treatment was used less frequently in the delgocitinib group (12 [5%] of 254 patients) than in the alitretinoin group (21 [8%] of 259 patients; appendix p 15). Baseline demographics and patient characteristics were similar in both treatment groups (table 1; appendix pp 17–18).

The primary and key secondary endpoints were tested hierarchically, and all comparisons were statistically significant (table 2). The primary endpoint of change in HECSI score from baseline to week 12 was significantly greater in patients in the delgocitinib group (least squares mean –67·6 [SE 3·4]) versus those in the alitretinoin group (–51·5 [3·4]; difference –16·1 [95% CI –23·3 to –8·9], p<0·0001). The change in HECSI score was consistently larger in the delgocitinib cream group than in the alitretinoin group (figure 3A).

The least squares mean change in HECSI score at week 24 was also significantly greater in the delgocitinib cream group versus the alitretinoin group (table 2). Differences between treatment groups in terms of the change in HECSI score were observed at all timepoints starting from week 1 and continued to increase from week 12 to week 24 (figure 3A). A significantly greater proportion of patients in the delgocitinib cream group versus the alitretinoin group reached HECSI-90 at week 12 (table 2). From week 1 to week 24, the proportion of patients who responded to treatment was higher in the delgocitinib cream group than in the alitretinoin group (figure 3B). Moreover, the least squares mean AUC for HECSI-90, which signified the number of days spent with a 90% reduction in HECSI score, was significantly higher at week 24 in patients in the delgocitinib group versus those in the alitretinoin group (table 2, figure 3C).

At week 12, a significantly greater proportion of patients in the delgocitinib group than in the alitretinoin group reached IGA-CHE treatment success (table 2). The proportion of patients who had IGA-CHE treatment success was consistently higher in the delgocitinib group than in the alitretinoin group from week 1 (figure 3D).

For the weekly HESD itch score, a greater least squares mean change from baseline to week 12 was observed in patients in the delgocitinib group versus alitretinoin (table 2). Similarly, for the HESD pain assessments, a greater least squares mean change in the weekly average from baseline to week 12 was observed in the delgocitinib group versus the alitretinoin group (table 2). For both HESD itch and HESD pain assessments, the least squares mean decrease in the weekly average from baseline was consistently greater in patients in the delgocitinib group than in patients in the alitretinoin group starting from week 1 (figure 3E, F).

AUC for the reduction from baseline in DLQI score was higher with delgocitinib cream than with alitretinoin at week 24 (table 2). Differences between treatment groups were observed from week 1 and consistently increased to week 24 (figure 3G). The numbers of missing values imputed with worst observation carried forward or non-response for each outcome and treatment group, as well as the results from the efficacy sensitivity analysis, are summarised in the appendix (pp 22–24).

	Total (n=513)	Delgocitinib cream (n=254)	Alitretinoin (n=259)
(Continued from previous page)			
HESD pain (weekly average)¶			
n	484	240	244
Mean (SD)	5·5 (2·9)	5·2 (2·9)	5·8 (2·8)
Median (IQR)	6·0 (3·3–7·9)	5·6 (3·1–7·6)	6·1 (3·6–8·0)
≥4	339/484 (70%)	163/240 (68%)	176/244 (72%)

Data are n, n (%), median (IQR), or mean (SD). IGA-CHE scores range from 0, meaning clear, to 4, meaning severe. HECSI scores range from 0–360. DLQI scores range from 0–30. HESD itch and HESD pain scores range from 0–10. DLQI=Dermatological Life Quality Index. HECSI=Hand Eczema Severity Index. HESD=Hand Eczema Symptom Diary. IGA-CHE=Investigator's Global Assessment for Chronic Hand Eczema. *As determined by the unmasked investigator. †Trial centres are listed in the appendix (pp 2–6). ‡Chronic hand eczema subtypes were assessed by the investigator on the basis of medical history, morphology of the present lesions at baseline, and a mandatory diagnostic patch test completed so results were available before baseline assessments on day 1. For patients who had a diagnostic patch test performed within 3 years before screening, the results from the most recent patch test were used for the chronic hand eczema subtype classification. §One patient with a baseline IGA-CHE score of 2 was excluded from the full analysis set due to inclusion criteria not being met. ¶Baseline weekly average was defined as the average of the daily observations during the 7 days preceding the randomisation date.

