Clinical trial protocol

LP0133-1402

A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2)

Phase 3 – efficacy and 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:**	**LP0133-1402**
	Date:	**20-Aug-2021**
	EudraCT no:	**2020-002961-32**
	Version:	**4.0, Final**

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:

PPD , MD
Vice president, Medical Sciences

PPD , MSc Stat
Biostatistics lead, Medical Sciences

PPD , MD
Medical lead, Medical Sciences

PPD MA
Clinical operations lead, Global Clinical Operations

Sibylle Schliemann, PD Dr. med.
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)	20-Aug-2021	Global
Original protocol (Protocol version 3.0)	04-Feb-2021	NA

Amendment 1 (20-Aug-2021)

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 was written to comply with requests from health authorities and to proceed with administrative and editorial changes.

Section no. and title	Description of change	Brief rationale
Section 4 Schedule of trial procedure	Number of sites (approximately 10 trial sites) removed. Added that if deemed necessary, photographs can be retaken at an unscheduled visit.	To allow more flexibility on the number of sites participating in the clinical photography and thus increase the number of subjects that can participate. To allow more flexibility to the subjects and investigators.
Section 4 Schedule of trial procedure Section 9.8.4 Treatment compliance	Deleted that at the end-of-treatment/early termination visit, the subject will be asked about their overall compliance with the IMP.	To avoid data duplication and inconsistencies in the data.

Section no. and title	Description of change	Brief rationale
Section 4 Schedule of trial procedure	Added that the subject has the possibility to choose for which purpose (scientific and/or commercial) the photographs can be used.	To give the possibility to the subjects to choose the purpose.
Section 11.7.2 Photography (selected trial sites)	Specified that photography assessments will be done to capture disease status and not to show disease progression.	For clarity, as the disease does not have a linear development.
	Specified that the photographs will be of the whole hands (back and front) including wrists and not only of representative lesions.	To more accurately capture disease status, including clear skin.
Section 5.5 Benefit/risk assessment	Clarification that treatment with other therapies will be withheld from the subjects for up to 22 weeks added.	VHP requests.
	Text on potential skin reactions, such as pain (burning and stinging), sensitisation to IMP, allergic and irritant contact dermatitis, local immunosuppression, and skin infections added.	
Section 9.2 Administration of IMP	Fingertips added in the list of areas to be treated.	For completeness.
Section 9.6 Concomitant medication and concurrent procedures, Section 9.7 Prohibited medications and procedures	Guidance regarding COVID-19 vaccines added. COVID-19 vaccines can be administered to subjects without the need to pause or discontinue IMP.	MHRA request.
Section 10.2 Reasons for permanent discontinuation of IMP	Positive patch test reaction to the IMP added as a reason for permanent discontinuation of IMP.	For consistency with Section 11.5.5.1.

Section no. and title	Description of change	Brief rationale
Section 11.1 Overview, Section 13.2 Collection of adverse events reports	Text regarding assessment of AEs updated. AEs will be assessed by a physician.	To clarify the responsibilities and who should perform certain tasks.
Section 11.2.1 Demographics	Asian - Chinese added as race.	To support a potential future submission in China.
Section 11.4.3.1 Overview Section 11.7.1.5 Patient's Global Assessment of disease severity (PaGA) Section 14.3.5 Testing strategy Section 14.3.8 Analysis of keys secondary endpoints Section 14.3.9 Analysis of exploratory endpoints Section 14.3.10 Analysis of patient-reported outcomes	PaGA TS is removed from the list of secondary endpoints. PaGA score will be analysed descriptively as an exploratory endpoint.	The modified PaGA used in this trial is considered less informative as an endpoint for the evaluation of the clinical relevance of delgocitinib in CHE. As a consequence, PaGA TS is removed from the confirmatory testing procedure.
Section 11.5.1 Vital signs	Text regarding vital signs updated. The vital signs will be measured in a sitting position.	Vital signs are not critical data, thus a supine position for measuring is not required.
Section 11.5.5.1 IMP patch test procedure	Added that photographs of a positive patch test reaction should be taken if a device is available at the site.	For clarity
Section 11.8 End of trial	Specification added to indicate that for subjects not completing the trial, it will be recorded if the reason for not completing the trial was related to COVID-19.	This information is needed to fully assess and report the impact of COVID-19 on the trial.

Section no. and title	Description of change	Brief rationale
Section 13.3 Reporting of adverse events	Text regarding cutaneous AEs updated.	To provide more guidance for the reporting of cutaneous AEs.
Section 13.4.1 Investigator reporting responsibilities	A more detailed specification on the timing of reporting of SAEs added (i.e., immediately, without undue delay).	To align with updated text in the EU CT regulation on reporting of SAEs.
Section 14.1 Sample size	Basis for the assumptions on response rate for delgocitinib and vehicle for sample size calculation added.	VHP request.
Section 14.3.12.1 Adverse events	Paragraph added indicating that other events will be tabulated and listed.	For completeness.
Appendix 1	Hospitalisation definition clarified.	For clarity.
Appendix 2	Instructions were added regarding reporting of AEs with onset prior to initiation of IMP that worsen after administration of IMP.	To align with the updated procedure for AE reporting.
Appendix 3D	Specified that clinical assessments/safety evaluations must be signed and dated by physicians.	To clarify the responsibilities and who should perform certain tasks.
Appendix 4	Added that for Canada all essential trial documents and source documents will be archived for 25 years.	Health Canada request.
Throughout document	References to US, US sites, and US-specific provisions removed.	No US sites will be involved in this trial.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarised.

Protocol version summary of changes table

Document history

Document	Date	Type of protocol version
Protocol version 3.0	04-Feb-2021	Version with reduction in sample size from N=600 to N=450. Version created after internal approval of version 2.0, but before submission to any regulatory authorities or IECs/IRBs.
Protocol version 2.0	26-Jan-2021	Version with updates made after receipt of EMA scientific advice; i.e. after internal approval of version 1.0, but before submission to any regulatory authorities or IECs/IRBs.
Protocol version 1.0	09-Nov-2020	Version for internal use

Overall rationale for protocol version 3.0 (04-Feb-2021)

Description of change	Brief rationale
Reduction in sample size from N=600 to N=450.	The sample size has been reduced based on the trial design as agreed with EMA during the scientific advice procedure.
Reduction in number of sites from 75 to 55.	The reduction in sample size led to a reduction in the number of sites to safeguard data quality.

Overall rationale for protocol version 2.0 (26-Jan-2021)

Description of change	Brief rationale
Addition of inclusion criterion related to avoidance of irritants and allergens.	Based on EMA scientific advice dated 16-Nov-2020, it was decided to add an inclusion criterion on avoidance of irritants and allergens as mean to evaluate inadequate response to standard non-medicated skin care.
Assessment of pharmacokinetics (PK) was moved from companion trial LP0133-1401 to this trial.	Based on EMA scientific advice dated 16-Nov-2020, it was decided to increase the number of subjects who will have PK samples collected from 80-90 subjects at selected trial sites in trial LP0133-1401 to all subjects participating in a trial. As PK samples are not to be taken at sites where tape stripping assessments are planned (only in trial LP0133-1401), it was decided to move the PK assessments to trial LP0133-1402.
Minor editorial revisions throughout document.	Minor, have therefore not been summarised.

Table of contents

List of panels

List of abbreviations and definition of terms

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
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
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicine Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension Health Questionnaire 5 Level
EU	European Union
FAS	full analysis set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
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
HEIS	Hand Eczema Impact Scale
HESD	Hand Eczema Symptom Diary
HIV	human immunodeficiency virus

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 at least 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
LEO 124249	delgocitinib
LEO Pharma	LEO Pharma A/S
LP0133-1403	open-label long-term extension trial with delgocitinib cream 20 mg/g for 36 weeks
LTE trial	long-term extension trial (LP0133-1403)
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
PaGA	Patient's Global Assessment of disease severity
PDAL	Proximal Daily Activity Limitations
PDE-4	phosphodiesterase-4
PGA	Physician's Global Assessment
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PUVA	psoralen ultraviolet A
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SD	standard deviation
SOC	system organ class
STAT	signal transducer and activator of transcription
TCS	topical corticosteroid(s)
TS	treatment success
ULN	upper limit of normal
UVA1	ultraviolet A1
UVB	ultraviolet B
VHP	Voluntary Harmonization Procedure
WPAI:CHE	Work Productivity and Activity Impairment: Chronic Hand Eczema
WOCF	worst observation carried forward

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td>LP0133-1402
2020-002961-32</td></tr>
<tr><td>Title of trial</td><td>A phase 3 clinical trial to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a 16-week treatment period in adult subjects with moderate to severe chronic hand eczema (DELTA 2).</td></tr>
<tr><td>Short title of trial</td><td>Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema.</td></tr>
<tr><td>Main objectives, estimands, and endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Estimand type and strategy</th><th>Endpoints</th></tr>
<tr><td>Primary objective:
To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.</td><td>Primary.
‘Composite’ strategy.
First supplementary.
‘Pandemic modified composite’ strategy.
Second supplementary for endpoints at Week 16.
‘Treatment policy’ strategy.</td><td>Primary endpoint:
• IGA-CHE[1] TS at Week 16.
Key secondary endpoints:
• HECSI-75 at Week 16.
• HECSI-75 at Week 8.
• HECSI-90 at Week 16.
• IGA-CHE TS at Week 8.
• IGA-CHE TS at Week 4.
• Percentage change in HECSI[2] score from baseline to Week 16.</td></tr>
<tr><td>Secondary objective:
To confirm 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 adult subjects with moderate to severe CHE.</td><td>Primary.
‘Composite’ strategy.
First supplementary.
‘Pandemic modified composite’ strategy.
Second supplementary for endpoints at Week 16.
‘Treatment policy’ 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 itch score (weekly average) of ≥4 points from baseline at Week 8.[4]
• Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 4.[4]
• Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 2.[4]
• Reduction of HESD 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 8.[5]
• Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4.[5]</td></tr>
</table>
</td></tr>
</table>

		• Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.[6] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 8.[6] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 4.[6] • Reduction of DLQI score of ≥4 points from baseline at Week 16.[7] • Change in HESD itch score (weekly average) from baseline to Week 16. • Change in HESD score (weekly average) from baseline to Week 16. • Change in HESD pain score (weekly average) from baseline to Week 16. • Change in HEIS[8] score from baseline to Week 16. • Change in HEIS PDAL score from baseline to Week 16. • Change in DLQI score from baseline to Week 16.
Secondary objective: To evaluate the safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Not applicable.	***Secondary endpoint:*** • Number of treatment-emergent[9] AEs from baseline up to Week 16 (Week 18 for subjects not participating in the LTE trial) per subject.

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 in each of the 5 hand regions (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales. The HECSI score will range from 0 (lowest possible score) to 360 (highest possible score).

3) The HESD is an eDiary in which subjects will assess the worst severity of [redacted] individual signs and symptoms of CHE ([redacted]) over the past 24 hours using an 11-point numeric rating scale throughout the trial on a daily basis.

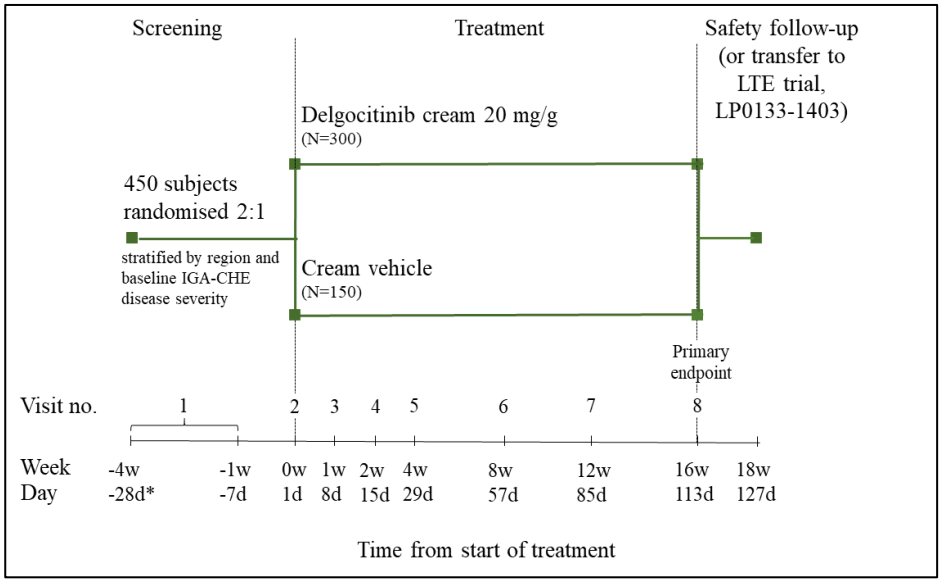
4) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.

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

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

7) Among subjects with a baseline DLQI score ≥4 points.

