Cover Page

Study title: A phase 3 clinical trial to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adolescents 12-17 years of age with moderate to severe chronic hand eczema (DELTA TEEN)
LEO Pharma number: LP0133-1426
NCT number: NCT05355818
Date: 11-Dec-2023

Updated clinical trial protocol

LP0133-1426

A phase 3 clinical trial to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adolescents 12-17 years of age with moderate to severe chronic hand eczema
(DELTA TEEN)

Phase 3 – efficacy/safety

A randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and the applicable regulatory requirement(s).

LEO Pharma A/S	**Trial ID:**	**LP0133-1426**
	Date:	**11-Dec-2023**
	EudraCT no:	**2021-006340-27**
	Version:	**2.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within LEO Pharma Clinical Vault are legally binding equivalent of traditional handwritten signatures. The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

[redacted], MD, MSc.
Vice president, Global Clinical Development

[redacted], MSc. Eng. PhD
Biostatistics lead, Global Clinical Development

[redacted], MD
Medical lead, Global Clinical Development

[redacted] BSc. Chemistry
Clinical operations lead, Global Clinical Operations

[redacted] MD
Signatory investigator

Acknowledgement statement investigators

Each participating investigator must agree to the approved clinical trial protocol by signing a clinical trial protocol acknowledgement form or similar document.

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 1 (substantial)	11-Dec-2023	Global
Original protocol	13-Jan-2022	NA

Amendment 1 (11-Dec-2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment

This amendment is mainly written to change the statistical methodology to a Bayesian analysis where data from the adult population from recently completed pivotal phase 3 trials (LP0133-1401 and LP0133-1402) is leveraged to analyze efficacy endpoints in the adolescent population. LEO Pharma believes that, based on results from the completed clinical development program for delgocitinib, there is now sufficient understanding of CHE pathophysiology and the pharmacology of delgocitinib to support using efficacy results from the adult trials as prior information to the Bayesian analysis of the adolescent data.

In addition, a maximum 35% of subjects originating from the same country has been added to avoid a bias in the estimated efficacy and safety assessments potentially occurring due to homogeneity of the population.

Minor clarifications and editorial changes have been made throughout the document.

Section no. and title	Description of change	Brief rationale
Section 4, Schedule of trial procedures and Section 11.4.3.2, Hand Eczema Symptom Diary	Added that a minimum of 4 HESD scores per week are required to calculate the average.	For clarification.
Section 7.2, Number of subjects needed	Added that a maximum of 35% of subjects are allowed to originate from the same country.	To avoid a bias in the estimated efficacy and safety assessments potentially occurring due to homogeneity of the population.
Section 9.5, Rescue treatment	Recording of 'rescue medication' changed to 'rescue treatment.'	To accommodate that a rescue treatment can be either a rescue medication or a rescue procedure.
Sections 14.3.4 to 14.3.17	The confirmatory evidence for the trial, i.e. the testing hierarchy, has been updated to use the Bayesian analyses for the primary and key secondary endpoints.	By using the Bayesian methodology, efficacy data from adult trials will support the analysis of data in adolescents.
Section 14.3.17, Description of the Bayesian analyses and design characteristics	New section including a detailed description of the Bayesian analyses and its design characteristics	To provide an evaluation/justification for use of the Bayesian analyses of primary and key secondary endpoints.
Appendix 4, Country-specific requirements	Archiving period for essential trial documents and source documents in Canada changed from 25 to 15 years	Change in archival requirements by Health Canada.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

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List of panels

List of abbreviations and definitions of terms

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
Akaike information criterion	a mathematical method for evaluating how well a model fits the data it was generated from
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
cDLQI	Children's Dermatology Life Quality Index
CHE	Chronic hand eczema
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMO	contract manufacturing organisation
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organisation
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicine Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
ePRO	electronic patient-reported outcome
ESS	effective sample size
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HCP	healthcare professional
HECSI	Hand Eczema Severity Index

HESCI-90	at least 90% improvement in HECSI score from baseline
HESD	Hand Eczema Symptom Diary©
HIV	human immunodeficiency virus
IA	informed assent
IC	informed consent
IAF	informed assent form
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IE	intercurrent event
IEC	independent ethics committee
IGA-CHE	Investigator's Global Assessment for chronic hand eczema©
IGA-CHE TS	IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline
IgE	Immunoglobulin E
IL	Interleukin
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
JAK	Janus kinase
LP0133-1273	A randomized, vehicle-controlled, double-blind, dose-ranging phase 2b trial to investigate the efficacy, safety and PK/PD of twice-daily topical applications of delgocitinib cream 1, 3, 8, and 20 mg/g for 16 weeks in adult subjects with mild to severe chronic hand eczema
LP0133-1401	A randomized, vehicle-controlled, double-blind, phase 3 trial to investigate efficacy, safety and PD of twice-daily topical applications of delgocitinib cream 20 mg/g for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema
LP0133-1402	A randomized, vehicle-controlled, double-blind, phase 3 trial to investigate efficacy, safety and PK of twice-daily topical applications of delgocitinib cream 20 mg/g for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema
MAP	meta-analytic-predictive
MAR	missing at random
MCMC	Markov chain Monte Carlo

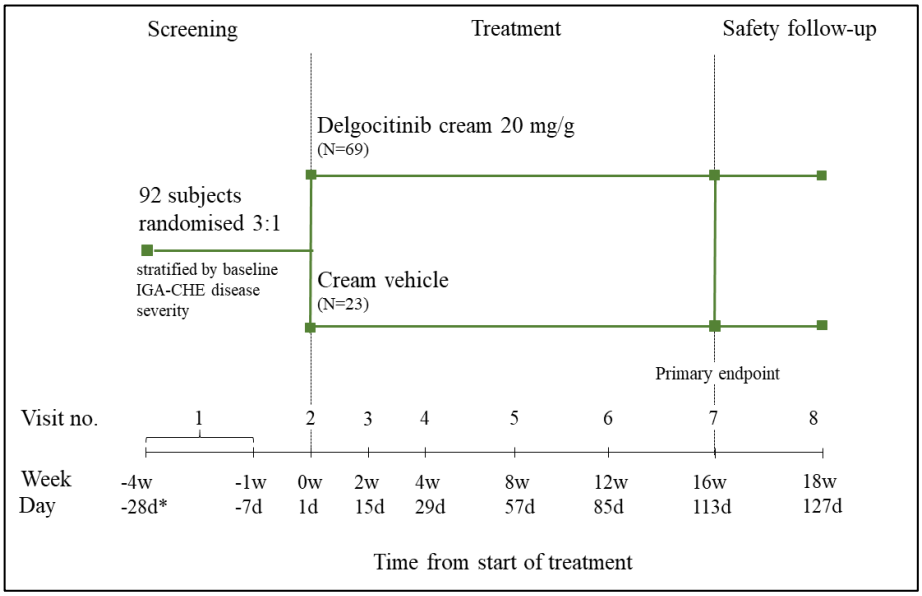
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
PD	pharmacodynamic(s)
PDE-4	phosphodiesterase-4
PGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen ultraviolet A
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
STAT	signal transducer and activator of transcription
Tau (τ)	the between-trial heterogeneity parameter
TCS	topical corticosteroid(s)
TS	treatment success
ULN	upper limit of normal
UVA1	ultraviolet A1
UVB	ultraviolet B
vs.	versus
WOCF	worst observation carried forward

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td colspan="3">LP0133-1426
2021-006340-27</td></tr>
<tr><td>Title of trial</td><td colspan="3">A phase 3 clinical trial to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in adolescents 12-17 years of age with moderate to severe chronic hand eczema</td></tr>
<tr><td>Short title of trial</td><td colspan="3">Efficacy and safety of delgocitinib cream in adolescents 12-17 years of age with moderate to severe chronic hand eczema</td></tr>
<tr><td>Main objectives, estimands, and endpoints</td><td colspan="3"><table>
<tr><th>Objectives</th><th>Estimand type and strategy</th><th>Endpoints</th></tr>
<tr><td rowspan="3">Primary objective:
To evaluate the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.</td><td>Primary:
• Composite strategy.

Supplementary:
• Treatment policy strategy.</td><td>Primary endpoint:
• IGA-CHE[1] TS at Week 16. (IGA-CHE TS refers to a score of 0 [clear] or 1 [almost clear] with a ≥2-step improvement from baseline).</td></tr>
<tr><td>Primary:
• Composite strategy.</td><td>Key secondary endpoint:
• HECSI-90[2] at Week 16.</td></tr>
<tr><td>Primary:
• Composite strategy</td><td>Secondary endpoint:
• IGA-CHE TS at Weeks 2, 4, 8, and 12.</td></tr>
<tr><td>Secondary objective:
To evaluate the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.</td><td>Primary:
• Composite strategy</td><td>• Key secondary endpoints:
• Reduction of HESD[3] itch score (weekly average) of ≥4 points from baseline at Week 16.[4]
• Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.[5]
• Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16.[6]
• Secondary endpoint:
• Change in cDLQI score from baseline to Week 16.</td></tr>
<tr><td>Secondary objective:
To evaluate the safety of twice-daily</td><td>Not applicable.</td><td>Secondary endpoint:
• Number of treatment-emergent[7] AEs</td></tr>
</table></td></tr>
</table>

	applications of delgocitinib cream 20 mg/g in the treatment of adolescents with moderate to severe CHE. | | from baseline up to Week 18. 1) The IGA-CHE is an instrument used in clinical trials to rate the severity of the subject's global CHE and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). 2) The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the 5 hand areas (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales. 3) The HESD is an eDiary in which subjects will assess the worst severity of 6 symptoms of CHE (itch, pain, cracking, redness, dryness, flaking) over the past 24 hours using an 11-point scale. 4) Among subjects with a baseline HESD itch score (weekly average) ≥4 points. 5) Among subjects with a baseline HESD pain score (weekly average) ≥4 points. 6) Among subjects with a baseline HESD score (weekly average) ≥4 points. 7) An event will be considered treatment emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP. **Abbreviations:** AE = adverse event; cDLQI = Children's Dermatology Life Quality Index; CHE = chronic hand eczema; eDiary = electronic diary; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI score from baseline; 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©; IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline; TS = treatment success.
Final collection of data for the primary endpoint	Week 16.
Trial design	The trial is a phase 3 randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial in which adolescent 12-17 years of age with moderate to severe CHE will be treated with delgocitinib cream 20 mg/g or cream vehicle for 16 weeks. The trial consists of a screening period, a treatment period, and a follow-up period. <u>Screening period</u> The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked, and wash-out of treatments listed as exclusion criteria will be initiated if applicable. The subjects will receive an eDiary device and training in completion of the eDiary.

	Treatment period At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. Eligible subjects will be randomised 3:1 to treatment with delgocitinib cream 20 mg/g or cream vehicle. The randomisation will be stratified by the baseline severity of CHE according to IGA-CHE (moderate to severe). The first application of IMP will occur at the trial site at baseline (Day 1). All subsequent IMP application will be performed by the subjects/caregivers at home twice daily for 16 weeks. During the treatment period, the subjects will be required to return to the trial site for the visits scheduled at Weeks 2, 4, 8, 12, and 16. The subject will apply the last IMP application prior to the scheduled visit at Week 16. Follow-up period Subjects will be followed-up via phone (can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety.  * For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 8.3. In view of a 28-day wash-out for some of these treatments and the allowed visit window (+3 days), the screening period can be extended up to 31 days. **Abbreviations:** d = day; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; N = number of subjects; w = week.
Main assessments	Investigator assessment of efficacy: • IGA-CHE for assessment of disease severity. • HECSI for assessment of the clinical signs of CHE. Subject assessment of efficacy and health-related quality of life; PROs • HESD. • cDLQI.

	Safety assessments: Vital signs, physical examination, ECG, laboratory testing, subject assessment of local tolerability, and AE reporting.
Main criteria for inclusion	• Age 12 to 17 years at screening and baseline. • Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. • Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 3 or 4). • Subjects who have a documented history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks). – Inadequate response is defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score of ≤2) despite treatment with a daily regimen of TCS of class III-IV (potent to very potent) for Europe and Australia and class IV-I (medium potency to very/ultra-high potency) for Canada, applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter. – Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, and significant skin atrophy as assessed by the physician.
Main criteria for exclusion	• Concurrent skin disease on the hands, e.g tinea manuum. • Clinically significant infection (e.g. impetiginised hand eczema) on the hands. • Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed). • Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline. • Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical. • Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline. • Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline. • Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline. • Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline.

	• Any disorder which is not stable and could: − Affect the safety of the subject throughout the trial. − Impede the subject's ability to complete the trial. Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders, and major physical impairment.
Investigational medicinal product	• Name of IMP: delgocitinib cream. • Active substance: delgocitinib. • Dosage form: cream. • Concentration: 20 m/g and cream vehicle. • Dose: twice-daily. • Method of administration: topical administration.
Duration of trial participation	The duration of trial participation will be approximately 22 weeks, consisting of a screening period of up to 4 weeks, a treatment period of 16 weeks, and a safety follow-up period of 2 weeks.
Number of subjects	A total of 92 subjects will be randomised 3:1 to delgocitinib cream 20 mg/g or cream vehicle.
Number and distribution of trial sites	Approximately 40 sites in Europe, Canada, and Australia.
Statistical methods	The Bayesian analyses of the primary estimand for the primary and key secondary endpoints are considered the confirmatory evidence for the trial. The treatment effect (defined as proportion of responders for delgocitinib cream 20 mg/g minus the proportion of responders for cream vehicle) for all the binary confirmatory endpoints will be evaluated based on the calculated difference of posterior distributions for delgocitinib cream 20 mg/g and cream vehicle. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥0. Hierarchical evaluation, which is applied for the Bayesian analyses, will be used to control the overall type I error at a nominal one-sided 2.5% level. This is based on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before sequential testing for additional benefits (key secondary endpoints) related to efficacy. The primary estimand will use a composite strategy to handle IEs. With a composite strategy, the occurrence of an IE is a component of the endpoint. For the primary and the key-secondary endpoints, Frequentist analyses will be conducted in addition to the Bayesian analysis. The Frequentist analyses for the primary estimand for the binary endpoints will be a logistic regression model including treatment group and baseline IGA-CHE score as factors. The logistic regression model will be applied to estimate the risk difference and associated 95% confidence interval. Other estimands for the primary and key-secondary endpoints as well as secondary endpoints will only be analysed using the Frequentist approach.

Signatory investigator	[redacted], MD. [redacted], Canada
Sponsor	LEO Pharma A/S, Industriparken 55, DK 2750 Ballerup, Denmark

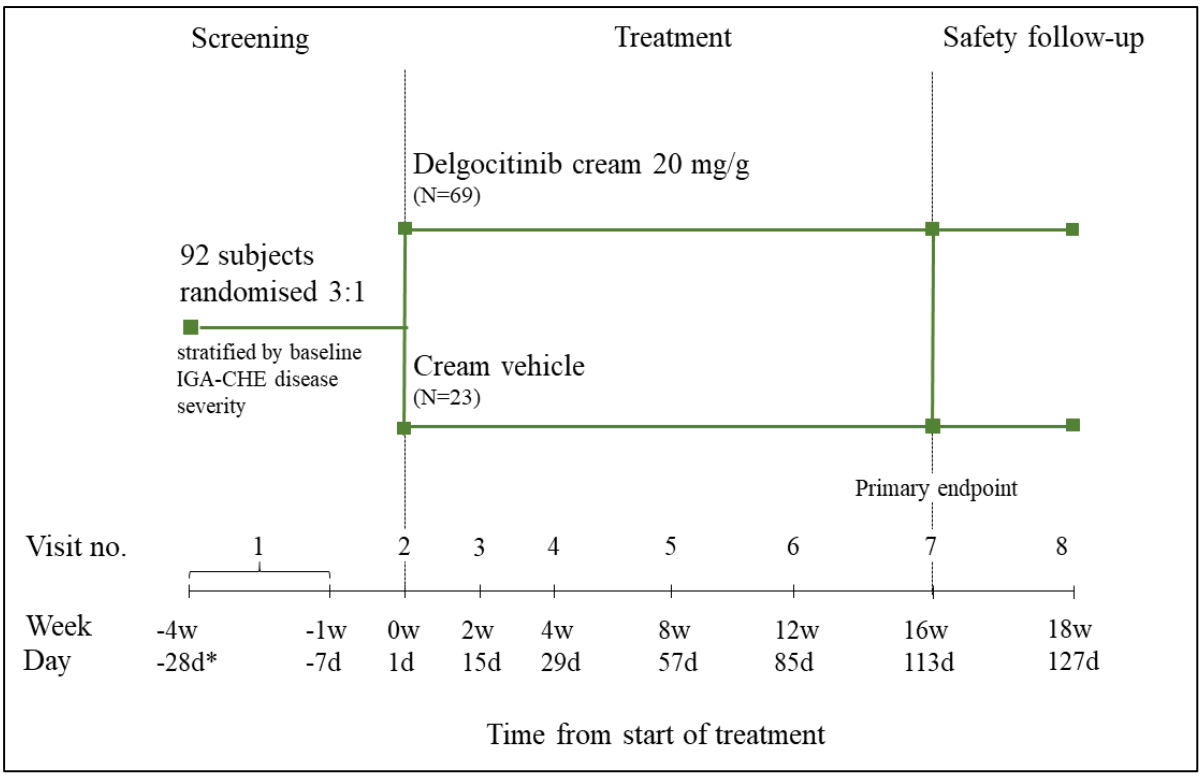
2 Trial identification

EudraCT number: 2021-006340-27.

The clinical trial protocol will be registered in local registries if required by local legislation.

3 Schematic of trial design

Panel 1: Trial design



* For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 8.3. In view of a 28-day wash-out for some of these treatments and the allowed visit window (+3 days), the screening period can be extended up to 31 days.

Abbreviations: d = day; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; N = number of subjects; w = week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening	Treatment period					End of treatment	Early termination, if applicable[1]	Primary endpoint visit at Week 16, if applicable[3]	Follow-up[2]	Unscheduled visit, if applicable[4]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**(8)**	**(9)**	**10**	
Week	**-4 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**-**	**-**	**18**	
Day	**-28[5] to -7**	**1**	**15**	**29**	**57**	**85**	**113**	**-**	**-**	**127[6]**	
Visit window (days)[7]	**+3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**±3**	
Trial population and eligibility											
IC/IA[8]	X										
Subject eligibility	X	X									
Investigator assessments at screening/baseline only											
Demographics	X										
Fitzpatrick skin type	X										
Medical history (including CHE treatment history)[9]	X										
Classification of CHE (including patch test if standard clinical practice)[10]	X										(X)
Height and weight		X					X				

	Screening	Treatment period					End of treatment	Early termination, if applicable[1]	Primary endpoint visit at Week 16, if applicable[3]	Follow-up[2]	Unscheduled visit, if applicable[4]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**(8)**	**(9)**	**10**	
Week	**-4 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**-**	**-**	**18**	
Day	**-28[5] to -7**	**1**	**15**	**29**	**57**	**85**	**113**	**-**	**-**	**127[6]**	
Visit window (days)[7]	**+3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**±3**	
Determination of treatment area(s)		X									(X)
eDiary handout/training	X										
Treatment and randomisation											
Randomisation		X									
Dispensing of IMP		X	X	X	X	X					(X)
Instruction for IMP application		X									
Application of IMP		Twice-daily									
Treatment compliance		Daily[11]					X[11]	X[11]			
Return of IMP and accountability[12]			X	X	X	X	X	X			(X)
Concomitant medication and concurrent procedures[13]	X	X	X	X	X	X	X	X	X	X	X
Investigator assessments of efficacy											
IGA-CHE	X	X	X	X	X	X	X	X	X		
HECSI		X	X	X	X	X	X	X	X		

	Screening	Treatment period					End of treatment	Early termination, if applicable[1]	Primary endpoint visit at Week 16, if applicable[3]	Follow-up[2]	Unscheduled visit, if applicable[4]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**(8)**	**(9)**	**10**	
Week	**-4 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**-**	**-**	**18**	
Day	**-28[5] to -7**	**1**	**15**	**29**	**57**	**85**	**113**	**-**	**-**	**127[6]**	
Visit window (days)[7]	**+3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**±3**	
Subject assessment of efficacy – daily											
eDiary completion: HESD[14]	Daily								X		
Subject assessments of efficacy and health-related quality of life – during trial visits											
cDLQI	X	X		X			X	X			
Subject assessment of safety											
Subject assessment of local tolerability		Weekly[15]					X	X			
Investigator assessments of safety											
Vital signs	X	X					X	X			(X)
Physical examination	X						X	X			(X)
ECG	X						X	X			(X)
Chemistry, haematology (central laboratory)[16]	X	X			X		X	X			(X)
Serology, total IgE (central laboratory)	X										
Urine pregnancy test[17]	X	X		X	X	X	X	X			(X)

	Screening	Treatment period					End of treatment	Early termination, if applicable[1]	Primary endpoint visit at Week 16, if applicable[3]	Follow-up[2]	Unscheduled visit, if applicable[4]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**(8)**	**(9)**	**10**	
Week	**-4 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**-**	**-**	**18**	
Day	**-28[5] to -7**	**1**	**15**	**29**	**57**	**85**	**113**	**-**	**-**	**127[6]**	
Visit window (days)[7]	**+3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**-**	**±3**	
Urinalysis (urine dipstick)	X						X	X			(X)
AEs	X	X	X	X	X	X	X	X	X	X	X
Other assessments											
New CHE lesions			X	X	X	X					(X)
PK blood sample[18]					X		X				
Return of eDiary (if applicable)[19]							X	X	X		
End of treatment/trial											
End-of-treatment form							X	X			
End-of-trial form[20]								X	X	X	(X)

1. Subjects who discontinue IMP prior to Week 16 or withdraw from trial will be asked to return to the trial site for an early termination visit as soon as possible after the last IMP application for completion of all trial procedures scheduled for the visit at Week 16 except PK blood sample. Subjects who discontinue IMP treatment will also be asked to return to the trial site at Week 16 (see footnote 3).
2. Subjects will be followed-up via phone (can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety.
3. Subjects who discontinue IMP treatment prior to Week 16 will be asked to return to the trial site at Week 16 (scheduled 113 days after baseline) for a primary efficacy endpoint visit.

4. Unscheduled visits may occur if subjects need to make a visit in between the scheduled visit dates e.g. due to an AE or due to a significant change in their disease state. Assessment of AEs and concomitant medication will always be performed at unscheduled visits; other assessments to be performed at unscheduled visits will be at the discretion of the investigator.
5. For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in the relevant exclusion criteria. In view of a 28-day wash-out for some of these treatments and the allowed visit window (+3 days), the screening period can be extended up to 31 days.
6. As the follow-up visit will be scheduled approximately 2 weeks after the last IMP application, the follow-up visit can occur before Week 18/Day 127 for subjects who discontinue IMP prior to Week 16.
7. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline (Day 1) (except for the follow-up visit which should be planned relative to the last application of IMP, see footnote 2).
8. The ICF(s)/IAF(s) must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and initiation of wash-out of treatments listed as exclusion criteria.
9. Medical history (including CHE treatment history) within the previous 12 months should be recorded (see Section11.2.2).
10. CHE subtype(s) will be classified according to local standard clinical practice (see Panel 9). Patch testing is recommended to be performed in accordance with the guideline (1) and if this is considered standard clinical practice at the trial site. For subjects who have had a patch test done within 3 years prior to screening, the results of the most recent patch test will be recorded in the eCRF. For subjects who have not had a patch test within 3 years prior to screening, a patch test will be done. Final reading of the patch test should preferably be performed prior to the baseline visit. If this is not possible, the patch test can be performed later but final reading must be available no later than the Week 8 visit.
11. Treatment compliance will be recorded daily by the subject in the eDiary from Day 1 onwards up to end of treatment/early termination.
12. All returned, opened IMP tubes will be weighed at the trial site.
13. Concomitant medication should be included from 3 months prior to baseline (Day 1) until end of trial (see Section 9.6).
14. Completion of the HESD eDiary will be initiated at least 1 week prior to baseline (Day 1), but preferably already from the date the subjects receive the eDiary. Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. Subjects who discontinue IMP but remain in the trial will be asked to continue completing the eDiary until the primary endpoint visit at Week 16. A minimum of 4 HESD scores per week are required throughout the trial to calculate the average. The baseline HESD weekly average will be calculated based on daily assessments during the 7 days immediately preceding the baseline visit (Day -7 to Day -1).
15. Subjects' assessment of local tolerability will be evaluated weekly by the subject in the eDiary from Day 7 onwards up to end of treatment/early termination.
16. Subjects do not have to be fasting for safety laboratory samples.
17. For female subjects of childbearing potential (as defined in the relevant inclusion criterion).
18. The PK blood samples should be taken 2-6 hours post application of IMP.
19. Not applicable at the early termination visit if the subject does not withdraw from the trial, as subjects who discontinue IMP but remain in the trial will continue completing the eDiary until the primary efficacy endpoint visit at Week 16.

20. An end-of-trial form must be completed for all screened subjects. The form will be completed at the subjects' last visit.

Abbreviations: AE = adverse event; CHE = chronic hand eczema; cDLQI = Children's Dermatology Life Quality Index: ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; HECSI = Hand Eczema Severity Index; HESD = Chronic Hand Eczema Symptom Diary©; IA = informed assent; IC = informed consent; IAF = informed assent form; ICF = informed consent form; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; IgE = immunoglobulin E; IMP = investigational medicinal product; PK = pharmacokinetic.

5 Introduction and trial rationale

5.1 Chronic hand eczema

CHE is an inflammatory skin disorder located anywhere on the hands or wrists. It is clinically characterised by erythema, infiltration, hyperkeratosis, oedema, and vesicles. Secondary signs include scaling, fissures, and erosions, and the condition may be exacerbated by bacterial infections. Important symptoms include itch and pain, and the disease is often characterised by chronic relapses and a poor prognosis.

