



The pan-JAK inhibitor delgocitinib in a cream formulation demonstrates dose response in chronic hand eczema in a 16-week randomized phase IIb trial*

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Summary

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Conflicts of interest

The full list of Conflicts of interest is given in [Appendix S1](#).

Data availability

The data that support the findings of this study are available upon reasonable request. Further information can be obtained at: <https://www.leopharmatrials.com/en/for-professionals>

*Plain language summary available online

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Background Chronic hand eczema (CHE) is a burdensome disease, and new well-documented, safe and efficacious treatments are warranted. In a recent CHE phase IIa trial, the pan-Janus kinase (JAK) inhibitor delgocitinib in an ointment formulation was found to be efficacious and well tolerated.

Objectives This trial assessed the dose response, efficacy and safety of delgocitinib cream in CHE.

Methods In this double-blind, phase IIb dose-ranging trial, adults with CHE and a recent history of inadequate response or contraindication to topical corticosteroids were randomized to delgocitinib cream 1, 3, 8, 20 mg g⁻¹ or vehicle treatment twice daily for 16 weeks. The primary endpoint was the Investigator's Global Assessment for CHE (IGA-CHE) treatment success [0 (clear) or 1 (almost clear) with a ≥ two-point improvement from baseline to week 16]. Secondary endpoints were the time to IGA-CHE treatment success and changes in Hand Eczema Severity Index (HECSI); other endpoints were itch and pain numerical rating scale (NRS) scores, and Patient's Global Assessment (PaGA) at week 16.

Results Patients (n = 258) were randomized 1 : 1 : 1 : 1 : 1 to delgocitinib cream 1, 3, 8, 20 mg g⁻¹ or vehicle. A significant dose–response relationship was established for IGA-CHE (P < 0.025). IGA-CHE treatment success at week 16 was achieved in 21.2% (1 mg g⁻¹), 7.8% (3 mg g⁻¹), 36.5% (8 mg g⁻¹), 37.7% (20 mg g⁻¹) and 8.0% (vehicle) of patients. Delgocitinib 8 and 20 mg g⁻¹ showed a treatment effect against vehicle (P < 0.001). Similarly, there were improvements in HECSI, itch and pain NRS scores, and PaGA. Delgocitinib cream was well tolerated with the majority of adverse events being mild or moderate and considered unrelated to treatment. The most frequently reported adverse events were nasopharyngitis (17.3–29.4% in delgocitinib groups vs. 40% in vehicle group), eczema (5.8–11.3% in delgocitinib groups vs. 16.0% in vehicle group) and headache (3.8–11.5% in delgocitinib groups vs. 4.0% in vehicle group).

Conclusions In this trial, delgocitinib cream showed a dose–response relationship in terms of efficacy and was well tolerated.

Hand eczema (HE) has a lifetime prevalence of up to 20% and a 1-year prevalence of approximately 10% in adults.¹ HE is a pruritic, inflammatory and often painful noninfectious skin disorder of the hands and wrists.^{2–4} Exogenous (e.g. irritants, allergens⁵) and endogenous factors (e.g. skin barrier or immune dysfunction with associated dysregulated skin microbiome^{6–9}) drive the aetiopathogenesis. Risk factors associated with HE are female sex, prior/current atopic dermatitis, and occupations involving exposure to irritants and/or allergens, in particular wet-work occupations.^{5,10}

HE often has a chronic persistent but also a relapsing and remitting course. Chronic hand eczema (CHE) is defined as HE lasting for ≥ 3 months or with episodes at least twice per year.^{2,5} CHE is associated with high physical, psychological, occupational and socioeconomic burden.^{11–15} No topical treatment has been specifically developed and approved for CHE.⁴ Potent topical corticosteroids (TCS) are commonly used, but long-term use may be associated with atrophy and impairment of skin barrier, in turn preventing resolution.⁵ Alitretinoin, a systemic retinoid, is the only treatment specifically approved for severe CHE unresponsive to TCS in some EU countries, Canada, Israel and South Korea. Alitretinoin treatment may require medical and laboratory monitoring, and a pregnancy prevention programme for women of child-bearing age/potential.¹⁶ Due to the limitations of current treatment options, CHE disease management remains difficult and unsatisfactory.^{2,4,5,16–20} Consequently, safe and effective treatment options specifically developed for long-term control of CHE across subtypes are needed.¹⁷

Delgocitinib is a small-molecule pan-Janus kinase (JAK) inhibitor blocking all four members of the JAK family (JAK1–3, tyrosine kinase 2).²¹ The JAK–STAT (signal transducer and activator of transcription protein) pathway plays a key role in the pathogenesis of many dermatological diseases.^{21–24} Delgocitinib also inhibits the activation of innate and adaptive immune cells, improves skin barrier function by modulating keratinocyte differentiation, inhibits T-helper (Th)1-, Th2-, Th17- and Th22-type inflammatory responses, and has antipruritic properties.^{21,25–27} In a phase IIa trial, delgocitinib in an ointment formulation was shown to be effective and well tolerated in adults with CHE.²⁸ For the phase IIb trial described here, a cream formulation was used to support skin delivery and increase patient user-friendliness. The aim of this trial was to investigate a dose–response relationship as well as efficacy and safety of delgocitinib cream in the treatment of adults with mild, moderate and severe CHE.

