CLINICAL TRIAL

BJD
British Journal of Dermatology

Efficacy and safety of topical delgocitinib in patients with chronic hand eczema: data from a randomized, double-blind, vehicle-controlled phase IIa study

M. Worm,[1] A. Bauer,[2] P. Elsner,[3] V. Mahler,[4] S. Molin[5] and T.S.S. Nielsen[6]

[1]Division of Allergy and Immunology, Department of Dermatology and Allergy, Charité Universitätsmedizin Berlin, Berlin, Germany
[2]Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University, Dresden, Germany
[3]Department of Dermatology, University Hospital Jena, Jena, Germany
[4]Department of Dermatology, University Hospital Erlangen, Erlangen, Germany
[5]Division of Dermatology, Queen's University, Kingston, ON, Canada
[6]LEO Pharma A/S, Ballerup, Denmark

Linked Comment: Strowd and Feldman. Br J Dermatol 2020; **182**:1078.

Summary

Background Management of chronic hand eczema (CHE) remains a challenge; effective topical treatment is limited to corticosteroids.
Objectives To assess the efficacy and safety of a novel, pan-Janus kinase inhibitor (delgocitinib) in patients with CHE.
Methods In this randomized, double-blind, phase IIa study, patients with CHE received delgocitinib ointment 30 mg g^{-1} or vehicle ointment for 8 weeks. The primary end point was the proportion of patients achieving treatment success ['clear'/'almost clear' skin with ≥ 2-point improvement in the Physician's Global Assessment of disease severity (PGA)] at week 8. Secondary end points included Hand Eczema Severity Index (HECSI) score changes and the proportion of patients achieving treatment success on the Patient's Global Assessment of disease severity (PaGA).
Results Ninety-one patients were randomized. More patients receiving delgocitinib (46%) than vehicle (15%) [odds ratio 4·89, 95% confidence interval (CI) 1·49–16·09; P = 0·009] achieved treatment success (PGA). Adjusted mean HECSI score at week 8 was lower with delgocitinib (13·0) than with vehicle (25·8) (adjusted mean difference −12·88, 95% CI −21·47 to −4·30; P = 0·003). More patients receiving delgocitinib than vehicle achieved treatment success by PaGA, but this did not reach statistical significance. The incidence of adverse events was similar with delgocitinib and vehicle; none led to discontinuation of delgocitinib.
Conclusions Delgocitinib ointment was efficacious and well tolerated. As a plateau of efficacy was not observed, a longer treatment period may lead to increased efficacy. Further clinical studies are warranted to confirm these findings in patients with CHE.

Correspondence
Margitta Worm
E-mail: margitta.worm@charite.de

Accepted for publication
24 August 2019

Funding sources
This study was sponsored by LEO Pharma. Medical writing support was provided by Andrew Jones PhD, from Mudskipper Business Limited, funded by LEO Pharma A/S.

Conflicts of interest
M.W. and A.B. have been investigators for and have received lecture honoraria from LEO Pharma. P.E. has been a study investigator for, has received research funding (departmental) and has received speaker honoraria from LEO Pharma. V.M. has been a study investigator for LEO Pharma. S.M. has been a study investigator and has received speaker honoraria from LEO Pharma. T.S.S.N. is an employee of LEO Pharma.

The present address for V.M. is Paul-Ehrlich-Institut, Langen, Germany

DOI 10.1111/bjd.18469

What's already known about this topic?

- Chronic hand eczema (CHE) has a significant burden.
- Few randomized controlled studies have evaluated current treatments for CHE; only limited data are available to inform and guide clinical practice decisions.
- There is currently an unmet need for efficacious and well-tolerated topical treatment options for patients with CHE.

What does this study add?

- Delgocitinib is a novel, pan-Janus kinase (JAK) inhibitor specific for JAK1, JAK2, JAK3 and tyrosine kinase 2.

- Topical use of delgocitinib ointment resulted in clearance of CHE after 8 weeks of treatment in a significantly greater number of patients than vehicle; delgocitinib was also well tolerated.
- Results from this proof-of-concept clinical study suggest that topical delgocitinib may provide therapeutic benefit to patients with CHE with inadequate responses to topical corticosteroids.