CHE refers to hand eczema which persists for more than 3 months or returns twice or more often within 12 months (1).

Hand eczema is usually multifactorial, and it is generally agreed that no simple relationships exist between clinical patterns and aetiological diagnoses (2). Several different classifications have been proposed (1, 3, 4), and the most common subtypes of CHE are found to be irritant contact dermatitis, atopic hand eczema, and hyperkeratotic eczema (5). Other subtypes include allergic contact dermatitis, contact urticaria/protein contact dermatitis, and recurrent vesicular hand eczema (pompholyx) (1).

The reported prevalence and incidence rates of hand eczema vary considerably, depending on the methodology in the collection of data. In a review of data available from 1964 to 2007, the point prevalence of hand eczema in the general population was approximately 4%, 1 year prevalence about 10%, and life time prevalence approached 15% (6). In another study by Thyssen et al. (7), approximately 7–10% of patients with hand eczema reported symptoms ‘nearly all the time’, implying a chronic state of the disease. Based on data from 7 studies, the incidence rate of hand eczema was 5.5 cases/1000 person years with a higher median incidence rate among women (1). Several risk factors, such as pre-existing AD, female sex, wet work, and contact allergy have been identified (6, 8). The prevalence of hand eczema is different across age groups (6) with a mean/median first onset in the early or mid-20’ies (9-11). However, approximately one third of men and women report their first hand eczema before the age of 20 (12).

Only few studies have dealt with hand eczema in paediatric populations and limited information on the prevalence of hand eczema in paediatrics is available. One study (13) reported a 1-year prevalence of hand eczema of 7.3% in paediatrics aged 12-16 years and the prevalence seems to be lower in the paediatric population than in adults. This is likely to be explained by the occupational exposure in adults (13). A more recent study (14) reported a 1-year prevalence of hand eczema of 5.2% and a life-time prevalence of hand eczema of 9.7%

in adolescents at the age of 16 years. This study also confirmed a strong association between hand eczema in adolescence and AD in childhood (15). The observation that AD in childhood may lead to more persistent and chronic hand eczema in adolescence may be explained by an impairment of the skin barrier of patients affected with AD that can facilitate allergic sensitisation to several substances (15, 16).

The socioeconomic burden of CHE is significant. 5 studies in adults from 4 countries have found that total societal costs (direct and indirect) ranged between USD $1,924 and USD $8,212 (inflated to 2017 cost) per patient per year (1, 17-20).

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 cytokine responses representing Th2 pathway (IL-4, IL-13), Th22 pathway (IL-22), Th17 pathway (IL-17), Th1 pathway (interferon-γ), and the JAK/STAT pathway. As the JAK proteins are required for signalling of most cytokines, blocking of JAKs reduces cytokine signalling and thereby abrogates the vicious cycle that leads to the development of CHE (16, 21, 22).

CHE is generally difficult to treat and presents with periods of flares and periods of remissions. Long-term disease control of CHE may require reactive treatment of flares and proactive treatment for the prevention of flares.

Treatment of CHE involves different disease management strategies such as elimination of triggers, general skin care, and anti-inflammatory therapy in a step wise approach. General skin care in terms of emollients is widely used and recommended by physicians, but evidence of efficacy is sparse (1). Elimination of triggers such as allergens and irritants can be effective and a necessary prerequisite for successful therapy on a longer term, but elimination may in many circumstances be difficult to achieve. Although lacking documented treatment effect, TCS remain the mainstay of topical anti-inflammatory therapy for hand eczema. However, long-term use of TCS is restricted due to side effects such as skin atrophy and potential inhibition of skin barrier repair.

Whereas mild CHE to some extent may be managed by elimination of triggers and general skin care, management of moderate to severe CHE is more cumbersome. Alitretinoin (23) is the only approved product specifically indicated for treatment of CHE but is only indicated for severe CHE and only approved in few countries worldwide. Alitretinoin treatment has various safety limitations and is therefore only indicated for use in adults who have severe

CHE that is unresponsive to treatment with potent TCS. There are currently no available treatment options indicated specifically for CHE in adolescents.

Considering the paucity of approved therapies for the treatment of CHE in both adults and adolescents, other therapeutic options are limited to those approved for other skin diseases with an inflammatory pathophysiology. These treatments lack the clinical documentation for use in CHE and are restricted to short-term use which is not suitable in a chronic disorder characterised by relapsing features often resulting in long-term treatment exposure. As the currently available treatment options either lack documented treatment effect or are limited by restrictions of long-term use due to safety concerns (1, 24), there is a high unmet medical need for new topical treatment of moderate to severe CHE with high efficacy in combination with a favourable safety profile. Delgocitinib has the potential to address the unmet medical need associated with this serious skin disorder.

5.2 Experience with investigational medicinal product

Delgocitinib (LEO 124249) is a pan JAK inhibitor, which blocks various cytokine mediated signalling pathways and widely suppresses the activation of immune and inflammatory cells such as T cells, B cells, mast cells, and monocytes activated by these cytokines (25).

In nonclinical studies, topically administered delgocitinib suppressed skin inflammation in rat and mouse AD- and psoriasis-like models and reduced IL-31-induced scratching in mice (current investigator's brochure). Topical administration of delgocitinib was also shown to improve the impaired skin barrier function in mouse models and in human skin (26).

The efficacy and safety of delgocitinib cream in CHE has been demonstrated in in a phase 2b dose-ranging trial (LP0133-1273) with delgocitinib cream (1, 3, 8, and 20 mg/g).

In the phase 2b dose-ranging trial (LP0133-1273), delgocitinib cream (1, 3, 8, or 20 mg/g) was applied twice daily for 16 weeks in adult subjects with mild to severe CHE. For the 2 highest doses of delgocitinib cream (8 mg/g and 20 mg/g), a statistically significant treatment effect was observed in terms of IGA-CHE TS at Week 16 (defined as achieving an IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥2-step reduction from baseline) and change from baseline in HECSI score at Week 16 compared with cream vehicle. For the population selected for the present trial (subjects with moderate to severe CHE), 40.2% of subjects on delgocitinib cream 8 mg/g and 20 mg/g (pooled data based on the results from the phase 2b dose-ranging trial) achieved IGA-CHE TS at Week 16 vs. 10.5% in the cream vehicle group ($p<0.05$) (27).

For all doses, delgocitinib cream was well tolerated, and a low systemic exposure to delgocitinib was observed.

Based on currently available nonclinical and clinical data, delgocitinib cream has the potential to become a novel local-acting immunomodulatory agent for topical treatment of CHE with a favourable safety profile.

5.3 Trial rationale

The purpose of this phase 3 trial is to evaluate efficacy and safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in adolescents 12-17 years of age with moderate to severe CHE. The trial will evaluate efficacy and safety after 16 weeks of twice-daily double-blind vehicle-controlled treatment.

The strength of delgocitinib cream is selected based on results from the dose-ranging phase 2b trial LP013-1273, where delgocitinib cream 20 mg/g was shown to be effective and well-tolerated (i.e. the majority of AEs were mild or moderate and not considered related to the treatment) in adult subjects with mild to severe CHE (see Section 5.2 for details and Section 12 for the rationale for the selected dose and treatment duration).

Based on the available nonclinical and clinical data, delgocitinib cream has the potential to become an effective and user-friendly treatment for CHE and thereby improve the everyday lives of affected patients.

The primary endpoint defined for the primary estimand, addressing the primary objective, is selected to be IGA-CHE TS (an IGA-CHE score of 0 [clear] or 1 [almost clear] with a two-step improvement from baseline) at Week 16 without IEs (initiation of rescue treatment or permanent discontinuation of IMP). IGA-CHE is a static global assessment of the disease severity of CHE rated by the investigator and is a feasible instrument in clinical practice. Initiation of rescue treatment or discontinuation of IMP may occur at the discretion of the investigator or the subject. Since such IEs most often are due to lack of efficacy or treatment features considered unacceptable by the subject, a composite strategy is chosen where the IEs are part of the primary estimand for the endpoint (i.e. subjects who experience IEs are considered non-responders to treatment).

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (28) and ICH GCP (29), and in compliance with the approved protocol and applicable regulatory requirements.

The trial design chosen is regarded as scientifically justified (see Section 12.1) and adheres to ethical standards that ensure the rights, safety, and wellbeing of the trial subjects. The efficacy and safety of delgocitinib cream 20 mg/g will be evaluated in adolescents 12-17 years of age with moderate to severe CHE who may benefit from treatment in the trial. Risks associated with treatment in this clinical trial (i.e. significant adverse reactions associated with dermal or systemic exposure to delgocitinib) are considered minimal due to the low systemic exposure observed in previous clinical trials with topically applied delgocitinib (see Section 5.2).

A 3:1 randomisation is planned to increase the opportunity for subjects to receive active treatment. Trial subjects/subject's parent/guardian will be informed at the screening visit that trial procedures prior to baseline may warrant an alteration of the subject's ongoing concomitant treatments. To ensure subjects' safety, investigators are informed only to enroll subjects who are considered able to stop prohibited treatment during the screening period without experiencing intolerable worsening of CHE symptoms. To mitigate the risk for worsening of CHE signs and/or symptoms during the treatment and follow-up period, rescue treatment may be prescribed to trial subjects at the discretion of the investigator (see Section 9.5). Subjects/caregivers will be instructed to contact the investigator if subject's CHE worsens significantly.

Female subjects of childbearing potential must agree to use an acceptable birth control method to prevent pregnancy throughout the trial up until the last application of IMP.

Age-appropriate explanations will be given prior to any investigation or procedure to decrease the likelihood of anxiety and distress.

The subject's and the parent's/guardian's right to withdraw from the trial or discontinue IMP at any time is ensured. If subjects are withdrawn from the trial, they will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

In accordance with the current version of ICH GCP, qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by Global Safety at LEO Pharma and by an independent Data Monitoring Committee (see Appendix 3H) to ensure that prompt action is taken, if needed to maximise patient safety.

5.4.1 Parent/guardian

The parent/guardian is the subject's legally authorised representative(s) authorised under applicable law to grant permission on behalf of the subject for their participation in trial

activities. The subject's parent/guardian may also act as the subject's caregiver (see Section 5.4.2), but not necessarily vice versa.

5.4.2 Caregiver

By 'caregiver' is understood an individual (often a parent or other family member) who can provide general care for the paediatric subject during the trial, e.g. assist in applying trial product on the subject's skin. The caregiver will be trained via instructions for use, and such training must be documented by the trial site.

5.5 Benefit/risk assessment

There are currently no approved treatment options indicated for adolescents with moderate to severe CHE and thus there is a high unmet medical need for new therapies for these subjects.

Treatment with other therapies will be withheld from the subjects for up to 22 weeks. During the 16-week treatment period, 3 out of 4 subjects will receive active treatment with delgocitinib cream 20 mg/g which was shown to be effective in CHE in a phase 2b trial in adults (LP0133-1273, see Section 5.2). 1 out of 4 subjects will receive cream vehicle. All subjects may receive rescue treatment if required (Section 9.5), regardless of their treatment allocation.

Delgocitinib is a topically applied JAK inhibitor. Systemic JAK inhibitors are associated with potential safety concerns of serious infections, all-cause mortalities, major adverse cardiovascular events, malignancies, deep vein thrombosis and pulmonary embolisms, lipid elevations and low blood cell counts. The potential safety concerns for systemic JAK inhibitors have also been included in the label for a topically applied JAK inhibitor approved for treatment of AD in the US. These potential safety concerns are however not considered a risk for delgocitinib cream due to the low systemic exposure and the current safety profile observed in completed and ongoing trials with delgocitinib in patients with CHE.

No important identified risks of delgocitinib have been documented during the overall nonclinical and clinical development to date. Nevertheless, as observed with other topical therapies, local skin reactions, such as pain (burning and stinging), sensitisation to IMP, allergic and irritant contact dermatitis, local immunosuppression, and skin infections, may occur. A detailed overview of nonclinical and clinical data on delgocitinib is available in the current investigator's brochure.

The risk to subjects in this trial will be minimised by fulfilment of all eligibility criteria and by close clinical monitoring. To ensure the safety and wellbeing of subjects participating in

this trial, safety will be monitored during the trial, and stopping criteria have been defined (Section 10.2).

The blood sampling procedure poses the same low risk as normally associated with this procedure (i.e. infection, bleeding into the surrounding tissue, and, very rarely, inflammation of the vein, or formation of blood clots). Blood sampling will only be conducted by authorised personnel and topical anaesthesia may be applied before venipuncture to minimise pain.

Altogether, the risks associated with participating in this clinical trial are considered low and are expected to be outweighed by the benefit of a potential future treatment option for CHE.

Participation in clinical trials may currently be associated with increased risk and added challenges due to the COVID-19 pandemic caused by SARS-CoV-2. The proposed trial is not believed to put subjects with CHE at an increased risk for viral infections including SARS-CoV-2. However, a risk of exposure to infected people cannot be excluded as the trial subjects may enter public areas (e.g. commute to the trial site) and have additional human contact (e.g. with trial site staff). Appropriate risk assessments and mitigation measures must be considered to protect the subjects and trial site staff and to ensure the integrity of the trial data. It is unknown whether treatment with delgocitinib cream 20 mg/g may predispose to COVID-19, but ongoing safety monitoring will ensure that all adverse events are continuously monitored.

EMA (30), FDA (31), and national health authorities in Europe, Canada, and Australia have issued new guidelines that aim to provide recommendations for conduct of clinical trials during the COVID-19 pandemic. Given the circumstances of the potentially relapsing pandemic situation with regard to the spread of COVID-19 in the future, special attention will be paid to protecting subjects participating in the trial and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the EMA or national guidelines.

During the trial, the investigators will be trusted to take appropriate actions to ensure the safety of the individual subjects according to local authority issued preventive measures. As these can differ across countries and regions, no general instruction from the sponsor can be provided concerning subject safety and the need for postponing trial visits. In case of local authority issued preventive measures, the investigator can convert on-site visits into phone or video consultations. At phone/video visits, no investigator assessments of efficacy can be done. Safety monitoring remains an obligation to LEO Pharma, and it is considered feasible to

collect safety data such as AE data remotely (via electronic communication) where on-site visits are not possible. Other mitigating measures include collecting PRO data via a web-based solution and ensuring supply of IMP to the subjects to overcome local authority issued preventive measures due to the COVID-19 pandemic (see Appendix 7 for details).

6 Trial objectives, estimands, and endpoints

Panel 3 presents the objectives and estimands for the primary, key secondary endpoints, and secondary endpoints. Further details about the testing strategy, estimand strategy, and analysis of the primary, key secondary, and secondary endpoints are provided in Sections 14.3.4 to 14.3.10.

The secondary and exploratory objectives and endpoints are presented in Panel 4. The estimands and analyses for the exploratory efficacy endpoints are described in Section 14.3.11.

Panel 3: Objectives and estimands for primary, key secondary, and secondary endpoints

Objectives	**Statistical approach**	**Estimands**				**Endpoints**
	Bayesian/ Frequentist	Estimand type (Primary/ Supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
Primary objective: To evaluate the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Primary endpoint:** • IGA-CHE TS at Week 16. (IGA-CHE TS refers to a score of 0 [clear] or 1 [almost clear] with a ≥2-step improvement from baseline).
	Frequentist.	Supplementary.	Response achieved regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Treatment policy strategy.		
	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Key secondary endpoint:** • HECSI-90 at Week 16.
	Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Secondary endpoint:** • IGA-CHE TS at Weeks 2, 4, 8, and 12.

Objectives	Statistical approach	Estimands				Endpoints
	Bayesian/ Frequentist	Estimand type (Primary/ Supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
Secondary objectives: To evaluate the health-related quality of life of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE.	Bayesian and Frequentist.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Risk difference.	**Key secondary endpoints:** • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 16.[1] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.[2] • Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16.[3]
	Frequentist.	Primary.	Change from baseline to Week 16 without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. Composite strategy.	Difference in mean change.	**Secondary endpoint:** • Change in cDLQI score from baseline to Week 16.

1) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
3) Among subjects with a baseline HESD score (weekly average) ≥4 points.

Abbreviations: cDLQI = Children's Dermatology Life Quality Index; CHE = chronic hand eczema; HECSI = Hand Eczema Severity Index; HECSI-90 = at least 90% improvement in HECSI score from baseline; HESD = Hand Eczema Symptom Diary©; IE = intercurrent event; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline; TS = treatment success.

Panel 4: Secondary and exploratory objectives and endpoints

Objectives	Statistical approach	Endpoints
Secondary objective		**Secondary endpoint[1]**
To evaluate the safety of twice-daily applications of delgocitinib cream 20 mg/g in the treatment of adolescents with moderate to severe CHE.	Frequentist.	• Number of treatment-emergent[2] AEs from baseline up to Week 18.
Exploratory objectives		**Exploratory endpoints**
To evaluate the health-related quality of life and efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adolescents with moderate to severe CHE over time.	Frequentist.	**Efficacy** • HECSI-90 at Weeks 4 and 8. • HECSI-75 at Weeks 4, 8, and 16. • Percentage change in HECSI score from baseline to Weeks 4, 8, and 16. **Health-related quality of life and efficacy** • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[3] • Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16.4. • Change in HESD itch score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[5] • Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16.[6] • Change in HESD pain score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8.[7] • Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16.[8] • Change in HESD score (weekly average) from baseline to Weeks 2, 4, 8, and 16. • Change in cDLQI score from baseline to Week 4.

1) In addition to the secondary safety endpoint listed, clinical laboratory tests, vital signs, and physical examination at screening and end of treatment; use of rescue treatment; and subjects' assessment of local tolerability will be evaluated.
2) An event will be considered treatment emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first dose of IMP.
3) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
4) Among subjects with a baseline HESD itch score (weekly average) ≥3 points.
5) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
6) Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
7) Among subjects with a baseline HESD score (weekly average) ≥4 points.
8) Among subjects with a baseline HESD score (weekly average) ≥3 points.

Abbreviations: AE = adverse event; cDLQI = Children's Dermatology Life Quality Index; CHE = chronic hand eczema; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI score from baseline; HECSI-90 = at least 90% improvement in HECSI score from baseline; HESD = Hand Eczema Symptom Diary©.

7 Trial design

7.1 Overall trial design

This trial is a phase 3, randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial. The trial is designed to evaluate the efficacy and safety of delgocitinib cream 20 mg/g applied twice-daily for 16 weeks in adolescents 12-17 years of age with moderate to severe chronic hand eczema. The trial design is illustrated in Section 3.

Screening period (Week -4 to Week 0)

The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks (i.e. screening visit should take place between Week -4 and Week -1). For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 8.3. In view of a 28-day wash-out for some of these treatments and the allowed visit window (+3 days), the screening period can be extended up to 31 days. Only subjects who are considered able to stop prohibited treatment during the screening period without experiencing intolerable worsening of CHE signs and symptoms should be included in the trial.

At the screening visit, the subjects' eligibility to enter the trial will be checked. Trial-specific measurements will be performed as outlined in the schedule of trial procedures (Section 4). Subjects will receive an eDiary and training on how to fill it out during the screening period and the initial 16 weeks of treatment. Completion of the eDiary will be initiated preferably from the date the subjects receive the eDiary, and at the latest 1 week prior to the baseline visit on Day 1 (see Section 11.3).

The subjects' CHE subtype(s) will be classified according to standard clinical practice in Europe, Canada, and Australia. Patch testing is recommended to be performed in accordance with the guideline (1) and if this is considered standard clinical practice at the trial site. For subjects who have had a patch test performed within the last 3 years, the results from the most recent patch test can be used; otherwise, a new patch test should be performed. Final reading of the patch test should preferably be performed prior to the baseline visit. If this is not possible, the patch test can be done later but final reading must be available no later than the Week 8 visit.

Treatment period (Week 0 to 16)

At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. Eligible subjects will be randomised 3:1 to either delgocitinib cream 20 mg/g or cream vehicle.

Subjects/caregivers will apply the IMP (delgocitinib cream 20 mg/g or cream vehicle) twice-daily for 16 weeks. The first application of IMP will occur at the trial site at baseline (Day 1) after all baseline assessments have been carried out. All subsequent IMP applications will be performed by the subjects/caregivers at home.

During the 16-week treatment period, subjects will return to the trial sites for efficacy and safety assessments at the visits outlined in Section 4.

Follow-up period (Week 16-18)

Subjects will be followed-up via phone (can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Note that for subjects who discontinue treatment with IMP prematurely, the 2-week follow-up period will start at the time of last IMP application.

7.2 Number of subjects needed

92 subjects will be randomised 3:1 to delgocitinib cream 20 mg/g or cream vehicle. The statistical power considerations for this sample size are described in Section 14.3.17

This trial will be conducted at approximately 40 sites in Europe, Canada, and Australia. The targeted minimum number of randomised subjects per trial site is 4, and the maximum number of subjects per trial site is 30.

To avoid a bias in the estimated efficacy and safety assessments potentially occurring due to homogeneity of the population, a maximum 35% of subjects are allowed to originate from the same country.

7.3 End-of-trial definition

A subject is considered to have completed the trial if, regardless of permanent discontinuation of IMP, the subject attends the Week 16 visit (primary endpoint visit) and the follow-up visit.

The end of the trial overall is defined as the date of the last visit of the last subject in the trial globally.

Final collection of data for the primary endpoint occurs at Week 16. The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome will determine the timelines for trial results disclosure on ClinicalTrials.gov.

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial, and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be verified according to the inclusion and exclusion criteria specified in Panel 2. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and IRBs/IECs, as applicable.

8.2 Inclusion criteria

The subjects must fulfil all of the following criteria to be eligible for the trial:

1. Signed and dated IC has been obtained prior to any protocol-related procedures. Signed and dated IC must be provided by the subject's parent/guardian and/or by the subject in the form of a signed and dated IC/IA (as applicable according to national laws or regulation).
2. Age 12 to 17 years at screening and baseline.
3. Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
4. Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 3 or 4).
5. Subjects who have a documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks).
    - Inadequate response is defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score of ≤2) despite treatment with a daily regimen of TCS of class III-IV (potent to very potent) for Europe and Australia and class IV-I (medium potency to very/ultra-high potency) for Canada, applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter.
    - Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, and significant skin atrophy as assessed by the physician.
6. Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.

7. A woman of childbearing potential* must use an acceptable** method of birth control throughout the trial up until the last application of IMP.

   * A woman of childbearing potential is defined as a female subject aged ≥ 12 years who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

   ** Acceptable methods of birth control are listed in Appendix 8.

8.3 Exclusion criteria

Subjects are not eligible for the trial if they violate any of the following criteria:

1. Known or suspected hypersensitivity to any component(s) of the IMP (refer to Panel 9.1 for an overview of all excipients).
2. Concurrent skin diseases on the hands, e.g. tinea manuum.
3. Active AD requiring medical treatment in regions other than the hands and feet.
4. Active psoriasis on any part of the body.
5. Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
6. Clinically significant infection (e.g. impetiginised hand eczema) on the hands.
7. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed).
8. Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.
9. Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical.
10. Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.
11. Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.
12. Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline.
13. Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline.
14. Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab):
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.

- Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.

15. Treatment with any non-marketed drug substance (that is, an agent that has not yet been made available for clinical use following registration) within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.
16. Clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial.

    Clinically significant infections are defined as:

    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
17. History of any known primary immunodeficiency disorder including a positive HIV virus test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
18. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
19. History of cancer:
    - Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to screening.
    - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to screening.
20. Any disorder which is not stable and could:
    - Affect the safety of the subject throughout the trial.
    - Impede the subject's ability to complete the trial.

    Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders, and major physical impairment.
21. Any abnormal finding which may:
    - Put the subject at risk because of their participation in the trial.
    - Influence the subject's ability to complete the trial.

    The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis.
22. Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening[a].
23. ALT or AST level ≥2.0×ULN at screening.
24. Current participation in any other interventional clinical trial.

25. Previously randomised in this clinical trial.
26. Subjects or parents/guardians who have a current or recent chronic alcohol or drug abuse, or any other condition associated with poor compliance as judged by the investigator.
27. Employees of the trial site, or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
28. Subjects who are legally institutionalised.
29. Women who are pregnant or lactating.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written IC/IA is obtained. Refer to Appendix 3B for details on the IC/IA process. Once IC/IA is obtained, a subject identification number (subject ID) will be assigned by a central interactive response technology (IRT) system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the ICF/IAF was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written IC/IA to participate in the trial (the parent/guardian must have given IC, as appropriate and according to national laws and regulation) and who have been assigned a subject ID are considered 'screened' subjects.

The investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID.

In addition, the investigator will maintain a log of all consented subjects at the trial site (subject identification list). This log will include each subject's identity, date of consent, and corresponding subject ID, so that any subject may be identified if required for any reason. The log must not be copied or retained by LEO Pharma.

Screening failures

Screening failures are defined as subjects who fail to meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (32) and to respond to queries from regulatory authorities. As a minimum, the following data will be collected in the eCRF for screening failures:

- Date of IC/IA.

- Demographics (date of birth [if full date of birth is not allowed to be recorded, month and/or year (as allowed by local legislation) of birth should be collected], age, sex, ethnicity, race).
- Reason for screen failure: Failure to meet eligibility criteria (to be specified which inclusion and/or exclusion criteria have been violated).
- Date of screen failure.
- Any adverse events (AEs) and serious AEs (SAEs).

In case of any SAEs, these must be followed up as described in Section 13.7.

Re-screening of screening failures is not allowed. However, if the reason for screening failure is not due to the subject failing to meet the eligibility criteria but is administrative (e.g. delayed test results or temporary site closure due to the COVID-19 pandemic), re-screening may be permitted. This will require approval by the sponsor. Individuals who are re-screened will get a new subject ID and they (and/or their parent/guardian) will need to sign a new ICF/IAF.