Materials and methods

Trial design and oversight

This was a double-blind, randomized, five-arm, vehicle-controlled, parallel-group, multicentre, phase IIb dose-ranging trial in which adults with mild-to-severe CHE were treated with delgocitinib cream 1, 3, 8, 20 mg g⁻¹ or cream vehicle twice daily for 16 weeks. The trial was conducted from

November 2018 through April 2020 at 26 medical research sites and hospitals in three countries (USA, Denmark, Germany). The trial consisted of an up to 4-week screening period, a 16-week treatment period, and a 2-week safety follow-up period.

The trial was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements, and was approved by the local institutional review board or independent ethics committee of each institution. All patients provided written informed consent.

The sponsor, LEO Pharma A/S, developed the trial protocol, provided delgocitinib cream and vehicle, performed data analysis, and wrote the manuscript drafts. All authors interpreted the data, provided critical input to manuscript drafts, and approved the submission of the manuscript for publication. All authors take responsibility for the accuracy and completeness of the data and analyses and vouch for the fidelity of the trial to the protocol. All investigators had confidentiality agreements with the sponsor. The trial is registered at ClinicalTrials.gov (registration number: NCT03683719).

Patients

Eligible participants were adults ≥ 18 years old with CHE. Their CHE had to be of at least mild severity based on the Investigator's Global Assessment for CHE (IGA-CHE; five-point scale: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe). Patients had to have a recent history (within 1 year before screening) of inadequate response or contraindication to TCS. Patch testing (according to local practice) had to be performed within 3 years prior to screening. Patch testing was used to identify possible contact-allergic CHE subtypes but the result of patch testing was not restrictive for inclusion into the trial. Patients were excluded if they were using medications that could influence treatment efficacy (e.g. TCS, immunosuppressive drugs, systemic antibiotics). Patients with any skin diseases that could influence the assessment of the treatment outcome were also excluded. A full list of eligibility criteria is provided in [Appendix S2](#).

Trial intervention

Patients were randomized 1 : 1 : 1 : 1 : 1 to delgocitinib cream 1, 3, 8, 20 mg g⁻¹ or vehicle. The first application was done at the trial site at baseline; subsequent applications were performed by the patients at home twice daily to the areas affected by CHE, over a 16-week treatment period. Areas initially affected and potential new areas were to be treated regardless of clearance status up until week 16. Trial site visits were scheduled at weeks 1, 2, 4, 6, 8, 10, 12, 14 and 16.

Randomization was performed via a central interactive web response system and stratified by severity of CHE according to IGA-CHE (mild, moderate and severe) and region (Europe and North America). A lower limit of 20% and an upper limit of 30% were imposed on the number of patients randomized

with mild and severe IGA-CHE baseline severity, respectively. Treatment allocation was blinded to all individuals (including patients, investigators and trial personnel). Blinded, coded kits containing delgocitinib creams or vehicle were used to mask the assigned treatment.

Patients were instructed to not change their usual skin care routine regarding use of emollients. However, emollients were not allowed to be used within 2 h before and after application of the study treatment.

Rescue treatment for CHE could be provided to patients at the investigator's discretion if medically necessary (i.e. to control intolerable CHE symptoms). If rescue treatment was initiated, the patient stopped the study treatment immediately and could not restart it.

Trial outcomes

The primary endpoint was 'IGA-CHE treatment success (TS) at week 16'. IGA-CHE TS was defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a two-step point improvement from baseline to week 16. The IGA-CHE scale (adapted from Ruzicka *et al.*²⁹) was used to rate the severity of the patient's global disease stage and is based on a five-point scale ranging from 0 (clear) to 4 (severe).

Secondary endpoints were change in Hand Eczema Severity Index (HECSI) score from baseline to week 16 and time to IGA-CHE TS. HECSI³⁰ was used to grade severity of the six clinical signs of HE and the extent of the lesions on each of five hand areas by use of standard scales. HECSI scores ranged from 0 to 360, with higher values indicating greater disease severity.