Hand eczema is a chronic inflammatory skin disease,[1] with varying and potentially interlinked aetiology, such as irritant or allergic contact dermatitis or atopic hand dermatitis. It is common in the general population, with an overall reported 1-year prevalence of around 10%.[2–4] Hand eczema is considered chronic (CHE) if it lasts at least 3 months or relapses twice or more in 1 year.[4] Common signs of CHE include erythema, oedema, blistering, thickening and fissures, while itch and pain are symptoms experienced by many patients.[5,6] CHE has a marked negative impact on patients' medical well-being and quality of life (QoL);[7–11] in particular, itch can have a negative impact on QoL.[8,12] Although the molecular mechanisms underlying CHE are not fully understood, a large panel of cytokine-mediated signalling cascades have been identified as part of the pathophysiology, including T-helper 2 (Th2) [interleukin (IL)-4, IL-13], Th22 (IL-22), Th17 (IL-17), Th1 (interferon-γ) and the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway.[13–15]

Emollients and topical corticosteroids are the mainstay of CHE treatment.[4,16] In addition, many patients with CHE do not receive adequate treatment,[6] which may be the result of misperceptions about CHE or to treatment-specific concerns.[4] For example, it is recommended that corticosteroids should not be used for > 6 weeks because of side-effects, such as skin atrophy and barrier impairment.[4,17] Also, systemic treatments for CHE are limited, with alitretinoin currently being the only approved treatment with an indication for CHE in Europe.

Delgocitinib is a novel, pan-JAK inhibitor specific for JAK1, JAK2, JAK3 and tyrosine kinase 2.[18] It blocks several cytokine-mediated signalling cascades, thereby inhibiting inflammation, and might, therefore, be a suitable therapeutic agent for topical use in CHE. The aim of this study was to evaluate the efficacy and safety of delgocitinib ointment over 8 weeks of treatment in adult patients with CHE refractory to topically applied steroids.

Patients and methods

Study design

This prospective, randomized, double-blind, parallel group, vehicle-controlled phase IIa proof-of-concept clinical study was conducted at 13 study sites in Germany (NCT02664805). Patients were randomized 2 : 1 to delgocitinib ointment (30 mg g^{-1}) or vehicle ointment applied twice daily (~12 h apart) in a thin layer to the areas of the hands affected by CHE, over an 8-week treatment period. Randomization was performed via a central Interactive Web Response System and stratified according to predominant disease subtype (irritant or nonirritant), as determined by the investigator at baseline. The number of patients in the irritant strata was limited to 45.

The institutional review board or independent ethics committee at all investigational sites approved the protocol and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Patients

Patients enrolled in the study were aged 18–65 years and had CHE with/without atopic aetiology of at least mild baseline severity based on the Physician's Global Assessment of disease severity (PGA),[19] and a history of inadequately controlled disease with topically applied corticosteroids. Patients were excluded if they were using medications that could influence treatment efficacy. Systemic drugs (immunosuppressive drugs, retinoids or corticosteroids), psoralen ultraviolet A or B therapy on the hands, topical treatment (immunomodulators or corticosteroids) on the hands or antibiotics were not permitted within 6, 4, 2 or 1 week(s) prior to randomization, respectively. Other exclusion criteria included concurrent skin diseases or significant clinical infection of the hand, a diagnosis of exfoliative dermatitis, severe renal or hepatic disorders, or an immunocompromising disease. The use of hand emollients was permitted during the study; however, they were not allowed within 2 h before and after treatment application. To explore gene expression profiles, skin biopsies were obtained from patients who provided consent. The results of these analyses are exploratory in nature and outside the scope of this paper.

End points and assessments

The primary end point was the proportion of patients achieving 'treatment success' at week 8 in each treatment group, based on the 5-point PGA. Treatment success was defined as achieving 'clear' or 'almost clear' skin with at least 2-point improvement from baseline. Secondary end points included treatment group differences at week 8 in mean Hand Eczema Severity Index (HECSI) score,[20] which is a composite measure of the severity and extent of coverage of morphological symptoms, including erythema, infiltration, vesicles, fissures, scaling and oedema on each of the five hand areas [fingertips,