9 Treatments

9.1 Trial product description

Panel 5: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size	Manufacturer responsible for batch release
Delgocitinib cream 20 mg/g	Cream	Delgocitinib, 20 mg/g	30 g	LEO Pharma A/S
Cream vehicle	Cream	Vehicle	30 g	LEO Pharma A/S

Panel 6: Excipients of delgocitinib cream 20 mg/g and cream vehicle

Excipients
Citric acid monohydrate
Sodium citrate
Benzyl alcohol
Disodium edetate
Hydrochloric acid
Purified water
Macrogol cetostearyl ether
Cetostearyl alcohol
Liquid paraffin
Butylhydroxyanisole
Sodium hydroxide (may be used to adjust pH)

9.2 Administration of investigational medicinal product

The IMP will be applied as a topical application twice daily for 16 weeks. The applications will be performed approximately 12 hours apart. Instructions for use will be provided to subjects and caregivers.

The IMP will be applied to clean, dry hands, fingers, fingertips, and wrists in a thin layer covering the affected areas. The amount of IMP to be used depends on the size of the affected area and the size of the hands, fingers, and wrists. 1 tube of 30 g delgocitinib cream is considered sufficient for treatment of the whole surface of hands, fingers, and wrists

twice daily for 2 weeks; however, a few subjects may need more (based on experience from the LP0133-1273 trial), which will be allowed at the discretion of the investigator.

The first application of IMP will occur at the trial site. Prior to the first IMP application, the subject/caregiver will be instructed on how much cream to apply and which area(s) to treat.

Only the affected area(s) on the hand(s), finger(s), fingertip(s), and wrist(s) will be treated. If new CHE lesions occur on initially untreated area(s) of the hand(s), finger(s), fingertip(s), and wrist(s), these new lesions will be treated with IMP as well. The subjects/caregivers will be advised to contact the investigator before initiating treatment of new lesions. The IMP application on initially affected areas and new lesions will continue until end of the treatment period regardless of clearance status. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16.

At the scheduled trial visits, investigator assessments of efficacy should preferably be done at least 2 hours after application of IMP and/or emollient. Recommendations for bathing, washing, and hand sanitising in relation to IMP application are provided in Section 9.6.

The IMP will be dispensed by the investigational staff at scheduled visits as outlined in Section 4. The IRT system will assign the required kit number(s) for each subject at each dispensing visit. Returned, opened IMP tubes will be weighed at the trial site to determine the amount of IMP used (see Section 9.8.3).

The investigator will use clinical judgement to treat any symptoms connected with an overdose.

9.3 Treatment assignment and blinding

9.3.1 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised at baseline (Day 1) in a 3:1 ratio to receive treatment with either delgocitinib cream 20 mg/g or cream vehicle. The randomisation will be stratified by baseline IGA-CHE score (3 or 4).

The IRT system will be used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking.

9.3.2 Blinding

This is a double-blind trial. The packaging and labelling of the IMPs will contain no evidence of their identity. It is not considered possible to differentiate between the IMPs solely by sensory evaluation.

9.3.3 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigators, HCPs who are not members of the trial staff, or authorised LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment via an unblinding function in the IRT system or unblinding CRO. Only the investigator should be unblinded and keep treatment allocation confidential. LEO Pharma must remain blinded until the end of the trial (except designated unblinded personnel).

For a requester who is not a member of the trial staff and who does not have access to the IRT system (e.g. a physician at an emergency room), a local contact number for the emergency unblinding CRO is provided on the subject card (see Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation without further medical consultation.

9.4 Background treatment

No background treatment is required in this trial. The subjects should not change their usual skin care routine for the hands regarding use of emollients. However, emollients should preferably not be used on the affected areas within 2 hours before and after application of IMP. Use of concomitant medication and concurrent procedures is further described in Section 9.6.

9.5 Rescue treatment

If medically necessary (i.e. to control intolerable CHE symptoms), rescue treatment for CHE may be prescribed to trial subjects at the discretion of the investigator. The investigators should make every attempt to conduct efficacy and safety assessments (e.g. disease severity scores, safety laboratory assessments) immediately before administering any rescue treatment. If rescue treatment is initiated, the subject must stop treatment with IMP immediately and will not be allowed to restart treatment with IMP. Subjects who discontinue IMP will be asked to attend an early termination visit, a follow-up visit (performed via phone, but can be a site visit if needed) approximately 2 weeks after the last application of IMP, and also the primary endpoint visit at Week 16 (see Section 10.3 for details).

Rescue treatment is defined as treatment (medication or procedure) initiated to treat intolerable CHE symptoms during the treatment and follow-up periods. It will be recorded in the eCRF if a treatment is given as rescue treatment.

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 3 months prior to baseline (Day 1) through safety follow-up must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name or therapy.
- Primary indication.
- Whether the medication or therapy is a rescue medication for the indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration (oral, topical, subcutaneous, transdermal, ophthalmic, intramuscular, respiratory [inhalation], intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other [if other, a specification must be provided]). For topical treatments, the dosage form (cream, lotion, ointment, foam, other) will also be recorded.
- For cutaneous treatment, it must also be recorded if the treatment is within 5 cm (appr. 2-inches) of the treatment area.

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded: procedure name (including anatomical area, if relevant), primary indication, and start and stop date (it will also be recorded if the procedure is ongoing). It will also be recorded if the procedure is inside the treatment area.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

As a rule, the subjects should not change their usual skin care routine for the hands if possible; however, emollients should preferably not be used on the treatment areas within 2 hours before and after application of IMP. Emollients are not considered concomitant medication and should not be recorded as such. The subjects will be allowed to apply other skin treatments/products to other areas of the body for other skin conditions (including foot dermatitis) during the trial, as long as this does not interfere with the trial (i.e. treatment should be applied by the caregiver or the subjects will need to wear disposable gloves, of a type recommended by the investigator, when applying treatment). If possible, normal bathing, washing of hands, and use of hand sanitisers should be avoided within 2 hours following application of IMP. Use of cosmetic body care products (e.g. body lotion, shampoo, bath oil), which are routinely used by the subjects, is allowed as per instructions for use, but the products should preferably not be changed during the trial and application should be avoided within 2 hours of IMP application or alternatively using disposable gloves.

Excessive sunlight and sunlamps should be avoided. Sunscreen products on the body and protective gloves on the hands are recommended when exposure cannot be avoided.

Assessment of the benefit-risk of the concomitant use of COVID-19 vaccine and IMP in delgocitinib trials was performed. The result of the risk assessment is that, for topical delgocitinib, COVID-19 vaccine should be recorded as a concomitant medication with no need to pause or discontinue IMP administration.

9.7 Prohibited medications and procedures

The medications and procedures listed in Panel 7 are prohibited during the trial.

Panel 7: Prohibited medications and procedures

Medication/procedure	Prohibited from	Prohibited to
Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine), retinoids (e.g. alitretinoin), or corticosteroids (steroid eyedrops[1] and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed).	28 days prior to baseline.	End of trial.
JAK inhibitors, systemic or topical (except for the IMP).	The subject's birth.	End of trial.
Tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands.	28 days prior to baseline.	End of trial.
Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands.	14 days prior to baseline.	End of trial.
Cutaneously applied antibiotics on the hands.	14 days prior to baseline.	End of trial.
Other cutaneously applied therapy on the hands (except for the IMP and the subject's own emollient).	7 days prior to baseline.	End of trial.
Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern.[2]	7 days prior to baseline.	End of trial.
Treatment with any marketed biological therapy[3] or investigational biologic agents (including immunoglobulin, anti-IgE, and anti-IL-4/IL-13 e.g. dupilumab):		
• Any cell-depleting agents including but not limited to rituximab.	6 months prior to baseline or until lymphocyte count returns to normal, whichever is longer.	End of trial.
• Other biologics.	3 months or 5 half-lives, whichever is longer, prior to baseline.	End of trial.
Any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration).	28 days prior to baseline or 5 half-lives, whichever is longer.	End of trial.

1) Note that steroid eyedrops should be recorded with the administration route 'ophthalmic', not 'cutaneous'.
2) This allows for the treatment of eczema and other skin conditions in regions other than the hands, as long as this does not interfere with the trial (i.e. treatment should be applied by the caregiver or the subject needs to use gloves when applying treatment).
3) Subjects are allowed to receive vaccines during the trial.

Abbreviations: IgE = immunoglobulin E; IL= Interleukin; IMP = investigational medicinal product; JAK = Janus kinase; PDE-4 = phosphodiesterase-4; PUVA = psoralen ultraviolet A; TCS = topical corticosteroids; UVA1 = ultraviolet A1; UVB = ultraviolet B.

As TCS only require 14 days of wash-out prior to baseline, subjects can be instructed to use TCS until 14 days before the baseline visit (Day 1) to alleviate significant worsening of their CHE.

As described in Section 9.5, prohibited medications or procedures used as rescue treatment for intolerable CHE symptoms are allowed, but subjects using rescue treatment must discontinue IMP immediately and will not be allowed to restart treatment with IMP.

All prohibited medications used must be recorded as concomitant medication.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMP will be packaged in individually numbered kits. Primary and secondary packaging materials will be individually labelled.

The labelling of IMP will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 (33), local regulations, and trial requirements. Label text will be translated into local languages as required.

The subjects will receive instructions for use which will be translated into local languages.

9.8.2 Storage of trial products

All LEO Pharma supplied IMPs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

Do not store the IMP above 25°C at the trial site. Do not freeze. The temperature during storage should be monitored by a calibrated, stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer.

A temperature log must be kept to document the storage within the right temperature interval. Storage facilities should be checked at least every working day.

Storage of IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable, and must be documented in the site signature and designation of responsibility log.

In the situations listed below, site staff should not use the affected IMPs and should immediately contact their CRA for further guidance:

- Temperature excursion upon receipt or during storage at the trial site.
- Damaged kit upon receipt.

Damaged IMP should be documented in the IRT system and reported as a product complaint as described in Section 9.10. Damaged IMP may not be used.

Further details regarding storage (including handling of temperature excursions upon receipt or during storage at the trial site) and handling of damaged IMPs (including kits damaged upon receipt) are provided in the trial product handling manual.

9.8.3 Investigational medicinal product accountability

The investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

Dispensing of IMPs may be delegated, e.g. to a hospital pharmacy, as locally applicable, and must be documented in the site signature and designation of responsibility log.

Documentation of IMP accountability must be kept for the IMPs administered to each individual subject randomised in the trial. This documentation must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMPs. IMP accountability information will be recorded in the IRT system. The IRT system will also maintain the inventory status of all IMPs at the trial site.

The subject will return used, partly used, and unused IMPs (including packaging material) at the visits specified in the schedule of trial procedures (Section 4).

Returned, opened IMP tubes will be weighed at the trial site to determine the amount of IMP used. The weight of the returned tubes will be recorded in the individual drug accountability form and in the eCRF (in grams with 1 decimal).

Returned trial product (used, partly used, and unused IMPs [including packaging material]) must be stored separately from non-allocated trial product.

Refer to the trial product handling manual for information on returning trial products.

All IMP (including packaging material) supplied by the CMO on behalf of LEO Pharma will be returned to the CMO on an ongoing basis. Prior to return, the IMPs must be fully

accounted for by the CRA with the help of site staff responsible for dispensing the IMPs. Accountability must be documented on the individual drug accountability form and in the IRT system.

9.8.4 Treatment compliance

The first application of IMP will occur at the trial site with clear instructions from the site staff on which areas of the hands, fingers, and wrists the IMP must be applied and which amount of IMP to be used per application.

Treatment days will be recorded by the subjects in the eDiary. The subject will be asked the following question once daily: 'Did you apply trial cream today?'.

The investigator (or designee) should review the compliance data entered in the eDiary before each visit. In case of non-compliance, the investigator should remind the subject of the importance of following the instructions given, including applying the IMP as prescribed.

Reporting in eCRF

At baseline, the date of first application of IMP will be recorded.

9.8.5 Trial product destruction

All IMP should be shipped to the CMO for destruction according to approved procedures and/or local requirements.

9.9 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

9.10 Reporting product complaints

Any defects or issues with the IMP must be reported to the Quality department via Global Safety at LEO Pharma on the trial-specific (paper) complaint form within 3 days of first knowledge.

Critical complaints (defined as any defect or issue that has or potentially could have a serious impact on the subject [e.g. SAE]) must be reported to the Quality department via Global Safety, within 24 hours of knowledge.

Complaint forms should contain a detailed description of the defect or issue, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the IMP will be reported by the investigator as described in Sections 13.3and 13.4.

Refer to the trial product handling manual for information on how to update the kit status in the IRT system and handling of trial product during investigation of a product compliant.

During the investigation of the product complaint, the IMP must be stored separately from other trial medication and at labelled conditions unless otherwise instructed; the trial site will be notified whether the IMP needs to be returned for further investigation or may be destroyed.

Global Safety, LEO Pharma contact information for reporting product complaints:

Fax number: +45 6910 2468

E-mail address: drug.safety@leo-pharma.com

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (prior to first dose or during the treatment period) or permanently discontinue trial treatment at any time if the subject, the parent/guardian, the investigator, or LEO Pharma considers that it is not in the subject's best interest to continue.

If a subject permanently discontinues IMP, the subject will be asked to attend an early termination visit, the primary endpoint visit, and the safety follow-up visit. If a subject or the subject's parent/guardian do not agree to attend these visits, the subject withdraws from the trial. To obtain a comprehensive efficacy evaluation of delgocitinib, it is of importance to assess the efficacy for each subject at the planned primary endpoint visit at Week 16.

Subjects who withdraw from the trial and subjects who permanently discontinue IMP will not be replaced.

If a subject withdraws from the trial, the subject or the subject's parent/guardian may request destruction of any samples taken and not tested, and the investigator must document this in the subject's medical record.

10.2 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Evidence of pregnancy.
- Initiation of rescue treatment.
- Clinically important laboratory abnormalities:
    - ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
    - Confirmed ALT and/or AST values >5×ULN (for more than 2 weeks).

It is not allowed to restart IMP treatment after discontinuation of IMP.

Data to be recorded in the eCRF

The primary reason for permanent discontinuation of IMP must be recorded in the medical records and on the end-of-treatment form in the eCRF where the following options are available:

- Adverse event.
- Death.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by subject.
- Withdrawal by parent/guardian.
- Lack of efficacy.
- Other.

If 'adverse event' is selected, the AE in question will be linked to the discontinuation of IMP. If 'other' is selected as a reason, a specification must be provided in the eCRF.

It will also be recorded whether the discontinuation of IMP was related to the COVID-19 pandemic to support the statistical analysis.

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP and return to the trial site for 2 additional visits as indicated below. See the schedule of trial procedures (Section 4) for data to be collected at these visits. The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Subjects who permanently discontinue IMP prior to Week 16 will be asked to attend the following visits:

- Early termination visit (as soon as possible after last administration of IMP).
- Safety follow-up visit (2 weeks after last administration of IMP, performed via phone, but can be a site visit if needed).
- Primary endpoint visit (16 weeks after randomisation).

Withdrawal from trial

Subjects who withdraw from the trial for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP (see the schedule of trial procedures [Section 4] for data to be collected at an early termination visit). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject or parent/guardian agrees.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 11.9.

10.4 Lost to follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and if the trial site is not able to get in contact with the subject or their parent/guardian.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The trial site must attempt to contact the subject or their parent/guardian and reschedule the missed visit as soon as possible and counsel the subject or their parent/guardian on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject or their parent/guardian. These contact attempts should be documented in the subject's medical record. Should the subject or their parent/guardian continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

11 Trial assessments and procedures

11.1 Overview

Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4. Refer to Section 7.1 for further details on the trial design.

Subjects participating in the trial will be under careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be experienced in treating CHE, have documented experience and completed training in use of the assessments required by the protocol, and must be physicians.

AEs must be assessed by a physician (Section 13.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Date of birth. If full date of birth is not allowed to be recorded, month and/or year (as allowed by local legislation) of birth should be collected together with the subject's age.
- Sex: female, male.
- Ethnic origin (self-reported by the subject): 'Hispanic or Latino', 'not Hispanic or Latino'.
- Race (self-reported by the subject): American Indian or Alaska Native, Asian – Chinese, Asian, Black or African American, native Hawaiian or other Pacific Islander, White, other (requires a specification to be provided). More than 1 race can be recorded per subject in the eCRF.
  Fitzpatrick skin type.

The subject's skin type will be recorded using the Fitzpatrick skin classification (Panel 8).

Panel 8: Fitzpatrick skin classification

Skin type	Description
I	Individuals who never tan and always sunburn if exposed to any appreciable amount of sunlight, primarily red-headed individuals and lightly complected blondes.
II	Individuals who frequently burn but are able to tan to a small degree after extended sun exposure.
III	Individuals who burn infrequently and tan readily.
IV	Individuals who rarely burn and tan heavily with moderate sun exposure, especially individuals of Asian, American Indian, Mediterranean, and Latin American descent.
V	Individuals who have dark constitutive pigmentation but become noticeably darker with sun exposure, especially lightly complected Black individuals, those of Indian descent.
VI	Individuals who have the heaviest constitutive pigmentation, especially dark-skinned Black individuals.

11.2.2 Medical history

All medical and surgical history within the previous 12 months, including concurrent/ongoing diagnoses, must be recorded. In addition, all relevant medical history including all past and current skin diseases (e.g. history of atopic diseases, foot dermatitis, and psoriasis) will be collected from the subject's date of birth. For each condition, diagnosis, or surgical procedure, the start date and stop date or whether it is ongoing will be recorded. It will be recorded if the disease is/has been present on the hands.

Relevant medical history also includes diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria (see Section 8.3).

CHE history:

- Date of diagnosis of CHE.
- Number of flares experienced during the past year.
- Results of relevant previous diagnostic procedures other than diagnostic patch testing (e.g. prick test).
- Presence of atopy.
- Presence of atopy in the subject's family history.

CHE treatment history:

- Previous treatments for CHE (name and type of treatment, rationale for discontinuation of treatment). Note that for TCS, previous treatments will only be collected for the last 12 months and the following additional details will be recorded: strength, dose, and date(s) of treatment.
- To support selection of trial subjects specifically on inclusion criterion no. 5:

- Has the subject fulfilled the trial inclusion criterion no. 5based on having inadequate response to treatment with TCS during the last 12 months? (yes, no).
- Has the subject fulfilled the trial inclusion criterion no. 5 based on TCS being medically inadvisable for the subject? (yes, no).
- If yes: reason for TCS use being medically inadvisable.

Exogenous risk factors for CHE:

- Environmental trigger factors (yes, no, unknown).
  - If yes: Occupational relevance (yes, no, unknown).
- Attended classes in school in the past year (yes/no).
  - a) If yes: Missed due to CHE (yes/no).
  - b) If yes: Number of days missed due to CHE (days).
  - c) If yes: Negative impact of CHE on school work in the past year (yes/no).
- Employed during the past year (working for pay, including part time work) (yes/no).
  - If yes: Hours working for pay per week (hours).
- Onset and worsening of CHE symptoms:
  - a) at work (yes, no, unknown).
  - b) during school (yes, no, unknown).
- Improvement of CHE symptoms:
  - a) when not at work (yes, no, unknown).
  - b) when not in school (yes, no, unknown).
- Healing of CHE on vacations (yes, no, unknown).
- Recurrence of CHE symptoms upon returning to:
  - a) work (yes, no, unknown).
  - b) school (yes, no, unknown).
- Worsening of CHE symptoms when:
  - a) not at work (yes, no, unknown).
  - b) not in school (yes, no, unknown).
- Number of daily hand washes (0-10, 11-20, >20).
- Tobacco smoking history (Never smoked, previous smoker [non-smoker for more than 1 year], current smoker [smoker for the past year]).
  - If current smoker: Type of tobacco (cigarettes, other).
  - If current smoker: Average daily number of smoked cigarettes during the past year (1-4, 5-10, 11-20, >20). For tobacco types other than cigarettes, 1 g of tobacco will be considered equal to 1 cigarette.

11.2.3 Height and weight

The subject's height (without shoes) will be measured; the subject's weight (in indoor clothing and without shoes) will be measured. Both assessments will be recorded with one decimal accuracy.

11.2.4 Determination of treatment area

Prior to the first application of IMP at baseline, the investigator will determine the treatment area(s) on the left and the right hand using the following 5 areas: fingertips, fingers (except fingertips), palm of hands, back of hands, and wrists. The treatment areas affected will be marked on a scheme showing the back and the front of the left and the right hand as from the perspective of the subject. If new CHE lesions occur, the scheme will be updated to document these.

11.2.5 Classification of CHE

The investigator will determine the CHE subtype(s) according to the definitions in Panel 9. The classification of CHE will be done according to standard clinical practice and thus may differ across regions and countries.

If standard clinical practice at the site, the classification of CHE is recommended to include diagnostic patch testing with at least a relevant baseline series including the most important contact allergens relevant to the locality of the site. For subjects who have had a diagnostic patch test performed within 3 years prior to screening, the results from the most recent patch test will be used for the classification. For subjects who have not had a patch test within 3 years prior to screening, a patch test should be performed. Final reading of the patch test should preferably be performed prior to the baseline visit. If this is not possible, the patch test can be performed later but final reading must be available no later than the Week 8 visit (Section 4). Patch testing is recommended to be performed at trial sites where the staff are experienced in performing and reading patch tests and where this is considered standard clinical practice.

The diagnostic patch test is done by applying patches containing standardised samples of allergens to the subjects' upper back. The patches will stay in place for approximately 48 hours under occlusion, after which they are removed during a visit at the trial site. The subjects will return to the trial site for assessment of patch test reactions according to standard clinical practice at the trial site.

Reporting in eCRF

The result of the diagnostic patch test (positive, negative, or inconclusive, i.e. unknown in the eCRF) will be recorded in the eCRF. If positive, it will be recorded if any of the identified allergies are considered relevant for the CHE (yes, no). The CHE subtype being the main diagnosis will be recorded, and additional CHE subtypes will be recorded if applicable.

Panel 9: Definition of subtypes of hand eczema

Subtype	Definition
Allergic contact dermatitis	Hand eczema caused by relevant contact allergens or cross-reactors identified by patch testing. Relevance means that there is a current exposure of the allergens to the hands.
Irritant contact dermatitis	Hand eczema with documented irritant exposure, which is quantitatively likely to cause dermatitis. No relevant contact allergy (no current exposure to allergens to which the patient has reacted positive in patch test).
Contact urticaria/protein contact dermatitis	Hand eczema in patients exposed to proteins (food, latex, and other biological material) with a positive prick test, or proven specific IgE, to suspected items. A considerable proportion of patients with contact urticaria will also have atopic symptoms.
Atopic hand eczema	Hand eczema in a patient with a medical history of atopic eczema, previous or current. No documented irritant exposure and/or relevant contact allergen likely to cause eczema.
Vesicular hand eczema (pompholyx)	Recurrent hand eczema with vesicular eruptions. No relevant contact allergy, no documented irritant exposure likely to cause dermatitis.
Hyperkeratotic eczema (hyperkeratotic dermatitis of the palms)	Chronic eczema with hyperkeratosis in the palms, or pulpitis, and no vesicles or pustules. No documented irritant exposure to the involved skin areas, likely to cause irritant exposure.

Reference: Adapted from (1). Note that the terms eczema and dermatitis are used interchangeably in the referenced publication.

Abbreviation: IgE = immunoglobulin E.

11.3 eDiary assessments

At the screening visit, the subjects will receive an eDiary device and eDiary training. The eDiary will be open for entry from 4 pm until midnight. The subjects must start completing the HESD in the eDiary at least 1 week prior to baseline, but preferably from the date the subjects receive the eDiary. The HESD must be completed in the eDiary every evening until Week 16, regardless of IMP discontinuation. Treatment compliance (daily) and subject assessment of local tolerability (weekly) will be evaluated by the subject in the eDiary from baseline up to end of treatment/early termination. Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial.

Handout, training, and return of the eDiary is outlined in the schedule of trial procedures (Section 4). Return of the eDiary is not applicable for subjects who discontinue IMP and attend an early termination visit, but do not withdraw from the trial. These subjects will continue completing the eDiary until the primary endpoint visit at Week 16 and will return the eDiary at that visit.

The following assessments will be completed in the eDiary by the subjects in the listed order:

- Daily: HESD (see Section 11.4.3.2).
- Daily: treatment compliance (see Section 9.8.4).
- Weekly: subject assessment of local tolerability (see Section 11.5.4).

11.4 Efficacy assessments

11.4.1 Investigator's Global Assessment for chronic hand eczema©

The IGA-CHE© (referred to in the protocol as IGA-CHE) is an instrument used in the phase 3 trials with delgocitinib cream in adults (LP0133-1401 and LP0133-1402). The IGA-CHE rates the severity of the subject's global disease and is based on a 5 point scale ranging from 0 (clear) to 4 (severe) (Panel 10). The IGA-CHE score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New lesions that occur on previously untreated areas will be included in the assessment. The IGA-CHE score will be recorded in the eCRF.

Panel 10: Investigator's Global Assessment for chronic hand eczema©

IGA-CHE severity	IGA-CHE score	Sign and intensity
Clear	0	No signs of erythema, scaling, hyperkeratosis/lichenification, vesiculation, oedema or fissures
Almost clear	1	Barely perceptible erythema No signs of scaling, hyperkeratosis/ lichenification, vesiculation, oedema or fissures
Mild	2	At least one: • Slight but definite erythema (pink) • Slight but definite scaling (mostly fine scales) • Slight but definite hyperkeratosis/lichenification and at least one: • Scattered vesicles, without erosion • Barely palpable oedema • Superficial fissures
Moderate	3	At least one: • Clearly perceptible erythema (dull red) • Clearly perceptible scaling (coarse scales) • Clearly perceptible hyperkeratosis/lichenification and at least one: • Clustered vesicles, without visible erosion • Definite oedema • Definite fissures
Severe	4	At least one: • Marked erythema (deep or bright red) • Marked and thick scaling • Marked hyperkeratosis/lichenification and at least one: • High density of vesicles with erosions • Marked oedema • One or more deep fissures

Abbreviation: IGA-CHE = Investigator's Global Assessment for chronic hand eczema©.