Table 1: **Patient demographics and baseline characteristics in DELTA FORCE (randomised population)**

Among patients in the full analysis set with a baseline HESD itch or pain score of 4 points or higher, compared with patients in the alitretinoin group, a higher proportion of patients in the delgocitinib group had a 4-point or more improvement in the weekly average of HESD itch scores (91 [52%] of 175 patients in the delgocitinib group *vs* 64 [36%] of 180 in the alitretinoin group; difference 16·4 percentage points [95% CI 6·2–26·6], p=0·0019) and HESD pain scores (86 [53%] of 161 *vs* 67 [39%] of 172; difference 14·5 percentage points [95% CI 3·9–25·1], p=0·0083) from baseline to week 24 (exploratory endpoints); differences between treatment groups were observed from week 1 (data not shown).

Among patients with a baseline DLQI score of 4 points or higher, compared with patients in the alitretinoin group, a higher proportion of patients in the delgocitinib cream group had a 4-point or more improvement in their DLQI scores from baseline to week 12 (158 [72%] of 219 *vs* 129 [56%] of 229; difference 15·8 percentage points [95% CI 7·1–24·5], p=0·0005) and from baseline to week 24 (156 [71%] of 219 *vs* 109 [48%] of 229; difference 23·6 percentage points [14·8–32·5], p<0·0001; exploratory endpoints).

The overall safety profile of delgocitinib cream 20 mg/g administered for 16–24 weeks was more favourable than the safety profile of alitretinoin administered for 12–24 weeks, with no treatment-emergent safety concerns identified for delgocitinib cream. Overall, fewer patients reported adverse events in the delgocitinib cream group (125 [49%] of 253 patients; rate [R; ie, number of events per person-years observed ×100] 231·5) than in the

	Delgocitinib cream (n=250)	Alitretinoin (n=253)	Difference (95% CI)	p value
Primary endpoint				
Change in HECSI score*, week 12	−67·6 (3·4; n=249)	−51·5 (3·4; n=250)	−16·1 (−23·3 to −8·9)	<0·0001
Key secondary endpoints				
HECSI-90,† week 12	96/249 (39%)	65/250 (26%)	12·6% (4·3 to 20·8)	0·0027
IGA-CHE treatment success†, week 12	68/250 (27%)	42/253 (17%)	10·6% (3·3 to 17·9)	0·0041
Change in HESD itch*, week 12	−3·0 (0·2; n=238)	−2·4 (0·2; n=238)	−0·7 (−1·1 to −0·2)	0·0051
Change in HESD pain*, week 12	−2·9 (0·2; n=238)	−2·3 (0·2; n=238)	−0·6 (−1·1 to −0·1)	0·018
AUC of HECSI-90‡, week 24	49·2 (4·0; n=249)	34·9 (4·0; n=250)	14·3 (5·8 to 22·9)	0·0010
AUC of reduction in DLQI score‡§, week 24	1124·7 (61·4; n=230)	790·7 (62·7; n=236)	334·0 (195·7 to 472·3)	<0·0001
Change in HECSI score*, week 24	−69·6 (3·8; n=249)	−45·1 (3·8; n=250)	−24·5 (−32·6 to −16·4)	<0·0001