fingers (except tips), palms, back of hands and wrists], with a final score ranging from 0 to 360 points. The proportion of patients achieving treatment success in each treatment group at week 8, based on the 5-point Patient's Global Assessment of disease severity (PaGA), was also assessed as a secondary end point, where treatment success was defined as achieving 'clear' skin in patients with 'mild' or 'very mild' baseline disease, or achieving 'clear' or 'very mild' skin in patients with 'moderate' or 'severe' baseline disease. Other end points included the proportion of patients reporting no itching, burning or pain at week 8, based on an 11-point numerical rating scale (NRS; 0–10, where 0 is 'none' and 10 is 'worst') and assessment of patient's QoL based on the Quality of Life in Hand Eczema Questionnaire (QOLHEQ). The QOLHEQ comprises 30 questions associated with four subscales (symptoms, emotions, function and treatment), with responses to most questions being 'never', 'rarely', 'sometimes', 'often' and 'all the time', corresponding to scores of 0–4.[21] Safety was assessed by evaluating adverse events (AEs), using terms as defined by Medical Dictionary for Regulatory Activities (MedDRA) version 19·0, and by monitoring vital signs, electrocardiograms (ECGs) and laboratory parameters.

PGA, HECSI and PaGA scores, and patient assessment of itching, burning and pain were assessed at baseline and at weeks 1, 2, 4, 6 and 8, with QOLHEQ scores assessed at baseline and at week 8.

Statistical analysis

The study sample size was determined based on 60 patients receiving delgocitinib and 30 patients receiving vehicle, providing an 80% power to reject the null hypothesis of no between-group difference for the primary end point, based on a two-sided test at the 5% significance level, assuming that 20% of patients in the vehicle group and 50% in the delgocitinib group had 'clear' or 'almost clear' disease, according to PGA. Therefore, 113 patients were screened to obtain 90 patients who were randomized, assuming a screen failure rate of 20%.

Efficacy was assessed based on the full analysis set (FAS), which comprised all randomized patients. Supportive analyses for the primary end point were conducted using the per protocol analysis set (PPS), which comprised the FAS, excluding patients: who received no treatment, the wrong treatment or missed $\geq$ 25% of the planned treatment; who provided no efficacy data; and who used prohibited medication and/or did not meet the disease-defining inclusion criteria. Safety was assessed based on the safety analysis set (SAS), which comprised the FAS, excluding patients who received no treatment and/or for whom no postbaseline safety evaluations were available. The proportion of patients achieving treatment success with PGA and PaGA, as well as the proportion of patients with no itching, burning or pain, was compared between treatment groups at week 8 using the Cochran–Mantel–Haenszel test, adjusted for predominant subtype (i.e. irritant or nonirritant). The homogeneity of the odds ratio (OR) across predominant CHE subtypes was investigated using the Breslow–Day test at the 10% significance level for the primary analysis. As a post-hoc sensitivity analysis, the difference in PGA response rate between treatment groups at week 8 was analysed using the Cochran–Mantel–Haenszel test, adjusted for predominant subtype and baseline PGA. The HECSI score at week 8 was compared between the treatments using analysis of covariance, including predominant CHE subtype, treatment, and baseline HECSI score as covariates. A post-hoc analysis of the proportion of patients who had a clinically relevant reduction of $\geq$ 4 in NRS itch at week 8 was performed in patients who had a baseline NRS itch score $\geq$ 4 using the Cochran–Mantel–Haenszel test, adjusted for predominant subtype (i.e. irritant or nonirritant).

For the primary and secondary end points, multiple imputation was used to handle missing data, assuming that the missing data were 'missing at random', i.e. the probability that an observation was missing depended on observed data but was unrelated to the data that were not observed. For QOLHEQ scores, the last observation carried forward (LOCF) approach was used to impute missing data at week 8.

Results

Patients

In total, 132 patients were screened and 91 patients were randomized between February and April 2016; 60 (66%) patients received delgocitinib and 31 (34%) received vehicle (Fig. 1). All 91 patients were included in the FAS and SAS; 76 patients were included in the PPS (51 receiving delgocitinib and 25 receiving vehicle, respectively). Eighty-six (95%) patients completed the study, of whom 59 (98%) were treated with delgocitinib and 27 (87%) with vehicle. One (2%) patient in the delgocitinib group discontinued treatment because of patient withdrawal and four (13%) patients in the vehicle group discontinued: three (10%) because of AEs and one (3%) because of a lack of efficacy. For the delgocitinib and vehicle groups, respectively, the mean $\pm$ SD duration of exposure was 8·1 $\pm$ 0·5 and 7·5 $\pm$ 1·8 weeks, and the extent of exposure to treatment was 488 and 231 patient-treatment weeks.

Patient baseline demographics and characteristics were generally well balanced between treatment groups, although there was a greater proportion of patients with severe disease in the vehicle group than in the delgocitinib group, as reflected by the PGA and PaGA scores (Table 1). Nonirritant CHE was reported in 53 (58%) patients, with irritant CHE reported in 38 (42%) patients. Most (n = 53/91; 58%) patients had 'moderate' disease, as assessed by PGA.