Other endpoints included change in itch and pain numerical rating scale (NRS) scores (weekly averages) from baseline to week 16, and proportion of patients achieving Patient's Global Assessment (PaGA) TS at week 16. For itch and pain NRS scores, patients assessed the worst severity of itch and pain symptoms of CHE over the past 24 h using an 11-point scale with 0 indicating, e.g. 'no itch' and 10 indicating 'severe itch'. Scores were evaluated by patients daily and recorded in an electronic diary: for analysis, weekly mean scores were calculated by averaging daily scores from the preceding 7 days. For PaGA, patients made a global assessment of the severity of their CHE using a five-point scale ranging from 0 (clear) to 4 (severe). PaGA TS was defined as a PaGA score of 0 when classified at baseline as 1 or 2, or a PaGA score of 0 or 1 when classified at baseline as 3 or 4.

Statistical analysis

The sample size of 250 patients was based on the following pairwise consideration: when comparing two treatment groups and assuming IGA-CHE TS rates of 45% for delgocitinib cream and 15% for vehicle, 50 patients per treatment group would provide a power $\geq 90\%$ to detect statistically significant different success rates between treatment groups with a significance level of 5%. Efficacy was assessed based on

the full analysis set comprising all randomized patients who received at least one application of study treatment. The safety analysis set was identical to the full analysis set.

Dose-response modelling of the primary endpoint 'IGA-CHE TS at week 16' was performed using Multiple Comparison Procedure-Modelling.^{31,32} Several candidate parametric models were prespecified, and selection of the dose-response model that fit the data best was controlled using a family-wise error rate of 2.5%. The null hypothesis of no treatment effect was tested at a one-sided significance level of 2.5% against the alternative hypothesis of treatment effect (nonflat dose-response curve).

For binary endpoints, the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity was used to analyse differences in response rates between each delgocitinib dose and vehicle separately. Data collected prior to or on the date when patients initiated rescue medication or permanently discontinued study treatment were used in the analysis. Non-responder imputation was done for each scheduled assessment visit after initiation of rescue medication or premature discontinuation of study treatment, as well as for any other missing data. Time to IGA-CHE TS was defined as the time from first study treatment application to first assessment of IGA-CHE TS, and Kaplan-Meier curves by treatment groups were estimated and compared using log-rank tests stratified by region and baseline disease severity.

For continuous endpoints, least square (LS) means were estimated using a mixed model for repeated measurements with an unstructured covariance matrix, Kenward-Roger denominator degrees of freedom approximation, adjusting for region and baseline disease severity and including an interaction between time and treatment as well as time and baseline assessment. Observed data collected prior to or on the visit of premature discontinuation of study treatment or initiation of rescue medication were included in the analysis. Missing data were imputed using the mixed model for repeated measurements predicted values.

Besides the multiple comparison adjustment for the dose-response analyses, there were no adjustments for multiple testing. The widths of the reported confidence intervals have not been adjusted for multiplicity and the inferences drawn may not be reproducible.

Results

Patients

All 258 randomized patients started study treatment and were included in the full analysis set and safety analysis set. Overall, 204 patients (79.1%) completed all periods of the trial (screening, treatment and safety follow-up) and attended the primary endpoint visit at week 16: 168 patients (80.8%) in the delgocitinib groups (any dose) and 36 patients (72.0%) in the vehicle group (Figure 1). More patients completed the trial in the two highest delgocitinib dose groups (84.6% for 8 mg g⁻¹, 86.8% for 20 mg g⁻¹) compared with vehicle and the two lowest