	8) The HEIS addresses [redacted] items within the following domains: CCI [redacted]. Each item is scored on a 5-point scale ranging from 0 (not at all) to 4 (extremely). 9) 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:** CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index; 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; HEIS = Hand Eczema Impact Scale; 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; IMP = investigational medicinal product;; PDAL = Proximal Daily Activity Limitations.
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 adult subjects 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. In view of a 28-day wash out for some of these treatments, the screening period can be extended up to 31 days. The subjects will receive an eDiary device and training in completion of the eDiary. <u>Treatment period</u> At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. If still eligible, the subjects will be randomised 2:1 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 and severe) and region (Europe and North America). The first application of IMP will occur at the trial site at baseline (Day 1). The subsequent IMP applications will be performed by the subjects 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 1, 2, 4, 8, 12, and 16. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16. <u>Follow-up period</u> The subjects will attend a follow-up visit (performed via phone, but can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Eligible subjects who complete the treatment period (i.e. who do not permanently discontinue IMP prior to Week 16) will be invited to

	participate in an open-label LTE trial (LP0133-1403, conducted under a separate protocol). Subjects who continue in the LTE trial will not be required to complete the follow-up period, as collection of safety data and safety surveillance will continue in the LTE trial.  * 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, 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; LTE = long term extension; w = week.
Main assessments	<u>Investigator assessments of efficacy:</u> • IGA-CHE for assessment of disease severity. • HECSI for assessment of the clinical signs of CHE. <u>Subject assessments of efficacy and health-related quality of life; PROs:</u> • Hand Eczema Symptom Diary (HESD). • Hand Eczema Impact Scale (HEIS). • Dermatology Life Quality Index (DLQI). <u>Safety assessments:</u> Vital signs, physical examination, ECG, laboratory testing, subject assessment of local tolerability, and AE reporting.
Main criteria for inclusion	• Age 18 years or above at screening. • 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). • HESD itch score (weekly average) of ≥4 points at baseline. • 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).

	• Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.

Main criteria for exclusion	• Concurrent skin diseases on the hands, e.g. tinea manuum.
	• Active AD requiring medical treatment in regions other than the hands and feet.
	• Active psoriasis on any part of the body.
	• Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
	• 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 transdermal or 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.
	• Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab):
	  o 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.
	  o Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
	• 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:
	  o A systemic infection.
	  o A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
	• History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.

	• Any disorder which is not stable and could: o Affect the safety of the subject throughout the trial. o 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. • Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
Investigational medicinal product	• Name of IMP: delgocitinib cream. • Active substance: delgocitinib. • Dosage form: cream. • Concentration: 20 mg/g and cream vehicle. • Dose and method of administration: topical application twice daily.
Duration of trial participation	The duration of trial participation will be up to 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 (safety follow-up period not applicable for subjects participating in the LTE trial).
Number of subjects	A total of 450 eligible subjects will be randomised in a 2:1 ratio to delgocitinib cream 20 mg/g or cream vehicle.
Number and distribution of trial sites	Approximately 55 sites in Europe and Canada.
Statistical methods	For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand. A closed testing procedure with hierarchical tests, alpha splitting, and alpha recycling will be used to control the overall type I error at a nominal one-sided 2.5% level. The statistical testing strategy is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life. The primary estimand for the primary and key secondary endpoints will use a 'composite' strategy where the occurrence of pre-defined IEs (initiation of rescue treatment and permanent discontinuation of IMP) is a component of the endpoint. A first supplementary estimand will use a 'pandemic modified composite' strategy which follows a 'composite' strategy for IEs independent of the COVID-19 pandemic, attempting to quantify the effect of the randomised treatment in a world without COVID-19 pandemic. A second supplementary estimand will use a 'treatment policy' strategy which attempts to quantify the effect of the randomised treatment regardless of whether an IE occurs. The second supplementary estimand will be used for endpoints related to Week 16 (primary endpoint visit). The primary analysis for the primary estimand for the binary endpoints will be CMH test stratified by region and baseline IGA-CHE score. The primary analysis for the primary estimand for the continuous endpoints will be

	ANCOVA with effects of treatment group, region, baseline IGA-CHE score, and baseline value (endpoint of interest).
Signatory investigator	Sibylle Schliemann, PD Dr. med. Department of Dermatology, University Hospital Jena, Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

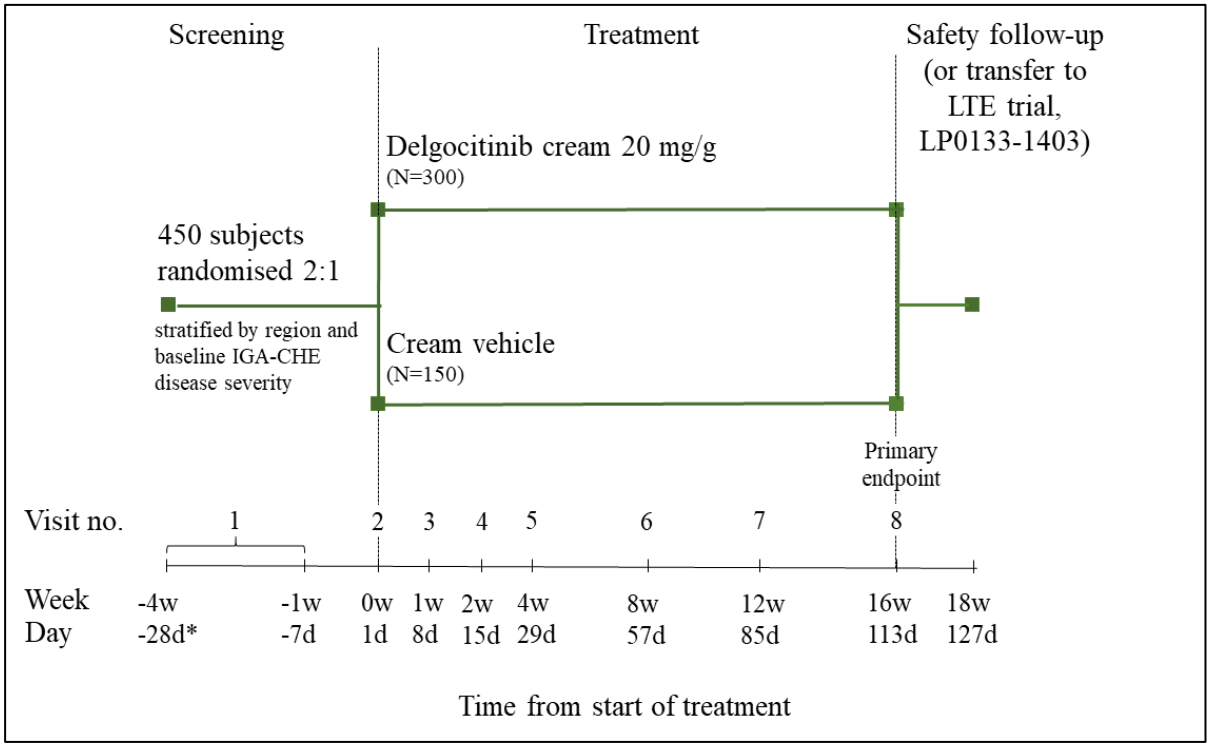
2 Trial identification

EudraCT number: 2020-002961-32.

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, 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; LTE = long-term extension; w = week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening	Treatment period						End of treatment[1]	Early termination, if applicable[2]	Follow-up[3]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**(9)**	**10**			
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**-**	**18[4]**			
Day	**-28[7] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**-**	**127[4]**			
Visit window (days)[8]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**			
Trial population and eligibility													
Informed consent(s)[9]	X						(X)[10]	(X)[10]					Appendix 3B
Subject eligibility	X	X											8.2, 8.3
Investigator assessments at screening/baseline only													
Demographics	X												11.2.1
Fitzpatrick skin type	X												11.2.2
Medical history (including CHE treatment history)	X												11.2.3
Classification of CHE (including patch test if standard clinical practice)[11]	X											(X)	11.2.4
Height and weight		X											11.2.5
Determination of treatment area(s)		X										(X)	11.2.6
eDiary handout/training	X												11.3
Treatments and randomisation													
Randomisation		X											9.3

	Screening	Treatment period						End of treatment[1]	Early termination, if applicable[2]	Follow-up[3]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**(9)**	**10**			
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**-**	**18[4]**			
Day	**-28[7] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**-**	**127[4]**			
Visit window (days)[8]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**			
Dispensing of IMP		X	X	X	X	X	X					(X)	9.2
Instruction for IMP application		X											9.2
Application of IMP		Twice daily											9.2
Treatment compliance		Daily[12]						X[12]	X[12]				9.8.4
Return of IMP and accountability[13]			X	X	X	X	X	X	X			(X)	9.8.3
Concomitant medication and concurrent procedures[14]	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Investigator assessments of efficacy													
IGA-CHE	X	X	X	X	X	X	X	X	X		X		11.4.1
HECSI		X	X	X	X	X	X	X	X		X		11.4.2
Subject assessment of efficacy – daily													
eDiary completion: HESD[15]	Daily										X		11.4.3.2
Subject assessments of efficacy and health-related quality of life – during trial visits													
PGI-S[16]		X		X	X	X		X	X				11.7.1.2
PGI-C[17]				X	X	X		X	X				11.7.1.3
HEIS		X	X	X	X	X	X	X	X				11.7.1.4
PaGA		X	X	X	X	X	X	X	X				11.7.1.5

	Screening	Treatment period						End of treatment[1]	Early termination, if applicable[2]	Follow-up[3]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**(9)**	**10**			
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**-**	**18[4]**			
Day	**-28[7] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**-**	**127[4]**			
Visit window (days)[8]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**			
DLQI		X	X		X	X	X	X	X		X		11.7.1.6
EQ-5D-5L		X	X		X	X	X	X	X				11.7.1.7
WPAI:CHE		X			X	X		X	X				11.7.1.8
Subject assessment of safety													
Subject assessment of local tolerability		Weekly[18]						X	X				11.5.5
Investigator assessments of safety													
Vital signs	X	X						X	X			(X)	11.5.1
Physical examination	X							X	X			(X)	11.5.2
ECG	X		X					X	X			(X)	11.5.3
Chemistry, haematology (central laboratory)[19]	X	X		X	X	X	X	X	X			(X)	11.5.4
Serology, total IgE (central laboratory)	X												11.5.4
Urine pregnancy test[20]	X	X			X	X	X	X	X			(X)	11.5.4
Urinalysis (urine dipstick)[21]	X	X		X	X	X	X	X	X			(X)	11.5.4
Investigator assessment of local tolerability			X	X	X	X	X	X	X			(X)	11.5.5

	Screening	Treatment period						End of treatment[1]	Early termination, if applicable[2]	Follow-up[3]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**(9)**	**10**			
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**-**	**18[4]**			
Day	**-28[7] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**-**	**127[4]**			
Visit window (days)[8]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**			
Scoring of suspected local skin reaction related to IMP (if applicable)[22]			(X)	(X)	(X)	(X)	(X)	(X)	(X)			(X)	11.5.5
IMP patch test (if applicable)[22]			(X)	(X)	(X)	(X)	(X)	(X)	(X)			(X)	11.5.5.1
AEs	X	X	X	X	X	X	X	X	X	X	X	X	13
Other assessments													
New CHE lesions			X	X	X	X	X	X	X	X	X	(X)	9.2, 11.2.6
PK blood sample[23]			X		X			X	X				11.6
Photography of the whole hands, including wrists (selected trial sites)[24]		X			X	X		X	X			(X)	11.7.2
Return of eDiary (if applicable)								X[25]	X[26]		X		11.3
End of treatment/trial													
End-of-treatment form								X	X				11.8
End-of-trial form[27]								X	X	X	X	(X)	11.8

1) End-of-treatment assessments will be conducted at Week 16. For subjects who participate in the LTE trial (LP0133-1403), the Week 16 visit in the present trial will coincide with the baseline visit in the LTE trial.

2) 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. Subjects who discontinue IMP will also be asked to return at Week 16 (see footnote 5).

3) All subjects not participating in the LTE trial will be asked to attend a follow-up visit (performed via phone, but can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Subjects who will participate in the LTE trial will not be required to complete the safety follow-up period, as collection of safety data and safety surveillance will continue in the LTE trial.
4) 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.
5) Subjects who discontinue IMP treatment prior to Week 16 will be asked to return to the trial site at Week 16 (scheduled 112 days after baseline) for a primary endpoint visit.
6) Unscheduled visits 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. Assessments to be performed at unscheduled visits will be at the discretion of the investigator.
7) 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, the screening period can be extended up to 31 days.
8) 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 3).
9) The ICF(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.
10) If applicable, the ICF for the LTE trial should preferably be signed no later than the Week 16 visit in the present trial. The screening visit in the LTE trial will ideally coincide with the Week 12 visit in the present trial. The baseline visit of the LTE trial will coincide with the Week 16 visit in the present trial. Applicable data from the screening, baseline, Week 12, and Week 16 visits in the present trial will be transferred to the LTE trial to avoid duplicate assessments.
11) CHE subtype(s) will be classified according to local standard clinical practice. This includes patch testing in the EU. For subjects who have had a patch test done within 3 years prior to screening, the results of the most recent patch test (i.e. the CHE subtype[s]) 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. The patch test should preferably be completed prior to the baseline visit. If this is not possible, the patch test can be postponed but must be completed no later than the Week 8 visit. Patch testing is not mandatory in Canada but is recommended to be performed if this is considered standard clinical practice at the trial site.
12) Treatment compliance will be recorded daily by the subject in the eDiary from Day 1 onwards up to end of treatment/early termination.
13) All returned, opened IMP tubes will be weighed at the trial site.
14) Relevant prior/concomitant medication should be included from 3 months prior to baseline (Day 1) until end of trial (see Section 9.6).
15) Completion of HESD in the eDiary will be initiated at least 1 week prior to baseline (Day 1), but preferably 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 continue completing HESD in the eDiary until the primary endpoint visit at Week 16.
16) Includes Itch PGI-S, Pain PGI-S, and HESD PGI-S.
17) Includes Itch PGI-C, Pain PGI-C, and HESD PGI-C.
18) Subject 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.