Data are n (%) or least squares mean (SE) unless otherwise specified. Missing data were imputed with worst observation carried forward (WOCF; continuous endpoints) or non-response (binary endpoints). Data after initiation of rescue treatments or permanent discontinuation of trial drug were treated as missing. The numbers of missing values imputed with WOCF or non-response for each outcome and treatment group are shown in the appendix (pp 22–23). Two-sided p values are reported. The order of endpoints in this table reflects the order of the testing hierarchy. IGA-CHE treatment success was defined as an IGA-CHE score of 0 or 1 with at least a two-step improvement from baseline. AUC=area under the curve. DLQI=Dermatology Life Quality Index. HECSI=Hand Eczema Severity Index. HECSI-90=at least 90% improvement in HECSI score from baseline. HESD=Hand Eczema Symptom Diary. IGA-CHE=Investigator's Global Assessment for Chronic Hand Eczema. *ANCOVA, adjusted for hyperkeratotic or non-hyperkeratotic subtype and baseline value of the score. †Cochran–Mantel–Haenszel test stratified for hyperkeratotic or non-hyperkeratotic subtype. ‡Robust ANCOVA, adjusted for hyperkeratotic or non-hyperkeratotic subtype, and baseline value of the score. §The AUC of reduction from baseline in DLQI score up to week 24 was based on all changes of DLQI score values until week 24.

Table 2: **Summary of efficacy results for the primary and all key secondary endpoints in DELTA FORCE (full analysis set)**