11.4.2 Hand Eczema Severity Index

The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, oedema) and the extent of the lesions on each of the 5 hand areas (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales (34).

For each hand region (total of both hands, e.g. 10 fingers), the investigator rates the average severity of each of the 6 clinical signs of hand eczema using a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) (Panel 11). The investigator also rates the extent of the lesions by assessing the percentage of the hand regions these lesions occupy and converting it to a score based on a 5-point scale (the area score) (Panel 11). For each of the hand regions, the region score will be calculated by adding up the severity scores for the 6 clinical signs of hand eczema and multiplying with the area score (Panel 12). The HECSI score equals the sum

of the region scores and will range from 0 (lowest possible score) to 360 (highest possible score).

The HECSI will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New CHE lesions that occur on previously untreated areas will be included in the assessment.

Panel 11: HECSI severity score scale and area score scale

Severity score (SS) scale (based on both hands)	
0	None/absent
1	Mild
2	Moderate
3	Severe

Note: half-scores (0.5, 1.5, 2.5) are not allowed.

Area score (AS) scale (based on the affected area of both hands)	
0	0% affected area
1	1% to 25% affected area
2	26% to 50% affected area
3	51% to 75% affected area
4	76% to 100% affected area

Note: half-scores (0.5, 1.5, 2.5, 3.5) are not allowed.

Panel 12: Calculation of the total HECSI score

Hand region	Erythema	Infiltration/ papulation	Vesicles	Fissures	Scaling	Oedema	Area score	Score
Fingertips	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Fingers (except fingertips)	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Palm of hands	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Back of hands	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
Wrists	(SS +	SS +	SS +	SS +	SS +	SS)	× AS	
The total HECSI score equals the sum of the 5 above region scores:								_____ (range 0-360)

Abbreviations: AS = area score; HECSI = Hand Eczema Severity Index: SS = severity score.

11.4.3 Patient-reported outcomes (efficacy)

11.4.3.1 Overview

Each subject must make individual assessments relating to their perception of their disease independently of the investigator and trial site staff.

The PRO HESD is considered an efficacy assessment in this trial. The HESD will be completed daily as an eDiary.

11.4.3.2 Hand Eczema Symptom Diary©

The HESD© (referred to in the protocol as HESD) is an instrument used in the phase 3 studies with delgocitinib cream in adults (LP0133-1401 and LP0133-1402). The HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Subjects will assess the worst severity of 6 individual signs and symptoms of CHE (itch, pain, cracking, redness, dryness, and flaking) over the past 24 hours using an 11-point numeric rating scale with anchors of 0 =‘no (symptom)’ and 10 =‘severe (symptom)’. The HESD score is derived as an average of the 6 items; a high score is indicative of severe CHE signs and/or symptoms. A minimum of 4 HESD scores per week are required throughout the trial to calculate the average. The baseline HESD weekly average will be calculated based on daily assessments during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). Subjects will complete the HESD on a daily basis in an eDiary as outlined in Section 4.

11.5 Safety assessments

11.5.1 Vital signs

Vital signs (resting blood pressure and pulse) must be assessed according to the schedule of trial procedures (Section 4). Vital signs will be measured following at least 5 minutes of rest.

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial (respecting exclusion criterion no. 21).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false and the second measurement should be recorded in the eCRF. If the third measurement confirms the first measurement (abnormal), the second measurement will be considered false and the first measurement should be recorded in the eCRF.

Reporting in eCRF

It will be recorded in the eCRF if vital signs were measured; if not, a reason should be provided. Vital signs (resting blood pressure and pulse) will be recorded in the eCRF. Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a

pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.5.2 Physical examination

A physical examination of the subject including general appearance and dermatologic examination of the skin must be performed according to the schedule of trial procedures (Section 4). Presence of foot dermatitis will be documented. The investigator should perform the same examinations as in clinical practice as a minimum.

If an abnormal physical finding at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the clinical trial (respecting exclusion criterion 21). In case only CHE is identified, the physical examination should be considered as normal.

Reporting in eCRF

It will be recorded in the eCRF if a physical examination was performed and, if applicable, the investigator's evaluation ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). If a physical examination was not performed, a reason should be given.

Clinically significant abnormal findings at the screening visit, will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.5.3 Electrocardiography

A single 12-lead resting digital ECG will be recorded after the subject has been supine for at least 5 minutes at the visits indicated in the schedule of trial procedures (Section 4).

A pre-evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. At a minimum, the date of ECG recording will be documented in the source.

The ECG data will be transferred to a central ECG service company for central evaluation. A cardiologist at the ECG service company will analyse and interpret the ECG data. The ECG service company will provide ECG evaluation reports to the trial sites.

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date. The investigator has the final decision on the clinical significance of any ECG abnormalities. The investigator will document the review of the

ECG result by signing the ECG report at the trial site or in an electronic portal hosted by the ECG vendor.

If an abnormal ECG finding at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the clinical trial (respecting exclusion criterion nr. 21.

The collection and transmission of ECG data will be described in a separate ECG manual. Test dummy transmissions will be undertaken prior to trial conduct to ensure that transmissions can be made, and that date and time settings are correctly set.

Reporting in eCRF
It will be recorded in the eCRF if an ECG was performed and, if applicable, the investigator's assessment of ECG results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). If an ECG was not performed, a reason should be given.

Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.5.4 Local tolerability

Subjects will provide an assessment of local tolerability according to the schedule of trial procedures (Section 4).

The subject will complete a weekly assessment of stinging/burning in connection with the IMP applications in the eDiary from Day 7 onwards. The subject will be asked to retrospectively assess the worst stinging/burning in connection with the IMP application during the last week. In addition, the subjects will be asked by the investigator at the end-of-treatment/early termination visit to assess the local tolerability during the last week (see Section 4). The assessment will be done using the 4-point scale shown in Panel 13.

The subject's assessment of local tolerability may be reported as an AE at the discretion of the investigator, even if the investigator does not suspect a local skin reaction related to application of IMP (reporting of e.g. pain or stinging/burning by the subject).

Panel 13: Subject assessment of local tolerability after IMP application

Grade (severity)	Stinging/burning
0 (none)	No stinging or burning.
1 (mild)	Slight warm, tingling sensation, not really bothersome.
2 (moderate)	Definitive warm, tingling sensation, that is somewhat bothersome.
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort.

Abbreviation: IMP: investigational medicinal product.

Reporting in eCRF

For the subject's assessment of local tolerability, the highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF.

11.5.5 Laboratory testing

11.5.5.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4).

The evaluations shown in Panel 14 will be performed by the central laboratory.

Panel 14: Clinical laboratory tests performed by the central laboratory

Chemistry	Haematology[2]
Liver and renal parameters:	Haemoglobin
Albumin	Thrombocytes
Creatinine	**White blood cells:**
Alkaline phosphatase	Leukocytes
Aspartate aminotransferase	Neutrophils
Alanine aminotransferase	Lymphocytes
Bilirubin[1]	Monocytes
Electrolytes and glucose:	Eosinophils
Sodium	Basophils
Potassium	**Serology[2,3]**
Glucose (non-fasting)	Hepatitis B virus surface antigen
Cholesterol	Hepatitis C virus antibody
LDL cholesterol	HIV-1 antibody
HDL cholesterol	HIV-2 antibody
Triglycerides	
Urinalysis[4]	
Protein	
Glucose	
Ketones	
Leukocytes	
Erythrocytes	
Nitrite	

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) In case additional analysis are needed to support the interpretation of the initial test results for hepatitis B, hepatitis C, or HIV, these will be performed by the central laboratory as applicable.
3) Measured at screening only.
4) Urinalysis will only be performed if considered required by the investigator based on dipstick results.

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein.

11.5.5.2 Investigator evaluation of laboratory samples

Central laboratory

Chemistry, haematology, urinalysis (if applicable), and serology will be analysed by a central laboratory which will provide results to the trial sites. Laboratory parameters will be classified as 'low', 'normal', or 'high', depending on whether the value is below, within, or above the reference range for the relevant age group, respectively. The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date the evaluation. The signed and dated version will be filed with the investigator's trial documentation. In case of clinically significant abnormal results, appropriate action, as judged by the investigator, must be taken.

If a screening laboratory result is abnormal and clinically significant, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criterion no. 21).

A laboratory manual will be provided to the trial sites specifying the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this trial.

In case of an increase of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5×ULN re-sampling for alkaline phosphatase (ALP), ALT, AST, and bilirubin (BILI) should be done immediately, without undue delay and no later than within 72 hours from initial sampling time to confirm abnormalities. Re-sampling may be relevant at lower levels at the discretion of the investigator.

Abnormal liver function tests of concurrent measurements of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×ULN and bilirubin (BILI) ≥2× ULN (Hy's law) should be reported as an SAE (see Section 13.4 for reporting of SAEs).

Tests performed at the trial site

Urine samples will be tested with a dipstick according to the schedule of trial procedures (Section 4). It will be at the investigators discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.

Female subjects of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomisation. The test will be repeated every 4 weeks as shown in the schedule of trial procedures in Section 4.

Reporting in eCRF

At each visit, the site staff will record in the eCRF if a blood sample was taken. If not, a reason should be provided. The investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

It will be recorded in the eCRF if a urine dipstick was performed and whether urinalysis is required for further assessment, as judged by the investigator. If so, a urine sample should be sent to the central laboratory. If the urine sample was not tested with a dipstick, a reason will be provided. The investigator's assessment of the urine dipstick results ('normal', 'abnormal') will be recorded in the eCRF. In case urinalysis is performed, the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

It will be recorded in the eCRF if the subject is a woman of childbearing potential and if a urine pregnancy test was performed. If not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition will be reported as an AE. Any new clinically significant sign, symptom, or illness occurring after screening will be reported as an AE in accordance with Section 13.3.

11.6 Pharmacokinetic assessments

Blood samples for PK assessments should be collected according to the schedule of trial procedures (Section 4).

Collection, handling, and shipment instructions for PK blood samples are provided in a laboratory manual.

PK samples for determination of delgocitinib concentrations will be analysed by a laboratory using a validated bioanalytical method. Details of the analytical method used will be described in the bioanalytical report.

PK samples from vehicle-treated subjects will not be analysed. Written procedures are in place to avoid unblinding of the trial and any trial subjects in relation to analysis of the PK samples.

Reporting in eCRF

It will be recorded in the eCRF if the PK sample was taken; if not, a reason will be provided. The data and time of the last IMP application prior to the PK sample must be recorded in the eCRF.

11.7 Pharmacodynamics assessments

Not applicable.

11.8 Other assessments

11.8.1 Patient-reported outcomes

Each subject must make individual assessments relating to their perception of their disease and quality of life. These are recommended to be performed independently of the investigator and trial site staff, and prior to the investigator performing his/her efficacy assessments.

The PRO HESD (eDiary) is considered an efficacy assessment in this trial and is described in Section 11.4.3.

The PRO cDLQI (completed in an electronic device by the subjects at the trial sites) is described in Section 11.8.1.1 below.

11.8.1.1 Children Dermatology Life Quality Index

The cDLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, friendships, leisure, school or holiday, adverse comments, sleep, and the treatment (35). Each item is scored on a 4-point Likert scale (0 = 'not at all⁄not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life. The cDLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.9 End of trial

End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all randomised subjects when exposed to IMP when they have had their last administration of IMP. This form will also be completed for subjects who permanently discontinue IMP prior to Week 16 and subjects who withdraw from trial, unless they were never exposed to IMP (see Section 10.3 for early termination assessments).

The date of last administration of IMP will be recorded on the end-of-treatment form. It will also be recorded if the subject completed the treatment (i.e. did not discontinue IMP prior to the Week 16 visit) and, if not, whether the reason for not completing the treatment period was related to COVID-19. If the subject did not complete the treatment, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2).

End-of-trial form

An end-of-trial form must be completed in the eCRF for all screened subjects when they have had their last visit. The following data will be collected:

- Date of last contact.
- Did the subject complete the trial? Refer to Section 7.3 for a definition of trial completion.
- Primary reason for not completing the trial based on the following categories: death, adverse event, lack of efficacy, lost to follow-up, withdrawal by subject or parent/guardian, screen failure (failure to meet eligibility criteria), or other.
- Was the reason for not completing the trial related to COVID-19?

If ‘adverse event’ is selected, the AE in question will be linked to the non-completion of the trial. If ‘other’ is selected as a reason, a specification must be provided in the eCRF. If ‘withdrawal by subject or parent/guardian’ is selected, it will be recorded whether the subject or parent/guardian withdrew informed consent or not.

11.10 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, and PK. The total volume of blood to be drawn is approximately 42 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value, but total volume of blood drawn will be kept to a minimum as required in the clinical guideline regarding investigation of medicinal products in the paediatric population (36).

11.11 Storage of biological samples

The blood and urine samples for laboratory testing (serology, haematology, chemistry, and urinalysis) are only taken to ensure and monitor subject safety during this trial and will only be stored until the analysis is completed by the central laboratory.

PK samples will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This trial is a randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial. The trial will be conducted in accordance with the protocol, ICH GCP, and applicable regulatory requirements. The trial will be conducted at multiple trial sites located in Europe, Canada, and Australia. High quality trial sites with shared standards of practice will be selected.

Subjects with CHE represent a heterogeneous population as CHE is associated with different aetiologies, morphologies, and severities. To mitigate any potential difference in trial outcome based on baseline characteristics, the trial subjects will be randomised in a stratified manner. Randomisation and blinding will minimise selection bias and minimise influence of confounding factors, and the stratification will ensure a balance of the treatment groups with respect to baseline disease severity (IGA-CHE score 3 or 4). IGA-CHE severity is viewed as a strong prognostic factor for persistent disease (37).

The vehicle control group included in the trial will serve as reference and has been added to establish the efficacy and safety of delgocitinib cream in the adolescent population in a blinded trial design. The randomisation ratio of 3:1 allows the majority of subjects to receive active treatment with delgocitinib cream 20 mg/g. Subjects who have intolerable CHE symptoms may receive rescue treatment if needed.

Topical application is considered the preferred route of administration for treatments for CHE, since CHE is a cutaneous disease characterised by local lesions affecting localised areas of the skin. Topical administration will minimise the systemic exposure to the IMP and hence reduce the risk of AEs due to systemic exposure.

The dose and treatment duration of delgocitinib cream are based on data from the phase 2b dose-ranging trial in adults with mild to severe CHE (LP0133-1273), showing a treatment effect of delgocitinib cream 8 mg/g and 20 mg/g vs. cream vehicle ($p<0.05$) according to IGA-CHE TS (IGA-CHE score of 0 [clear] or 1 [almost clear] with a ≥2 step improvement from baseline) at Week 16. Since the benefit/risk profile for both strengths was favourable, it warranted the use of delgocitinib cream 20 mg/g to ensure a dose that is sufficient for the more severe segment of subjects and likely to provide the best possible treatment effect for all subjects across the moderate to severe population.

Although the underlying pathophysiological mechanism of CHE has not been studied in adolescents, there is no reason to believe that it is different from adult pathophysiology, and as the systemic exposure with delgocitinib cream is low and has shown to be comparable between adults and adolescents with atopic dermatitis (LP0133-1181 trial, part 1), it is considered to be appropriate to extrapolate the dose for adults (20 mg/g) to adolescents.

In trial LP0133-1273, a clear treatment effect of delgocitinib cream 20 mg/g vs. cream vehicle ($p<0.05$) was demonstrated in terms of IGA-CHE TS and change from baseline in HECSI score from Week 8 in the moderate to severe population. Further, an increase in the IGA-CHE TS response rate was observed from Week 12 to Week 16 in both the delgocitinib cream 20 mg/g and cream vehicle groups, supporting a treatment duration with a primary efficacy endpoint at Week 16.

The trial population is selected to reflect the adolescent population with CHE to ensure that the trial results will be generalisable to this part of the target population. The eligibility criteria are designed to comply with standard safety precautions and to avoid confounding diagnoses (e.g. psoriasis on the hands) which may interfere with the trial results. The target population is subjects with moderate to severe CHE based on the pronounced unmet medical need for this population, whereas subjects with mild CHE are generally well managed by elimination of trigger factors, general skin care, and TCS treatment.

The trial endpoints have been selected to evaluate the efficacy and safety of delgocitinib cream in improving the severity and extent of CHE in adolescents. The trial endpoints will also address subject's perception of disease severity and the impact on health-related quality of life.

12.2 Appropriateness of assessments

The clinical efficacy of delgocitinib cream will be assessed by IGA-CHE and HECSI. The IGA-CHE is an instrument based on a modification of the Physician's Global Assessment for hand eczema (PGA) by removing the subjective subject assessments, area scoring, and by adjusting the description of score 1. The IGA-CHE is used in the phase 3 trials in adults (LP0133-1401 and LP0133-1402). HECSI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of CHE (38).

By validated PROs, this trial will also address the subjects' perception of disease severity and the impact on health-related quality of life.

Safety will be assessed using standard clinical methods such as AE reporting, ECG, vital signs, and clinical laboratory measurements.

13 Adverse events

13.1 Definition and classification of adverse events

Adverse events and serious adverse events are defined in Appendix 1.

Classification of AEs in terms of severity, causality, and outcome is defined in Appendix 2.

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject and/or the parent/guardian has signed the ICF/IAF until subject's completion of the clinical trial (as defined in Section 7.3).

AEs must be assessed by a physician.

At all visits, the subject and/or the parent/guardian will be asked a non-leading question by the investigator about AEs, e.g.: "How have you felt since I saw you last?" No specific symptoms should be asked for, except subject-reported local tolerability which will be queried specifically (see Section 11.5.4) and reported as AE(s) if deemed relevant by the investigator. If the AE qualifies as an SAE, expedited reporting is required (Section 13.4). It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

Refer to Sections 11.5.1 to 11.5.5 for principles for data entry in the eCRF.

13.3 Reporting of adverse events

AEs reported by the subject or observed by the investigator must be recorded on the AE form of the eCRF and should be described in the following manner:

The AE term must be in precise English medical terminology (that is, not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (e.g. 'allergic contact dermatitis').

For cutaneous AEs, the location must be part of the AE description and may be described as e.g. the face, scalp, back, chest, arm, leg, trunk, or limb. Additionally, the location should be described using:

- Lesional/perilesional (≤2 cm from the border of lesion(s) treated with IMP).
- Distant (>2 cm from the border of lesion(s) treated with IMP).

The duration of the AE must be reported by the start date and stop date of the event, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first administration of IMP.

AEs must be classified in terms of severity, causality, and outcome according to the definitions in Appendix 2.

Action taken with IMP: any action taken with IMP as a consequence of the AE must be recorded (dose not changed, drug withdrawn, not applicable, unknown).

Withdrawal from trial due to this AE: it must be recorded whether the AE led to withdrawal from the trial.

Other action taken: any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1. SAE criteria are also listed on the SAE form.

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form immediately, without undue delay and no later than 24 hours of obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE.

The actual reporter, if not the investigator, should also sign and date the SAE form.

The completed SAE form must be faxed or scanned and e-mailed to Global Safety at LEO Pharma using the e-mail address or fax number below:

Global Safety at LEO Pharma

E-mail address: drug.safety@leo-pharma.com

Fax number: +45 6910 2468

If relevant, the investigator will enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Safety at LEO Pharma may request further information in order to fully assess the SAE. The investigator must forward such information to LEO Pharma upon request by fax or e-mail (see contact details above).

The investigator must notify the local IRB(s)/IEC(s) of SAEs, as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported immediately without undue delay and no later than 24 hours of obtaining knowledge to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether an SAE is expected. The relevant reference safety information document for this clinical trial is:

- For the IMP, investigator's brochure Section 7.3, current edition and subsequent updates must be used.

Global Safety at LEO Pharma will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned countries.

The IRB(s)/IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned countries.

For all countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma (39), and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, and IEC(s)/IRB(s), according to the current

applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or termination, and outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Section 13.4.1.

Pregnant subjects must immediately discontinue IMP permanently (Sections 10.2 and 10.3).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 15 are considered AESIs in this trial and will require additional details to be recorded. LEO Pharma may request that the investigator forward additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting via the SAE form as described in Section 13.4 in addition to the requirements specified in Panel 15. AESIs will be part of the data that a DMC will have access to.

Panel 15: Adverse events of special interest

Adverse event of special interest	Additional data to be recorded
Eczema herpeticum	Skin findings: • Lesion type (papules, vesicles, crusts, eroded pits, other). • Disseminated / localised. • Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Present in an area with visible eczema / no visible eczema / present in areas with and without eczema. • Monomorphic / polymorphic. • Confirmation of herpes simplex virus (not confirmed, polymerase chain reaction [PCR], viral culture, Tzanck, other).

13.6.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP.

Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, incorrect route of product administration, wrong product administered, and expired product administered].

Accidental overdose or underdose where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Inappropriate schedule of product administration where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Treatment non-compliance (incl. missed doses) where no clinical consequence occurred or could have occurred should not be recorded as medication errors. See Section 9.8.4 for recording of treatment non-compliance.

Medication error must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.3 Misuse or abuse

The terms misuse and abuse are similar in that they both represent the intentional use of a drug in a way other than intended.

Misuse refers to situations where the IMP is intentionally and inappropriately used for therapeutic purposes not in accordance with the protocol.

Abuse refers to intentional use of an IMP for what could be considered desirable non-therapeutic effects (e.g. sedative, stimulant, euphoric effects).

Misuse and abuse must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of misuse or abuse must be recorded as separate AEs on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.4 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared to screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.

As CHE is a fluctuating disease, consider to only report an AE if aggravation/exacerbation exceeds normal disease fluctuation or if lesions appear in an area which is normally not affected by CHE.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP for 14 days after end of treatment, or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome.

All SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, e.g. chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilised or is chronic, should be added to the narrative description of the SAE on the SAE form.

Any pregnancy occurring during the trial will be followed up as described in Section 13.5.1.

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (40).

If the investigator becomes aware of information that requires an immediate change in a clinical trial procedure or a temporary halt of the clinical trial to protect clinical trial subjects

from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO Pharma, regulatory authorities, or IRBs/IECs.

The investigator must immediately inform LEO Pharma – by contacting the clinical project manager or medical expert – of this change in a clinical trial procedure or of the temporary halt; the investigator will provide full details of the information and the decision-making process leading to the implementation of the urgent safety measure.

LEO Pharma must act immediately upon receipt of the urgent safety measure notification in accordance with internal procedures and local legislation.

14 Statistical methods

Endpoints will be analyzed using 2 different statistical approaches: the Bayesian and the Frequentist approach.

14.1 Sample size

92 subjects will be randomised 3:1 to delgocitinib cream 20 mg/g or cream vehicle.

Based on response rates from the phase 2b dose-ranging trial in adults (LP0133-1273), a one-sided significance level at 2.5% and a sample size of 92 subjects will provide at least 80% power for detecting a treatment difference in the primary endpoint assuming an IGA-CHE TS response at Week 16 of 40.2% for delgocitinib cream 20 mg/g and 10.5% for cream vehicle.

When the response rates from LP0133-1401 and LP0133-1402 are included in the sample size calculation, this will result in a power which is lower than first anticipated.

The power obtained when using the Bayesian approach on a sample size of 92 subjects is explained in Section 14.3.17.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomised and exposed to IMP will be included in the full analysis set and will be analysed for efficacy. Exclusions from the full analysis set can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a randomised subject exposed to IMP from the full analysis set, a justification addressing ICH E9 will be given.

A safety analysis set will be defined as all subjects exposed to IMP.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the analysis set definition document before breaking the randomisation code.

14.3 Statistical analysis

14.3.1 Disposition of subjects

The reasons for permanent discontinuation of IMP or withdrawal from trial will be presented for all randomised subjects by last visit attended and by treatment group.

An overall summary of subject disposition will be presented for all randomised subjects. The disposition summary will include information on the number of randomised, exposed, included in the full analysis set, permanently discontinuing IMP, and not completing the trial by treatment group and overall.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and by treatment group. Presentations of age, sex, ethnicity, race, and baseline IGA-CHE by treatment will also be given.

Other baseline characteristics include height, weight, body mass index, region, country, Fitzpatrick skin type, CHE history, CHE treatment history, past and current medical history, and prior and concomitant medication. In addition, the baseline assessment for the primary and key secondary endpoints will be presented.

14.3.3 Exposure and treatment compliance

The duration of exposure to treatment in a specific visit interval will be calculated as the number of days from date of first application of IMP in that period to the date of last application of IMP in that period, both days included.

Exposure to treatment will be presented for the safety analysis set as days of exposure per treatment group.

The average weekly and total amount of IMP used will be presented for the safety analysis set by treatment group for each visit interval and for the total treatment period.

Treatment compliance will be presented for the safety analysis set per treatment group.