Treatment success: Physician's Global Assessment

At week 8, the primary end point of treatment success, measured by PGA, was achieved in 46% of patients receiving delgocitinib and 15% of patients receiving vehicle [OR 4·89, 95%

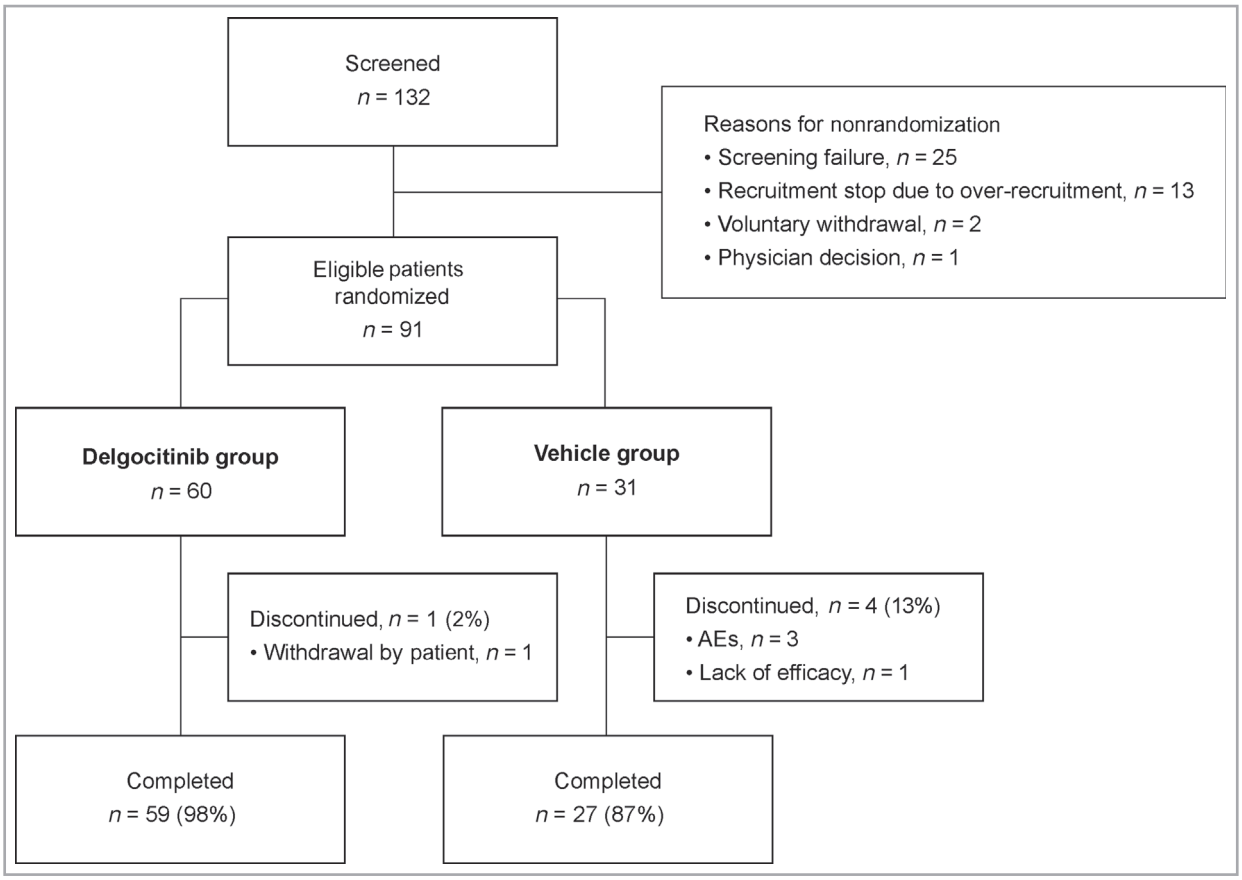

Fig 1. Patient disposition. AE, adverse event

confidence interval (CI) 1·49–16·09; P = 0·009], with missing values imputed. All supportive analyses (Tables S1 and S2; see Supporting Information), as well as the sensitivity analysis adjusting for both predominant subtype and baseline PGA, led to a similar conclusion as that of the primary analysis. The proportion of patients achieving treatment success continuously increased over time in the delgocitinib group without reaching a plateau, whereas fewer and generally similar proportions of patients in the vehicle group achieved treatment success over time (Fig. 2). In the delgocitinib group, treatment success was achieved in 54% and 40% of patients with irritant and nonirritant CHE, respectively, and in 15% and 14%, respectively, in the vehicle group. A Breslow–Day test assessing homogeneity of OR between patients with irritant and nonirritant CHE determined that treatment success was not driven by a predominant CHE subtype (P = 0·7). When assessing the primary end point by baseline disease severity, the subgroup with 'moderate' baseline PGA scores had the greatest proportion of patients achieving treatment success, with most (53%) being in the delgocitinib group (Table 2).

Hand Eczema Severity Index

Mean HECSI scores decreased over time in both treatment groups (Fig. S1; see Supporting Information). At week 8, the mean HECSI score, adjusted for baseline HECSI and predominant CHE subtype, was 13·0 for patients receiving delgocitinib and 25·8 for patients receiving vehicle (adjusted mean difference −12·88, 95% CI −21·47 to −4·30; P = 0·003), with missing values imputed. Similar results were observed using an LOCF analysis (Table S2).

Other efficacy end points

Treatment success measured by PaGA at week 8 was achieved in 31% of patients receiving delgocitinib and 18% of patients receiving vehicle, although the difference between groups did not reach statistical significance (OR 2·11, 95% CI 0·69–6·46; P = 0·19), with missing values imputed. Similar results were observed using an LOCF analysis (Table S2).