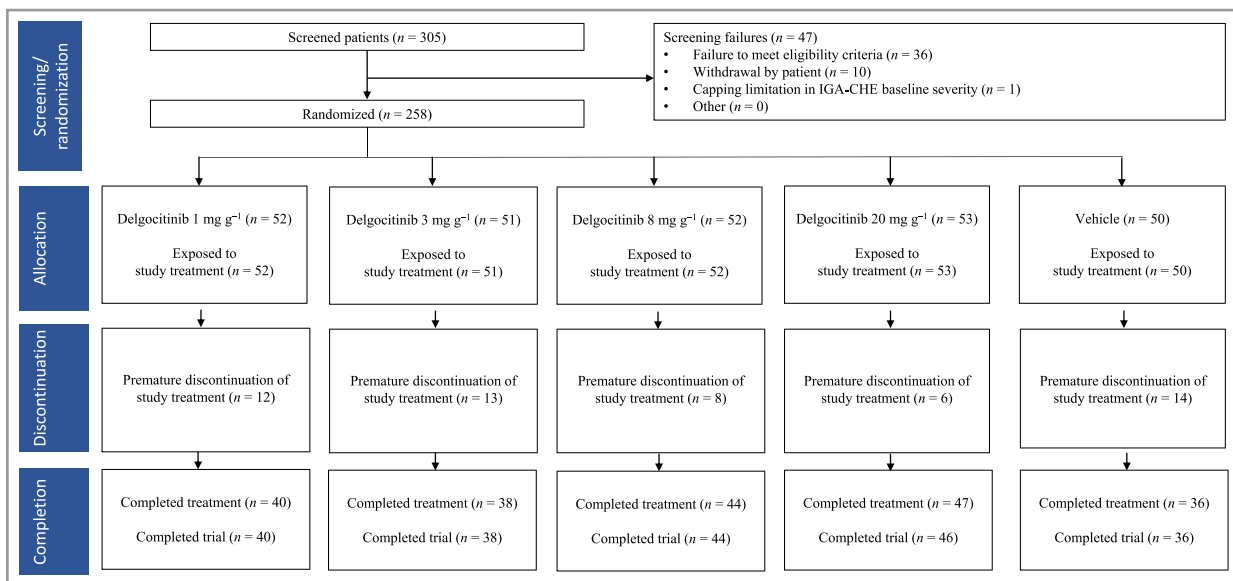


Figure 1 Flowchart of patient disposition. IGA-CHE, Investigator's Global Assessment for chronic hand eczema.

delgocitinib dose groups (72.0% for vehicle, 76.9% for 1 mg g⁻¹, 74.5% for 3 mg g⁻¹).

Baseline demographics and characteristics were comparable with no relevant differences between the treatment groups (Table 1).

Dose–response relationship

A statistically significant dose–response relationship was established for the primary endpoint 'IGA-CHE TS at week 16' ($P < 0.025$, Table S1).

Clinical efficacy

The primary endpoint 'IGA-CHE TS at week 16' was achieved in 21.2% of patients in the delgocitinib 1 mg g⁻¹ group, 7.8% in 3 mg g⁻¹, 36.5% in 8 mg g⁻¹, 37.7% in 20 mg g⁻¹, and 8.0% in vehicle (Table 2). Delgocitinib 8 and 20 mg g⁻¹ showed a statistically significant treatment effect against vehicle at week 16 ($P < 0.001$). The clinical efficacy was apparent from week 4 (8 mg g⁻¹) and week 6 (20 mg g⁻¹) (Figure 2A). The estimated median time to IGA-CHE TS was 82 days (11.7 weeks) for the 8 mg g⁻¹ group and 98 days (14 weeks) for the 20 mg g⁻¹ group.

Accordingly, a change in HECSI was observed. LS Mean (SE) changes from baseline to week 16 were -39.8 (3.7) in 1 mg g⁻¹, -35.9 (3.8) in 3 mg g⁻¹, -46.7 (3.6) in 8 mg g⁻¹, -42.0 (3.6) in 20 mg g⁻¹ and -26.4 (3.8) in vehicle (Figure 2B and Table 2). The percentage changes in LS Mean (SE) from baseline to week 16 were -70.1 (10.9) in 1 mg g⁻¹, -67.0 (11.0) in 3 mg g⁻¹, -80.2 (10.6) in 8 mg g⁻¹, -70.5 (10.5) in 20 mg g⁻¹ and -41.6 (11.1) in vehicle.

These clinical findings were paralleled by scores reflecting symptom relief. LS Mean (SE) in itch NRS score (weekly average) from baseline to week 16 were -3.1 (0.4) in

1 mg g⁻¹, -2.5 (0.4) in 3 mg g⁻¹, -3.2 (0.4) in 8 mg g⁻¹, -3.2 (0.3) in 20 mg g⁻¹ and -1.7 (0.4) in vehicle (Figure 2C and Table 2). LS Mean (SE) in pain NRS score (weekly average) from baseline to week 16 were -2.7 (0.3) in 1 mg g⁻¹, -2.4 (0.3) in 3 mg g⁻¹, -3.0 (0.3) in 8 mg g⁻¹, -3.2 (0.3) in 20 mg g⁻¹ and -1.4 (0.3) in vehicle (Figure 2D and Table 2).

Finally, PaGA TS at week 16 was achieved in 17.3% of patients in the delgocitinib 1 mg g⁻¹ group, 19.6% in 3 mg g⁻¹, 23.1% in 8 mg g⁻¹, 34.0% in 20 mg g⁻¹ and 6.0% in vehicle (Figure 2E and Table 2).

Safety

A comparable proportion of patients receiving delgocitinib and vehicle reported adverse events (AEs, Table 3). Across all delgocitinib groups, a total of 142 of 208 patients (68.3%) had AEs. In the vehicle group, 30 of 50 patients (60.0%) had AEs. No deaths were reported. Serious AEs were reported in three patients: postural dizziness and bullous pemphigoid (3 mg g⁻¹ group) and 'anxiety' (8 mg g⁻¹ group); none of these were considered related to treatment. Most frequently reported AEs ($\geq 5\%$ in any treatment group) were nasopharyngitis, eczema and headache. Most AEs were mild or moderate and considered unrelated to treatment. There was no dose–response relationship in the safety profile, no clinically important changes in vital signs, electrocardiogram or laboratory parameters, and no AEs suggestive of a relationship to systemic exposure. No events of eczema herpeticum, herpes zoster or malignancies were reported. Delgocitinib cream was well tolerated according to the patient's own assessment of local tolerability. The number of AEs leading to withdrawal from the trial or permanent discontinuation of the study treatment was low across all delgocitinib groups and comparable with the vehicle group.