14.3.4 Testing strategy and establishing confirmatory evidence using Bayesian analysis

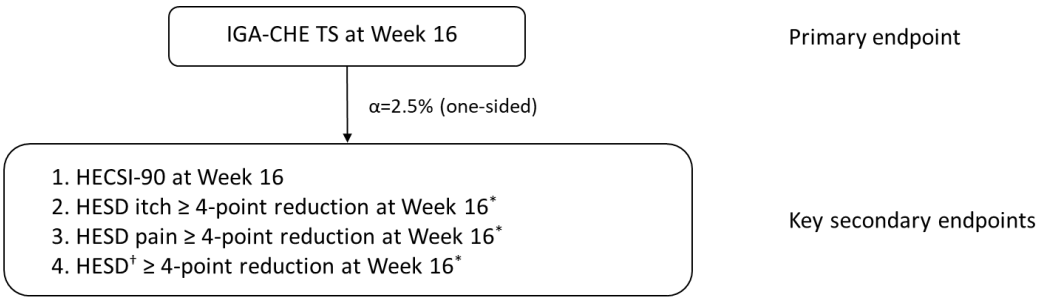
The Bayesian analyses of the primary estimand for the primary and key secondary endpoints are considered the confirmatory evidence for the trial. The treatment effect (defined as proportion of responders for delgocitinib cream 20 mg/g minus the proportion of responders for cream vehicle) for all the binary confirmatory endpoints will be evaluated based on the calculated difference of posterior distributions for delgocitinib cream 20 mg/g and cream vehicle. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥0.

Hierarchical evaluation, which is applied for the Bayesian analyses, will be used to control the overall type I error at a nominal one sided 2.5% level. This is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before sequential testing for additional benefits (key secondary endpoints) related to efficacy.

If superiority is claimed for the primary endpoint, then evaluation of the next endpoints will be done in a fixed sequential order as specified in Panel 16. This process will be repeated until no further tests are significant.

Only analyses based on the Bayesian approach will be part of the testing hierarchy.

Panel 16: Graphical display of the testing procedure for primary and secondary endpoints



* From baseline in subjects with baseline ≥ threshold of response
† Average score of 6 symptom items, i.e., itch, pain, cracking of the skin, redness, dryness, and flaking

Abbreviations: 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©; IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.

14.3.5 Estimand strategy

14.3.5.1 Overview

The analysis of endpoints related to efficacy and health-related quality of life will be based on the full analysis set.

For the analyses based on the Bayesian approach, only the primary estimand using the composite strategy will be used.

For the analyses based on the Frequentist approach, both the primary estimand (using the composite strategy) and the supplementary estimand (using the treatment policy strategy) will be considered for the primary endpoint while only the primary estimand will be considered for the key secondary endpoints (remaining binary endpoints) and other continuous endpoints.

The primary estimand will use a composite strategy to handle IEs. With a composite strategy, the occurrence of an IE is a component of the endpoint.

A supplementary estimand will use a treatment policy strategy which attempts to quantify the effect of the randomised treatment, ignoring the occurrence of IEs. Data collected for the endpoint of interest are used regardless of whether an IE occurred.

For the composite and treatment policy estimands, prespecified sensitivity analyses will be conducted to assess the robustness of the results with respect to the handling of missing data. The pre-specified sensitivity analysis will only be performed for the primary endpoint as a low IMP discontinuation rate is anticipated in the relatively small sample size (69 subjects on delgocitinib cream vs. 23 subjects on cream vehicle) and the expected low amount of the missing data. These sensitivity analyses will only be performed for the analyses based on the Frequentist approach when mentioned.

In addition, sensitivity analyses of the influence of weight on the non-informative part of the prior will be made for the Bayesian approach, see Section 14.3.17.

The following IEs are considered to affect the interpretation of the estimated treatment effects:

- **Initiation of rescue treatment:** This IE occurs when a subject initiates rescue treatment. This IE can occur at the discretion of the investigator. If rescue treatment is initiated, the subject must stop treatment with IMP immediately and will not be allowed to restart treatment with IMP (refer to Section 9.5 for details).

- **Permanent discontinuation of IMP:** This IE occurs when a subject permanently discontinues IMP. This IE can occur at the subject's own initiative, at the subject's parent's/guardian's initiative, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up.

Panel 17 presents an overview of how observed and missing data will be handled according to the IEs for the primary analysis for estimands.

Panel 17: Handling of observed and missing data according to the intercurrent events for the primary analysis estimands

		Estimand strategy for binary endpoints		Estimand strategy for continuous endpoints
Intercurrent event	**Data observed or missing**	**Composite (Primary)**	**Treatment policy (Supplementary)[1]**	**Composite (Primary)**
Initiation of rescue treatment.	Observed.	Non-response.	Value will be used as observed.	WOCF (including baseline value).
	Missing.	Non-response.	MI (MAR).	WOCF (including baseline value).
Permanent discontinuation of IMP.	Observed.	Non-response.	Value will be used as observed.	WOCF (including baseline value).
	Missing.	Non-response.	MI (MAR).	WOCF (including baseline value).
No intercurrent events.	Observed.	Value will be used as observed.	Value will be used as observed.	Value will be used as observed.
	Missing.	Non-response.	MI (MAR).	WOCF (including baseline value).

1. Supplementary estimand will only be performed for the primary endpoint.

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; MI = multiple imputation; WOCF = worst observation carried forward.

14.3.5.2 Estimands for binary endpoints

The population level summary will be the risk difference between delgocitinib cream 20 mg/g and cream vehicle.

Primary estimand: composite strategy (used for both the Bayesian approach and the Frequentist approach)

This primary estimand evaluates the treatment effect in adolescents 12-17 years of age with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP.

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be considered non-response, reflecting an assumption that initiation of rescue treatment and permanent discontinuation of IMP indicate failure of the randomised treatment.

For example, the primary composite endpoint of IGA-CHE TS at Week 16 without initiation of rescue treatment or permanent discontinuation of IMP can take the values:

- '1' (response), if the subject achieves IGA-CHE TS at Week 16 and has not initiated rescue treatment nor permanently discontinued IMP prior to Week 16.
- '0' (non-response), if the subject has not achieved IGA-CHE TS at Week 16 or has initiated rescue treatment or permanently discontinued IMP prior to Week 16.

Supplementary estimand: treatment policy strategy (used for the Frequentist approach)

This supplementary estimand evaluates the treatment effect in adolescents 12-17 years of age with moderate to severe CHE, regardless of initiation of rescue treatment or permanent discontinuation of IMP.

Observed data will be used in the analysis, including the data observed after the occurrence of IEs. To support the treatment policy strategy, subjects who experience IEs prior to Week 16 will be asked to attend the primary endpoint visit at Week 16 for collection of data.

14.3.5.3 Estimand for continuous endpoints (used for the Frequentist approach)

The population level summary will be the difference in mean change (or percentage change) from baseline to the endpoint of interest between delgocitinib cream 20 mg/g and cream vehicle.

Primary estimand: composite strategy

This primary estimand evaluates the treatment effect in adolescents with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP.

For subjects who received rescue treatment or who have permanently discontinued IMP prior to the endpoint of interest, observed data after the IEs will be considered non-response by using WOCF (including the baseline value) which is considered an extremely unfavourable value.

14.3.6 Primary endpoint analysis, Frequentist approach

The primary endpoint will be analysed as follows: Let the treatment effect be defined as μ = (delgocitinib cream 20 mg/g minus cream vehicle), then the hypothesis to be tested is:

- $H_0: \mu \leq 0 \; against \; H_a: \mu > 0.$

The hypothesis will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand.

Primary analysis for the primary estimand

Missing data for subjects who do not attend the visit for the endpoint of interest and do not experience an IE prior to this visit will be imputed as non-response.

The risk difference between the 2 treatment groups will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval based on the standardised estimator presented in Ge M et al. (41).

Sensitivity analysis for the primary estimand

Missing data at the endpoint of interest, for subjects who do not experience the IEs prior to that, will be handled as follows. For subjects in the delgocitinib cream 20 mg/g group and the cream vehicle group, missing data will be imputed from a Bernoulli distribution with parameter p value 0.1. The same parameter p will be used for both treatment groups. The parameter value 0.1 is based on the response rate of IGA-CHE TS at Week 16 in the cream vehicle group in the phase 2b trial in adults (LP0133-1273) and will introduce uncertainty due to missing data. A MI procedure (100 iterations) will be used. For each of the 100 complete datasets, the risk difference will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated. In case of no missing data this analysis will not be performed.

Supplementary analysis for primary estimand using historical and trial data

Historical data used for this analysis is from trials LP0133-1401 and LP0133-1402.

The 95% CI of interaction between treatment and trial ID for the logistic regression model, (including the factors: treatment group, baseline IGA-CHE score, trial ID [i.e., trials LP0133-1401, LP0133-1402, and LP0133-1426] and interaction between treatment and trial ID) will be presented. The 95% confidence interval is based on the standardised estimator presented by Ge M et al. (41).

Analysis for the supplementary estimand
Missing data at Week 16 will be imputed using MI (100 iterations) assuming MAR within treatment group.

For each of the 100 imputed datasets, the risk difference will be based on a logistic regression model including treatment group and baseline IGA-CHE score as factors. The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated. This will only be performed for the primary endpoint. In case of no missing data this analysis will not be performed.

Sensitivity analysis for the supplementary estimand
Missing data at Week 16 will be imputed as non-response.

The risk difference will be analysed as described above for the primary analysis for the supplementary estimand. This will only be performed for the primary endpoint. In case of no missing data this analysis will not be performed.

14.3.7 Primary endpoint analysis, Bayesian approach

The Bayesian analysis of the primary endpoint is only done for the primary estimand. The treatment effect (defined as proportion of responders for delgocitinib cream 20 mg/g minus the proportion of responders for cream vehicle) will be evaluated based on the calculated posterior distribution of the treatment difference. Delgocitinib cream 20 mg/g is considered superior to cream vehicle if the 2.5% percentile of the posterior distribution of the treatment difference is ≥ 0.

The methodology for calculating the posterior distribution and extracting the mean treatment difference along with 95% credibility intervals and the likelihood that the treatment effect is larger than 0 is described in Section 14.3.17.

14.3.8 Key secondary endpoint analysis, Frequentist approach

The key secondary endpoints will be analysed in the same manner as described in Section 14.3.6 for the primary endpoint.

Panel 18 provides an overview of which estimand (the composite strategy) and missing data strategy (non-responder imputation) is to be used in the analyses of the key secondary endpoints.

Panel 18: Overview of estimand and missing data strategy used for the key secondary endpoints

Key secondary endpoint	Type of endpoint	Primary estimand	
		Strategy to handle IEs	Handling of missing data and data collected after IE
HECSI-90 at Week 16.	Binary.	Composite.	Non-response imputation.
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 16[1].			
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16[2].			
Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[3].			

1) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) Among subjects with a baseline HESD pain score (weekly average) of ≥4 points.
3) Among subjects with a baseline HESD score (weekly average) of ≥4 points.

Abbreviations: HECSI = Hand Eczema Severity Index; HECSI-90 = at least 90% improvement in HECSI from baseline; HESD = Hand Eczema Symptom Diary©; IE = intercurrent event.

14.3.9 Key secondary endpoint analysis, Bayesian approach

The confirmatory hypotheses for key secondary endpoints (for testing hierarchy, see Panel 16) will be tested based on the primary endpoint analysis (see Section 14.3.7) for the primary estimand described in Section 14.3.5.2. Missing data will be handled in the same manner as for the Frequentist approach, see Panel 18.

14.3.10 Secondary endpoint analysis, Frequentist approach

The analysis of secondary endpoints will be based on the full analysis set.

The analysis of the binary secondary endpoints will resemble the primary analysis for the primary estimand detailed in Section 14.3.6. Continuous endpoints will be analysed as follows:

Analysis of continuous endpoints for the primary estimand

Missing data for subjects who do not attend the visit for the endpoint of interest and do not experience an IE prior to this visit will be imputed as WOCF (including the baseline value).

The change (or percentage change) from baseline to the endpoint of interest will be analysed using an ANCOVA model with effects of treatment group, baseline IGA-CHE score, and baseline value (endpoint of interest).

Panel 19 provides an overview of the estimands and missing data strategy used for the secondary endpoints.

Panel 19: Overview of estimand and missing data strategy used for secondary endpoints

Secondary endpoints	Statistical approach	Type of endpoint	Primary estimand	
			Strategy to handle IEs	Handling of missing data and data collected after IE
Efficacy				
IGA-CHE TS at Weeks 2, 4, 8, and 12.	Frequentist.	Binary.	Composite.	Non-response imputation.
Health-related quality of life and efficacy				
Change in cDLQI score from baseline to Week 16.	Frequentist.	Continuous.	Composite.	WOCF (including baseline value).

Abbreviations: cDLQI = Children's Dermatology Life Quality Index; IE = intercurrent event; IGA-CHE = Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2 step improvement from baseline; WOCF = worst observation carried forward.

14.3.11 Exploratory analyses, Frequentist approach

The analysis of exploratory endpoints will be based on the full analysis set.

The analysis of exploratory endpoints will resemble the primary analysis for the primary estimand related to a specific endpoint type: binary or continuous. For details refer to Section 14.3.6 for binary endpoints and for continuous endpoints refer to Section 14.3.8).

Panel 20 provides an overview of the estimand and missing data strategy used for the exploratory endpoints.

Panel 20: Overview of estimand and missing data strategy used for exploratory endpoints

Exploratory endpoints	Statistical approach	Type of endpoint	Primary estimand	
			Strategy to handle IEs	Handling of missing data and data collected after IE
Efficacy				
HECSI-75 at Weeks 4, 8, and 16	Frequentist	Binary	Composite	Non-response imputation
HECSI-90 at Weeks 4 and 8	Frequentist	Binary	Composite	Non-response imputation
Percentage change in HECSI score from baseline to Weeks 4, 8, and 16	Frequentist	Continuous	Composite	WOCF (including baseline value)
Health-related quality of life and efficacy				
Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 2, 4, and 8[1]	Frequentist	Binary	Composite	Non-response imputation
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 2, 4, 8, and 16[2]	Frequentist	Binary	Composite	Non-response imputation
Change in HESD itch score (weekly average) from baseline to Weeks 2, 4, 8, and 16	Frequentist	Continuous	Composite	WOCF (including baseline value)
Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 2, 4, and 8[3]	Frequentist	Binary	Composite	Non-response imputation
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 2, 4, and 8[4]	Frequentist	Binary	Composite	Non-response imputation
Change in HESD pain score (weekly average) from baseline to Weeks 2, 4, 8, and 16	Frequentist	Continuous	Composite	WOCF (including baseline value)
Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 2, 4, 8, and 16[5]	Frequentist	Binary	Composite	Non-response imputation
Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 2, 4, 8, and 16[6]	Frequentist	Binary	Composite	Non-response imputation
Change in HESD score (weekly average) from baseline to Weeks 2, 4, 8, and 16	Frequentist	Continuous	Composite	WOCF (including baseline value)
Change in cDLQI score from baseline to Week 4	Frequentist	Continuous	Composite	WOCF (including baseline value)

1) Among subjects with a baseline HESD itch score (weekly average) ≥3 points.
2) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
3) Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
4) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
5) Among subjects with a baseline HESD score (weekly average) ≥3 points.

6) Among subjects with a baseline HESD score (weekly average) ≥4 points.

Abbreviations: cDLQI = Children's Dermatology Life Quality Index; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI from baseline; HECSI-90 = at least 90% improvement in HECSI from baseline; HESD = Hand Eczema Symptom Diary©; IE = intercurrent event; WOCF = worst observation carried forward.

14.3.12 Analysis of pharmacokinetics

Delgocitinib plasma concentration will be summarised for the safety analysis set by visit using geometric mean, coefficient of variation (derived based on a log-normal distribution assumption), median, 1st quartile, 3rd quartile, minimum, and maximum values.

14.3.13 Safety analysis

The analysis of safety will be based on the safety analysis set.

14.3.13.1 Adverse events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term and primary system organ class (SOC).

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An event will be considered treatment-emergent if started after the first application of IMP or if started before the first application of IMP and worsened in severity after first application of IMP. The tabulations described in the following will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

An overall summary of the number of events and the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, premature discontinuations from IMP and/ or withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be presented.

The number of AEs and number of subjects with each type of AEs will be tabulated by treatment group.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of related AEs and the number of subjects with each type of related AE will be tabulated.

SAEs will be evaluated separately, and a narrative will be given.

AESIs will be listed by treatment group. No narratives will be given.

AEs leading to withdrawal from trial or permanent discontinuation of IMP will be listed. The detailed listing will provide an overview of the individual cases and include the age and sex of the participant, treatment received at the time of AE onset, the AE preferred and reported terms, causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE, and number of days since first and last IMP administration. No narratives will be given.

Other events (medication error, misuse, and abuse of IMP) will be tabulated and listed. No narratives will be given.

14.3.13.2 Vital signs and physical examination

The change in vital signs (resting blood pressure and pulse) from baseline to Week 16 will be summarised as mean, standard deviation (SD), median, minimum, and maximum values for each treatment group.

14.3.13.3 Clinical laboratory evaluation

For laboratory parameters, the absolute values as well as the changes from baseline will be summarised by visit for each treatment group.

A shift table will be produced for relevant parameters showing the categories at baseline against those at end of treatment (Week 16).

14.3.14 Interim analysis

No interim analysis is planned.

14.3.15 General principles

All significance tests will be one-sided using the 2.5% significance level. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified.

An observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit).

Categorical data will be summarised using the number and percentage of subjects in each category and treatment group. Continuous data will be summarised using the mean, median, SD, 1st quartile, 3rd quartile, minimum, and maximum values.

All the analyses specified in the protocol will be reviewed in relation to the blinded data actually obtained, and the statistical analysis plan will be finalised before breaking the randomisation code.

Any changes from the statistical analyses planned in this clinical trial protocol will be described and justified in a protocol amendment, the statistical analysis plan and/or in the CTR, dependent on the type of change.

14.3.16 Handling of missing values

The methods for handling of missing values in the different analyses are described in Section 14.3.5.

14.3.17 Description of the Bayesian analyses and design characteristics

The design characteristics is based on 92 randomised subjects (69 in the delgocitinib cream 20 mg/g group and 23 in the cream vehicle group).

For each endpoint, the choice of the between-trial heterogeneity parameter (τ) and the weight on the non-informative part of the prior is described. In addition, the degree of borrowing is described by the ESS and finally, the influence of the type I error and power investigated.

14.3.17.1 Overview of the Bayesian procedure

The R Bayesian evidence synthesis tools (R package RBesT) (42, 43) will be applied. The steps in the analysis are listed below.

1. **Create informative prior:** The MAP approach, using a hierarchical model for between-study heterogeneity, will be applied to derive an informative prior from historical data (the pivotal trials LP0133-1401 and LP0133-1402 and where applicable, phase 2b trial LP0133-1273) for the cream vehicle as well as for the delgocitinib cream 20 mg/g treatment group.

2. **Parametric mixture densities:** The expectation maximization algorithm is used to approximate parametric mixture densities to the MCMC samples representing the MAP prior. The mixture providing the best Akaike information criterion value is selected.

3. **Robustification of the informative prior:** The informative mixture prior is robustified by adding a non-informative component which protects against type I error inflation in presence of prior-data conflict, i.e. if the adolescent trial data strongly deviate from the historical information. The weight put on the non-informative part is prespecified for each endpoint. The influence of the weight on the ESS, the type I error and power for the trial will be described.

4. **Posterior distribution:** Once the data from the adolescent trial is unblinded, the posterior distributions for the proportion of responders for each treatment group, given the robust mixture priors, are calculated.

5. **Treatment effect evaluation:** Conclusion on treatment effect will be based on the calculated difference in the posterior distributions.

a. Statistically significant treatment effect is concluded if the probability that the difference (delgocitinib cream 20 mg/g minus cream vehicle) is larger than zero, is larger than 0.975.
b. 95% credibility interval is generated as the 2.5% and 97.5% quantiles of the difference in posterior distributions.
c. Median and mean are calculated from the difference in posterior distributions.

6. **Sensitivity/tipping point analyses (given the unblinded results):** Will be done to evaluate the influence of the prespecified selected τ and the prespecified selected weight parameter for the non-informative part of the prior.

14.3.17.2 Evaluation of design characteristics (type I error, power and bias) for the Bayesian analysis of the primary endpoint

The between-trial heterogeneity for the primary endpoint IGA-CHE TS is set to $\tau = 0.5$, the weight on the non-informative part of the prior is set to 0.2 (20%).

This ensures a type I error <5% for efficacy rates <10% (average observed efficacy rates for cream vehicle was 8.4% in the adult trials LP0133-1401 and LP0133-1402) and a high power (>75%) for efficacy levels above observed efficacy levels (average difference in adult trials is 15.9%).

In the following sections, the selection of the parameters for the primary endpoint IGA-CHE TS are justified and discussed.

Results of primary endpoint from the pivotal phase 3 trials LP0133-1401 and LP0133-1402

Results are shown in Panel 21.

Panel 21: Results of primary endpoint IGA-CHE TS, trials LP0133-1401 and LP0133-1402

	Delgocitinib cream 20 mg/g Responders (%), N	**Cream vehicle** Responders (%), N	**Average response rate for cream vehicle**	**Average response rate for delgocitinib cream 20 mg/g**	**Average treatment effect**
LP0133-1401	64 (19.7), N = 325	16 (9.9), N = 162	8.4%	24.3%	15.9%
LP0133-1402	91 (29.1), N = 313	11 (6.9), N = 159			

Abbreviations: IGA-CHE: Investigator's Global Assessment for chronic hand eczema©; N: number of subjects.
Notes: IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.

14.3.17.2.1 Creating informative prior for cream vehicle

The variability in the estimated proportion of responders is low for cream vehicle. A summary of the MAP is shown in Panel 22.

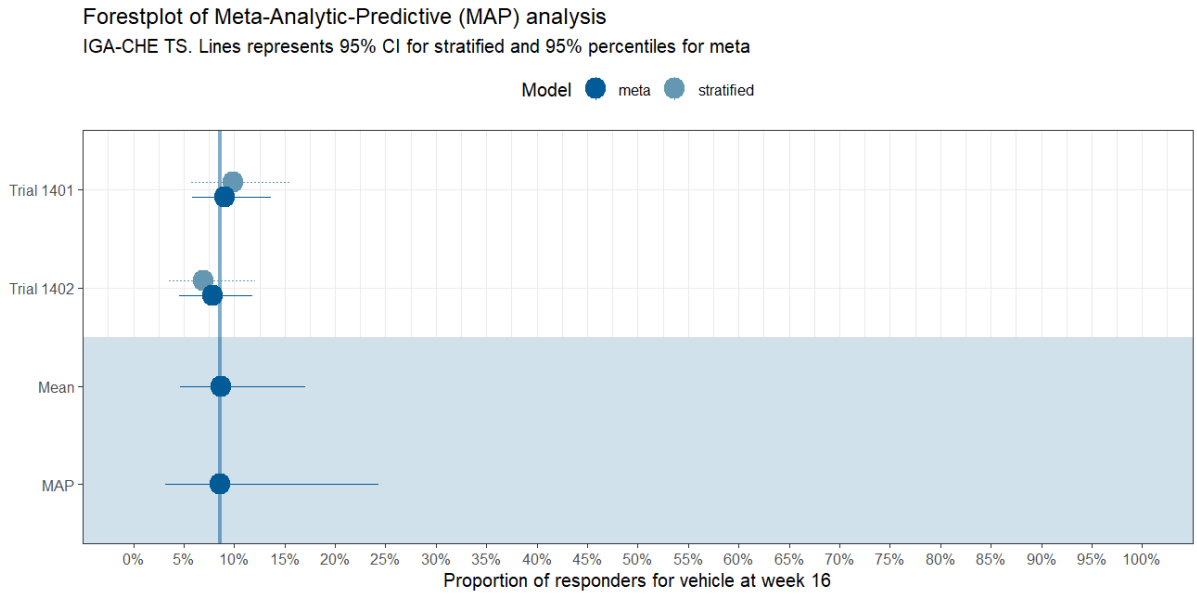
Panel 22: Summary of MAP for cream vehicle

	Mean	SD	Median	2.5% quantile	97.5% quantile
Between-trial heterogeneity of τ prediction stratum	0.33	0.26	0.27	0.01	0.97
MAP Prior MCMC sample	0.097	0.058	0.086	0.031	0.245

Abbreviations: MAP: meta-analytic-predictive, MCMC: Markov chain Monte Carlo, SD = standard deviation.

A forest plot of trials LP0133-1401 and LP0133-1402 and the MAP is shown in Panel 23.

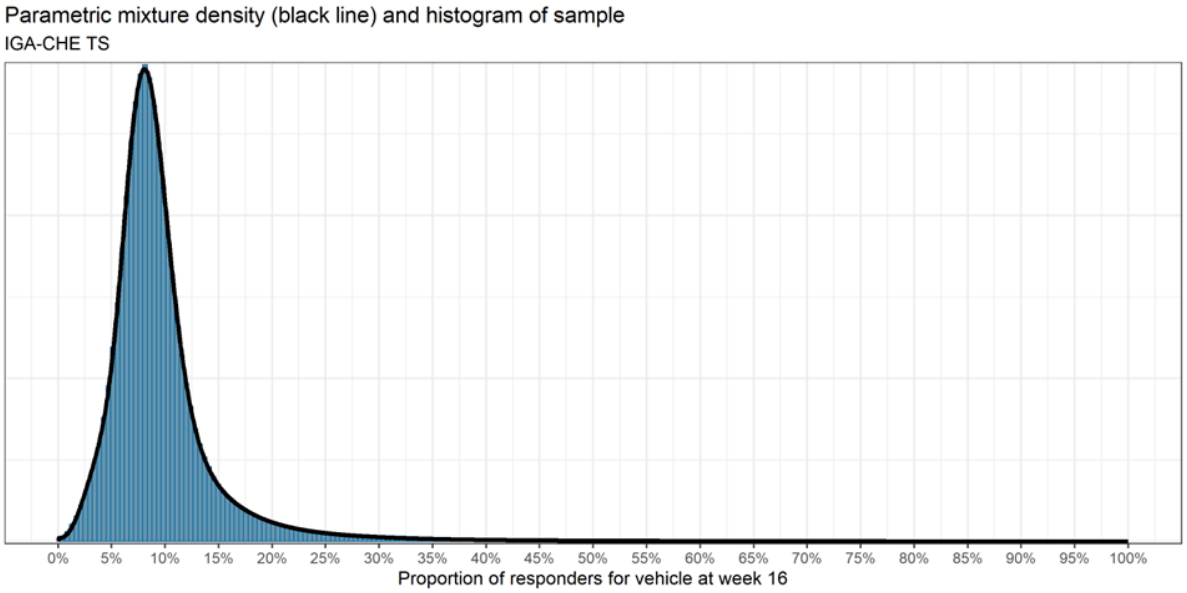
Panel 23: Forest plot for the MAP for cream vehicle



Abbreviation: MAP: meta-analytic-predictive.
Notes: Solid line represents the MAP model predictions. Dashed line represents the stratified estimates.