At week 8, a significantly greater proportion of patients in the delgocitinib group reported 'no burning' compared with the vehicle group (Table S1). The proportion of patients was also higher in the delgocitinib group for 'no itching' and 'no pain', although this did not reach statistical significance. A post-hoc responder analysis in patients who had a baseline NRS itch score ≥ 4 (n = 50) showed that a greater proportion of patients receiving delgocitinib (n = 16/29; 55%) than vehicle (n = 5/21; 24%) had a reduction of ≥ 4 in NRS itch at week 8 (OR 4·01, 95% CI 1·14–14·09; P = 0·029).

Table 1 Patient demographics and baseline characteristics (full analysis set)

	Delgocitinib (n = 60)	Vehicle (n = 31)	All patients (n = 91)
Mean ± SD age (years)	43·8 ± 13·0	40·8 ± 12·5	42·8 ± 12·8
Male : female	18 : 42 (30 : 70)	11 : 20 (35 : 64 to 65)	29 : 62 (32 : 68)
Ethnicity			
White	59 (98)	30 (97)	89 (98)
Asian	1 (2)	0	1 (1)
Other	0	1 (3)	1 (1)
Predominant subtype			
Irritant	25 (42)	13 (42)	38 (42)
Nonirritant	35 (58)	18 (58)	53 (58)
PGA			
Mild	13 (22)	5 (16)	18 (20)
Moderate	36 (60)	17 (55)	53 (58)
Severe	11 (18)	9 (29)	20 (22)
Mean ± SD HECSI	32·6 ± 21·5	40·5 ± 34·3	–
PaGA			
Clear	1 (2)	0	1 (1)
Very mild	5 (8)	2 (6)	7 (8)
Mild	16 (27)	6 (19)	22 (24)
Moderate	26 (43)	11 (35)	37 (41)
Severe	12 (20)	12 (39)	24 (26)
NRS score < 4/≥ 4[a]			
Itching	25 (46)/29 (54)	6 (21)/23 (79)	31 (37)/52 (63)
Burning	35 (65)/19 (35)	17 (59)/12 (41)	52 (63)/31 (37)
Pain	32 (59)/22 (41)	17 (59)/12 (41)	49 (59)/34 (41)
Mean ± SD QOLHEC			
Overall	50·6 ± 21·1	53·9 ± 22·8	–
Symptoms	15·3 ± 5·0	16·1 ± 5·0	–
Emotions	11·9 ± 6·6	13·0 ± 7·6	–
Functioning	11·2 ± 6·7	12·4 ± 7·6	–
Treatment/prevention	12·2 ± 5·4	12·4 ± 5·1	–

Data are n (%) unless otherwise indicated. PGA, Physician's Global Assessment of disease severity; HECSI, Hand Eczema Severity Index; PaGA, Patient's Global Assessment of disease severity; NRS, numerical rating scale; QOLHEC, Quality of Life in Hand Eczema Questionnaire. [a]Not all patients in the full analysis set had a reported value; hence, the denominator in the calculation of the proportions is lower (n = 54 for delgocitinib and n = 29 for vehicle).