Table 1 Patient demographics and baseline characteristics^a

	All randomized patients N = 258	Delgocitinib, dose (N)				Vehicle N = 50
		1 mg g ⁻¹ (52)	3 mg g ⁻¹ (51)	8 mg g ⁻¹ (52)	20 mg g ⁻¹ (53)	
Age (years), mean (SD)	46.0 (14.5)	44.3 (13.6)	46.1 (14.6)	47.9 (12.9)	43.9 (15.1)	47.8 (16.2)
Sex, n (%)						
Male	100 (38.8)	15 (28.8)	23 (45.1)	20 (38.5)	19 (35.8)	23 (46.0)
Female	158 (61.2)	37 (71.2)	28 (54.9)	32 (61.5)	34 (64.2)	27 (54.0)
Race, n (%)						
White	254 (98.4)	51 (98.1)	51 (100)	50 (96.2)	52 (98.1)	50 (100)
Asian	3 (1.2)	1 (1.9)	0	1 (1.9)	1 (1.9)	0
Other	1 (0.4)	0	0	1 (1.9)	0	0
Ethnicity, n (%)						
Hispanic or Latino	9 (3.5)	3 (5.8)	0	2 (3.8)	1 (1.9)	3 (6.0)
Not Hispanic or Latino	249 (96.5)	49 (94.2)	51 (100)	50 (96.2)	52 (98.1)	47 (94.0)
Age at onset of HE (years); median (range)	32.5 (0.0–78.0)	32.5 (0.0–67.0)	33.0 (0.0–69.0)	39.0 (0.0–66.0)	29.0 (0.0–72.0)	26.0 (0.0–78.0)
Duration of HE (years); median (range)	7.0 (0.0–53.0)	6.0 (0.0–48.0)	6.0 (0.0–34.0)	6.5 (0.0–47.0)	9.0 (0.0–53.0)	7.0 (0.0–49.0)
IGA-CHE score, n (%)						
0, Clear	0	0	0	0	0	0
1, Almost clear	0	0	0	0	0	0
2, Mild	61 (23.6)	13 (25.0)	13 (25.5)	11 (21.2)	12 (22.6)	12 (24.0)
3, Moderate	145 (56.2)	29 (55.8)	29 (56.9)	29 (55.8)	31 (58.5)	27 (54.0)
4, Severe	52 (20.2)	10 (19.2)	9 (17.6)	12 (23.1)	10 (18.9)	11 (22.0)
HECSI score						
Mean (SD)	55.9 (42.8)	59.0 (48.0)	52.4 (35.9)	49.5 (29.3)	65.7 (58.3)	52.7 (34.9)
Median (range)	44.5 (5.0–296.0)	45.0 (5.0–223.0)	44.0 (6.0–186.0)	40.0 (6.0–122.0)	48.0 (7.0–296.0)	45.5 (9.0–150.0)
CHE subtypes (main diagnosis), n (%)						
Allergic contact dermatitis	15 (5.8)	3 (5.8)	4 (7.8)	4 (7.7)	2 (3.8)	2 (4.0)
Irritant contact dermatitis	80 (31.0)	21 (40.4)	13 (25.5)	14 (26.9)	12 (22.6)	20 (40.0)
Contact urticaria/ protein contact dermatitis	0	0	0	0	0	0
Atopic hand eczema	97 (37.6)	16 (30.8)	17 (33.3)	20 (38.5)	28 (52.8)	16 (32.0)
Pompholyx	20 (7.8)	4 (7.7)	3 (5.9)	8 (15.4)	2 (3.8)	3 (6.0)
Hyperkeratotic eczema	46 (17.8)	8 (15.4)	14 (27.5)	6 (11.5)	9 (17.0)	9 (18.0)
Itch and pain NRS scores (weekly average) n ^b	252	51	50	50	52	49
Itch, mean (SD)	4.9 (2.7)	5.3 (2.8)	4.3 (2.3)	4.9 (3.0)	5.2 (2.6)	4.5 (2.6)
Pain, mean (SD)	4.1 (2.7)	4.7 (2.9)	4.1 (2.7)	3.9 (2.8)	4.0 (2.7)	3.6 (2.5)
PaGA score, n (%)						
0, Clear	0	0	0	0	0	0
1, Almost clear	5 (1.9)	0	1 (2.0)	0	2 (3.8)	2 (4.0)
2, Mild	63 (24.4)	12 (23.1)	10 (19.6)	18 (34.6)	9 (17.0)	14 (28.0)
3, Moderate	118 (45.7)	23 (44.2)	27 (52.9)	19 (36.5)	24 (45.3)	25 (50.0)
4, Severe	72 (27.9)	17 (32.7)	13 (25.5)	15 (28.8)	18 (34.0)	9 (18.0)