19) Subjects do not have to be fasting for safety laboratory samples.
20) For women of childbearing potential (as defined in inclusion criterion no. 8, Section 8.2).
21) It will be at the investigator's discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.
22) Only applicable if the investigator suspects a local skin reaction related to IMP application based on the initial inspection of the subject's hands and the subject's assessment of local tolerability (Section 11.5.5). The investigator will score the local skin reaction (Section 11.5.5) and perform an IMP patch test with the subject's (blinded) IMP to classify the aetiology of the reaction (see Section 11.5.5.1).
23) The PK blood samples should be taken 2-6 hours post application of IMP.
24) Photography will require additional informed consent with the possibility to choose for which purpose (scientific and/or commercial) the photographs can be used. If deemed necessary (e.g. in case of poor quality), photographs can be retaken at the next visit or at an unscheduled visit.
25) Subjects who continue to the LTE trial must bring the eDiary to the Week 16 visit so the trial site staff can set up the eDiary for the LTE trial. Daily completion of the eDiary will continue in the LTE trial.
26) 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 endpoint visit at Week 16.
27) An end-of-trial form must be completed for all screened subjects. The form will be completed at the subjects' last trial visit (for subjects not participating in the LTE trial) or at the baseline visit in the LTE trial (for subjects participating in the LTE trial).

Abbreviations: AE = adverse event; CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index: ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension Health Questionnaire 5 Level; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; ICF = informed consent form; IGA-CHE = Investigator's Global Assessment for chronic hand eczema; IgE = immunoglobulin E; IMP = investigational medicinal product; LTE = long-term extension; PaGA = Patient's Global Assessment of disease severity; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; WPAI:CHE = Work Productivity and Activity Impairment: Chronic Hand Eczema.

5 Introduction and trial rationale

5.1 Chronic hand eczema

CHE is a serious 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).

The socioeconomic burden of CHE is significant. 5 studies 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, 13-16). CHE is associated with increased sick leave (17, 18) as well as job loss and change in jobs (5, 19, 20). Overall, CHE has a

significant detrimental effect on quality of life, work productivity, daily activities, and health care costs (13).

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 (21-23).

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 (24) 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.

Considering the paucity of approved therapies for the treatment of CHE, other therapeutic options are limited to those approved for other skin diseases with an inflammatory pathophysiology. These applied 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, 25), there is a high unmet medical need for new topical treatment of moderate to severe CHE with high efficacy in combination with a good safety profile especially for long-term use. New and better treatments would potentially improve the everyday lives of patients with moderate to severe CHE. Delgocitinib has the potential to address the unmet medical need associated with this serious disease.

5.2 Experience with IMP

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 (26).

In nonclinical studies, topically administered delgocitinib inhibited inflammation in rat and mouse models of contact dermatitis and reduced IL-31-induced scratching in mice. Topical administration of delgocitinib was also shown to improve the impaired skin barrier function in mouse models and in human skin (27).

The efficacy and safety of delgocitinib in CHE has been demonstrated in a phase 2a trial (LP0133-1180) with delgocitinib ointment 30 mg/g and in a phase 2b dose-ranging trial (LP0133-1273) with delgocitinib cream (1, 3, 8, and 20 mg/g).

In the LP0133-1180 trial, delgocitinib ointment 30 mg/g was applied twice daily for 8 weeks in adult subjects with mild to severe CHE. A statistically significant difference between delgocitinib ointment 30 mg/g and ointment vehicle was observed for the primary endpoint PGA treatment success at Week 8 (defined as achieving a Physician's Global Assessment score of 0 [clear] or 1 [almost clear] with a ≥2-step reduction from baseline).

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 dose and population selected for the present trial (delgocitinib cream 20 mg/g and subjects with moderate to severe CHE), 39.0% of subjects achieved IGA-CHE TS at Week 16 vs. 10.5% in the cream vehicle group ($p<0.05$) (28).

In both trials and for all doses, delgocitinib was well tolerated, and a low systemic exposure to delgocitinib was observed.

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

5.3 Trial rationale

There is a clear unmet need for new long-term treatment options in the treatment of patients suffering from moderate to severe CHE. The purpose of this phase 3 trial is to confirm the efficacy and evaluate the safety of twice-daily applications of delgocitinib cream 20 mg/g for 16 weeks compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE. The strength of delgocitinib cream is selected based on results from the dose-ranging phase 2b trial LP0133-1273, where delgocitinib cream 20 mg/g was shown to be effective and well-tolerated 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 (Section 5.2), delgocitinib cream has the potential to become an effective, well-tolerated, 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]) 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 (29) and ICH GCP (30), and in compliance with the approved protocol and applicable regulatory requirements.

The trial design chosen is regarded as scientifically justified 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 adults 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.

Pregnant or breastfeeding women and women trying to become pregnant will not be included in the trial. Women of childbearing potential must agree to use an acceptable birth control method to prevent pregnancy during the trial.

Trial subjects will be informed at the screening visit that trial procedures prior to baseline may warrant an alteration of their ongoing concomitant treatments. To ensure subjects' safety, investigators are informed only to enrol 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 symptoms during the treatment and follow-up periods, rescue treatment may be prescribed to trial subjects at the discretion of the investigator (see Section 9.5). Subjects will be instructed to contact the investigator if their CHE worsens significantly.

The subject'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.

5.5 Benefit/risk assessment

There is a clear unmet medical need for new long-term therapies for subjects with moderate to severe CHE. The only currently approved treatment option indicated for patients with CHE is alitretinoin, which is associated with significant safety precautions and is only indicated for the most severe disease state. Alitretinoin is only approved in few countries worldwide.

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

not permanently discontinue IMP prior to Week 16 will be invited to participate in an open-label LTE trial (LP0133-1403, hereafter referred to as 'the LTE trial').

Delgocitinib is a topically applied JAK inhibitor. Systemic JAK inhibitors are associated with potential adverse reactions and a black box warning concerning the risk of serious infections, malignancy, and thrombosis. These risks are not considered relevant for delgocitinib cream due to the very low systemic exposure observed in previous trials with topically applied delgocitinib.

No specific adverse drug reactions or important identified risks have been identified for delgocitinib cream during the 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 non-clinical and clinical data on delgocitinib is available in the current investigator's brochure.(31).

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 qualified medical personnel.

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 (32), FDA (33), and national health authorities in Europe and Canada 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 guideline.

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 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 and key secondary endpoints. Further details about the testing strategy, estimand strategy, and analysis of the primary and key secondary endpoints are provided in Sections 14.3.5 to 14.3.8.

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 14.3.9.

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

Objectives	Estimands				Endpoints
	Estimand type (primary or supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
Primary objective: To confirm the efficacy of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Composite' strategy.	Difference in response rates.	***Primary endpoint:*** • IGA-CHE TS at Week 16. ***Key secondary endpoints:*** • HECSI-75 at Week 16. • HECSI-75 at Week 8. • HECSI-90 at Week 16. • IGA-CHE TS at Week 8. • IGA-CHE TS at Week 4.
	First supplementary.	Response achieved without IEs in a world without COVID-19 pandemic.	Initiation of rescue treatment, permanent discontinuation of IMP independent of the COVID-19 pandemic, permanent discontinuation of IMP related to the COVID-19 pandemic. 'Pandemic modified composite' strategy.		
	Second supplementary for endpoints at Week 16.	Response achieved regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Treatment policy' strategy.		
	Primary.	Percentage change from baseline to Week 16 without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Composite' strategy.	Difference in mean percentage change.	***Key secondary endpoint:*** • Percentage change in HECSI score from baseline to Week 16.
	First supplementary.	Percentage change from baseline to Week 16 without IEs in a world	Initiation of rescue treatment, permanent discontinuation of IMP independent of the COVID-19 pandemic, permanent discontinuation of		

Objectives	Estimands				Endpoints
	Estimand type (primary or supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
		without COVID-19 pandemic.	IMP related to the COVID-19 pandemic. 'Pandemic modified composite' strategy.		
	Second supplementary for endpoints at Week 16.	Percentage change from baseline to Week 16 regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Treatment policy' strategy.		
Secondary objective: To confirm 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 adult subjects with moderate to severe CHE.	Primary.	Response achieved without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Composite' strategy.	Difference in response rates.	***Key secondary endpoints:*** • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 16.[1] • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 8.[1] • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 4.[1] • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 2.[1] • Reduction of HESD 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 8.[2]
	First supplementary.	Response achieved without IEs in a world without COVID-19 pandemic.	Initiation of rescue treatment, permanent discontinuation of IMP independent of the COVID-19 pandemic, permanent discontinuation of IMP related to the COVID-19 pandemic. 'Pandemic modified composite' strategy.		
	Second supplementary for endpoints at Week 16.	Response achieved regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Treatment policy' strategy.		

Objectives	Estimands				Endpoints
	Estimand type (primary or supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
					• Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4.[2] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16.[3] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 8.[3] • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 4.[3] • Reduction of DLQI score of ≥4 points from baseline at Week 16.[4] •
	Primary.	Change from baseline to Week 16 without IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Composite' strategy.	Difference in mean change.	***Key secondary endpoints:*** • Change in HESD itch score (weekly average) from baseline to Week 16. • Change in HESD score (weekly average) from baseline to Week 16. • Change in HESD pain score (weekly average) from baseline to Week 16. • Change in HEIS score from baseline to Week 16.[5] • Change in HEIS PDAL score from baseline to Week 16.[5] • Change in DLQI score from baseline to Week 16.
	First supplementary.	Change from baseline to Week 16 without IEs in a world without COVID-19 pandemic.	Initiation of rescue treatment, permanent discontinuation of IMP independent of the COVID-19 pandemic, permanent discontinuation of IMP related to the COVID-19 pandemic. 'Pandemic modified composite' strategy.		

Objectives	Estimands				Endpoints
	Estimand type (primary or supplementary)	Interpretation	Intercurrent events and strategy	Population level summary	
	Second supplementary for endpoints at Week 16.	Change from baseline to Week 16 regardless of IEs.	Initiation of rescue treatment, permanent discontinuation of IMP. 'Treatment policy' strategy.		

Note: The order of endpoints in this panel does not reflect that in the testing hierarchy, see Section 14.3.5 for details.

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

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

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

4) Among subjects with a baseline DLQI score ≥4 points.

5) As the HEIS is not assessed at the primary endpoint visit, the second supplementary estimand is not applicable for this endpoint.

Abbreviations: CHE = chronic hand eczema; COVID-19 = coronavirus disease 2019; DLQI = Dermatology Life Quality Index; 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; HEIS = Hand Eczema Impact Scale; 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; IMP = investigational medicinal product; PDAL = Proximal Daily Activity Limitations.

Panel 4: Secondary and exploratory objectives and endpoints

Objectives	Endpoints
Secondary objective	**Secondary endpoint**
To evaluate the safety of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	• Number of treatment-emergent[1] AEs from baseline up to Week 16 (Week 18 for subjects not participating in the LTE trial) per subject.
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 adult subjects with moderate to severe CHE over time.	*Efficacy* • IGA-CHE TS at Weeks 1, 2, and 12. • HECSI-75 at Weeks 1, 2, 4, and 12. • HECSI-90 at Weeks 1, 2, 4, 8, and 12. • Percentage change in HECSI score from baseline to Weeks 1, 2, 4, 8, and 12. • Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 1 and 12.[2] • Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16.[3] • Time to reduction of HESD itch score (weekly average) of ≥4 points.[2] • Change in HESD itch score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12. • Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 1, 2, and 12.[4] • Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16.[5] • Time to reduction of HESD score (weekly average) of ≥4 points.[4] • Change in HESD score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12. • Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 1, 2, and 12.[6] • Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16.[7] • Time to reduction of HESD pain score (weekly average) of ≥4 points.[6] • Change in HESD pain score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12. • Change in HESD (weekly average for each individual symptom [excluding itch and pain]) score from baseline to Week 16. *Health-related quality of life and efficacy* • Change in HEIS score from baseline to Weeks 1, 2, 4, 8, and 12. • Reduction of HEIS score of ≥1.5 points at Weeks 1, 2, 4, 8, 12, and 16.[8] • Change in HEIS PDAL score from baseline to Weeks 1, 2, 4, 8, and 12.

	• Reduction of HEIS PDAL score of ≥1.5 points at Weeks 1, 2, 4, 8, 12, and 16.[9] • Change in HEIS (each individual domain [excluding PDAL]) score from baseline to Weeks 1, 2, 4, 8, 12, and 16. • Reduction in DLQI score of ≥4 points at Weeks 1, 4, 8, and 12.[10] • Change in DLQI score from baseline to Weeks 1, 4, 8, and 12.
To evaluate the effect of twice-daily applications of delgocitinib cream 20 mg/g on health-related quality of life and work productivity compared with cream vehicle in the treatment of adult subjects with moderate to severe CHE.	• Change in EQ-5D-5L index score from baseline to Weeks 1, 4, 8, 12, and 16. • Change in EQ-5D-5L visual analogue scale score from baseline to Weeks 1, 4, 8, 12, and 16. • Change in WPAI:CHE absenteeism score from baseline to Week 4, 8, and 16.[11] • Change in WPAI:CHE presenteeism score from baseline to Week 4, 8, and 16.[11] • Change in WPAI:CHE work productivity loss score from baseline to Week 4, 8, and 16.[11] • Change in WPAI:CHE activity impairment score from baseline to Week 4, 8, and 16.