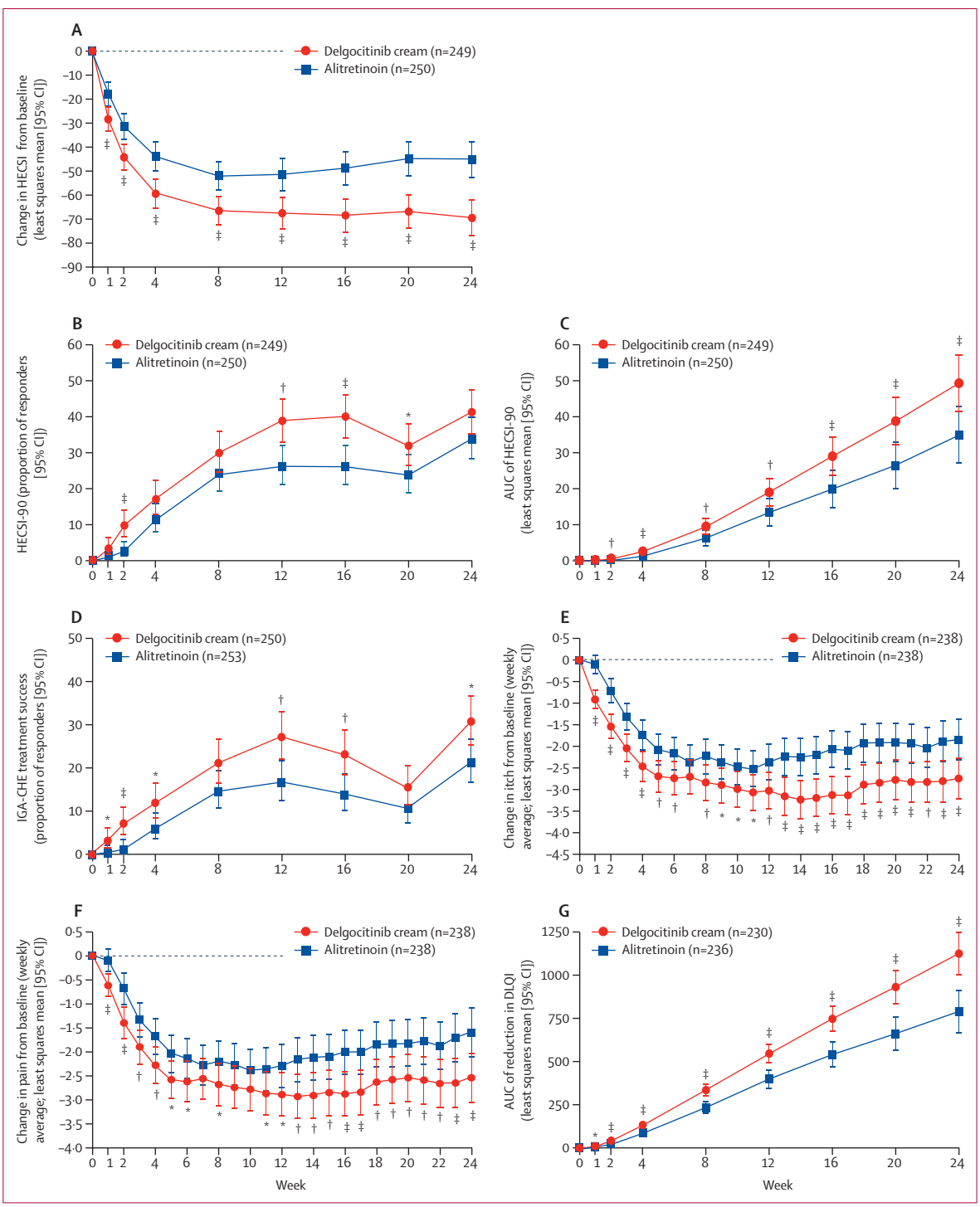
alitretinoin group (188 [76%] of 247 patients [R=596·1]; table 3). In both treatment groups, most adverse events were mild or moderate in severity. The most frequent adverse events (ie, reported in ≥5% of patients in any treatment group) were headache, nasopharyngitis, and nausea (table 3). Adverse events that were considered related to trial treatment were reported in 24 (9%) of 253 patients treated with delgocitinib cream versus 134 (54%) of 247 patients treated with alitretinoin (table 3, appendix pp 25–30). Fewer patients in the delgocitinib cream group (3 [1%] of 253) than in the alitretinoin group (25 [10%] of 247) reported adverse events leading to trial drug discontinuation (table 3, appendix pp 31–33). Serious adverse events were reported in five (2%) of 253 patients treated with delgocitinib cream versus 12 (5%) of 247 patients treated with alitretinoin (table 3, appendix pp 34–35). All serious adverse events in the delgocitinib cream group were assessed as not related to trial drug by both trial investigator and sponsor, LEO Pharma. Of the serious adverse events reported in the alitretinoin group, three (1%) were assessed as related to the trial drug (preferred terms [each n=1; <1%] international normalised ratio increased, headache, and hand dermatitis). No deaths were reported in the DELTA FORCE trial. No adverse events of special interest (ie, eczema herpeticum, deep vein thrombosis, or pulmonary embolism) were reported in the delgocitinib cream group. One (<1%) adverse event of special interest was reported in the alitretinoin group (table 3). This patient developed deep vein thrombosis 90 days after the first dose of alitretinoin following knee surgery; the event was assessed as not related to alitretinoin treatment by both trial investigator and sponsor. No changes in haematology, chemistry, or urinalysis parameters were assessed to be of clinical relevance in the delgocitinib cream group. In the alitretinoin group, post-baseline changes were observed for cholesterol and triglycerides that could be of clinical relevance.

Discussion

The DELTA FORCE trial provides evidence of the superior efficacy and more favourable safety profile of topical delgocitinib cream 20 mg/g compared with oral alitretinoin, currently the only approved systemic drug for treating severe chronic hand eczema over up to 24 weeks. In this head-to-head trial in a patient population with a high disease burden and unmet treatment needs,