^aTable is based on all randomized patients. ^bFor itch and pain NRS scores only, the number of patients with data (n) differed from the number of patients within a treatment group (N). For all other baseline assessments, n and N were identical and therefore equal to N provided in the header. CHE, chronic HE; HE, hand eczema; HECSI, Hand Eczema Severity Index; IGA-CHE, Investigator's Global Assessment for CHE; N, number of patients within a treatment group; n, number of patients with data; NRS, numerical rating scale; PaGA, Patient's Global Assessment.

Discussion

Delgocitinib cream treatment twice daily for 16 weeks in adults with mild-to-severe CHE and a recent history of inadequate response or contraindication to TCS demonstrated a statistically significant dose–response relationship for the primary

efficacy outcome IGA-CHE TS. Doses of 8 and 20 mg g⁻¹ showed a treatment effect vs. vehicle in all presented endpoints without raising any safety concerns.

The primary outcome, IGA-CHE TS at week 16, was met by more patients in the delgocitinib 8 and 20 mg g⁻¹ groups compared with vehicle and the lower-dose groups. These

Table 2 Efficacy outcomes at week 16. All outcomes are based on the full analysis set.

	Delgocitinib, dose (N)				Vehicle N = 50
	1 mg g ⁻¹ (52)	3 mg g ⁻¹ (51)	8 mg g ⁻¹ (52)	20 mg g ⁻¹ (53)	
IGA-CHE					
Patients with IGA-CHE TS at week 16, responders (%)	11 (21.2)	4 (7.8)	19 (36.5)	20 (37.7)	4 (8.0)
Difference in percentage from vehicle (95% CI)	13.3 (0.3–26.2)	–0.0 (–10.4 to 10.4)	28.2 (13.8–42.6) ^a	29.6 (14.6–44.7) ^a	–
Time to IGA-CHE TS, median, days (weeks)	– ^b	– ^b	82 (11.7) ^c	98 (14.0) ^d	– ^b
HECSI					
n	40	38	43	47	37
Change in HECSI score from baseline to week 16, LSMean (SE)	–39.8 (3.7)	–35.9 (3.8)	–46.7 (3.6)	–42.0 (3.6)	–26.4 (3.8)
Difference from vehicle, LSMean (95% CI)	–13.4 (–22.8 to –4.0)	–9.5 (–19.0 to –0.0)	–20.3 (–29.6 to –11.0)	–15.6 (–24.8 to –6.4)	–
Percentage change in HECSI score from baseline to week 16, LSMean (SE)	–70.1 (10.9)	–67.0 (11.0)	–80.2 (10.6)	–70.5 (10.5)	–41.6 (11.1)
Difference to vehicle, LSMean (95% CI)	–28.5 (–55.6 to –1.5)	–25.4 (–52.7 to 1.9)	–38.6 (–65.2 to –12.0)	–28.9 (–55.4 to –2.4)	–
Itch and pain NRS scores					
N	51	50	50	52	49
n	38	36	40	42	33
Change in itch NRS score (weekly average) from baseline to week 16, LSMean (SE)	–3.1 (0.4)	–2.5 (0.4)	–3.2 (0.4)	–3.2 (0.3)	–1.7 (0.4)
Difference to vehicle, LSMean (95% CI)	–1.4 (–2.3 to –0.4)	–0.8 (–1.7 to 0.1)	–1.5 (–2.4 to –0.6)	–1.5 (–2.4 to –0.6)	–
Change in pain NRS score (weekly average) from baseline to week 16, LSMean (SE)	–2.7 (0.3)	–2.4 (0.3)	–3.0 (0.3)	–3.2 (0.3)	–1.4 (0.3)
Difference to vehicle, LSMean (95% CI)	–1.3 (–2.2 to –0.4)	–1.0 (–1.9 to –0.1)	–1.6 (–2.4 to –0.7)	–1.8 (–2.7 to –0.9)	–
PaGA					
Patients with PaGA TS at week 16, responders (%)	9 (17.3)	10 (19.6)	12 (23.1)	18 (34.0)	3 (6.0)
Difference in percentage to vehicle (95% CI)	11.5 (–0.2 to 23.3)	13.8 (1.1–26.4)	16.8 (4.0–29.5)	28.2 (13.8–42.6)	–