1) 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.
2) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
3) Among subjects with a baseline HESD itch score (weekly average) ≥3 points.
4) Among subjects with a baseline HESD score (weekly average) ≥4 points.
5) Among subjects with a baseline HESD score (weekly average) ≥3 points.
6) Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
7) Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
8) Among subjects with a baseline HEIS score ≥1.5 points.
9) Among subjects with a baseline HEIS PDAL score ≥1.5 points.
10) Among subjects with a baseline DLQI score ≥4 points.
11) Among subjects with paid work at baseline.

Abbreviations: AE = adverse event; CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index; EQ-5D-5L = EuroQol 5-Dimension Health Questionnaire 5 Level; 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; HEIS = Hand Eczema Impact Scale; 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; PDAL = Proximal Daily Activity Limitations; WPAI:CHE = Work Productivity and Activity Impairment: Chronic Hand Eczema.

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 confirm the efficacy and evaluate the safety of delgocitinib cream 20 mg/g applied twice daily for 16 weeks in adult subjects with moderate to severe CHE. 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, 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 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. 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 Canada and Europe. This includes patch testing in Europe. 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 will be performed. The patch test should preferably be completed prior to the baseline visit. If this is not possible, the patch test can be postponed but must be completed no later than the Week 8 visit. Patch testing is not mandatory in Canada but is recommended to be performed if this is considered standard clinical practice at the trial site.

Treatment period (Week 0 to Week 16)
At baseline (Day 1), the subjects' eligibility to enter the trial will be confirmed. Eligible subjects will be randomised 2:1 to either delgocitinib cream 20 mg/g or cream vehicle.

Subjects 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 on Day 1 after all baseline

assessments have been carried out. All subsequent IMP applications will be performed by the subjects 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. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16. Efficacy and safety assessments during the treatment period will be performed as described in the schedule of trial procedures (Section 4).

At the Week 12 visit, subjects may be invited to participate in the LTE trial. For subjects who continue to the LTE trial, the following visits will (ideally) coincide to facilitate a seamless transition between the trials and continuous treatment with IMP (if applicable):

- The Week 12 visit in the present trial will ideally coincide with the screening visit in the LTE trial.
- The Week 16 visit in the present trial will coincide with the baseline visit in the LTE trial. Subjects must complete the 16-week treatment period (i.e. must not permanently discontinue IMP prior to Week 16) and the Week 16 visit in the present trial to be eligible for the LTE trial.

All eligible subjects who do not permanently discontinue IMP prior to Week 16 will be invited to participate in the LTE trial.

Follow-up period (Week 16 to Week 18)
Those subjects not participating in the LTE trial will attend a follow-up visit (performed via phone, but can be a site visit if needed) approximately 2 weeks after the last IMP application for assessment of safety. Note that for subjects who permanently discontinue IMP, the 2-week follow-up period will start at the time of last IMP application.

Subjects who will participate in the LTE trial will not be required to complete the follow-up period, as collection of safety data and safety surveillance will continue in the LTE trial.

7.2 Number of subjects needed

A total of 450 subjects will be randomised 2:1 to delgocitinib cream 20 mg/g or cream vehicle. The statistical power considerations for this sample size are described in Section 14.1.

This trial will be conducted at approximately 55 sites in Europe and Canada. The anticipated minimum number of randomised subjects per trial site is 6, and the maximum number of subjects per trial site is 30.

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 (for subjects not transferring to the LTE trial). For subjects transferring to the LTE trial, the subject is considered to have completed the trial if attending the Week 16 visit in this trial and the baseline visit of the LTE trial.

For subjects not participating in the LTE trial, end of trial is defined as attending the last visit in this trial. For subjects participating in the LTE trial, the end of the present trial is defined as attending the baseline visit in the LTE trial.

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.

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 at the visits specified in Panel 2. It will be recorded in the 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 informed consent has been obtained prior to any protocol-related procedures.
2. Age 18 years or above at screening.
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. HESD itch score (weekly average) of ≥4 points at baseline. The baseline weekly average will be calculated from daily assessments of itch severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 itch scores out of the 7 days is required to calculate the baseline average score.
6. 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 EU 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.

7. Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.
8. 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 or a younger girl 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 postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or 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 fulfil any of the following criteria:

1. Concurrent skin diseases on the hands, e.g. tinea manuum.
2. Active AD requiring medical treatment in regions other than the hands and feet.
3. Active psoriasis on any part of the body.
4. Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
5. Clinically significant infection (e.g. impetiginised hand eczema) on the hands.
6. 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).
7. Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.
8. Previous or current treatment with JAK inhibitors (including delgocitinib/ LEO 124249), systemic or topical.
9. Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.
10. Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.

11. Other transdermal or cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
18. 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.
19. 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.

20. 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.
21. Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
22. ALT or AST level ≥2.0×ULN at screening.
23. Known or suspected hypersensitivity to any component(s) of the IMP (refer to Section 9.1 for an overview of all excipients).
24. Current participation in any other interventional clinical trial.
25. Previously randomised in this clinical trial.
26. 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 informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject ID will be assigned by a central 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 informed consent form 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 informed consent to participate in the trial 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 (34) 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 informed consent(s).
- 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 AEs and 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 will need to sign a new ICF.

9 Treatments

9.1 Trial product description

Panel 5: Identification of IMPs

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	15 g	LEO Pharma A/S
Cream vehicle	Cream	Vehicle	15 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 IMP

The IMP (delgocitinib cream 20 mg/g or cream vehicle) 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.

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, fingertips, and wrists. 1 tube of 15 g delgocitinib cream is considered sufficient for treatment of the whole surface of hands, fingers, fingertips, and wrists twice daily for 1 week; 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 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 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 Week 16 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 the visits scheduled in Section 4. 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 2:1 ratio to receive treatment with either delgocitinib cream 20 mg/g or cream vehicle. The randomisation will be stratified by region (Europe or North America) and 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, healthcare professionals 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 the unblinding IRT system or unblinding CRO. Only the investigator should be unblinded and keep treatment allocation confidential. LEO Pharma staff must remain blinded until the end of the trial.

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) 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 initiated to treat intolerable CHE symptoms during the treatment and follow-up periods. It will be recorded in the eCRF if a medication 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 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 treatment for CHE (yes, no).
- 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, cutaneous, subcutaneous, transdermal, ophthalmic, intramuscular, respiratory [inhalation], intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other [if other, a specification must be provided]). For cutaneous 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 (approximately 2 inches) of the IMP 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 must 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. 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 (from screening until end of trial for the individual subject as defined in Section 7.3). Details regarding prohibited medications and procedures prior to screening and baseline are described in Section 8.3.

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] or 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 transdermal or cutaneously applied therapy on the hands (except for the IMP and the subject's own emollient).	7 days prior to baseline.	End of trial.

Medication/procedure	Prohibited from	Prohibited to
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 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 foot eczema, as long as this does not interfere with the trial (i.e. the subjects need to use gloves when applying treatment).
3) Subjects are allowed to receive vaccines during the trial.

Abbreviations: IgE = immunoglobulin E; 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 for the first 14 days of wash-out of systemic treatment to alleviate significant worsening of their CHE.

As described in Section 9.5, prohibited medications 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 IMPs will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 (35), 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 IMP 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.

In addition, all eligible subjects who complete the treatment period (i.e. who do not permanently discontinue IMP prior to Week 16) will be invited to participate in the LTE trial.

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 13.3 and 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 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

A subject may:

- withdraw from the trial (i.e. stop all further protocol-defined trial activities) or
- permanently discontinue trial treatment (i.e. stop all further trial treatment but continue to participate in protocol-defined trial activities as outlined in Section 10.3)

at any time if the subject, 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 the primary endpoint visit and the safety follow-up visit. If a subject does not agree to attend these visits, the subject withdraws from the trial. To obtain the most representative 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, they 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.
- Positive patch test reaction to the IMP
- 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.
- 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 agrees.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 11.8.

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.

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 and reschedule the missed visit as soon as possible and counsel the subject 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. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

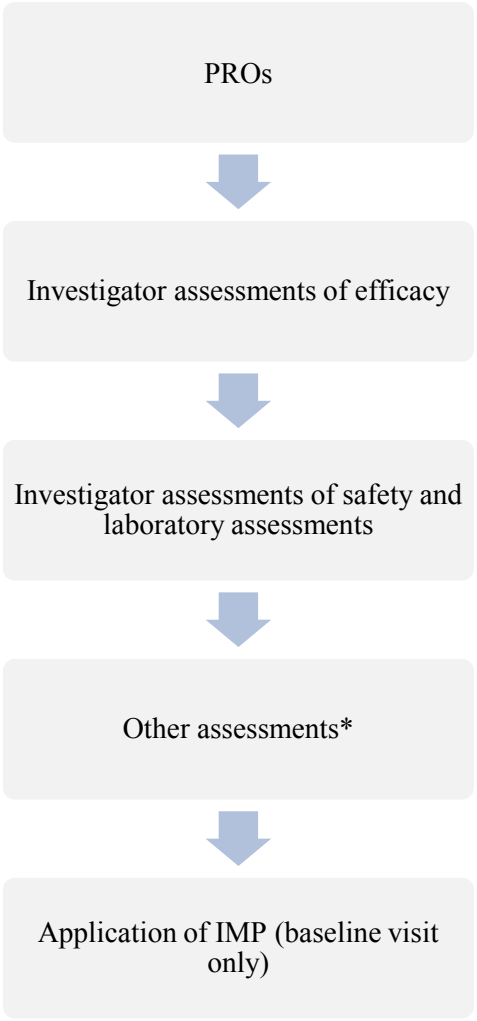
11 Trial assessments and procedures

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.

Assessments and procedures at each trial visit are recommended to be performed in the order shown in Panel 8.

Panel 8: Sequence of assessments



* PK samples and/or photographs.

Abbreviations: IMP = investigational medicinal product; PK = pharmacokinetic; PRO = patient-reported outcome.

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).

To reduce inter-rater variability, the same investigator should perform all the evaluations for a given subject throughout the entire trial period, whenever possible.

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.

11.2.2 Fitzpatrick skin type

The subject's skin type will be recorded using the Fitzpatrick skin classification (Panel 9).

Panel 9: 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.

11.2.3 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. 6:
  - Has the subject fulfilled the trial inclusion criterion no. 6 based on having inadequate response to treatment with TCS during the last 12 months? (yes, no).
  - Has the subject fulfilled the trial inclusion criterion no. 6 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).
- Onset and worsening of CHE symptoms during work (yes, no, unknown).
- Improvement of CHE symptoms when not at work (yes, no, unknown).
- Healing of CHE on vacations (yes, no, unknown).
- Recurrence of CHE symptoms upon returning to work (yes, no, unknown).
- Worsening of CHE symptoms when not at work (yes, no, unknown).
- Wet-work exposure (defined as skin exposed to liquids longer than 2 hours per day, using occlusive gloves longer than 2 hours per day, or more than 20 hand washes per day) (yes, no, unknown).
- Number of daily hand washes (0-10, 11-20, >20).
- Employment status during the past year (part-time employed, full-time employed, not employed). In case more than one option applies, the status that the subject had for the longest period during the past year should be captured.
  - If employed during the past year: Days home from work due to CHE during the last year (yes, no).
  - If yes: Total number of days home from work due to CHE during the last year (<7 days, 7-21 days, >21 days).
- 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.

11.2.4 Classification of chronic hand eczema

The investigator will determine the CHE subtype(s) according to the definitions in Panel 10. The classification of CHE will be done according to standard clinical practice and thus may differ across regions and countries.

In Europe, the classification of CHE will include mandatory 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 will be performed. The patch test should preferably be completed prior to the baseline visit. If this is not possible, the patch test can be postponed but must be completed no later than the Week 8 visit (Section 4). Patch testing is not mandatory in Canada but 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) 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 10: 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.

11.2.5 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.

11.2.6 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.

11.3 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. Subjects who will participate in the LTE trial must bring the eDiary to the Week 16 visit, so the trial site staff can set up the eDiary for the LTE trial. Daily completion of the eDiary will continue in the LTE trial.

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 11.5.5).

11.4 Efficacy assessments

11.4.1 Investigator's Global Assessment for chronic hand eczema (IGA-CHE)

The IGA-CHE is an instrument used in the phase 2b trial with delgocitinib (LP0133-1273) and has been further revised for the current trial. 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 11). 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 11: Investigator's Global Assessment for chronic hand eczema (IGA-CHE)

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 (HECSI)

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 regions (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales (36).

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 12). The investigator also rates the extent of the lesions by assessing82 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 12). 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 13). 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 12: 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 13: 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 (HESD)

The HESD is an instrument used in the phase 2b trial with delgocitinib (LP0133-1273) and has been further revised for the current trial. The HESD is a [redacted]-item PRO instrument designed to assess severity of CHE signs and symptoms. Subjects will assess the worst severity of [redacted] individual signs and symptoms of CHE ([redacted]) 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 [redacted] items. 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, pulse, and body temperature) must be assessed according to the schedule of trial procedures (Section 4). Vital signs will be measured in a sitting position 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. 20).