The MCMC samples are fitted with a mixture of beta models. A histogram of the MCMC samples and the fitted mixture model is shown in Panel 24.

Panel 24: Parametric mixture density and histogram of the MCMC samples for cream vehicle



Abbreviation: MCMC: Markov chain Monte Carlo.

Robustification of informative prior for cream vehicle

The informative prior is robustified by adding a non-informative part (here with a weight of 0.2, and thereby reducing weight for the other components with a factor of 0.8), see Panel 25.

Panel 25: Prior components for cream vehicle after robustification

Parameters	Component 1	Component 2	Component 3	Component 4	Robust
Weight in mix	0.41	0.31	0.05	0.03	0.20
a	18	4	3	1	1
b	190	39	17	3	1

a and b are parameter in the beta-distribution (Be(a,b)).

14.3.17.2.2 Creating informative prior for delgocitinib cream 20 mg/g

The variability in the estimated proportion of responders is slightly higher for delgocitinib cream 20 mg/g compared to cream vehicle. A summary of the MAP is shown in Panel 26.

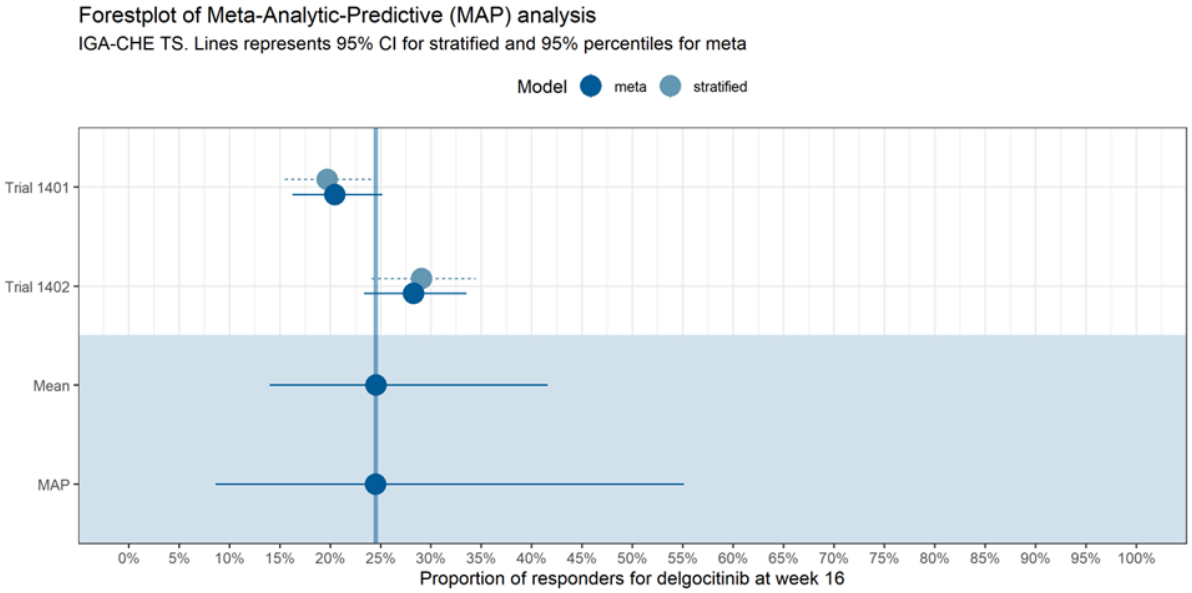
Panel 26: Summary of MAP for delgocitinib cream 20 mg/g

	Mean	SD	Median	2.5% quantile	97.5% quantile
Between-trial heterogeneity of τ prediction stratum	0.43	0.25	0.38	0.08	1.04
MAP Prior MCMC sample	0.26	0.11	0.25	0.09	0.55

Abbreviations: MAP: meta-analytic-predictive, MCMC: Markov chain Monte Carlo, SD = standard deviation.

A forest plot of trials LP0133-1401 and LP0133-1402 and the MAP is shown in Panel 27.

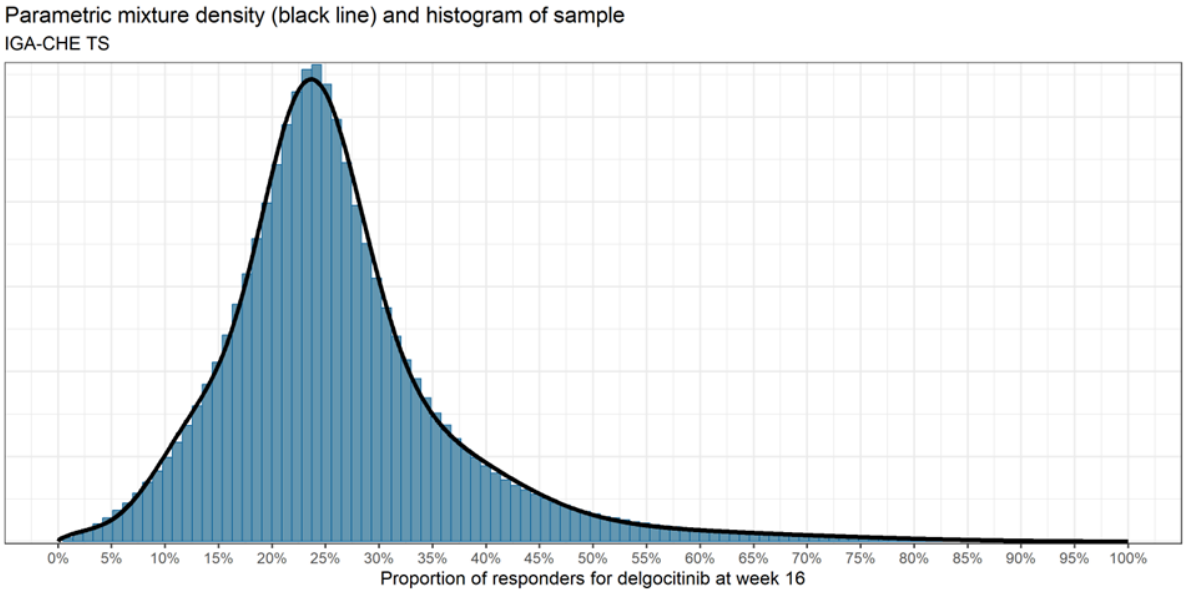
Panel 27: Forest plot for the MAP for delgocitinib cream 20 mg/g



Abbreviation: MAP: meta-analytic-predictive.
Notes: Solid line represents the MAP model predictions. Dashed line represents the stratified estimates.

The MCMC samples is fitted with a mixture of beta models. A histogram of the MCMC samples and the fitted mixture model is shown in Panel 28.

Panel 28: Parametric mixture density and histogram of the MCMC samples for delgocitinib cream 20 mg/g



Abbreviation: MCMC: Markov chain Monte Carlo.

Robustification of informative prior for delgocitinib cream 20 mg/g

The informative prior is robustified by adding a non-informative part (here with a weight of 0.2, and thereby reducing weight for the other components with a factor of 0.8), see Panel 29.

Panel 29: Prior components for delgocitinib cream 20 mg/g after robustification

Parameters	Component 1	Component 2	Component 3	Component 4	Robust
Weight in mix	0.38	0.17	0.13	0.13	0.20
a	22	7	14	2	1
b	67	32	26	3	1

a and b are parameter in the beta-distribution (Be(a,b)).

14.3.17.2.3 The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior

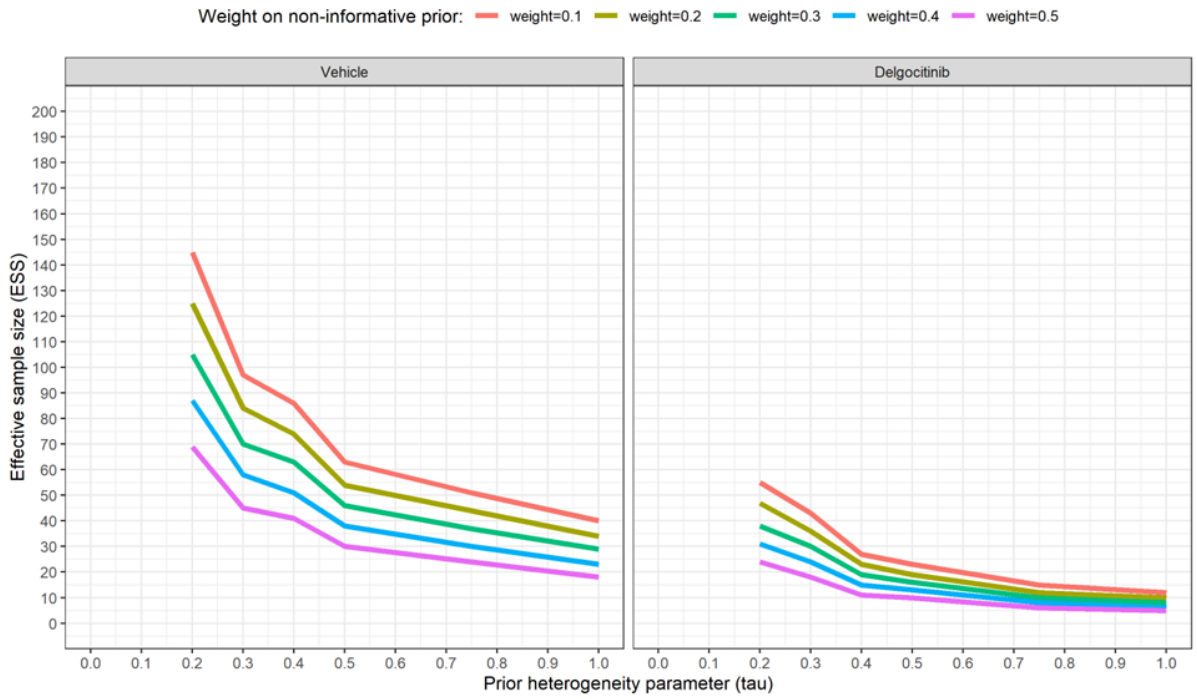
The ESS represents the additional information added to the trial data from the historical data and is a way to quantify the amount of information borrowed from the historical data. The ESS is calculated using the elir approach (44).

Adding a robust mixture component reduces the ESS of the MAP prior and thereby the degree of influence of the MAP prior in the final analysis. The ESS as a function of τ and weight on the non-informative part is shown in Panel 30. The curves level out as τ increases above 0.5.

The choice of τ = 0.5 and a weight = 0.2 corresponds to an ESS of approximately 55 for the cream vehicle arm and approximately 20 for the delgocitinib cream 20 mg/g arm. The larger

degree of borrowing of information in the cream vehicle arm as compared to the delgocitinib cream 20 mg/g arm is due to less variability in the historical data for cream vehicle.

Panel 30: The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior for the primary endpoint IGA-CHE TS at Week 16



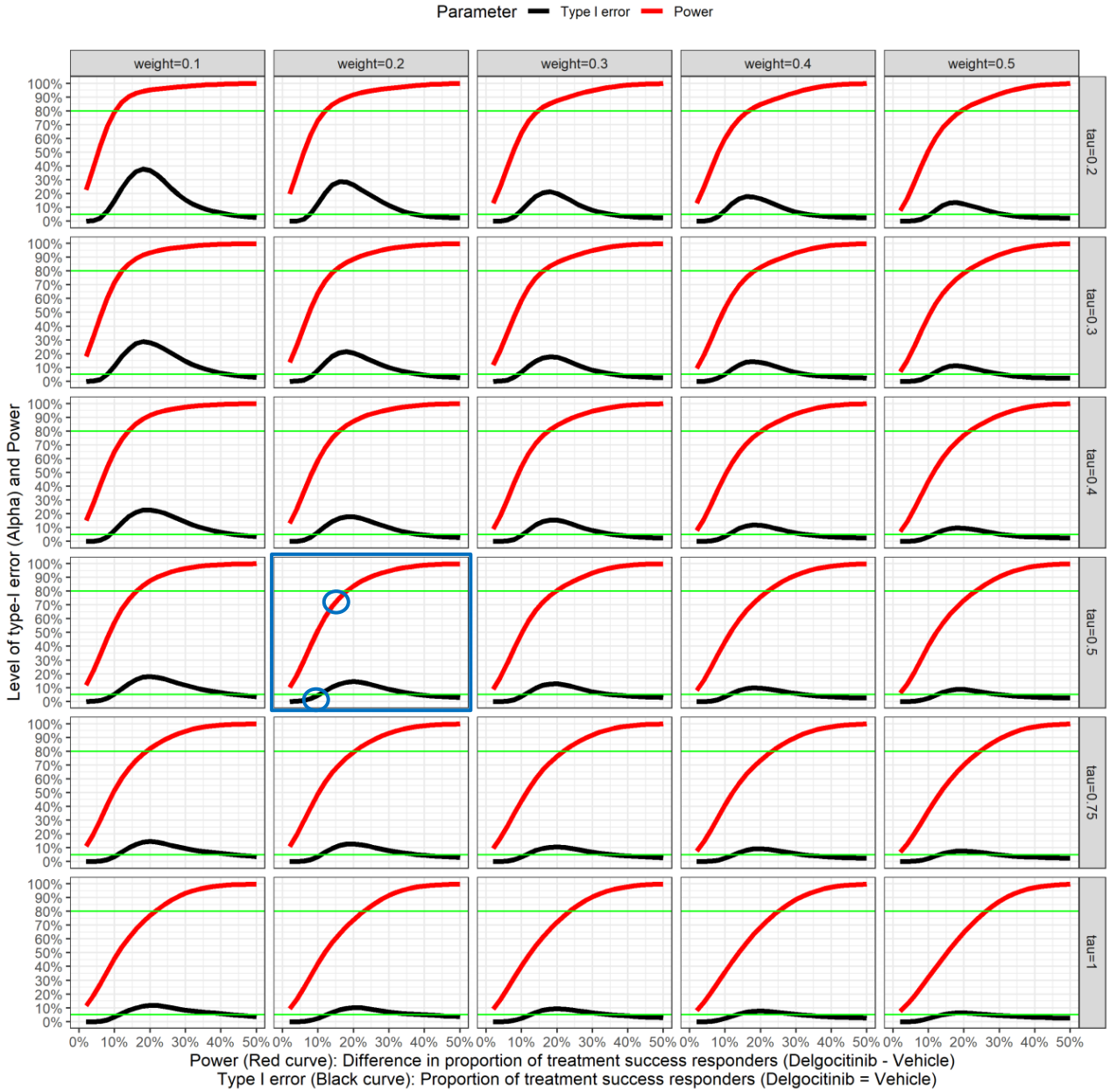
Abbreviation: ESS = effective sample size. IGA-CHE = Investigator's Global Assessment for chronic hand eczema©.

The level of type I error and power as a function of the difference in proportion of IGA-CHE TS at Week 16

The influence of τ and weight on the type I error and the power is shown in Panel 31. Overall, the type I error decreases as τ and weight increase, and it peaks just above the average observed response rate in the historical data. The power is increasing with increasing difference and lower τ and weight.

The average response rate for cream vehicle on IGA-CHE TS at Week 16 in the adult trials (LP0133-1401 and LP0133-1402) is 8.4% (Panel 21), corresponding to a type-I error of <5% (Panel 31). The average treatment effect is 15.9% (Panel 21), corresponding to a power of >75% (Panel 31).

Panel 31: The level of type I error and power as a function of the difference in proportion of IGA-CHE TS responders at Week 16, split on the level of τ and the weight put on the non-informative part of the robust prior



Abbreviations: IGA-CHE = Investigator's Global Assessment for chronic hand eczema©. IGA-CHE TS = IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2-step improvement from baseline.
Notes: tau = τ, the between-trial heterogeneity. Weigh represents the non-informative part of the prior. The blue circles mark the anticipated type I error and power with the predefined selections of τ = 0.5 and weight = 0.2, for the average response rates for cream vehicle and delgocitinib cream 20 mg/g in the adult trials.

Hypothetical sensitivity analyses of the influence of weight on the non-informative part of the prior

To illustrate the influence of a selection of $\tau = 0.5$ and weight = 0.2, 2 examples of hypothetical outcomes of the adolescent trial have been generated. In example 1, the efficacy is at par with the observed data and in example 2, the efficacy is markedly lower.

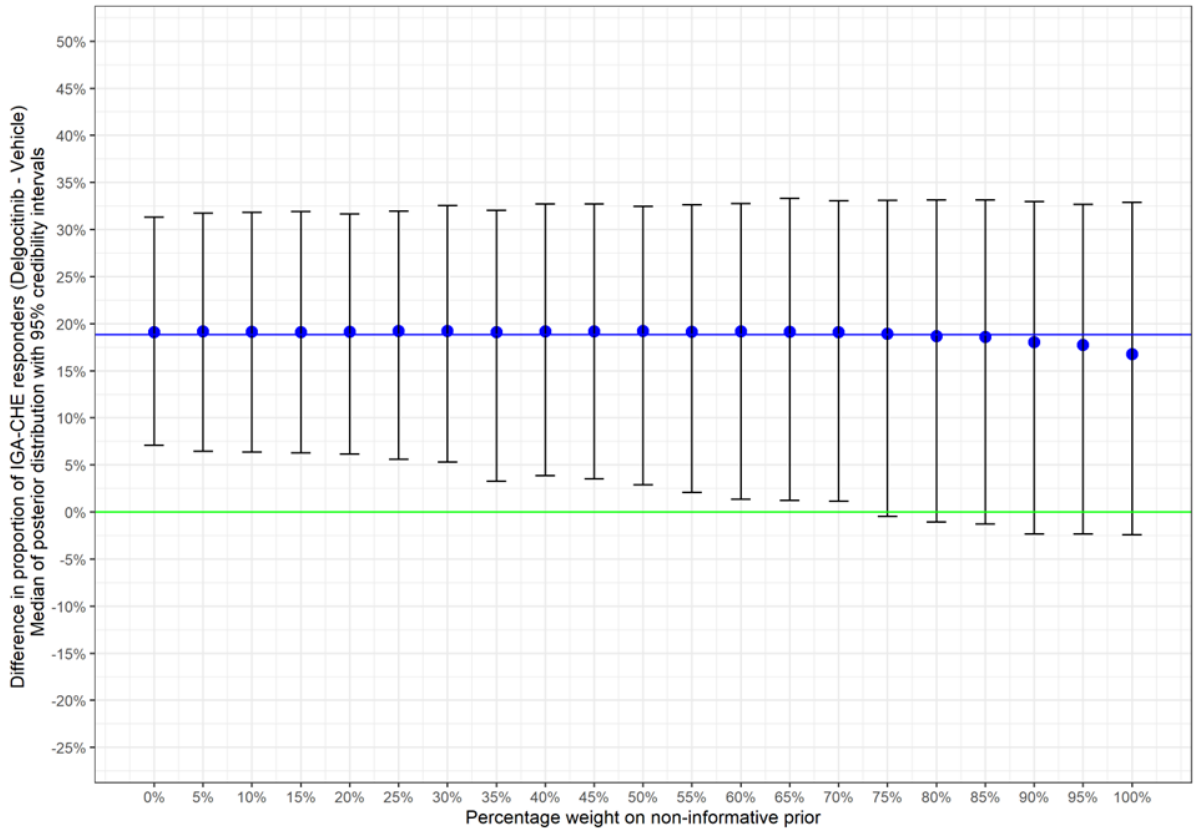
Example of sensitivity analysis if results from the adolescent trial (LP0133-1426) is close to the results from the adult trials (LP0133-1401 and LP0133-1402)

Panel 32: Hypothetical outcome in trial LP0133-1426, example 1

	Delgocitinib cream 20 mg/g	Cream vehicle	Observed difference in IGA-CHE TS response rates
Number of subjects randomized	69	23	-
Number of responders at week 16 (%)	22 (31.9%)	3 (13.3%)	18.8%

Using the hypothetical difference in response rate in trial LP0133-1426 (Panel 32), the result gets significant when the weight is below 70%, see Panel 33. This is seen as the 95% credibility bands no longer overlap 0. Very little bias is observed as the point estimate is fairly constant.

Panel 33: Sensitivity analysis of the influence of weight on non-informative part of prior when results in LP0133-1426 are close to the results in the adult trials (LP0133-1401 and LP0133-1402)



Abbreviation: IGA-CHE = Investigator's Global Assessment for chronic hand eczema©.

Example of sensitivity analysis if results from the adolescent trial (LP0133-1426) differ from the results from adult trials (LP0133-1401 and LP0133-1402)

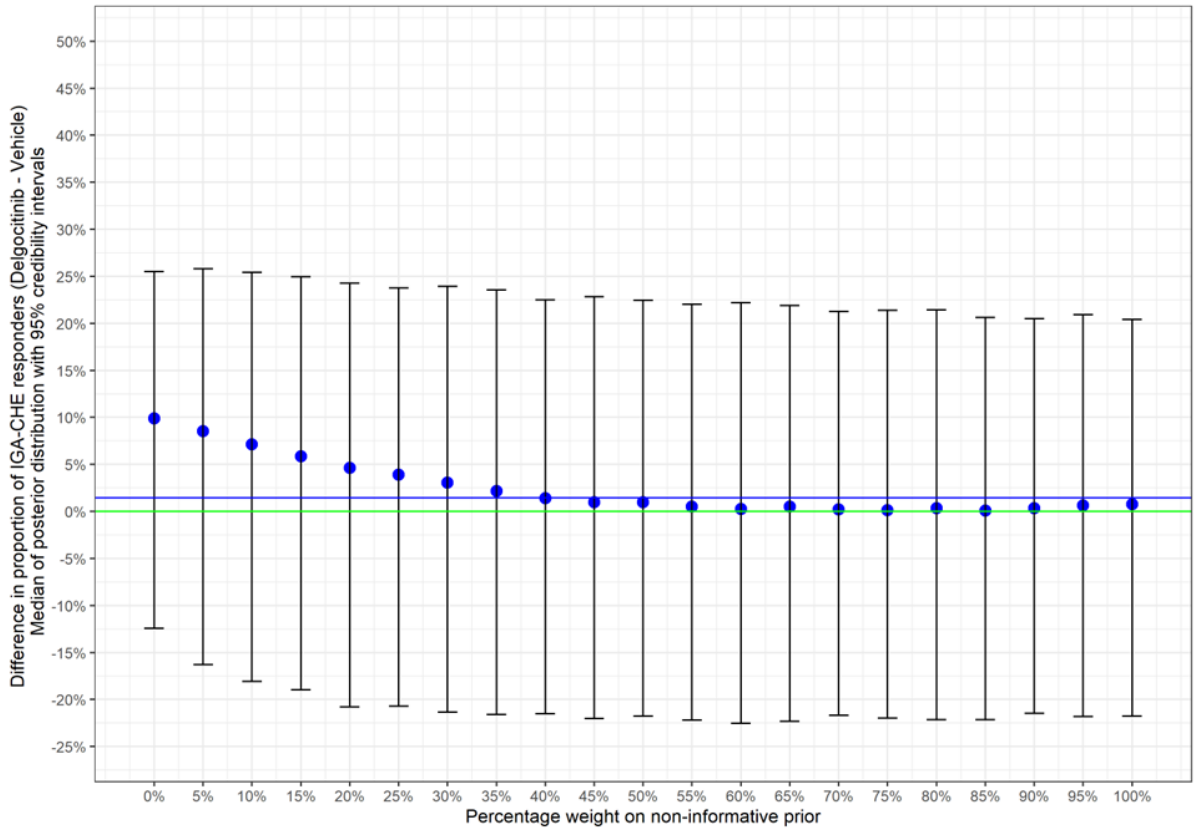
Panel 34: Hypothetical outcome in trial LP0133-1426, example 2

	Delgocitinib cream 20 mg/g	Cream vehicle	Observed difference in IGA-CHE TS response rates
Number of subjects randomized	69	23	-
Number of responders at week 16 (%)	22 (31.9%)	7 (30.4%)	1.4%

Panel 34 presents example where the hypothetical difference in response rates in trial LP0133-1426 is markedly lower than the observed data.

As shown in Panel 35, the results remain non-significant when the results are far from the observed data. The bias increases when the weight decreases below 20%.

Panel 35: Sensitivity analysis when results from the adolescent's trial differ from the results from the adult trials



Abbreviation: IGA-CHE = Investigator's Global Assessment for chronic hand eczema©.

Conclusion on hypothetical examples

The hypothetical examples illustrate that if the treatment difference between delgocitinib cream 20 mg/g and cream vehicle in trial LP0133-1426 is similar to the treatment difference in the adult trials (example 1), then the Bayesian analysis gives a confirmatory result for IGA-CHE TS. If the treatment difference is markedly lower in trial LP0133-1426 than in adult trials (example 2), then the Bayesian analysis will not confirm a difference between delgocitinib cream 20 mg/g and cream vehicle in IGA-CHE TS.

14.3.17.3 Evaluation of design characteristics (type I error and power) for the Bayesian analysis of key secondary endpoints

The between-trial heterogeneity (τ) and the weight on the non-informative part of the prior for key secondary endpoints are justified and discussed in the following. For all key secondary endpoints, $\tau = 0.5$ and weight = 0.2.