^aStatistically significant compared with vehicle ($P = 0.0004$). ^bIGA-CHE TS was reached in less than 50% of patients, therefore the median time was not estimable. ^cStatistically significant compared with vehicle ($P < 0.0001$). ^dStatistically significant compared with vehicle ($P = 0.022$). Risk difference was calculated using Mantel–Haenszel weighting. The P-value is derived from a Cochran–Mantel–Haenszel test, stratified by region and baseline IGA-CHE score. In case any of the stratification factor combinations resulted in strata with zero observations, a simpler model was investigated in a sequential manner (1, removing region only; 2, removing baseline IGA-CHE only; 3, removing both region and baseline IGA-CHE). Continuous endpoints were analysed using a mixed model for repeated measurements (treatment*week + baseline*week + region + baseline IGA-CHE). Missing data were imputed using the mixed model for repeated measurements predicted values. HECSI, Hand Eczema Severity Index; CI, confidence interval; IGA-CHE, Investigator's Global Assessment for chronic hand eczema; IGA-CHE TS, IGA-CHE treatment success, defined as an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a two-step improvement from baseline to week 16; LSMean, least squares mean; N, number of patients within a treatment group; n, number of patients with data; NRS, numerical rating scale; PaGA, Patient's Global Assessment; PaGA TS, PaGA treatment success, defined as a PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild), or a PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) or 4 (severe); SE, standard error.

improvements in skin clearance were statistically significant from week 4 (8 mg g⁻¹) and week 6 (20 mg g⁻¹) through week 16. PaGA TS at week 16 showed dose-dependent improvements in patients' own assessment of skin clearance.

The change in HECSI from baseline to week 16 showed improvements for all dose groups compared with vehicle.

Localized itch and pain are considered two of the most common and burdensome symptoms experienced by