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, pulse, and body temperature) 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 thorough physical examination of the subject including whole body inspection of the skin, auscultation of heart, lungs, and abdomen, palpation of the abdominal organs, and basic neurological status 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 trial (respecting exclusion criterion no. 20). 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 results 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 trial (respecting exclusion criterion no. 20).

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 Laboratory testing

11.5.4.1 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
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils % neutrophils Lymphocytes % lymphocytes Monocytes % monocytes Eosinophils % eosinophils Basophils % basophils Thrombocytes
Urinalysis[2]	**Serology[3,4]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Hepatitis B virus surface antigen Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody Immunoglobulin E

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Urine samples will be tested at the trial site (dipstick). It will be at the investigator's discretion to decide whether a urine sample should be sent to the central laboratory for microscopic examination (WBC; RBC; epithelial cells, squamous; epithelial cells, transitional; epithelial cells, renal tubular; hyaline casts; WBC casts; RBC casts; waxy casts; granular casts; calcium oxalate crystals; uric acid crystals; triphosphate crystals; yeast; and bacteria).
3) Measured at screening only.
4) In case additional analyses 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.

Abbreviations: HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein; RBC = red blood cells; WBC = white blood cells.

11.5.4.2 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, 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. 20).

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.

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 investigator's discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.

Women of childbearing potential will have a urine pregnancy test performed at the trial site at screening and 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 test 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 randomisation will be reported as an AE in accordance with Section 13.3.

11.5.5 Assessment of local tolerability

Subjects and investigators will each 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 subject 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 15.

Panel 15: 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.

The investigator will assess whether he/she suspects a local skin reaction related to application of the IMP. If the investigator suspects a local skin reaction related to application of the IMP, the skin reaction will be scored according to the Berger and Bowman scales in

Panel 16. The scoring should only assess skin signs suspected to be related to application of the IMP and not signs or symptoms related to the subject's CHE.

Following scoring according to the Berger and Bowman scales, an IMP patch test will be performed to confirm a possible diagnosis of allergic contact dermatitis caused by the IMP, see procedure described in Section 11.5.5.1. The aetiology of the local skin reaction will be captured in the eCRF and the final diagnosis will be captured as an AE.

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).

Reporting in eCRF
For the subject's assessment of local tolerability at the end-of-treatment/early termination visit, the highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF.

For the investigator's assessment of local tolerability, it will be reported in the eCRF if the investigator suspects a local skin reaction to be related to application of IMP (yes, no). If the investigator suspects a local skin reaction to be related to application of IMP, the scores in Panel 16 (one score for Scale 1 and zero, one, or multiple scores for Scale 2) will be recorded in the eCRF. The aetiology of the local skin reaction (irritant contact dermatitis caused by IMP, allergic contact dermatitis caused by IMP [requires a positive IMP patch test, see Section 11.5.5.1], or other [specify]) will be captured in the eCRF and the final diagnosis will be captured as an AE.

Panel 16: Berger and Bowman scoring scales if investigator suspects a local skin reaction related to IMP application

Scale 1	
Skin appearance	**Score**
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal oedema or minimal papular response	2
Erythema and papules	3
Definite oedema	4
Erythema, oedema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the test field	7

Select the appropriate score (only one score) if a local skin reaction is suspected to be related to application of the IMP.

Scale 2	
Other observations	**Letter score**
Slightly glazed appearance	A
Markedly glazed appearance	B
Glazing with peeling and cracking	C
Glazing with fissures	F
Film of dried serous exudates covering all or part of the patch site	G
Small petechial erosions and/or scabs	H

Other observations (multiple scores allowed) will be recorded if applicable.

11.5.5.1 IMP patch test procedure

Only if the investigator suspects a local skin reaction related to application of the IMP, an IMP patch test will be performed following scoring according to the Berger and Bowman scales described in Section 11.5.5. The subject's own (blinded) IMP will be used for the IMP patch test. To avoid contamination, approximately 1 cm of cream should be squeezed out of the tube before performing the IMP patch test. If this is not possible, a new tube of IMP will be used (dispensed at the given visit) for the procedure. The trial site staff will apply a small amount of IMP 'as is' in a patch test chamber which will be placed on the subject's upper back and secured with hypoallergenic tape. The patch will be removed after 2 days. The investigator will perform readings of any apparent patch test reaction 3-4 days and 5-7 days after applying the patch. If a photography device is available at the site, the positive patch test reaction

should be documented by photography. The patch test reaction will be scored (Panel 17) according to guidelines (37). If the subject has a positive reaction to the IMP patch test, the subject must discontinue treatment with IMP.

Further instructions for the IMP patch test procedure, scoring of the IMP patch test reactions, and photographing positive patch test reactions will be provided in a separate IMP patch test manual.

Panel 17: Patch test reading criteria

Morphology	Patch test reaction score
No reaction	Negative reaction
Faint erythema only	Doubtful reaction
Erythema, infiltration, possibly papules	Weak positive reaction
Erythema, infiltration, papules, vesicles	Strong positive reaction
Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Reading criteria for patch test reactions based on morphology, modified from Johansen et al. (37).

Reporting in eCRF

For the IMP patch test, the date of placement of the IMP patch test, the date of each reading, and the patch test reaction scores will be recorded in the eCRF (negative reaction, doubtful reaction, weak positive reaction, strong positive reaction, extreme positive reaction, or irritant reaction).

The photograph(s) of any positive patch test reactions will be uploaded to the eCRF.

11.6 Pharmacokinetic assessments

Blood samples for PK assessments should be taken 2-6 hours after application of IMP at the visits specified in 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 date and time of the last IMP application prior to the PK sample must be recorded in the eCRF.

11.7 Other assessments

11.7.1 Patient-reported outcomes (health-related quality of life and work productivity)

11.7.1.1 Overview

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 following PROs will be completed in an electronic device by the subjects at the trial sites at the visits specified in the schedule of trial procedures (Section 4) in the following order:

- Itch PGI-S.
- Itch PGI-C.
- Pain PGI-S.
- Pain PGI-C.
- HESD PGI-S.
- HESD PGI-C.
- HEIS.
- PaGA.
- DLQI.
- EQ-5D-5L.
- WPAI:CHE.

11.7.1.2 Patient Global Impression of Severity (PGI-S) questionnaires

The PGI-S is a 1-item questionnaire designed to assess the subject's global perception of their itch, pain, or chronic hand eczema signs and symptoms over the past week on a 4-point categorical response scale ('none', 'mild', 'moderate', or 'severe').

The subjects will be asked to complete 3 PGI-S questionnaires, one each to assess itch (Itch PGI-S), pain (Pain PGI-S), and their overall impression of their chronic hand eczema (HESD PGI-S) (Panel 18).

The PGI-S questionnaires will be completed at the trial site according to the schedule of trial procedures in Section 4.

Panel 18: Patient Global Impression of Severity (PGI-S) questionnaires

Itch PGI-S	**Pain PGI-S**	**HESD PGI-S**
Please choose the response below that best describes the severity of any **itch** on your hands over the **past week**	Please choose the response below that best describes the severity of any **pain** on your hands over the **past week**	Please choose the response below that best describes the severity of your **hand eczema signs and symptoms** over the **past week**
Response scale: □ None □ Mild □ Moderate □ Severe	Response scale: □ None □ Mild □ Moderate □ Severe	Response scale: □ None □ Mild □ Moderate □ Severe

11.7.1.3 Patient Global Impression of Change (PGI-C) questionnaires

The PGI-C is a 1-item questionnaire designed to assess the subject's impression of changes (38). From 5 response options ('much better', 'a little better', 'no change', 'a little worse', or 'much worse'), the subjects have to select the one response that best describes the overall change in their itch, pain, or chronic hand eczema signs and symptoms since they started IMP treatment.

The subjects will be asked to complete 3 PGI-C questionnaires, one each to assess the change in itch (Itch PGI-C), pain (Pain PGI-C), and their overall impression of their chronic hand eczema (HESD PGI-C) (Panel 19).

The PGI-C questionnaires will be completed at the trial site according to the schedule of trial procedures in Section 4.

Panel 19: Patient Global Impression of Change (PGI-C) questionnaires

Itch PGI-C	**Pain PGI-C**	**HESD PGI-C**
Please choose the response below that best describes the overall change in any **itch** on your hands since you started taking the study medication	Please choose the response below that best describes the overall change in any **pain** on your hands since you started taking the study medication	Please choose the response below that best describes the overall change in your **hand eczema signs and symptoms** since you started taking the study medication
Response scale: □ Much better □ A little better □ No change □ A little worse □ Much worse	Response scale: □ Much better □ A little better □ No change □ A little worse □ Much worse	Response scale: □ Much better □ A little better □ No change □ A little worse □ Much worse

11.7.1.4 Hand Eczema Impact Scale (HEIS)

The HEIS is an instrument used in the phase 2b trial with delgocitinib (LP0133-1273) and validated based on these data. HEIS includes [redacted] items addressing the subject's perception of the impact of hand eczema on [redacted] over the past 7 days. Each item is scored on a 5-point scale (0='not at all', 1='a little', 2='moderately', 3='a lot', 4='extremely'). The HEIS score is the average of the [redacted] items. The highest possible score is 4, and a high score is indicative of a high impact. 6 domain scores can be calculated for HEIS: PDAL (average of [redacted] items), [redacted]. The HEIS will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.5 Patient's Global Assessment of disease severity (PaGA)

Subjects will make a global assessment of the severity of their hand eczema. The assessment will be made using a 5-point scale (0='clear', 1='almost clear', 2='mild', 3='moderate', 4='severe') and will be based on the severity of their hand eczema at the time of the assessment (Panel 20). The PaGA will be completed by the subjects in an electronic device at the trial site according to the schedule of trial procedures in Section 4.

Panel 20: Patient's Global Assessment of disease severity (PaGA)

Rate the severity of your **hand eczema** right **now**. In making your rating you should think about the severity of **any hand eczema symptoms** you have right now, including scaling, blistering, cracking, swelling, redness, or thickening of the **skin on your hands**.

- □ Clear (No hand eczema symptoms)
- □ Almost clear (Only slight redness, no other hand eczema symptoms)
- □ Mild
- □ Moderate
- □ Severe

11.7.1.6 Dermatology Life Quality Index (DLQI)

The DLQI 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, daily activities, leisure, work or school, personal relationships, and the treatment (39). 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 DLQI score is the sum of the 10 items (score ranging from 0 to 30); a high score is indicative of a poor quality of life. The DLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.7 EuroQol 5-Dimension Health Questionnaire 5 Level (EQ-5D-5L)

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group to provide a simple, generic measure of health for clinical and economic appraisal (40). The EQ-5D-5L is a self-administered questionnaire used to assess health status 'today' and is divided into 2 sections.

The first section includes 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Each dimension will be assessed by the subject using a 5-point scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'unable to/extreme problems'). The EQ-5D-5L index score is derived from the 5 dimensions and has been converted from the 5L system to the 3L system using the EQ-5D-5L crosswalk value set. The index score ranges from -0.594 to 1.0 (based on the UK country-specific value set), with a higher score indicating a better health status.

The second section consists of a vertical visual analogue scale anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine'). The EQ-5D-5L will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.8 Work Productivity and Activity Impairment: Chronic Hand Eczema (WPAI:CHE)

The impact of CHE on the subject's ability to work and perform regular activities will be assessed by WPAI:CHE, which is an instrument to measure impairments in both paid work and unpaid work (41). The WPAI:CHE consists of 6 items, and scores can be calculated for 4 domains, each reflecting the percentage impairment due to CHE during the past 7 days, with higher numbers indicating greater impairment and less productivity:

- Absenteeism: percentage work time missed due to CHE for those who were currently employed.
- Presenteeism: percentage impairment while working due to CHE for those who were currently employed and actually worked in the past 7 days.
- Work productivity loss: percentage overall work impairment due to CHE for those who were currently employed.
- Activity impairment: percentage activity impairment due to CHE for all respondents.

The WPAI:CHE will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.2 Photography (selected trial sites)

Subjects at selected trial sites will be asked to participate in a photography component of the trial which involves digital photography assessments to capture disease status over time. Participation in this photography component requires that the subject provides additional informed consent with the possibility to choose for which purpose (scientific and/or commercial) the photographs can be used.

Digital colour photographs will be taken of the subjects' whole hands (front and back) including wrists according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the photo(s) was taken; if not, a reason should be provided. If deemed necessary (e.g. in case of poor quality), photographs can be retaken at the next visit or at an unscheduled visit.

Photography equipment, standards, and procedures are provided to the trial sites by the central photography vendor. Instructions for photography will be provided to the sites in a photography manual.

The photographs will have no other subject identifier than the subject ID, year of birth, visit number, and date, and will be transmitted electronically to the photography vendor using a secure file transfer protocol.

The photographs must be included as part of the individual subject source documentation.

Depending on the subject's consent, LEO Pharma may use the photographs in publications, posters, and similar types of information material or media targeting patients and healthcare professionals. The photographs may also be part of training material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected by blinding or covering any potential identifying features in the photos.

11.8 End of trial

End-of-treatment form
An end-of-treatment form will be completed in the eCRF for all randomised subjects exposed to IMP when they have had their last application 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 application 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 (for subjects not participating in the LTE trial) or attended the baseline visit for the LTE trial (for subjects participating in the LTE trial). 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, screen failure (failure to meet eligibility criteria), or other.
- Was the reason for not completing the trial related to COVID-19?
- Was the subject transferred to the extension trial (LP0133-1403)?