14.3.17.3.1 HECSI-90

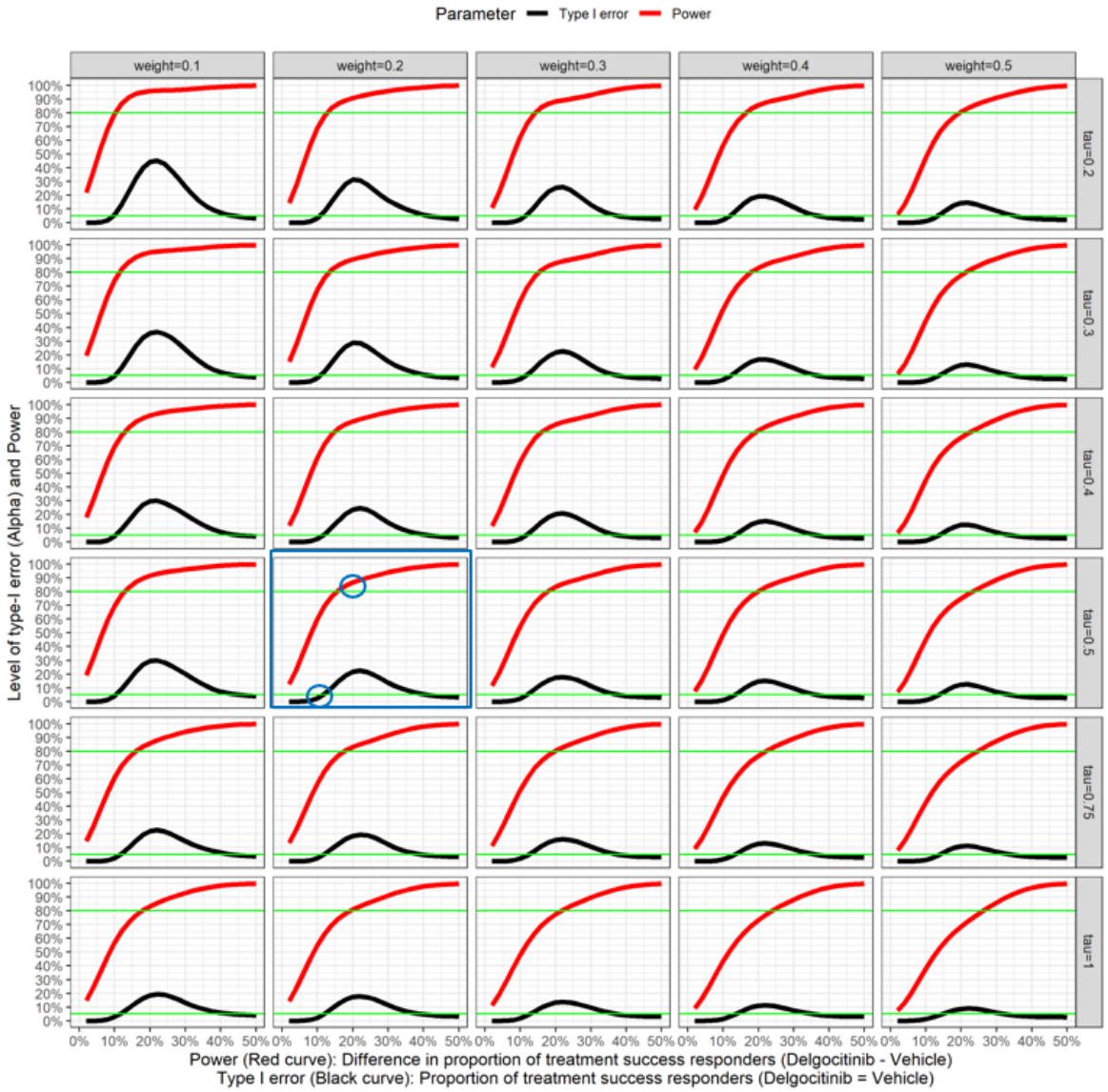
The average response rate for cream vehicle on HECSI-90 in the adult trials (LP0133-1273, LP0133-1401 and LP0133-1402) is 10.9% (Panel 36), corresponding to a type I error <5% (Panel 37). The average treatment effect is 19.3% (Panel 36), corresponding to a power >80% (Panel 37).

Panel 36: HECSI-90 results, trials LP0133-1273, LP013-1401, and LP0133-1402

	Delgocitinib cream 20 mg/g Responders (%), N	**Cream vehicle** Responders (%), N	**Average response rate for cream vehicle**	**Average response rate for delgocitinib cream 20 mg/g**	**Average treatment effect**	**Type 1 error**	**Power**
LP0133-1273	12 (29.3), N = 41	5 (13.2), N = 38	10.9%	30.2%	19.3%	<5%	>80%
LP0133-1401	96 (29.5), N = 325	20 (12.3), N = 162					
LP0133-1402	97 (31.0), N = 313	14 (8.8), N = 159					

Abbreviations: HECSI = Hand Eczema Severity Index. HECSI-90 = at least 90% improvement in HECSI from baseline. N = number of subjects

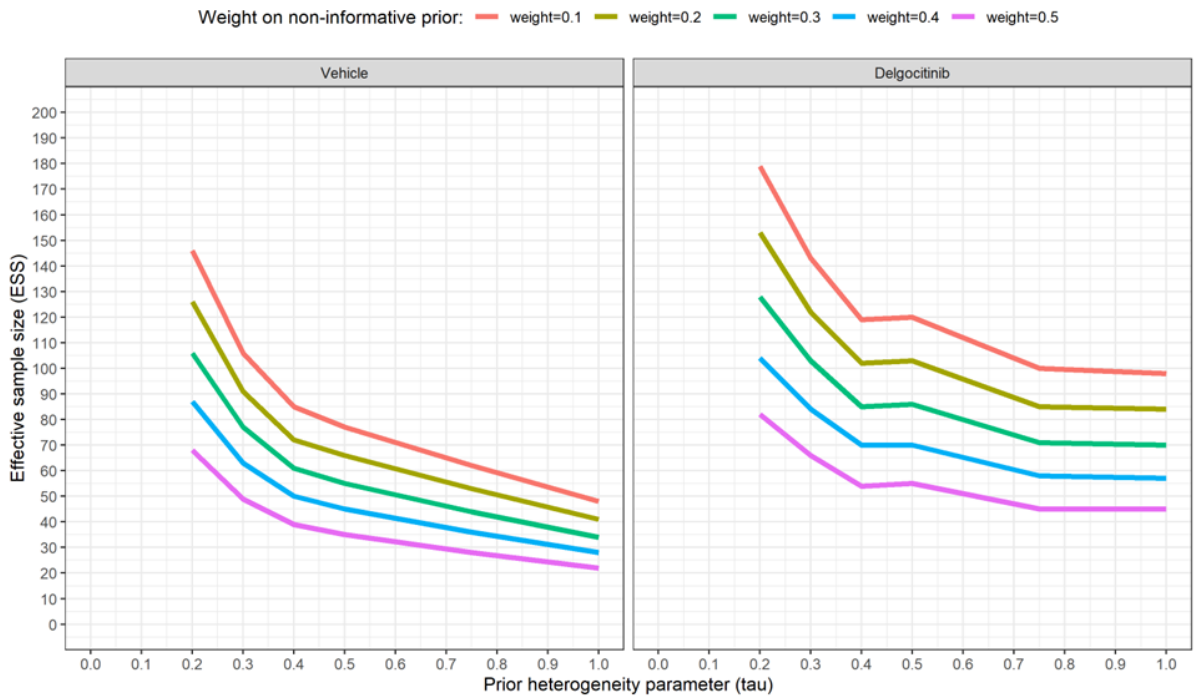
Panel 37: The level of type I error and power as a function of the difference in proportion of responders, split on the level of τ and the weight put on the non-informative part of the robust prior for HECSI-90



Abbreviation: HECSI = Hand Eczema Severity Index. HECSI-90 = at least a 90% improvement in HECSI score from baseline.
Notes: tau = τ, the between-trial heterogeneity. Weigh represents the non-informative part of the prior. The blue circles mark the anticipated type I error and power with the predefined selections of τ = 0.5 and weight = 0.2, for the average response rates for cream vehicle and delgocitinib cream 20 mg/g in the adult trials.

Panel 38 shows the ESS for various values of τ and weight. For τ = 0.5 and weight = 0.2, the ESS of using LP0133-1273, LP0133-1401, and LP0133-1402 is approximately 70 for cream vehicle arm and approximately 110 for delgocitinib cream 20 mg/g.

Panel 38: The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior for HECSI-90



Abbreviation: ESS = effective sample size; HECSI = Hand Eczema Severity Index. HECSI-90 = at least a 90% improvement in HECSI score from baseline.

14.3.17.3.2 Reduction of HESD≥4 from baseline

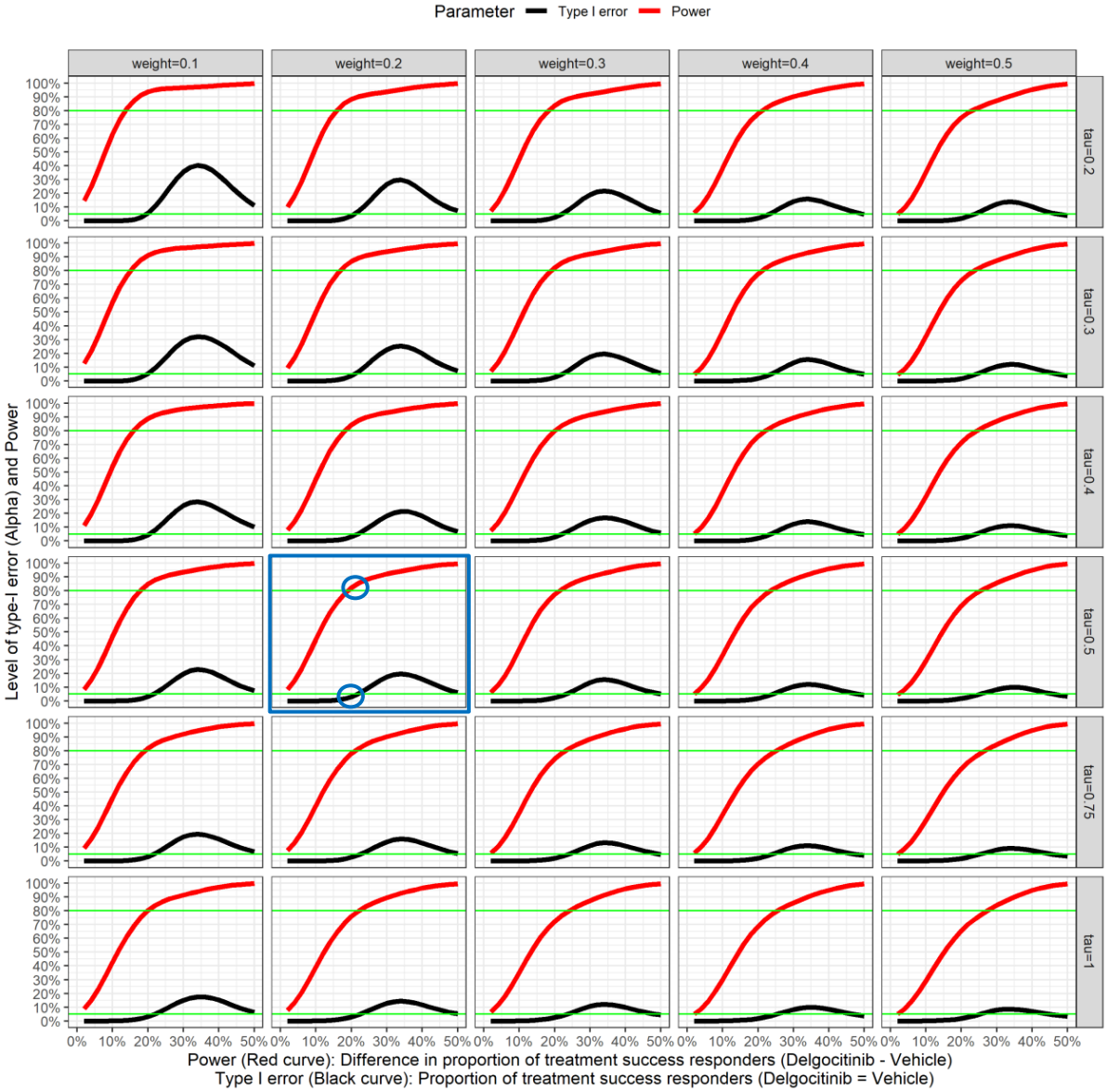
The average response rate for cream vehicle in the adult trials (LP0133-1273, LP0133-1401 and LP0133-1402) is 21.6% (Panel 39), corresponding to a type I error of <5% (Panel 40). The average treatment effect is 23.9% (Panel 39), corresponding to a power > 80% (Panel 40).

Panel 39: Reduction of HESD ≥4 from baseline, trials LP0133-1273, LP0133-1401, and LP0133-1402

	Delgocitinib cream 20 mg/g Responders (%), N	**Cream vehicle** Responders (%), N	**Average response rate for cream vehicle**	**Average response rate for delgocitinib cream 20 mg/g**	**Average treatment effect**	**Type 1 error**	**Power**
LP0133-1273	10 (37.0), N = 27	2 (8.3), N = 24	21.6%	45.5%	23.9%	<5%	>80%
LP0133-1401	146 (47.2), N = 309	38 (24.4), N = 156					
LP0133-1402	137 (44.5), N = 308	32 (20.9), N=153					

Abbreviations: HESD = Hand Eczema Symptom Diary©. N = number of subjects.

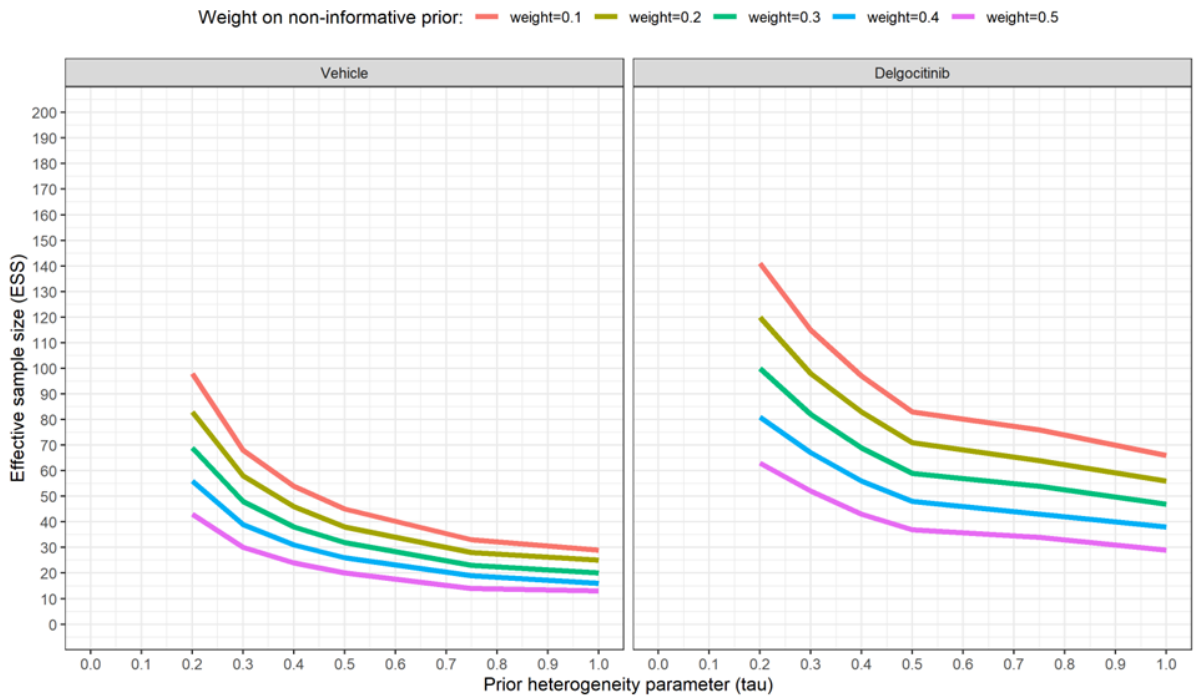
Panel 40: The level of type I error and power as a function of the difference in proportion of responders, split on the level of τ and the weight put on the non-informative part of the robust prior for HESD≥4



Abbreviation: HESD = Hand Eczema Symptom Diary©.
Notes: tau = τ, the between-trial heterogeneity. Weigh represents the non-informative part of the prior. The blue circles mark the anticipated type I error and power with the predefined selections of τ = 0.5 and weight = 0.2, for the average response rates for cream vehicle and delgocitinib cream 20 mg/g in the adult trials.

Panel 41 shows the ESS for various values of τ and weight. For τ = 0.5 and weight = 0.2, the ESS of using LP0133-1273, LP0133-1401, and LP0133-1402 is approximately 40 for the cream vehicle arm and approximately 90 for the delgocitinib cream arm.

Panel 41: The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior for HESD≥4



Abbreviation: ESS = effective sample size; HESD = Hand Eczema Symptom Diary©.

14.3.17.3.3 Reduction of HESD itch≥4 from baseline

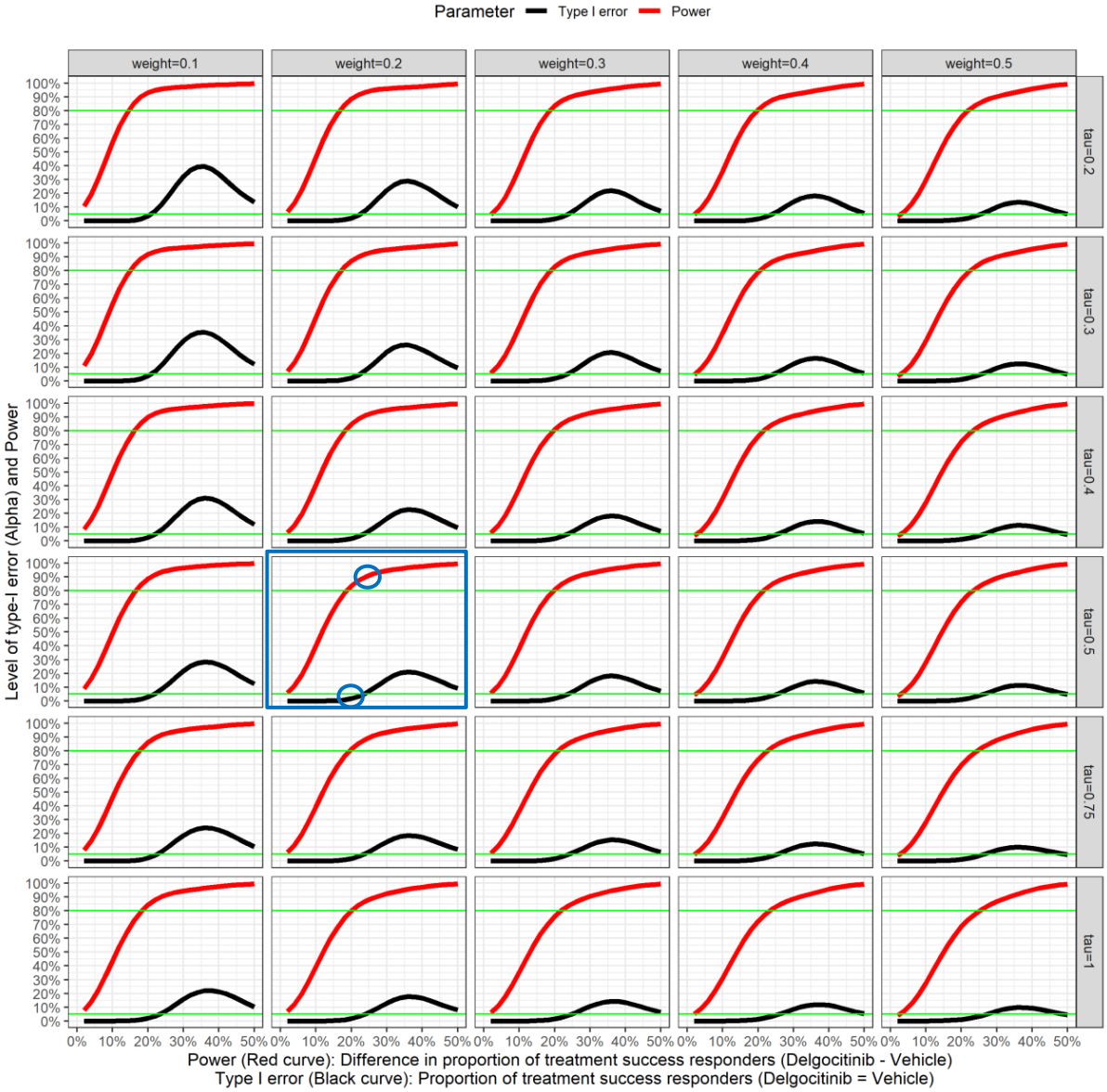
The average response rate for cream vehicle in the adult trials (LP0133-1273, LP0133-1401 and LP0133-1402) is 21.1% (Panel 42), corresponding to a type-I error of <5% (Panel 43). The average treatment effect is 26.3% (Panel 42), corresponding to a power > 80% (Panel 43).

Panel 42: HESD itch ≥4 from baseline, trials LP0133-1273, LP0133-1401, and LP0133-1402

	Delgocitinib cream 20 mg/g Responders (%), N	**Cream vehicle** Responders (%), N	**Average response rate for cream vehicle**	**Average response rate for delgocitinib cream 20 mg/g**	**Average treatment effect**	**Type 1 error**	**Power**
LP0133-1273	14 (53.8%), N = 26	4 (16.7%), N = 24	21.1%	47.4%	26.3%	<5%	>80%
LP0133-1401	152 (47.1%), N = 323	37 (23.0%), N = 161					
LP0133-1402	146 (47.2%), N = 309	31 (19.9%), N = 156					

Abbreviations: HESD = Hand Eczema Symptom Diary©. N = number of subjects.

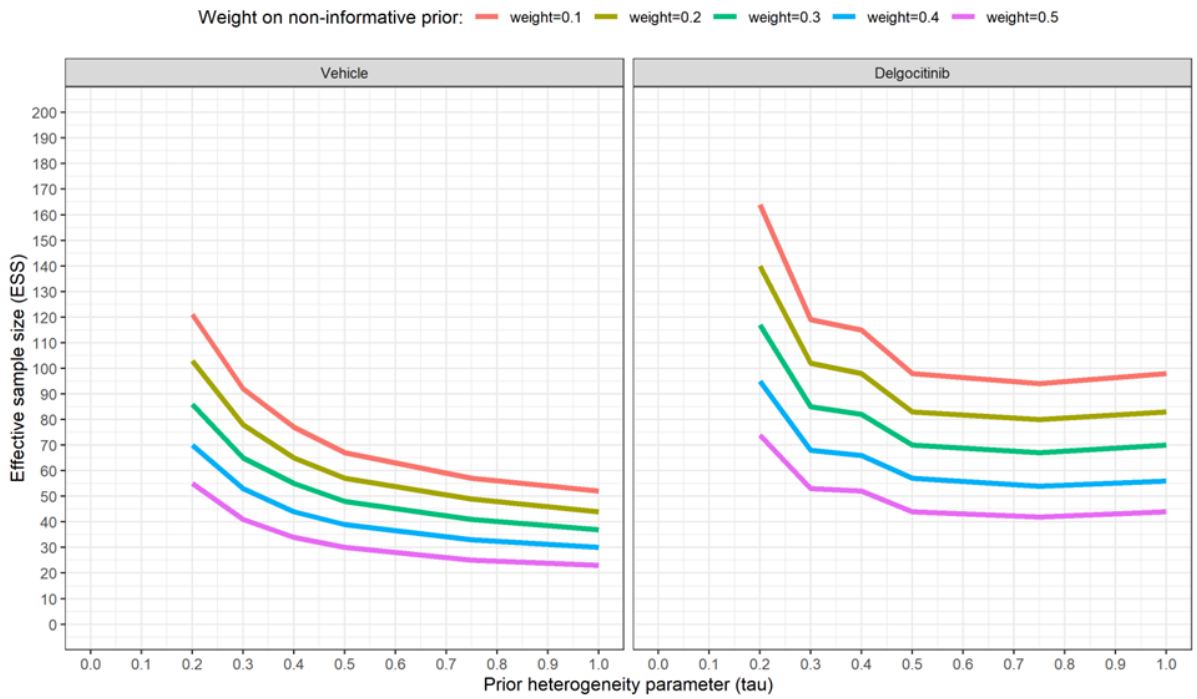
Panel 43: The level of type I error and power as a function of the difference in proportion of responders, split on the level of τ and the weight put on the non-informative part of the robust prior for HESD itch≥4



Abbreviation: HESD = Hand Eczema Symptom Diary©.
Notes: tau = τ, the between-trial heterogeneity. Weigh represents the non-informative part of the prior. The blue circles mark the anticipated type I error and power with the predefined selections of τ = 0.5 and weight = 0.2, for the average response rates for cream vehicle and delgocitinib cream 20 mg/g in the adult trials.

Panel 44 shows the ESS for various values of τ and weight. For τ = 0.5 and a weight = 0.2, the ESS of using LP0133-1273, LP0133-1401, and LP0133-1402 is approximately 60 for the cream vehicle arm and approximately 90 for the delgocitinib cream arm.

Panel 44: The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior for HESD itch≥4



Abbreviation: ESS = effective sample size; HESD = Hand Eczema Symptom Diary©.