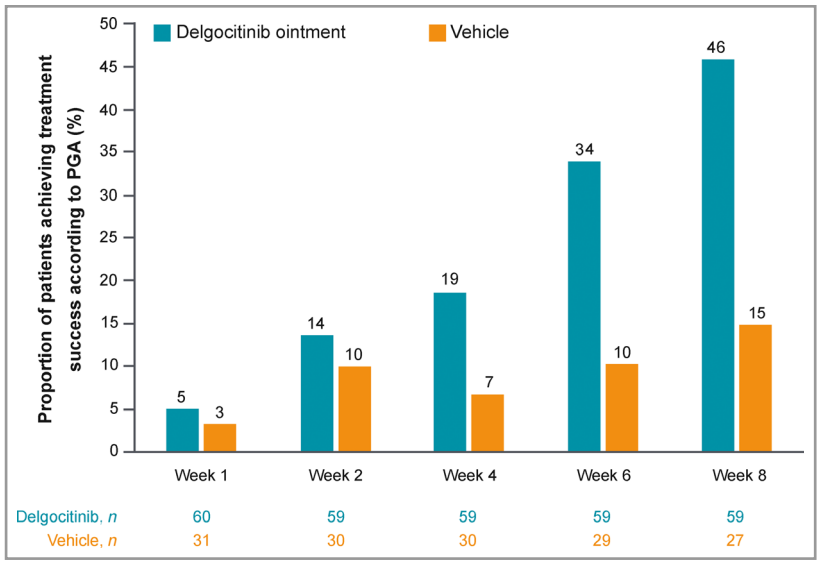

Fig 2. Treatment success by visit, measured by Physician's Global Assessment of disease severity (PGA) (observed cases;[a] full analysis set). [a]Values based on observed cases, i.e. there was no imputation of missing data.

Table 2 Treatment success at week 8, measured by the Physician's Global Assessment of disease severity, by baseline severity (observed cases;[a] full analysis set)

	Delgocitinib (n = 59)	Vehicle (n = 27)
Mild[b]		
Yes	4 (33)	0 (0)
No	8 (67)	5 (100)
Moderate		
Yes	19 (53)	3 (20)
No	17 (47)	12 (80)
Severe		
Yes	4 (36)	1 (14)
No	7 (64)	6 (86)

Data are n (%). [a]Values based on observed cases, i.e. there was no imputation of missing data; [b]the odds ratio for the mild subgroup could not be calculated because treatment success rate in the vehicle group for patients with mild baseline disease was 0.

Patients in both treatment groups reported lower overall QOLHEC scores, indicating improved QoL, than baseline. The mean change from baseline at week 8, adjusted for baseline QOLHEC score and predominant CHE subtype, was −19·1 in the delgocitinib group and −11·0 in the vehicle group (adjusted mean difference −8·1, 95% CI −15·4 to −0·8; P = 0·031). For the four QOLHEC subscales, adjusted means at week 8 were significantly lower in the delgocitinib group than the vehicle group for 'symptoms' and 'emotions', but no significant differences were found for 'functioning' and 'treatment and prevention' (Table 3).

Table 3 Adjusted mean differences from baseline in Quality of Life in Hand Eczema Questionnaire (QOLHEQ) scores at week 8 (last observation carried forward; full analysis set)[a]

	Delgocitinib (n = 60)	Vehicle (n = 31)
Overall score		
Adjusted mean	−19·1	−11·0
Difference −8·1 (95% CI −15·4 to −0·8); P = 0·031		
Symptoms subscore		
Adjusted mean	−6·2	−3·3
Difference −2·9 (95% CI −5·1 to −0·7); P = 0·01		
Emotions subscore		
Adjusted mean	−5·3	−3·2
Difference −2·1 (95% CI −4·2 to −0·03); P = 0·046		
Functioning subscore		
Adjusted mean	−4·6	−2·6
Difference −2·0 (95% CI −4·2 to −0·3); P = 0·089		
Treatment and prevention subscore		
Adjusted mean	−3·1	−1·8
Difference −1·3 (95% CI −3·1 to −0·6); P = 0·18		

[a]Adjusted for baseline QOLHEQ score and predominant subtype (irritant or nonirritant chronic hand eczema). CI, confidence interval.