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' is selected, it will be recorded whether the subject withdrew informed consent or not.

11.9 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 77 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value; however, the total volume of blood drawn will be less than that taken during a blood donation (approximately 500 mL).

11.10 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 is a randomised, double-blind, vehicle-controlled, parallel-group, multi-site trial, which 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 and North America. High-quality trial sites with shared standards of practice will be selected.

Subjects with hand eczema represent a heterogeneous population as hand eczema 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. The randomisation 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) and region (Europe or North America). IGA-CHE severity is viewed as a strong prognostic factor while regional differences could occur given the heterogeneous population.

The vehicle control group will serve as reference and has been added to establish the efficacy and safety of delgocitinib cream in a blinded trial design. The randomisation ratio of 2:1 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. Eligible subjects who complete the Week 16 visit (and who do not permanently discontinue IMP prior to Week 16) will be invited to continue in the LTE trial (conducted under a separate clinical trial protocol).

Topical application is considered the preferred route of administration for treatments for CHE, since CHE is a cutaneous disease characterised by few lesions affecting small 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. Furthermore, a patient insights meeting supports that topical treatment for CHE is preferred over systemic treatment from a patient point of view.

The dose and treatment duration of delgocitinib cream are based on data from the phase 2b dose-ranging trial LP0133-1273, showing a clear 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. The IGA-CHE TS response rates at Week 16 were similar in the delgocitinib cream 8 mg/g and

20 mg/g groups (41.5% and 39.0%, vs. 10.5% in the cream vehicle group). The complete absence of safety concerns at both strengths 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. Thus, the 20 mg/g dose was selected.

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. However, 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 endpoint at Week 16.

The trial population is selected to reflect the general adult population with CHE to ensure that the trial results will be generalisable to the target population. No upper age limit is included, and 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 confirm the efficacy of delgocitinib in improving the severity and extent of CHE. 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 score 1 adjustment as recommended by the FDA. The IGA-CHE was used in the phase 2b trial (LP0133-1273) and has been further revised for the current trial. HECSI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of CHE (42).

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 (AEs) and serious adverse events (SAEs) 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 has signed the ICF until end of trial (as defined in Section 7.3).

AEs must be assessed by a physician.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, e.g.: 'How have you felt since I saw you last?'. Subject-reported local tolerability will be queried specifically (see Section 11.5.5) and reported as AE(s) if deemed relevant by the investigator. In case of suspected local skin reaction related to IMP application, the final diagnosis based on the IMP patch test result (see Section 11.5.5.1) must be recorded as an AE. 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.

To avoid duplicate reporting of AEs in the present trial and the LTE trial, any AE with onset before the baseline visit in the LTE trial should be recorded as an AE in the present trial. If ongoing at the screening or baseline visit in the LTE trial, the AE should also be recorded as medical history in the LTE trial. An AE with onset after the baseline visit in the LTE trial should be recorded as an AE in the LTE trial.

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 but not later than within 24 hours of first 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 7226 3287

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 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, the Investigator's Brochure Section 7.3, edition 4.0 and subsequent updates must be used (31).

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 (30), 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 21 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 21.

Panel 21: 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)
Deep vein thrombosis	Risk factors: • Previous thromboembolism (record as medical history) • Family history of deep vein thrombosis/pulmonary embolism or other cardiovascular/blood-clotting disorders • Genetic disorders that might increase the risk for thrombosis (record as medical history) • History of cancer (record as medical history) • Recent venous catheter placement (record as medical history) • Current smoker (record as tobacco smoking history) • Hormonal contraception/hormonal replacement therapy (record as concomitant medication) • Trauma or surgery (record as per protocol) • Immobilisation (e.g. prolonged bed rest or sitting for long periods) Method of verification: • Clinical evaluation • Image-verified • Laboratory test(s)
Pulmonary embolism	

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 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 defined in the protocol.

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 the 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) until the subject's last visit in the trial. For subjects completing the treatment period and not participating in the LTE trial, this will be the safety follow-up visit. For subjects prematurely discontinuing IMP prior to Week 16, the last visit will in most cases be the primary endpoint visit. For subjects who will participate in the LTE 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 in the present trial, or until the final outcome is determined, whichever comes first. This could be at a safety follow-up visit via phone or at an LTE trial site visit. 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 period, 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.*" (43).

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

14.1 Sample size

A total of 450 subjects will be randomised 2:1 to delgocitinib cream 20 mg/g or cream vehicle. The sample size is chosen to ensure that sufficient safety information including adequate long-term exposure data is collected.

With a one-sided significance level of 2.5%, a sample size of 450 subjects randomised will provide at least 99% power for detecting a treatment difference for the primary endpoint, assuming an IGA-CHE TS response rate at Week 16 of 40% vs. 10% for delgocitinib cream 20 mg/g and cream vehicle, respectively. The assumptions on response rates are based on results from the phase 2b dose-ranging trial (LP0133-1273).

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 FAS and will be analysed based on the randomised treatment allocation. Exclusions from the FAS 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 subject from the FAS, 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 Aspects related to the COVID-19 pandemic

As the implications of the COVID-19 pandemic might, extraordinarily, influence trial events and data in manners not foreseen by the protocol, this section introduces the statistical considerations for handling of events related to the pandemic for primary and key secondary endpoints.

A supplementary estimand, 'pandemic modified composite', is introduced for analysis of the primary and key secondary endpoints. This estimand addresses permanent discontinuation of IMP related to the pandemic as an IE. Details are described in Section 14.3.6.

Interruption of IMP during the treatment period is not expected as per protocol and hence not considered as an IE. This is supported by the assumption that LEO Pharma will secure availability of IMP at all times. In addition, as the IMP supply is secured, the IE initiation of rescue medication will be considered independent of the pandemic (see Appendix 7).

The causal relationship of permanent discontinuation of IMP related to the pandemic will be recorded in the eCRF (see also Section 10.2).

Missing or 'treated as missing' data related to the COVID-19 pandemic
At scheduled visits, it will be recorded in the eCRF whether data are missing due to the pandemic. As a consequence of the pandemic and associated local preventive measures, subjects may miss an entire visit, or visits may be performed via phone or video, thereby only allowing for a subset of planned assessments to be collected.

Observed data after permanent discontinuation of IMP related to the pandemic will be 'treated as missing' and imputed assuming MAR. Missing data related to the pandemic will be imputed assuming MAR.

It should be noted that a subject may have missing data related to the pandemic, even though the subject has not experienced an IE related to the pandemic.

An overview of how observed and missing data will be handled according to the IEs and their relatedness to the pandemic is presented in Panel 23 for the primary analysis for estimands. Details of the analysis are described in Section 14.3.6.

14.3.2 Disposition of subjects

The reasons for permanent discontinuation of IMP and for not completing the trial will be presented for all randomised subjects 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 FAS, permanently discontinuing IMP, and not completing the trial by treatment group and overall.

14.3.3 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and by treatment group.

Demographics include age, sex, ethnicity, and race. Other baseline characteristics include height, weight, body mass index, region, country, total IgE, Fitzpatrick skin type, CHE history, CHE treatment history, exogenous risk factors for CHE, 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.

Baseline investigator efficacy assessments and baseline HESD assessments related to the primary and key secondary endpoints will be presented by region, baseline IGA-CHE score, and CHE subtype (main diagnosis).

14.3.4 Exposure and treatment compliance

The duration of exposure to treatment in a specific week 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 for each treatment group.

14.3.5 Testing strategy

For the primary and key secondary endpoints, confirmatory one-sided (superiority) hypotheses will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand. Let the treatment effect be defined as μ = (delgocitinib cream 20 mg/g minus cream vehicle), then:

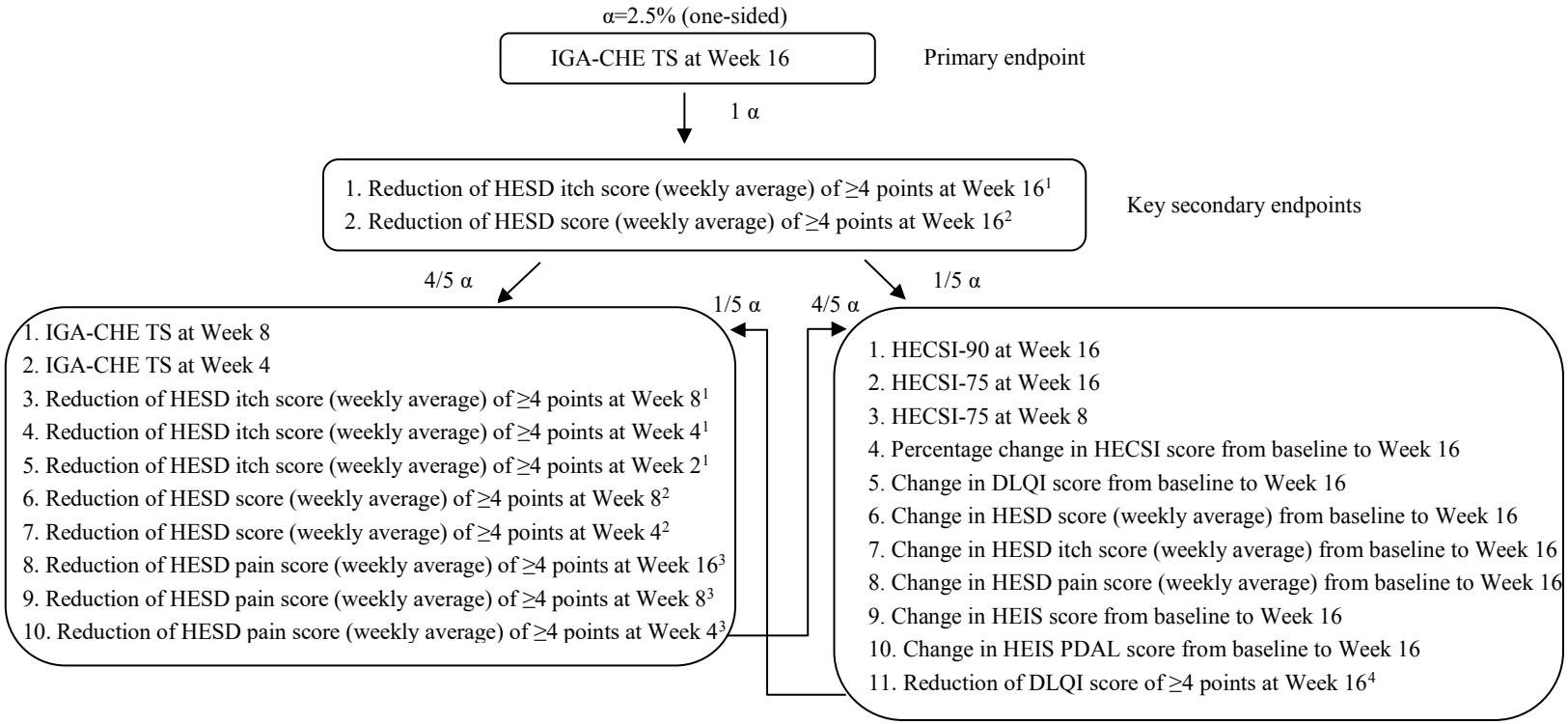
- For binary endpoints: H_0:$\mu \leq 0$ against H_a:$\mu > 0$.
- For continuous endpoints: H_0:$\mu \geq 0$ against H_a:$\mu < 0$.

A closed testing procedure with hierarchical tests, alpha splitting and alpha recycling will be used to control the overall type I error at a nominal one-sided 2.5% level. The statistical

testing strategy is built on the principle that the IGA-CHE TS superiority at Week 16 will have to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life.

The first hypothesis to be tested is superiority of delgocitinib cream 20 mg/g in terms of IGA-CHE TS at Week 16. It will be tested at the overall one-sided significance level of 2.5%. In general, if a test is significant, the significance level will be reallocated according to the weight and the direction of the arrows as specified in Panel 22. Each of the following hypotheses will be tested at their local significance level (α-local). This process will be repeated until no further tests are significant.

Panel 22: Graphical display of closed testing procedure for primary and key secondary endpoints



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

Abbreviations: DLQI = Dermatology Life Quality Index; 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; HEIS = Hand Eczema Impact Scale; 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; PDAL = Proximal Daily Activity Limitations.

14.3.6 Estimand strategy

14.3.6.1 Overview

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

The following primary and supplementary estimands will be defined for binary and continuous endpoints (primary and key secondary 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 (see also Section 5.3).

A first supplementary estimand will use a ‘pandemic modified composite’ strategy. The strategy follows a ‘composite’ strategy for IEs independent of the COVID-19 pandemic. However, data collected after the IE related to the pandemic will be ‘treated as missing’ and imputed assuming MAR.

A second 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 (independent of the pandemic) occurred. Data collected after an IE related to the pandemic will be ‘treated as missing’ and imputed assuming MAR. This second supplementary estimand will be used for endpoints related to Week 16 (primary endpoint visit).

For the ‘composite’ and ‘treatment policy’ estimands, pre-specified sensitivity analyses will be conducted to assess the robustness of the results with respect to the handling of missing data.