Figure 3: **Key efficacy results of the DELTA FORCE trial**
(A) Change in HECSI score. (B) Proportion of patients who reached HECSI-90. (C) AUC of HECSI-90. (D) Proportion of patients who reached IGA-CHE treatment success (defined as an IGA-CHE score of 0 or 1 with at least a two-step improvement from baseline). (E) Change in HESD itch score. (F) Change in HESD pain score. (G) AUC of reduction from baseline in DLQI score. Data collected after initiation of rescue treatments or permanent discontinuation of trial drug were treated as missing. The ANCOVA model in graphs A, E, and F was change in score from baseline=treatment + hyperkeratotic or non-hyperkeratotic subtype + baseline score; missing data were imputed with WOCF. For graphs B and D, missing data were imputed with non-response. The ANCOVA model in graph C is AUC of HECSI-90=treatment + hyperkeratotic or non-hyperkeratotic + baseline HECSI score; missing data were imputed with non-response. The ANCOVA model in graph G is AUC of reduction from baseline in DLQI score=treatment + hyperkeratotic or non-hyperkeratotic + baseline DLQI score; missing data were imputed with WOCF. The numbers of missing values imputed with worst observation carried forward (WOCF) or non-response for each outcome and treatment group are shown in the appendix (p 22). AUC=area under the curve. DLQI=Dermatology Life Quality Index. HECSI=Hand Eczema Severity Index. HECSI-90=at least 90% improvement in HECSI score from baseline. HESD=Hand Eczema Symptom Diary. IGA-CHE=Investigator's Global Assessment for Chronic Hand Eczema. *p<0·05. †p<0·01. ‡p≤0·001. Exact p values can be found in the appendix (pp 20–21).

delgocitinib cream showed statistically significantly greater change in the primary endpoint (a reduction in HECSI score from baseline to week 12) compared with alitretinoin. Statistically significantly greater treatment effects with delgocitinib cream were also observed for all key secondary endpoints, including reaching IGA-CHE treatment success and improvements in patient-reported HRQoL measures (ie, HESD itch, HESD pain, and DLQI scores), compared with alitretinoin. Differences between treatment groups were observed from week 1, and efficacy rates for the primary endpoint and all key secondary endpoints were consistently higher in the delgocitinib cream group throughout the treatment period compared with the alitretinoin group.



The primary endpoint (change in HECSI score) and key secondary endpoints (HECSI-90, IGA-CHE treatment success, and change in HESD itch or pain scores) were assessed at week 12 in the DELTA FORCE trial due to the alitretinoin product label, which advises treatment discontinuation should be considered after 12 weeks.[6] This timing ensured that patients in both treatment groups received continuous treatment up to the time of assessment. Despite the shorter delgocitinib cream treatment duration compared with the pivotal DELTA 1 and DELTA 2 trials,[12] which assessed efficacy endpoints following 16 weeks of treatment, differences between the delgocitinib cream and alitretinoin groups were statistically significant at week 12 in the DELTA FORCE trial. These data, together with the results from DELTA 1, DELTA 2, and DELTA 3 in patients with moderate to severe chronic hand eczema over 16–52 weeks,[12,13] support the broad mechanism of action of the topical pan-JAK inhibitor delgocitinib cream 20 mg/g as a well suited treatment for chronic hand eczema.[11]

Treatment with delgocitinib cream resulted in clinically meaningful changes, assessed via validated tools and measures, for patients with severe chronic hand eczema in the DELTA FORCE trial. HECSI is the most frequently used validated instrument in clinical trials to score both the extent and severity of hand eczema.[21,22] IGA-CHE score has been validated as a reliable and responsive measure of chronic hand eczema severity that can be used in clinical trials and settings to monitor clinically meaningful changes (defined as a two-step improvement in IGA-CHE score, as a conservative threshold) and treatment response.[17] Patients who reached IGA-CHE treatment success in the DELTA FORCE trial had at least a three-step improvement from baseline, as enrolled patients had a baseline IGA-CHE score of 4. The decrease in the proportion of patients who had HECSI-90 and IGA-CHE treatment success observed at week 20 can probably be explained by patients stopping treatment due to response at week 16. HESD has been validated as the first chronic hand eczema-specific patient-reported outcome measure to have shown strong reliability and ability to identify clinically meaningful changes in itch and pain (defined as ≥4-point improvement in the 7-day average of the HESD scores).[19] HESD itch and HESD pain differences between treatment groups in the DELTA FORCE trial were small