Safety

Overall, 34 (57%) patients in the delgocitinib group experienced 59 AEs and 14 (45%) patients in the vehicle group experienced 29 AEs, most of which were of mild intensity [n = 47/59 (80%) and n = 19/29 (66%), respectively] (Table 4). The reported AEs of postoperative wound infection were related to the skin biopsies that were taken for gene expression analyses. All AEs were of mild intensity and considered unrelated to treatment, and all patients recovered at the end of the study, although two patients in the vehicle group also experienced a worsening of CHE and discontinued from the study.

Treatment-related AEs were reported in three (5%) patients receiving delgocitinib [hand dermatitis in two (3%) patients; eczema in one (2%) patient] and eight (26%) patients receiving vehicle [hand dermatitis in seven (23%) patients; atopic dermatitis, application site pain and hypoaesthesia in one (3%) patient]. One serious AE of back pain was reported in a patient receiving delgocitinib and was considered unrelated to treatment. None of the AEs in the delgocitinib group led to discontinuation from the study, whereas three (10%) patients in the vehicle group experienced AEs of worsening hand dermatitis leading to study discontinuation. No clinically relevant changes in vital signs, ECG measurements or laboratory values were observed in either treatment group during the study.

Discussion

We hypothesized that delgocitinib, a pan-JAK inhibitor, would be an efficacious treatment for CHE through inhibition of JAK-dependent signalling pathways and the underlying inflammation responsible for CHE. In this phase IIa clinical study, delgocitinib ointment 30 mg g^{-1} was an efficacious and well-tolerated treatment for adults with CHE when applied twice daily over an 8-week treatment period.

The effectiveness of delgocitinib in CHE was demonstrated by the primary end point, where a significantly greater proportion of patients receiving delgocitinib than vehicle achieved treatment success. These data were supported by the assessment of HECSI.[20] The consistency of data between PGA and HESCI aligns with observations from a previous clinical trial,[19] as well as a study that compared different methods for the

Table 4 Most common adverse events (≥ 5% of patients in either treatment group) reported during the study

Adverse event	Delgocitinib (n = 60)	Vehicle (n = 31)
Nasopharyngitis	15 (25)	4 (13)
Postoperative wound infection	4 (7)	2 (6)
Hand dermatitis (worsening)	3 (5)	9 (29)
Headache	4 (7)	1 (3)
Creatine phosphokinase increased	0 (0)	2 (6)

Data are n (%).

assessment of hand eczema.[22] The efficacy of delgocitinib in the present study was also assessed from the patients' perspective, using PaGA. Treatment success measured by PaGA was numerically higher for delgocitinib than vehicle, although this did not reach statistical significance. However, the study was not powered for this end point and there was no inclusion criterion based on the assessment of PaGA. Importantly, delgocitinib was effective irrespective of the predominant CHE subtype (i.e. in patients with both 'irritant' and 'nonirritant' forms) or of baseline PGA severity (i.e. in patients with 'mild', 'moderate' or 'severe' disease), suggesting that it may have value across a wide range of patients with CHE.

CHE is a long-standing condition; therefore, it is encouraging that 46% of patients achieved treatment success during the relatively short treatment period in this study. As a plateau in treatment success with delgocitinib was not observed after 8 weeks, we could speculate that a longer treatment period may lead to increased efficacy. However, this needs to be explored further in future studies.

Itch is one of the most common and burdensome symptoms experienced by patients with CHE and has a substantial negative impact on QoL.[8] In this study, a numerically higher proportion of patients receiving delgocitinib than vehicle achieved 'no itching' at week 8. Furthermore, a post-hoc analysis showed that a greater number of patients receiving delgocitinib than vehicle responded with a clinically relevant improvement in NRS itch; although not confirmed in CHE, a reduction of ≥ 4 in NRS itch was considered clinically relevant based on studies in patients with other dermatological conditions such as atopic dermatitis.[23] Taken together, these data suggest that delgocitinib has a substantial positive impact on itch in CHE.

Overall, treatment with delgocitinib was well tolerated with an acceptable safety profile; most of the AEs reported in patients receiving delgocitinib were of mild intensity. The incidence of AEs and treatment-related AEs was low and similar in the delgocitinib and vehicle groups, and there were no AEs leading to discontinuation in the delgocitinib group. Postoperative wound infection, related to skin biopsies taken optionally to explore gene expression profiles of CHE subtype, was one of the most common AEs reported in the delgocitinib group (7%); all of these AEs were of mild intensity and considered unrelated to treatment, and had resolved by the end of the study.