The primary estimand for ‘time-to-event’ endpoints (exploratory endpoints) will use a ‘while on treatment’ strategy. Under the ‘while on treatment’ strategy, the actual duration of treatment is not important for determining treatment benefit. The interest lies in assessing the treatment response prior to the occurrence of IEs. This strategy will be implemented to handle IEs for time-to-event endpoints.

Analysis to summarise and assess the effect of patterns of missing data related to the pandemic will be specified in the statistical analysis plan prior to breaking the randomisation code.

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, regardless of relatedness to the COVID-19 pandemic, 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). This IE is handled without assessing relatedness to the pandemic.
- **Permanent discontinuation of IMP independent of the COVID-19 pandemic:** This IE occurs when a subject permanently discontinues IMP independent of the pandemic. This IE can occur at the subject's own initiative, at the discretion of the investigator or the sponsor, or if the subject is lost to follow-up.
- **Permanent discontinuation of IMP related to the COVID-19 pandemic**: This IE occurs when a subject permanently discontinues IMP due to circumstances related to the pandemic; not attributed to lack of efficacy or randomised treatment features considered unacceptable by the subject.

Panel 23 presents an overview of how observed and missing data will be handled according to the IEs for the primary analysis for estimands.

Panel 23: Handling of observed and missing data according to the intercurrent events for the primary analysis for estimands

		Estimand strategy for binary endpoints			Estimand strategy for continuous endpoints		
Intercurrent event	**Data observed or missing**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**
Initiation of rescue treatment[1]	Observed	Non-response	Non-response	Value will be used as observed	WOCF (including baseline value)	WOCF (including baseline value)	Value will be used as observed
	Missing	Non-response	Non-response	MI (MAR)	WOCF (including baseline value)	WOCF (including baseline value)	MI (MAR)
Permanent discontinuation of IMP **independent of** the pandemic	Observed	Non-response	Non-response	Value will be used as observed	WOCF (including baseline value)	WOCF (including baseline value)	Value will be used as observed
	Missing	Non-response	Non-response	MI (MAR)	WOCF (including baseline value)	WOCF (including baseline value)	MI (MAR)
Permanent discontinuation of IMP **related to** the pandemic	Observed	Non-response	Treated as missing, MI (MAR)	Treated as missing, MI (MAR)	WOCF (including baseline value)	Treated as missing, MI (MAR)	Treated as missing, MI (MAR)
	Missing	Non-response	MI (MAR)	MI (MAR)	WOCF (including baseline value)	MI (MAR)	MI (MAR)
No intercurrent events	Observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed

		Estimand strategy for binary endpoints			Estimand strategy for continuous endpoints		
Intercurrent event	**Data observed or missing**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**
	Missing **independent of** the pandemic	Non-response	Non-response	MI (MAR)	WOCF (including baseline value)	WOCF (including baseline value)	MI (MAR)
	Missing **related to** the pandemic	Non-response	MI (MAR)	MI (MAR)	WOCF (including baseline value)	MI (MAR)	MI (MAR)

1) Initiation of rescue treatment is considered an intercurrent event regardless of the relatedness to the COVID-19 pandemic.

Abbreviations: COVID-19 = coronavirus disease 2019; MAR = missing at random; MI = multiple imputation; WOCF = worst observation carried forward.

14.3.6.2 Estimand strategy for binary endpoints

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

Primary estimand: 'composite' strategy
This primary estimand evaluates the treatment effect in adult subjects 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.

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 difference in response rates between the two treatment groups will be analysed using the CMH test stratified by region and baseline IGA-CHE score. The difference in response rates with 95% CI will be calculated by the Mantel-Haenszel method stratified by region and baseline IGA-CHE score.

First 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 values 0.1 and 0.2. The same parameter p will be used for both treatment groups. The parameter values 0.1 and 0.2 are based on the response rates of IGA-CHE TS and HESD itch score (weekly average) ≥4 points, respectively, at Week 16 in the cream vehicle group in LP0133-1273 and will introduce uncertainty due to missing data. A MI procedure (100 iterations) will be used for each value of p. For each of the 100 complete datasets, the

difference in response rates will be analysed using a CMH test stratified by region and baseline IGA-CHE score. 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.

Second sensitivity analysis for the primary estimand

A tipping point analysis will be performed. Missing data at the endpoint of interest, for subjects who did not experience the IEs prior to that, will be handled as follows:

- For subjects in the delgocitinib cream 20 mg/g group, missing data will be imputed as non-response.
- For subjects in the cream vehicle group, missing data will be imputed from a Bernoulli distribution with parameter p (ranging from 0 to 1). By varying the parameter p, different percentages of subjects in the cream vehicle group will be assumed to be responders, deviating from the default zero percent used in the primary analysis. A MI procedure (100 iterations) will be used for each value of p.

For each of the 100 complete datasets, the difference in response rates will be analysed using a CMH test stratified by region and baseline IGA-CHE score. 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.

The tipping point is then found as the value of p which changes the conclusion from statistically significant to non-significant and will be judged from a clinical perspective.

First supplementary estimand: 'pandemic modified composite' strategy

This first supplementary estimand evaluates the treatment effect in adult subjects with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP in a world without COVID-19 pandemic, where interest lies in the treatment effect as it would have been observed had the COVID-19 pandemic not happened.

For subjects who experience IEs independent of the pandemic prior to the endpoint of interest, observed data after the IEs will be considered non-response.

For subjects who experience an IE related to the pandemic prior to the endpoint of interest, observed data after the IE will be 'treated as missing' and imputed assuming MAR.

Primary analysis for the first supplementary estimand
Missing data for subjects who do not attend the visit for the endpoint of interest and do not experience IEs prior to this visit will be imputed as non-response, unless data is missing due to the pandemic in which case it will be imputed assuming MAR.

The procedure for imputing values will be implemented in a 2-step procedure, where all missing or 'treated as missing' data will be imputed using MI (100 iterations) assuming MAR within treatment groups. Once the 100 complete data sets have been generated by MI, non-responder imputation of relevant data points not affected by the pandemic will be applied according to the rules described above.

For each of the 100 complete datasets, the difference in response rates will be analysed using the CMH test stratified by region and baseline IGA-CHE score. 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.

Second supplementary estimand for endpoints at Week 16: 'treatment policy' strategy
This supplementary estimand evaluates the treatment effect in adult subjects with moderate to severe CHE, regardless of initiation of rescue treatment or permanent discontinuation of IMP in a world without COVID-19 pandemic.

Observed data will be used in the analysis, including the data observed after the occurrence of IEs independent of the pandemic. 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.

For subjects who experience an IE related to the pandemic prior to Week 16, observed data at Week 16 will be 'treated as missing' and imputed assuming MAR.

Primary analysis for the second supplementary estimand
Missing data at Week 16 independent of the pandemic will be imputed using MI (100 iterations) assuming MAR within 4 groups defined according to treatment group and whether the subject has experienced an IE (independent of the pandemic).

Missing data or 'treated as missing' data at Week 16 due to the pandemic will be imputed using MI assuming MAR within treatment group using data from subjects who have not experienced an IE.

For each of the 100 imputed datasets, the difference in response rates will be analysed using the CMH test stratified by region and baseline IGA-CHE score. 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.

Sensitivity analysis for the second supplementary estimand
Missing data at Week 16 will be imputed as non-response, unless data is missing or 'treated as missing' due to the pandemic in which case it will be imputed using MI (100 iterations) assuming MAR within treatment group using data from subjects who have not experienced an IE.

The difference in response rates will be analysed as described above for the primary analysis for the second supplementary estimand.

14.3.6.3 Estimand strategy for continuous endpoints

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 adult subjects 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).

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 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, region, baseline IGA-CHE score, and baseline value (endpoint of interest).

Sensitivity analysis for the primary estimand
Missing data at the endpoint of interest, for subjects who did not experience IEs prior to that, will be handled as follows:

- For subjects in the delgocitinib cream 20 mg/g group, missing data will be imputed as WOCF (including the baseline value).
- For subjects in the cream vehicle group, missing data will be imputed using MI (100 iterations) assuming MAR.

For each of the 100 complete datasets, the change (or percentage change) from baseline to the endpoint of interest will be analysed using the ANCOVA model with effects of treatment, region, baseline IGA-CHE score, and baseline value. The estimates and standard errors from the analyses will be combined using Rubin's rule to provide the estimate and associated standard error.

First supplementary estimand: 'pandemic modified composite' strategy
This first supplementary estimand evaluates the treatment effect in adult subjects with moderate to severe CHE, without initiation of rescue treatment or permanent discontinuation of IMP in a world without COVID-19 pandemic, where interest lies in the treatment effect as it would have been observed had the COVID-19 pandemic not happened.

For subjects who experience IEs independent of the pandemic prior to the endpoint of interest, observed data after the IEs will be considered non-response by using WOCF (including the baseline value).

For subjects who experience an IE related to the pandemic prior to the endpoint of interest, observed data after the IE will be 'treated as missing' and imputed assuming MAR.

Primary analysis for the first supplementary estimand
Missing data for subjects who do not attend the visit for the endpoint of interest and do not experience IEs prior to this visit will be imputed as WOCF (including the baseline value), unless data is missing due to the pandemic in which case it will be imputed assuming MAR.

The procedure for imputing values will be implemented in a 2-step procedure, where all missing or 'treated as missing' data will be imputed using MI (100 iterations) assuming MAR within treatment groups. WOCF imputation of relevant data points not affected by the pandemic will be applied according to the rules described above.

For each of the 100 complete datasets, the change (or percentage change) from baseline to the endpoint of interest will be analysed using the ANCOVA model with effects of treatment,

region, baseline IGA-CHE score, and baseline value. The estimates and standard errors from the analyses will be combined using Rubin's rule to provide the estimate and associated standard error.

Second supplementary estimand for endpoints at Week 16: 'treatment policy' strategy
This supplementary estimand evaluates the treatment effect in adult subjects with moderate to severe CHE, regardless of initiation of rescue treatment or permanent discontinuation of IMP in a world without COVID-19 pandemic.

Observed data will be used in the analysis, including the data observed after the occurrence of IEs independent of the pandemic. 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.

For subjects who experience an IE related to the pandemic prior to Week 16, observed data at Week 16 will be 'treated as missing' and imputed assuming MAR.

Primary analysis for the second supplementary estimand
Missing data at Week 16 independent of the pandemic will be imputed using MI (100 iterations) assuming MAR within 4 groups defined according to treatment group and whether the subject has experienced an IE independent of the pandemic.

Missing data or 'treated as missing' data at Week 16 due to the pandemic will be imputed using MI assuming MAR within treatment group using data from subjects who have not experienced an IE.

For each of the 100 complete datasets, the change (or percentage change) from baseline to Week 16 will be analysed using an ANCOVA model with effects of treatment, region, baseline IGA-CHE score, and baseline value. The estimates and standard errors from the analyses will be combined using Rubin's rule to provide the estimate and associated standard error.

Sensitivity analysis for the second supplementary estimand
Missing data at Week 16 independent of the pandemic will be imputed using a pattern-mixture model where data in the delgocitinib cream 20 mg/g group as well as the cream vehicle group will be imputed from the cream vehicle group (copy-reference approach). The data will be imputed using MI (100 iterations) assuming MAR within 2 groups: subjects in the cream vehicle group who have experienced an IE independent of the pandemic, and subjects in the cream vehicle group who have not experienced an IE.

Missing data or 'treated as missing' data at Week 16 due to the pandemic will be imputed using MI assuming MAR within treatment group using data from subjects who have not experienced an IE.

For each of the 100 completed datasets, the change (or percentage change) from baseline to Week 16 will be analysed using an ANCOVA model with effects of treatment, region, baseline IGA-CHE score, and baseline value. The results of the analysis will be combined using Rubin's rule to provide the estimate and associated standard error.

14.3.6.4 Estimand strategy for time-to-event endpoints

The difference in the estimates of the cumulative incidence functions for the event of interest between delgocitinib cream 20 mg/g and cream vehicle will be evaluated at Weeks 2, 4, and 8.

Primary estimand: 'while on treatment' strategy
With the 'while on treatment' strategy, response to treatment prior to the occurrence of the IEs is of interest. This strategy is chosen for the time-to-event endpoints with an expected early effect, e.g. reduction of HESD itch score (weekly average) of ≥4 points from baseline.

Let T represent the time from randomisation to the time-to-event endpoint and T_{IE} represent the time from randomisation to occurrence of the first IE. The 'while on treatment' estimand evaluates:

$$Pr(T < T_{IE} \wedge 16)$$

where $T_{IE} \wedge 16$ is the minimum of T_{IE} and the end of the treatment period (administrative censoring time), corresponding to Week 16 in this trial. Since interest lies in estimating the time to achieving the endpoint while remaining on the randomised treatment, the occurrence of the IEs can be accounted for through the formulation of a competing risks model. It is assumed that IEs indicate failure of the randomised treatment.

Primary analysis for the primary estimand
The null hypothesis, H_0: $\lambda_{delgo}(t) = \lambda_{vehicle}(t)$, $\forall\ t \in (0,16)$, where $\lambda(t)$ denotes the sub-distribution hazard rate associated with the time-to-event endpoint at time t (measured in weeks), will be tested against the alternative, H_a: $\lambda_{delgo}(t) \neq \lambda_{vehicle}(t)$ based on Gray's test.

To quantify the magnitude of the potential treatment effect, the estimated cumulative incidence functions for the competing risks model will be presented for the treatment groups, based on the Aalen-Johansen estimator, along with 95% CIs.