	Delgocitinib cream (n=253, PYO 120·9)			Alitretinoin (n=247, PYO 104·0)			Rate ratio (95% CI)	Risk difference (95% CI)
	N	Event	Rate*	N	Event	Rate*		
All adverse events	125 (49%)	280	231·5	188 (76%)	620	596·1	0·39 (0·34 to 0·45)	−26·7% (−34·5 to −18·3)
Serious adverse events	5 (2%)	5	4·1	12 (5%)	12	11·5	0·36 (0·13 to 1·02)	−2·9% (−6·5 to 0·4)
Deaths	0	0	0	0	0	0	NA	0·0% (−1·5 to 1·5)
Severity								
Mild	92 (36%)	168	138·9	151 (61%)	397	381·7	0·36 (0·30 to 0·44)	−24·8% (−32·9 to −16·1)
Moderate	68 (27%)	108	89·3	104 (42%)	198	190·4	0·47 (0·37 to 0·59)	−15·2% (−23·3 to −6·9)
Severe	4 (2%)	4	3·3	14 (6%)	25	24·0	0·14 (0·05 to 0·40)	−4·1% (−7·8 to −0·8)
Probably or possibly related to trial drug	24 (9%)	30	24·8	134 (54%)	311	299·0	0·08 (0·06 to 0·12)	−44·8% (−51·6 to −37·2)
Adverse events leading to permanent discontinuation of trial drug	3 (1%)	4	3·3	25 (10%)	44	42·3	0·08 (0·03 to 0·22)	−8·9% (−13·4 to −5·1)
Outcome								
Fatal	0	0	0	0	0	0	NA	0·0% (−1·5 to 1·5)
Not recovered or not resolved	26 (10%)	35	28·9	39 (16%)	66	63·5	0·46 (0·30 to 0·69)	−5·5% (−11·5 to 0·4)
Recovering or resolving	11 (4%)	13	10·7	29 (12%)	38	36·5	0·29 (0·16 to 0·55)	−7·4% (−12·4 to −2·6)
Recovered or resolved	111 (44%)	227	187·7	172 (70%)	513	493·2	0·38 (0·33 to 0·44)	−25·8% (−33·8 to −17·2)
Recovered or resolved with sequelae	0	0	0	1 (<1%)	1	1·0	NA	−0·4% (−2·3 to 1·1)
Unknown	2 (1%)	5	4·1	1 (<1%)	2	1·9	2·15 (0·42 to 11·1)	0·4% (−1·6 to 2·5)
Action taken with trial drug								
Dose not changed	110 (43%)	239	197·6	156 (63%)	466	448·1	0·44 (0·38 to 0·52)	−19·7% (−28·0 to −11·0)
Dose reduced	0	0	0	42 (17%)	67	64·4	NA	−17·0% (−22·2 to −12·6)
Drug withdrawn	3 (1%)	4	3·3	25 (10%)	44	42·3	0·08 (0·03 to 0·22)	−8·9% (−13·4 to −5·1)
Not applicable	28 (11%)	37	30·6	35 (14%)	43	41·3	0·74 (0·48 to 1·15)	−3·1% (−9·0 to 2·8)
Unknown	0	0	0	0	0	0	NA	0·0% (−1·5 to 1·5)
Adverse events of special interest								
Eczema herpeticum	0	0	0	0	0	0	NA	0·0% (−1·5 to 1·5)
Deep vein thrombosis	0	0	0	1 (<1%)	1	1·0	NA	−0·4% (−2·3 to 1·1)
Pulmonary embolism	0	0	0	0	0	0	NA	0·0% (−1·5 to 1·5)

(Table 3 continues on next page)