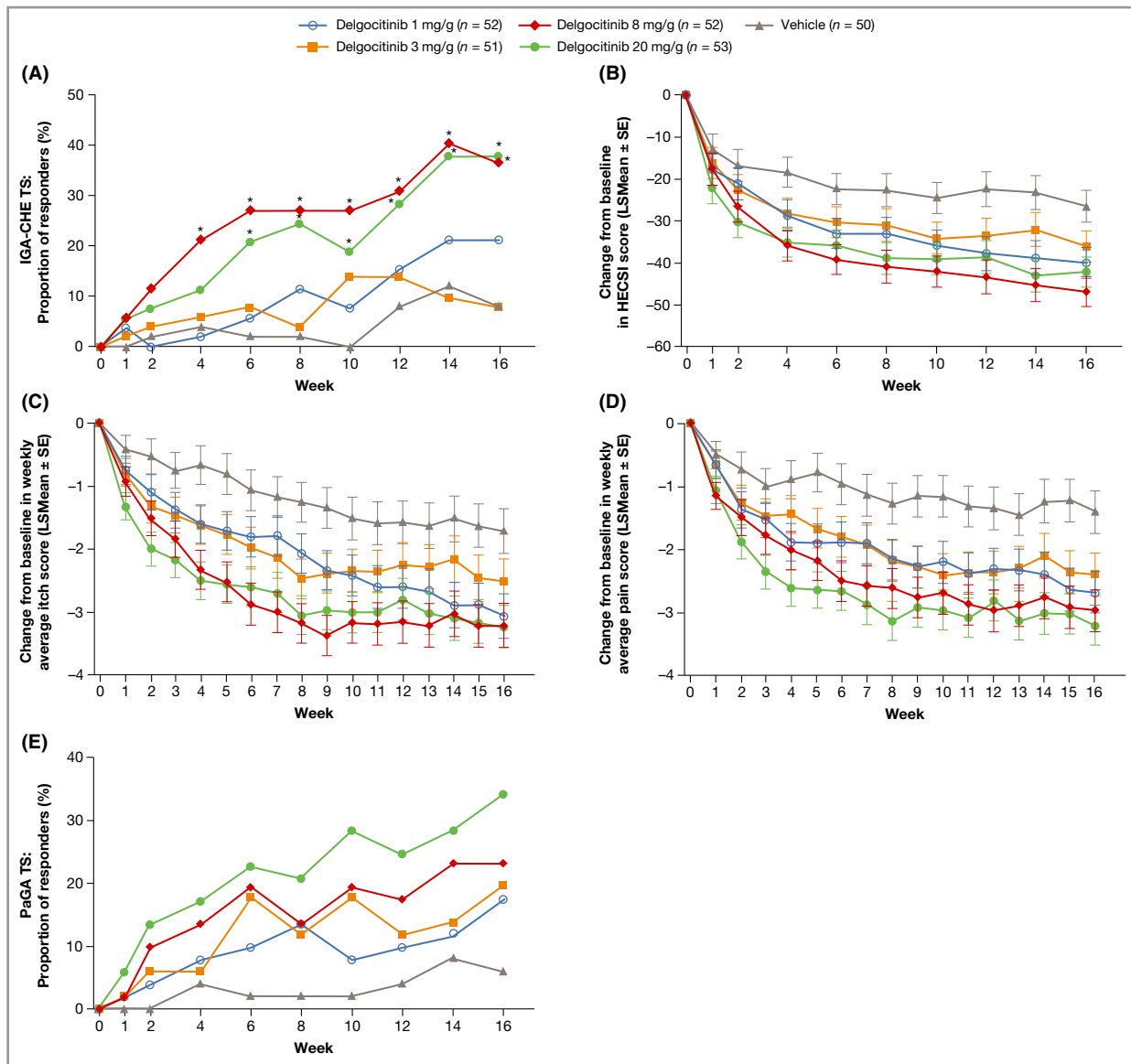


Figure 2 Efficacy outcomes from baseline to week 16. All outcomes are based on the full analysis set. (A) Proportion of patients achieving IGA-CHE TS, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a two-step improvement from baseline; (B) change from baseline in HECSE score; (C) change from baseline in itch score (weekly average); (D) change from baseline in pain score (weekly average); (E) proportion of patients achieving PaGA treatment success, i.e. a PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild), or a PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) to 4 (severe). Binary endpoints (A and E) were analysed using Cochran–Mantel–Haenszel. Data collected after premature discontinuation of the investigational medicinal product or initiation of rescue medication were imputed as nonresponders. Any other missing data were also imputed as nonresponders. Continuous endpoints (B–D) were analysed using a mixed model for repeated measurements (treatment*week + baseline*week + region + baseline IGA-CHE). Missing data were imputed using the mixed model for repeated measurements predicted values. CHE, chronic hand eczema; IGA-CHE, Investigator’s Global Assessment for CHE; HECSE, Hand Eczema Severity Index; LSMean, least squares mean; PaGA, Patient’s Global Assessment; SE, standard error; TS, treatment success. *Nominal $P < 0.05$.

patients with CHE and have a negative impact on their quality of life.¹¹ Itch and pain symptoms in this trial were captured through the Hand Eczema Symptom Diary (HESD). The response from patients indicated that delgocitinib cream brought about a rapid (within 1 week of initiation of therapy) and sustained reduction in itch and pain. Improvements in itch and pain NRS scores at week 16 were seen

for all dose groups, with the greatest improvement seen for 20 mg g^{-1} .

Overall, delgocitinib cream 8 and 20 mg g^{-1} had the highest efficacy compared with vehicle and lower-dose groups across all assessment scales. The treatment effect had not reached a plateau at the end of treatment, suggesting that longer-term use could offer additional benefits than what was observed in the trial.

Table 3 Summary of adverse events. All outcomes are based on the safety analysis set.

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

AEs presented are treatment-emergent with onset after the first application of study treatment. Related AEs are events considered by the investigator to be possibly or probably related to study treatment. Classification is according to MedDRA version 21.1. %, percentage of patients with one or more AE; AE, adverse event; E, number of patients within a treatment group, n, number of patients with one or more AE; R, rate number of AEs divided by person-years of exposure multiplied by 100 [person-years of exposure is calculated as days from first application of study treatment to last application of study treatment (both days included) divided by 365.25].

Delgocitinib cream was well tolerated. The most frequently reported AEs were nasopharyngitis, eczema and headache. No dose–response relationships were seen in the safety profile, and no safety concerns were identified.

Some potential limitations apply to the generalizability of this trial. Some of the efficacy assessment scales (IGA-CHE, HESD and PaGA) were developed more recently and have not been extensively used in clinical trials. Additionally, although the trial was well powered for its primary objective, the sample size does not allow for any conclusion on effectiveness in CHE subtypes. Phase III trials in CHE will further investigate the effects and safety of delgocitinib cream.

The pathogenesis of CHE involves cytokines that activate intracellular signalling through JAK–STAT pathways and are associated with Th1 (interferon- γ), Th2 [interleukin (IL)-4, IL-13], Th17 (IL-17) and Th22 (IL-22).⁴ The pathophysiology of CHE has been described based on aetiological classifications only.⁴ However, different triggers and risk factors associated with HE appear to converge towards common pathophysiological mechanisms in CHE.^{7,33} Delgocitinib's mode of action as a pan-JAK inhibitor would be expected to bring additional value to the management of CHE. The findings of this trial confirm the key role of the JAK–STAT pathway in CHE, supporting the use of delgocitinib because of its mode of action. Delgocitinib cream is expected to provide the benefits observed for other JAK inhibitors but without the safety concerns inherent to systemic administration due to the topical application to limited skin areas and limited systemic exposure. The successful outcomes of the trial support the potential of delgocitinib cream as an efficacious and safe topical treatment for patients with CHE.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Conflicts of interest statement

Appendix S2 Eligibility criteria

Table S1 Analysis of dose–response relationship of IGA-CHE treatment success at week 16.

Video S1 Author video.