In conclusion, use of delgocitinib ointment in adults with CHE was effective and well tolerated, thereby establishing clinical proof of concept. Additional studies are required to confirm the efficacy and safety of the topical use of delgocitinib in CHE.

References

1 Coenraads PJ. Hand eczema. *N Engl J Med* 2012; **367**:1829–37.
2 Johannisson A, Ponten A, Svensson A. Prevalence, incidence and predictive factors for hand eczema in young adults – a follow-up study. *BMC Dermatol* 2013; **13**:14.
3 Thyssen JP, Johansen JD, Linneberg A *et al.* The epidemiology of hand eczema in the general population – prevalence and main findings. *Contact Dermatitis* 2010; **62**:75–87.
4 Diepgen TL, Andersen KE, Chosidow O *et al.* Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges* 2015; **13**:e1–22.
5 Antonov D, Schliemann S, Elsner P. Hand dermatitis: a review of clinical features, prevention and treatment. *Am J Clin Dermatol* 2015; **16**:257–70.
6 Apfelbacher C, Molin S, Weisshaar E *et al.* Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. *Acta Derm Venereol* 2014; **94**:163–7.
7 Bohm D, Stock GS, Finkeldey F *et al.* Severe occupational hand eczema, job stress and cumulative sickness absence. *Occup Med (Lond)* 2014; **64**:509–15.
8 Cazzaniga S, Ballmer-Weber BK, Grani N *et al.* Medical, psychological and socio-economic implications of chronic hand eczema: a cross-sectional study. *J Eur Acad Dermatol Venereol* 2016; **30**:628–37.
9 Kouris A, Armyra K, Christodoulou C *et al.* Quality of life, anxiety, depression and obsessive-compulsive tendencies in patients with chronic hand eczema. *Contact Dermatitis* 2015; **72**:367–70.
10 Kuster D, Haufe E, Rethberg C *et al.* Health utilities for controlled and uncontrolled chronic hand eczema in healthcare employees. *Contact Dermatitis* 2018; **78**:18–27.
11 Fowler J. Chronic hand eczema: a prevalent and challenging skin condition. *Cutis* 2008; **82**:4–8.
12 Ruppert L, Apfelbacher C, Molin S *et al.* Itching in patients with chronic hand eczema: data from the CARPE registry. *Dermatology* 2014; **229**:146–53.
13 Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017; **139**:S65–76.
14 Pedersen MB, Skov L, Menne T *et al.* Gene expression time course in the human skin during elicitation of allergic contact dermatitis. *J Invest Dermatol* 2007; **127**:2585–95.
15 Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. *J Allergy Clin Immunol* 2013; **131**:300–13.
16 de Leon FJ, Berbegal L, Silvestre JF. Management of chronic hand eczema. *Actas Dermosifiliogr* 2015; **106**:533–44.
17 British Association of Dermatologists. Hand dermatitis/hand eczema. 2016. Available at: http://www.bad.org.uk/shared/getfile.ashx?id=166&itemtype=document (last accessed 29 September 2019).
18 Tanimoto A, Ogawa Y, Oki C *et al.* Pharmacological properties of JTE-052: a novel potent JAK inhibitor that suppresses various inflammatory responses *in vitro* and *in vivo*. *Inflamm Res* 2015; **64**:41–51.
19 Ruzicka T, Lynde CW, Jemec GB *et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**:808–17.
20 Held E, Skoet R, Johansen JD *et al.* The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. *Br J Dermatol* 2005; **152**:302–7.
21 Ofenloch RF, Weisshaar E, Dumke AK *et al.* The Quality of Life in Hand Eczema Questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. *Br J Dermatol* 2014; **171**:304–12.

22 Agner T, Jungersted JM, Coenraads PJ *et al.* Comparison of four methods for assessment of severity of hand eczema. *Contact Dermatitis* 2013; **69**:107–11.
23 Simpson EL, Bieber T, Guttman-Yassky E *et al.* Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**:2335–48.

Supporting Information

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

Fig S1. Mean ± SD change from baseline in Hand Eczema Severity Index by visit.

Table S1 Primary and secondary end points (multiple imputation).

Table S2 Primary and secondary end points (last observation carried forward).

Table S3 Proportion of patients with no itching, burning or pain at week 8.

Powerpoint S1 Journal Club Slide Set.