	Delgocitinib cream (n=253, PYO 120·9)			Alitretinoin (n=247, PYO 104·0)			Rate ratio (95% CI)	Risk difference (95% CI)
	N	Event	Rate*	N	Event	Rate*		
(Continued from previous page)								
Frequent adverse events (≥2% in any treatment group) by preferred term								
Infections and infestations								
Nasopharyngitis	30 (12%)	38	31·4	34 (14%)	46	44·2	0·71 (0·46 to 1·09)	–1·9% (–7·8 to 4·0)
Upper respiratory tract infection	6 (2%)	8	6·6	8 (3%)	8	7·7	0·86 (0·32 to 2·29)	–0·9% (–4·1 to 2·3)
COVID-19	5 (2%)	5	4·1	9 (4%)	9	8·7	0·48 (0·16 to 1·43)	–1·7% (–5·0 to 1·4)
Urinary tract infection	1 (<1%)	1	0·8	10 (4%)	11	10·6	0·08 (0·01 to 0·61)	–3·7% (–6·9 to –1·1)
Skin and subcutaneous tissue disorders								
Dry skin	3 (1%)	3	2·5	9 (4%)	9	8·7	0·29 (0·08 to 1·06)	–2·5% (–5·7 to 0·4)
Eczema	2 (1%)	2	1·7	5 (2%)	6	5·8	0·29 (0·06 to 1·42)	–1·2% (–3·9 to 1·1)
Hand dermatitis	2 (1%)	3	2·5	5 (2%)	5	4·8	0·52 (0·12 to 2·16)	–1·2% (–3·9 to 1·1)
Atopic dermatitis	1 (<1%)	1	0·8	5 (2%)	5	4·8	0·17 (0·02 to 1·47)	–1·6% (–4·3 to 0·5)
Erythema	1 (<1%)	1	0·8	9 (4%)	10	9·6	0·09 (0·01 to 0·67)	–3·2% (–6·4 to –0·8)
Musculoskeletal and connective tissue disorders								
Back pain	2 (1%)	2	1·7	6 (2%)	6	5·8	0·29 (0·06 to 1·42)	–1·6% (–4·5 to 0·8)
Investigations								
Blood triglycerides increased	2 (1%)	2	1·7	7 (3%)	8	7·7	0·22 (0·05 to 1·01)	–2·0% (–5·0 to 0·5)
Nervous system disorder								
Headache	10 (4%)	19	15·7	80 (32%)	114	109·6	0·14 (0·09 to 0·23)	–28·4% (–34·8 to –22·1)
Migraine	2 (1%)	2	1·7	6 (2%)	7	6·7	0·25 (0·05 to 1·18)	–1·6% (–4·5 to 0·8)
Dizziness	1 (<1%)	1	0·8	6 (2%)	6	5·8	0·14 (0·02 to 1·19)	–2·0% (–4·8 to 0·2)
Gastrointestinal disorders								
Nausea	1 (<1%)	1	0·8	14 (6%)	15	14·4	0·06 (0·01 to 0·43)	–5·3% (–8·9 to –2·4)
Diarrhoea	0	0	0	5 (2%)	5	4·8	NA	–2·0% (–4·7 to –0·1)
Lip dry	0	0	0	8 (3%)	8	7·7	NA	–3·2% (–6·3 to –1·1)
Respiratory, thoracic and mediastinal disorders								
Epistaxis	1 (<1%)	1	0·8	5 (2%)	6	5·8	0·14 (0·02 to 1·19)	–1·6% (–4·3 to 0·5)
Metabolism and nutrition disorders								
Hypertriglyceridaemia	3 (1%)	3	2·5	6 (2%)	7	6·7	0·37 (0·10 to 1·43)	–1·2% (–4·1 to 1·4)
Hypercholesterolaemia	0	0	0	9 (4%)	10	9·6	NA	–3·6% (–6·8 to –1·4)
Vascular disorders								
Flushing	0	0	0	5 (2%)	6	5·8	NA	–2·0% (–4·7 to –0·1)
Eye disorders								
Dry eye	0	0	0	7 (3%)	7	6·7	NA	–2·8% (–5·7 to –0·7)

Adverse events that started or worsened in severity after first trial drug dose and were reported on or before week 26 are presented. Relation to trial drug was based on investigator's assessment. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 24.0 dictionary. Rate ratios were estimated with CIs based on a Poisson regression model with treatment as fixed effect and natural logarithm of patient years of observation as offset. CIs for risk differences were Newcombe–Wilson CIs. NA=not applicable. PYO=patient years of observation. *Rate calculated as the number of events per PYO×100.