14.3.17.3.4 Reduction of HESD pain≥4 from baseline

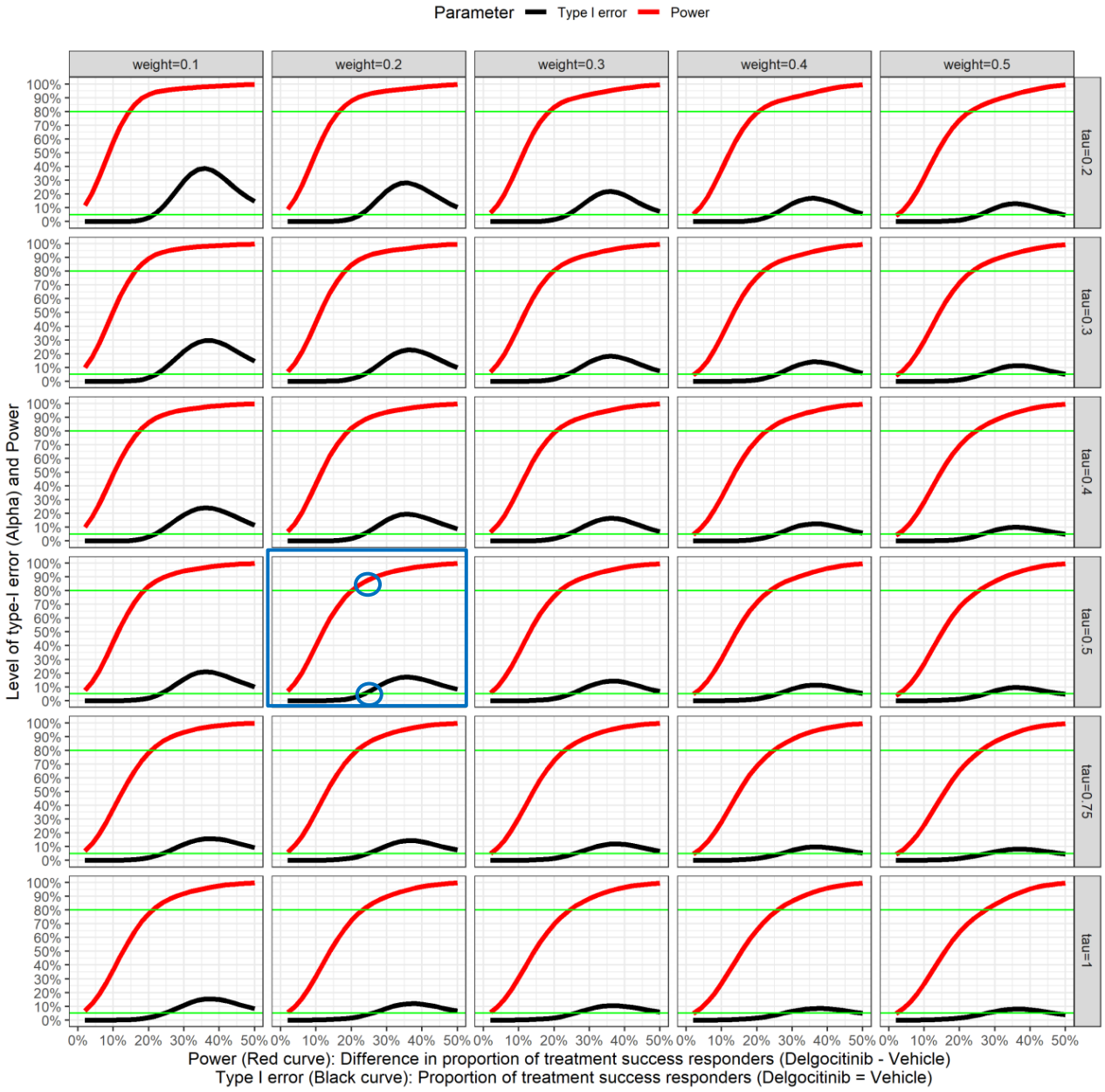
The average response rate for cream vehicle in the adult trials (LP0133-1273, LP0133-1401 and LP0133-1402) is 24.3% (Panel 45), corresponding to a type-I error of <5% (Panel 46). The average treatment effect is 25.3% (Panel 45), corresponding to a power of >80% (Panel 46).

Panel 45: Reduction of HESD pain ≥4, trials LP0133-1273, LP0133-1401, and LP0133-1402

	Delgocitinib cream 20 mg/g Responders (%), N	**Cream vehicle** Responders (%), N	**Average response rate for cream vehicle**	**Average response rate for delgocitinib cream 20 mg/g**	**Average treatment effect**	**Type 1 error**	**Power**
LP0133-1273	14 (70.0%), N = 20	1 (6.7%), N = 15	24.3%	49.6%	25.3%	<5%	>80%
LP0133-1401	143 (49.1%), N = 291	41 (27.5%), N = 149					
LP0133-1402	143 (48.6%), N = 294	32 (22.7%), N =141					

Abbreviations: HESD = Hand Eczema Symptom Diary©. N = number of subjects.

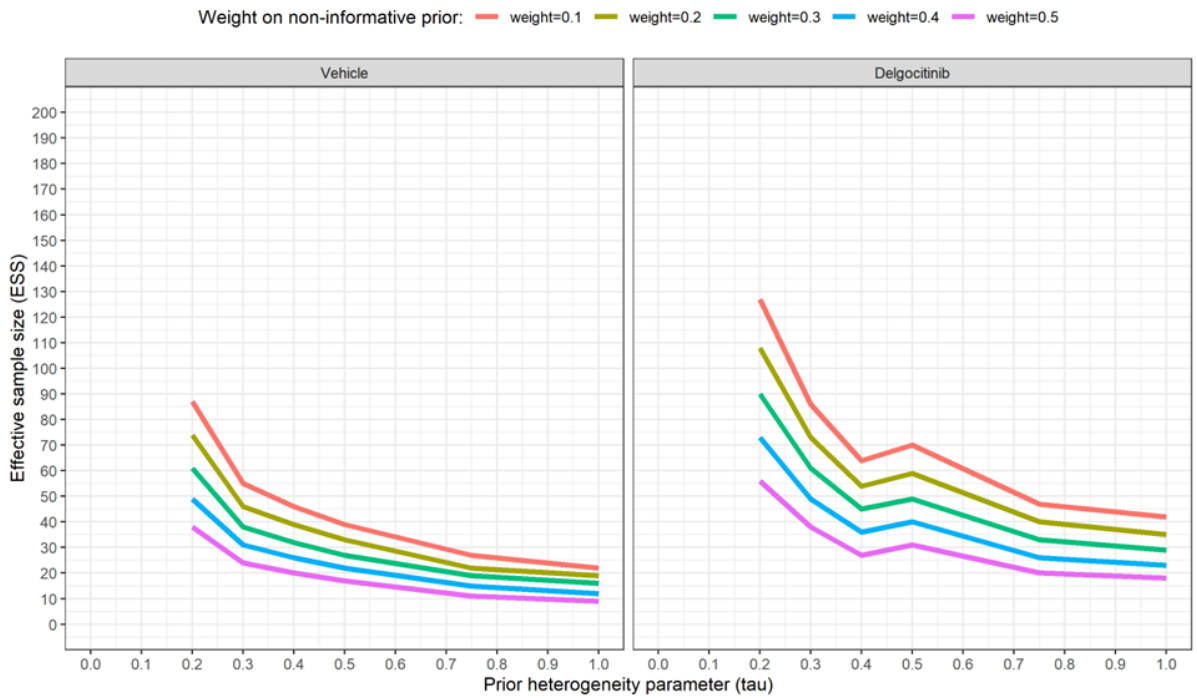
Panel 46: The level of type I error and power as a function of the difference in proportion of responders, split on the level of τ and the weight put on the non-informative part of the robust prior for HESD pain≥4



Abbreviation: HESD = Hand Eczema Symptom Diary©.
Notes: tau = τ, the between-trial heterogeneity. Weigh represents the non-informative part of the prior. The blue circles mark the anticipated type I error and power with the predefined selections of τ = 0.5 and weight = 0.2, for the average response rates for cream vehicle and delgocitinib cream 20 mg/g in the adult trials.

Panel 47 shows the ESS for various values of τ and weight. For τ = 0.5 and a weight = 0.2, the ESS of using LP0133-1273, LP0133-1401, and LP0133-1402 is approximately 35 for the cream vehicle arm and approximately 40 for the delgocitinib cream arm.

Panel 47: The ESS as a function of the level of τ and the weight put on the non-informative part of the robust prior for HESD pain≥4



Abbreviation: ESS = effective sample size; HESD = Hand Eczema Symptom Diary©.

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (45).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.5.5.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation*.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.

*Hospitalisation for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as an AE or SAE.
*Hospitalisation for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as an AE or SAE, even if not planned before consent to trial participation.
*Hospitalisation for routine scheduled treatment or monitoring of the studied indication not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as an AE or SAE.
*Hospitalisation for administrative, trial-related, or social purpose does not constitute an AE and should therefore not be reported as an AE or SAE.
*Complications that occur during hospitalisation are (S)AEs. If a complication prolongs hospitalisation, the event is an SAE.
*When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.

Additionally, all malignancies, incl. skin malignancies, should be reported as SAEs.

Definition of adverse events of special interest

An AESI (serious or non-serious) is an event type of scientific and medical concerns specific to the product or development programme, for which additional monitoring may be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the investigator to the sponsor and/or from the sponsor to other parties (e.g. regulators) might also be warranted.

AESIs are described in Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement. If the AE worsens in severity, the new severity, including date of worsening, should be recorded. However, if an AE with onset prior to IMP initiation worsens after IMP administration, a new AE should be recorded.

Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, or not related according to the investigator's clinical judgement.

Probably related	Follows a reasonable temporal sequence from administration of the IMP. Could not be reasonably explained by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. Follows a known pattern of response to the IMP. Disappears or decreases on cessation or reduction in dose of the IMP. Reappears or worsens upon re-challenge.
Possibly related	Follows a reasonable temporal sequence from the administration of the IMP. Could also be reasonably explained by the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. Follows a known pattern of response to the IMP.
Not related	Does not follow a reasonable temporal sequence from administration of the IMP. Is better explained by other factors like the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. Does not reappear or worsen upon re-challenge. Does not follow a known pattern of response to the IMP.

Outcome

The *outcome* of the event according to the investigator's clinical judgement should be classified using the categories below.

Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Not recovered/ not resolved	Event is still ongoing.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovered/ resolved with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded. In case of an SAE, the sequelae should be specified.
Unknown	Unknown to investigator, e.g. subject lost to follow-up.

LEO Pharma definitions versus CDISC definitions

Note that as per the above definition, LEO Pharma uses 'recovered/resolved' only if an event has actually stopped. According to the CDISC definition, the category 'recovered/resolved' also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as 'not recovered/not resolved' or 'recovering/resolving'.

Similarly, it should be noted that as per the above definition, LEO Pharma uses 'recovered/resolved with sequelae' only if an event has reached a state where the residual symptoms are assumed to persist. According to CDISC, an event is considered 'with sequelae', if it has 'retained pathological conditions'. Consequently, it is likely that some of the events classified by LEO Pharma with the outcome 'recovered/resolved with sequelae' could have been classified with the outcome 'recovered/resolved' according to the CDISC definition.

In summary, the definitions used by LEO Pharma are more conservative than those used by CDISC.

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (28) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (46).
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines (39).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial as required.

Any documents that the IRB/IEC may need to fulfil its responsibilities (such as the trial protocol, protocol amendments, investigator's brochure, subject information sheet, and informed consent and assent form(s), or advertisements) will be submitted to the IRB/IEC. These documents must be reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol must be approved by/receive favourable opinion from relevant regulatory authorities and IRBs/IECs, as required, prior to implementation.

The principal investigator will be responsible for the following, if required by local legislation:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Appendix 3B: Informed consent/assent process

Subjects and parents/guardians will receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects and parents/guardians will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated IC/IA to participate in the clinical trial and/or their parent's/guardian's signed and dated IC will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP and all applicable laws and regulations. The authorised person obtaining the IC/IA must also sign the ICF/IAF. The subject's decision not to participate or to withdraw will be respected, even if consent is given by the parent/guardian.

Subjects and parents/guardians will be re-consented/assented to the most current version of the ICF/IAF during their participation in the trial, if required. Subjects who become of legal age during the trial, will be consented to the most current version of the ICF for subjects being or becoming of legal age during the trial, if required by national laws and regulations. Subsequently, these subjects will be re-consented to the most current version of the ICF for subjects being or becoming of legal age during the trial, if applicable.

A copy of the ICF/IAF must be provided to the subject or the parent/guardian.

Subject card

At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address(es) and telephone number(s) of relevant trial site staff including the number for the investigator in case of emergency situations. The subject card also includes a local telephone number for the emergency unblinding CRO to be used if the investigator or delegated site staff cannot be reached or if unblinding in the IRT system cannot be performed.

Appendix 3C: Subject and data confidentiality

This clinical trial protocol as well as all other information, data, and results relating to this clinical trial and/or to the IMP is confidential information of LEO Pharma and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO Pharma may use any and all information, data, and results from this clinical trial in connection with the development of the IMPs and, therefore, may disclose and/or transfer information, data, and/or results to other investigators, regulatory authorities, and/or commercial partners.

Trial subjects will be assigned a unique identifier (subject ID) by LEO Pharma. Any subject's records or datasets that are transferred to LEO Pharma will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Trial subjects must be informed that their personal trial-related data will be used by LEO Pharma in accordance with local data protection law.

Trial subjects must be informed and agree to that their medical records may be examined by clinical quality assurance auditors or other authorised personnel appointed by LEO Pharma, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Trial subjects must be informed that LEO Pharma will keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research and for at least 25 years after the end of the clinical trial.

Processing of personal data
This protocol specifies the personal data on trial subjects (e.g. race, ethnicity, age, sex, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO Pharma, and third parties acting on behalf of LEO Pharma.

Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial as well as reporting obligations in the event of any data breach. In certain cases, an agreement on transfer of personal data may also be required.

Investigators and LEO Pharma must ensure that collection, processing, and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

Participation of the subjects in the clinical trial requires the collection, processing, and transfer of their personal data to EU and non EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services, and other related activities such as future research.

LEO Pharma has obtained the necessary authorisations for the processing of personal data collected in the trial.

Appendix 3D: Record keeping, quality control, and data handling

Source data at trial sites

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be 1 source defined at any time for any data elements.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed and dated by the physians.

The date and time of the sampling must be recorded at the laboratory requisition form.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Subject ID.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Randomisation code number.
- The fact that the subject is participating in a clinical trial in CHE including treatment with delgocitinib cream 20 mg/g or cream vehicle for 16 weeks.
- Other relevant medical information.

Trial monitoring

The trial will be monitored on an ongoing basis to verify that (i) the rights and well-being of the trial subjects is protected; (ii) the reported trial data are accurate, complete, and verifiable from source documents; and (iii) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and all applicable regulatory requirement(s).

The monitoring will be performed in a systematic, prioritised, risk-based approach, and as a combination of on-site, remote, and centralised monitoring. For more details, please refer to the trial-specific monitoring guideline and data review plan.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site

staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and important protocol deviations described in the CTR.

Sponsor audits, IRB/IEC review, and regulatory agency inspections
The clinical trial will be subject to audits conducted by LEO Pharma or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO Pharma staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify, and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO Pharma must be notified immediately.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into an electronic CRF (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.
The investigator must verify the correctness of the data entered by the site by electronically dating and signing the eCRF. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require re-signature by the investigator. The person making the change to the data, and the date, time, and reason for the change will be identified in the audit trail.

Subject data should be entered into the eCRF no later than 5 working days after each visit, unless a different deadline is stated in the clinical trial agreement. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor’s medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

An electronic PRO (ePRO) solution will be used to capture patient-reported data (data from questionnaires completed at the trial site and eDiary data). By the use of an ePRO, data will be available immediately after data entry and available for CRAs and site personnel, including the investigator, with reader access only. The ePRO system is a separate application from the eCRF and data captured from the eCRF and the ePRO will be stored on different servers during data capture. Data from both systems will be included in the final trial database.

External data transfers from vendors to LEO Pharma will be transmitted and handled via a secure file transfer protocol site.

Transmissions of data are documented in more detail in a data flow plan which is part of the trial master file.

Statistical programming standards
CDISC controlled terminology version 06 Nov 2020 or newer was used for definition of controlled terminology throughout this protocol. Standard data tabulation model (SDTM) version 1.4 will be used for data tabulations.

Archiving of trial documentation
The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (39). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (e.g. in case of an inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents even if the investigator leaves the trial site or retires before the end of the required storage period.

No documents may be destroyed during the retention period without the written approval of LEO Pharma. No documents may be transferred to another location or party without written acceptance from LEO Pharma.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

For archiving purposes, each investigator will be supplied with an electronic copy of the eCRFs and ePRO data for all screened subjects at the trial site. This is done after completion

of the trial and before access to the eCRF/ePRO is revoked. Audit trail information will be included. eCRFs and ePRO data must be available for inspection by authorised representatives from LEO Pharma, from regulatory authorities and/or IRBs/ IECs.

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

LEO Pharma is committed to be transparent with respect to its clinical trials.

Basic information of this clinical trial will be registered in the global data registry, www.ClinicalTrials.gov. before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this clinical trial will be posted at leopharmatrials.com in accordance with our Position on Public Access to Clinical Trial Information after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu, and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

Publications

The investigator shall be entitled to make publications of the results generated by the investigator in accordance with the process described here.

A multi-site publication will be submitted for publication within 12 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as final database lock of the clinical trial. After such multi-site publication is made public, or if no multi-site publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO Pharma a copy of all such manuscripts and/or presentations. LEO Pharma shall have rights to review and comment. The investigator shall consider comments provided by LEO Pharma but is not required to modify the manuscript and/or presentation based on such comments, provided, however, that the investigator upon the request of LEO Pharma remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO Pharma withhold the publication or presentation to allow LEO Pharma to protect its inventions and other intellectual property rights described in any such manuscripts.

In case no multi-site publication has been made public at the time of investigator's notification of an independent publication to LEO Pharma, LEO Pharma and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-site publication.

In case of publications made by the investigator after the first multi-site publication has been published, the above-mentioned requirements must still be followed.

Any publication must comply with Good Publication Practice (GPP3) standards.

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results, and authorship. LEO Pharma also follows the CONSORT reporting guidelines (32).

Appendix 3F: Insurance

LEO Pharma has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

Appendix 3G: Financial disclosure

Investigators will provide LEO Pharma with sufficient, accurate financial information as requested to allow LEO Pharma to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests and update this information, should any relevant change occur, during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 3H: Committee structure

Patient safety will be carefully assessed by an independent DMC. All members will be independent of the trial and of LEO Pharma. The DMC members are experienced with clinical trials and will be responsible for evaluating the safety of the subjects through

assessment of the safety of the treatment regimen during the trial and through monitoring of the overall conduct of the trial.

The DMC will review data on a regular basis. Additional meetings may also be called on an ad hoc basis, as requested by the DMC or LEO Pharma. All data collected at the time of the data cut-off/scheduled meetings will be included in the summaries for the DMC, including data from subjects still ongoing in the trial. The DMC will examine summaries and listings of AEs, specific laboratory parameters, and subject disposition data as detailed in the DMC charter. Full details of the analyses to be presented to the DMC will be specified in a separate DMC statistical analysis plan.

The DMC will have an independent statistician and an independent administrator who will remain independent of the trial management team.

Further details on all aspects relating to the DMC are provided in the DMC charter.

Appendix 3I: Trial and trial site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IRBs/IECs, or competent authorities may decide to stop the clinical trial, part of the trial, or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, the investigator or LEO Pharma must promptly inform IRBs/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, [S]AEs, and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

Reasons for the premature closure of a trial site by LEO Pharma or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO Pharma procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Screening activities will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Trial sites will be closed upon trial completion. LEO Pharma will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

When the randomisation code has been broken, the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites and will be asked to record this in the subject's medical record.

Appendix 3J: Responsibilities

The signatory investigator is responsible for the approval of the clinical trial protocol and the CTR on behalf of all clinical trial investigators and as agreed to in a signatory investigator agreement.

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a national coordinating investigator agreement.

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a clinical trial agreement.

Appendix 4: Country-specific requirements

This appendix describes requirements and procedures that are specific for France and Canada. For each section, the text from the protocol is presented in normal font. The specific country requirements or procedures are presented below in bold font.

France

Section 8.3 Exclusion criteria

Subjects are not eligible for the trial if they violate any of the following criteria:

30. Subject not affiliated with or not a beneficiary of a social security scheme.

Canada

As per Health Canada standards, all essential trial documents and source documents will be archived for 15 years.

Appendix 5: Short version eligibility criteria

	Inclusion criteria
No.	**Short version**
1	Signed and dated IC and IA (as applicable according to national laws or regulation) has been obtained prior to any protocol-related procedures.
2	Age 12 to 17 years at screening and baseline.
3	Diagnosis of CHE, defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
4	Disease severity graded as moderate to severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 3 or 4).
5	Subjects who have a documented recent history of inadequate response to treatment with TCS or TCS treatment being medically inadvisable.
6	Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.
7	A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the last application of IMP.

	Exclusion criteria
No.	**Short version**
1	Known or suspected hypersensitivity to any component(s) of the IMP.
2	Concurrent skin diseases on the hands, e.g. tinea manuum.
3	Active AD requiring medical treatment in regions other than the hands and feet.
4	Active psoriasis on any part of the body.
5	Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
6	Clinically significant infection (e.g. impetiginised hand eczema) on the hands.
7	Systemic treatment with immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids within 28 days prior to baseline.
8	Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.

9	Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical.
10	Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.
11	Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.
12	Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline.
13	Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 7 days prior to baseline.
14	Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab) within 6 months or 5 half-lives prior to baseline or until cell counts return to normal, whichever is longer.
15	Treatment with any non-marketed drug substance within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.
16	Clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 28 days prior to baseline.
17	History of any known primary immunodeficiency disorder including a positive HIV virus test at screening, or the subject taking antiretroviral medications.
18	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
19	History of cancer.
20	Any disorder which is not stable and could affect the safety of the subject, influence the findings of the trials, or impede the subject's ability to complete the trial.
21	Any abnormal finding which may put the subject at risk, influence the results of the trial, or influnece the subject's ability to complete the trial.
22	Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
23	ALT or AST level ≥2.0×ULN at screening.
24	Current participation in any other interventional clinical trial.
25	Previously randomised in this clinical trial.
26	Subject or parents/guardians who have a current or recent chronic alcohol or drug abuse, or any other condition associated with poor compliance as judged by the investigator.

27	Employees of the trial site, or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
28	Subjects who are legally institutionalised.
29	Women who are pregnant or lactating.

Appendix 6: Contact list

Contact details for the clinical project manager, national lead CRA, and sponsor's medical expert are provided to the trial sites as a separate contact list.

Sponsor

LEO Pharma A/S (referred to as 'LEO Pharma' or 'the sponsor' in this clinical trial protocol) is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

Coordinating investigator

[redacted], MD
[redacted]
[redacted]
[redacted], Canada

Appendix 7: COVID-19 pandemic contingency plan

Without compromising the safety of subjects and trial integrity, it is expected that efforts are made to secure attendance at sites for all visits, ensuring important efficacy and safety assessments for the trial.

If on-site visits are not possible due to local authority issued preventive measures, the affected site will postpone screening and randomisation of new subjects until on-site visits can be conducted. For already randomised subjects, post baseline visits can be done remotely via phone or video. At phone/video visits, no investigator assessments of efficacy can be done, but the following data will be collected remotely (according to the schedule of trial procedures in Section 4):

- AE reporting.
- Treatment compliance (daily completion in the eDiary).
- Concomitant medication and concurrent procedures.
- HESD (daily completion in the eDiary).
- Subject assessment of local tolerability (weekly completion in the eDiary).
- PRO (cDLQI). The subjects will receive a link to complete the cDLQI in a web browser from their own computer/laptop.
- New CHE lesions.
- Urine pregnancy test. Women of childbearing potential will receive 1 extra urine pregnancy test at the randomisation visit to keep at home in case on-site visits become impossible during the trial. The subject will perform the test at home and inform the investigator about the result via phone. Additional urine pregnancy tests can be shipped to the subject's home together with IMP (see below) if needed.

In the eCRF, it will be recorded whether a visit or a given assessment was done remotely or not done. If not done, it will be recorded if this was due to the pandemic.

It will be at the discretion of the investigator to decide whether clinical laboratory samples are considered necessary to ensure subject safety in periods when on-site visits are not possible. If possible, a home visit can be arranged for a healthcare professional to collect relevant clinical laboratory samples.

Contingency plans due to COVID-19 must follow the authorities' COVID-19 guidelines and local requirements. Written procedures describing the contingency plan must be in place at site/depot. To ensure availability of IMP, the trial sites may dispense additional IMP if considered relevant (i.e. if local authority issued preventive measures are to be expected at the

given trial site). This will allow subjects to continue treatment with IMP although they are not able to go to the trial site. If a subject will not be able to attend on-site visits due to the pandemic before running out of IMP, the trial site will ensure shipping of IMP to the subject's home. As the subjects' IMP supply is secured, the IE of initiation of rescue treatment will be considered independent of the pandemic in the statistical analysis.

If a subject is tested positive for COVID-19, the investigator will evaluate whether this is an AE that contraindicates further dosing, in which case the subject will permanently discontinue IMP as described in Section 10.2.

Appendix 8: Acceptable methods of birth control

Acceptable methods of birth control include:

- Bilateral tubal occlusion or ligation (tubal sterilisation methods).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal contraception (associated with inhibition of ovulation [oral, injectable, implantable] or without inhibition of ovulation as the primary mode of action [oral]).
- Sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject and not just being without a current partner).
- Same-sex partner.
- Vasectomised partner (given that the subject is monogamous).
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.

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