***Table 3*: Summary of adverse events in the DELTA FORCE trial (safety analysis set)**

but statistically significant, and more patients treated with delgocitinib cream with a baseline HESD itch or pain score of 4 or more points had the clinically meaningful 4-point or more improvement in the weekly average of these scores from baseline to week 24 compared with patients treated with alitretinoin (exploratory analyses).

Overall, the number of adverse events, serious adverse events, severe adverse events, related adverse events, and adverse events leading to treatment discontinuation were lower in the delgocitinib cream group compared with the alitretinoin group. No treatment-emergent safety concerns were identified for delgocitinib cream, and the overall safety profile and tolerability was consistent with that observed in the DELTA 1, DELTA 2,[12] and DELTA 3[13] trials. In the alitretinoin group, the post-baseline changes observed for cholesterol and triglycerides are consistent with the alitretinoin product label. Permanent discontinuations of trial drug due to adverse events, lack of efficacy, or withdrawal by patient, and use of rescue treatments, were more frequent in the alitretinoin group than in the delgocitinib cream group. Considering the relatively high number of permanent discontinuations of trial drug due to adverse events, lack of efficacy, or withdrawal by patient compared with the DELTA 1 and

DELTA 2 trials,[12] the composite estimand was considered appropriate for handling intercurrent events (defined as permanent discontinuations of trial drug and use of rescue treatments). Overall, the more frequent occurrence of intercurrent events in the alitretinoin group could be an indication of better efficacy, safety, and tolerability of delgocitinib cream compared with alitretinoin. Given the side-effect profile and limitations of use of alitretinoin, particularly in patients of childbearing potential, and the higher occurrence of chronic hand eczema among female individuals,[23] delgocitinib cream has the potential to provide a non-steroidal topical treatment option that combines effective disease control without the safety concerns associated with systemic treatment.

Trial limitations include the predominantly White patient population (93% White and 90% European) and the non-double-blind trial design. The assessor-masked trial design was implemented to ensure unbiased clinical efficacy assessments of HECSI and IGA-CHE scores; a double-blind and double-dummy trial design was not considered feasible as addition of a cream vehicle to alitretinoin-treated patients could have independent therapeutic effects[24,25] and potentially increase the clinical effect in the alitretinoin group. More analysis is needed of the effect of delgocitinib cream versus alitretinoin on work productivity and activity impairment and other HRQoL exploratory endpoints. Moreover, comparative efficacy across chronic hand eczema causes would be of additional interest for a separate comprehensive analysis to inform on any differences in response rates.

In the DELTA FORCE trial, topical delgocitinib cream 20 mg/g showed superior clinical treatment effects and HRQoL improvements, and a more favourable safety profile compared with oral alitretinoin over 24 weeks across the primary and all secondary endpoints in patients with severe chronic hand eczema. Delgocitinib cream was well tolerated over 24 weeks, with no treatment-emergent safety concerns identified. These data support the benefits of delgocitinib cream as an efficacious and well tolerated topical treatment in this patient population with high disease burden and unmet treatment needs.

Contributors

All authors made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work. All authors interpreted the data, provided critical input to manuscript drafts, and approved the submission of the manuscript for publication. AMG-A (coordinating investigator; not a LEO Pharma employee), NM, MLØ, UP, and LR directly accessed and verified the data reported in the manuscript. All authors had full access to the data in the trial and take responsibility for the accuracy and completeness of the data and analyses and the decision to submit for publication.

Declaration of interests

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Data sharing

Anonymised patient-level data that support the findings of this trial are available to qualified external researchers on reasonable request to LEO Pharma. These requests are reviewed on a case-by-case basis based on scientific merit.

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