Cause-specific hazard Cox regression models will be fit for the cause-specific hazard for the 2 competing risks. The estimated cause-specific hazard ratios will be presented along with 95% CIs.

14.3.7 Analysis of primary endpoint

The primary endpoint will be analysed as described in Sections 14.3.6.1 and 14.3.6.2. The confirmatory one-sided (superiority) hypothesis, described in Section 14.3.5, will be tested for delgocitinib cream 20 mg/g vs. cream vehicle based on the primary analysis for the primary estimand.

14.3.8 Analysis of key secondary endpoints

The confirmatory hypotheses for key secondary endpoints, presented in Sections 14.3.6.1 and 14.3.5, will be tested based on the primary analyses for the primary estimand strategies described in Sections 14.3.6.2 and 14.3.6.3.

Panel 24 provides an overview of the primary analysis of the key secondary endpoints related to the primary and supplementary estimands. For further details, including sensitivity analysis, refer to Section 14.3.6.

Panel 24: Overview of the primary analysis of the key secondary endpoints related to the primary and supplementary estimands

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 16[1] Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 16[2]	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
IGA-CHE TS at Week 8 IGA-CHE TS at Week 4	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Not applicable	Not applicable

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 8[1]	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Not applicable	Not applicable
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 4[1]							
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Week 2[1]							
Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 8[2]							
Reduction of HESD score (weekly average) of ≥4 points from baseline at Week 4[2]							

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 16[3]	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 8[3]	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Not applicable	Not applicable
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Week 4[3]							

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
HECSI-90 at Week 16 HECSI-75 at Week 16	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
HECSI-75 at Week 8	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Not applicable	Not applicable

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
Percentage change in HECSI score from baseline to Week 16 Change in DLQI score from baseline to Week 16 Change in HESD score (weekly average) from baseline to Week 16 Change in HESD itch score (weekly average) from baseline to Week 16 Change in HESD pain score (weekly average) from baseline to Week 16	Continuous	Composite	WOCF (including baseline value)	Pandemic modified composite	Independent of the COVID-19 pandemic: WOCF (including baseline value) Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
Change in HEIS score from baseline to Week 16 Change in HEIS PDAL score from baseline to Week 16	Continuous	Composite	WOCF (including baseline value)	Pandemic modified composite	Independent of the COVID 19 pandemic: WOCF (including baseline value) Related to the COVID 19 pandemic: MI assuming MAR within treatment group	Not applicable	Not applicable

Key secondary endpoint	Type of endpoint	Primary estimand		First supplementary estimand		Second supplementary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**	**Strategy to handle IEs**	**Handling of missing data and data collected after IE**
Reduction of DLQI score of ≥4 points from baseline at Week 16[4]	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group

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

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

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

4) Among subjects with a baseline DLQI score of ≥4 points.

Abbreviations: COVID-19 = coronavirus disease 2019; DLQI = 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; HEIS = Hand Eczema Impact Scale; 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; IMP = investigational medicinal product; MAR = missing at random; MI = multiple imputation; PDAL = Proximal Daily Activity Limitations; WOCF = worst observation carried forward.

14.3.9 Analysis of exploratory endpoints

The analysis of exploratory endpoints will be based on the FAS.

The analysis of exploratory endpoints will resemble the primary analysis for the primary estimand related to a specific endpoint type: binary, continuous, or time to event. For details refer to Section 14.3.6 (for binary endpoints refer to Section 14.3.6.2, for continuous endpoints refer to Section 14.3.6.3, and for time-to-event endpoints refer to Section 14.3.6.4).

Panel 25 provides an overview of the statistical analysis of the exploratory endpoints.

Panel 25: Overview of the statistical analysis of exploratory endpoints

Endpoints	**Type of endpoint**	**Primary estimand**	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**
Efficacy			
IGA-CHE TS at Weeks 1, 2, and 12	Binary	Composite	Non-response imputation
HECSI-75 at Weeks 1, 2, 4, and 12	Binary	Composite	Non-response imputation
HECSI-90 at Weeks 1, 2, 4, 8, and 12	Binary	Composite	Non-response imputation
Percentage change in HECSI score from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Reduction of HESD itch score (weekly average) of ≥4 points from baseline at Weeks 1 and 12[1]	Binary	Composite	Non-response imputation
Reduction of HESD itch score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16[2]	Binary	Composite	Non-response imputation
Time to reduction of HESD itch score (weekly average) of ≥4 points[1]	Time to event	While on treatment	Not applicable
Change in HESD itch score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Reduction of HESD score (weekly average) of ≥4 points from baseline at Weeks 1, 2, and 12[3]	Binary	Composite	Non-response imputation
Reduction of HESD score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16[4]	Binary	Composite	Non-response imputation

Endpoints	Type of endpoint	Primary estimand	
		Strategy to handle IEs	**Handling of missing data and data collected after IE**
Time to reduction of HESD score (weekly average) of ≥4 points[3]	Time to event	While on treatment	Not applicable
Change in HESD score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Reduction of HESD pain score (weekly average) of ≥4 points from baseline at Weeks 1, 2, and 12[5]	Binary	Composite	Non-response imputation
Reduction of HESD pain score (weekly average) of ≥3 points from baseline at Weeks 1, 2, 4, 8, 12, and 16[6]	Binary	Composite	Non-response imputation
Time to reduction of HESD pain score (weekly average) of ≥4 points[5]	Time to event	While on treatment	Not applicable
Change in HESD pain score (weekly average) from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Change in HESD (weekly average for each individual symptom [excluding itch and pain]) score from baseline to Week 16	Continuous	Composite	WOCF (including baseline value)
Health-related quality of life and efficacy			
Change in HEIS score from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Reduction of HEIS score of ≥1.5 points at Weeks 1, 2, 4, 8, 12, and 16[7]	Binary	Composite	Non-response imputation
Change in HEIS PDAL score from baseline to Weeks 1, 2, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Reduction of HEIS PDAL score of ≥1.5 points at Weeks 1, 2, 4, 8, 12, and 16[8]	Binary	Composite	Non-response imputation
Change in HEIS (each individual domain [excluding PDAL]) score from baseline to Weeks 1, 2, 4, 8, 12, and 16	Continuous	Composite	WOCF (including baseline value)
Reduction in DLQI score of ≥4 points at Weeks 1, 4, 8, and 12[9]	Binary	Composite	Non-response imputation
Change in DLQI score from baseline to Weeks 1, 4, 8, and 12	Continuous	Composite	WOCF (including baseline value)
Change in EQ-5D-5L index score from baseline to Weeks 1, 4, 8, 12, and 16	Continuous	Composite	WOCF (including baseline value)
Change in EQ-5D-5L visual analogue scale score from baseline to Weeks 1, 4, 8, 12, and 16	Continuous	Composite	WOCF (including baseline value)

Endpoints	Type of endpoint	Primary estimand	
		Strategy to handle IEs	Handling of missing data and data collected after IE
Change in WPAI:CHE absenteeism score from baseline to Week 4, 8, and 16[10]	Continuous	Composite	WOCF (including baseline value)
Change in WPAI:CHE presenteeism score from baseline to Week 4, 8, and 16[10]	Continuous	Composite	WOCF (including baseline value)
Change in WPAI:CHE work productivity loss score from baseline to Week 4, 8, and 16[10]	Continuous	Composite	WOCF (including baseline value)
Change in WPAI:CHE activity impairment score from baseline to Week 4, 8, and 16	Continuous	Composite	WOCF (including baseline value)

1) Among subjects with a baseline HESD itch score (weekly average) ≥4 points.
2) Among subjects with a baseline HESD itch score (weekly average) ≥3 points.
3) Among subjects with a baseline HESD score (weekly average) ≥4 points.
4) Among subjects with a baseline HESD 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 HEIS score ≥1.5 points.
8) Among subjects with a baseline HEIS PDAL score ≥1.5 points.
9) Among subjects with a baseline DLQI score ≥4 points.
10) Among subjects with paid work at baseline.

Abbreviations: DLQI = 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; HEIS = Hand Eczema Impact Scale; 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; IMP = investigational medicinal product; MAR = missing at random; MI = multiple imputation; PDAL = Proximal Daily Activity Limitations; WOCF = worst observation carried forward; WPAI:CHE = Work Productivity and Activity Impairment: Chronic Hand Eczema.

14.3.10 Analysis of patient-reported outcomes

The 3 PGI-S scores (Itch PGI-S, Pain PGI-S, and HESD PGI-S), the 3 PGI-C scores (Itch PGI-C, Pain PGI-C, and HESD PGI-C), and PaGA score will be summarised by visit for each treatment group.

14.3.11 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.

14.3.12 Analysis of safety

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

14.3.12.1 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 dose 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.

AEs will be summarised in terms of the number of subjects with at least 1 event, the percentage of subjects with at least 1 event, the number of events, and the event rate per 100 person years of observation time.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as ‘not related’.

An overall summary presenting any treatment-emergent AEs, deaths, SAEs, permanent discontinuations from IMP and/or withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be presented.

Tabulations by SOC and preferred term will be presented for all AEs, SAEs, related AEs, AESIs, AEs leading to withdrawal from trial, and AEs leading to permanent discontinuation of IMP. In addition, all AEs will be presented by severity and causal relationship to IMP, respectively. If an AE worsens in severity, the severity will be reported as the most severe recording for that AE.

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 subject, 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.

14.3.12.2 Vital signs and physical examination

For vital signs (resting blood pressure, pulse, and body temperature), the absolute values at baseline and Week 16 as well as the change from baseline to Week 16 will be summarised for each treatment group.

14.3.12.3 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).

14.3.12.4 Assessment of local tolerability

Assessment of local tolerability will be summarised by visit and treatment group.

14.3.13 Interim analysis

No interim analysis is planned.

14.3.14 General principles

Significance tests, for binary and continuous endpoints, will be one-sided using the 2.5% significance level. The Gray's test, used for time-to-event endpoints, will be two-sided using a 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. Continuous data will be summarised using the mean, median, SD, 1st quartile, 3rd quartile, minimum, and maximum values.

Baseline measurements will be defined as the latest available observation at or prior to the date of randomisation.

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.

14.3.15 Handling of missing values

The methods for handling of missing values in the different analyses are described in Section 14.3.6.

15 References

1. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ, Elsner P, English J, Fartasch M, Gimenez-Arnau A, Nixon R, Sasseville D, Agner T. Guidelines for diagnosis, prevention and treatment of hand eczema. J Dtsch Dermatol Ges. 2015;13(1):e1-22.

2. Agner T, Aalto-Korte K, Andersen KE, Foti C, Gimenez-Arnau A, Goncalo M, Goossens A, Le Coz C, Diepgen TL. Classification of hand eczema. J Eur Acad Dermatol Venereol. 2015;29(12):2417-2422.

3. Cronin E. Clinical patterns of hand eczema in women. Contact Dermatitis. 1985;13(3):153-161.

4. Johansen JD, Hald M, Andersen BL, Laurberg G, Danielsen A, Avnstorp C, Kristensen B, Kristensen O, Kaaber K, Thormann J, et al. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. Contact Dermatitis. 2011;65(1):13-21.

5. Apfelbacher C, Molin S, Weisshaar E, Bauer A, Elsner P, Mahler V, Weiss M, Ruzicka T, Diepgen TL. Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. Acta Derm Venereol. 2014;94(2):163-167.

6. Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75-87.

7. Thyssen JP, Carlsen BC, Menne T, Linneberg A, Nielsen NH, Meldgaard M, Szecsi PB, Stender S, Johansen JD. Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. Br J Dermatol. 2010;163(1):115-120.

8. Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood. Br J Dermatol. 2014;171(2):313-323.

9. Anveden I, Wrangsjo K, Jarvholm B, Meding B. Self-reported skin exposure -- a population-based study. Contact Dermatitis. 2006;54(5):272-277.

10. Hald M, Berg ND, Elberling J, Johansen JD. Medical consultations in relation to severity of hand eczema in the general population. Br J Dermatol. 2008;158(4):773-777.

11. Lind ML, Albin M, Brisman J, Kronholm Diab K, Lillienberg L, Mikoczy Z, Nielsen J, Rylander L, Toren K, Meding B. Incidence of hand eczema in female Swedish hairdressers. Occup Environ Med. 2007;64(3):191-195.

12. Meding B, Jarvholm B. Incidence of hand eczema - a population-based retrospective study. J Invest Dermatol. 2004;122(4):873-877.

13. Fowler JF, Ghosh A, Sung J, Emani S, Chang J, Den E, Thorn D, Person J, Duh MS. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. J Am Acad Dermatol. 2006;54(3):448-457.

14. Cortesi PA, Scalone L, Belisari A, Bonamonte D, Cannavo SP, Cristaudo A, De Pita O, Gallo R, Giannetti A, Gola M, et al. Cost and quality of life in patients with severe chronic hand eczema refractory to standard therapy with topical potent corticosteroids. Contact Dermatitis. 2014;70(3):158-168.

15. Augustin M, Kuessner D, Purwins S, Hieke K, Posthumus J, Diepgen TL. Cost-of-illness of patients with chronic hand eczema in routine care: results from a multicentre study in Germany. Br J Dermatol. 2011;165(4):845-851.

16. van Gils RF, Bosmans JE, Boot CR, Rustemeyer T, van Mechelen W, van der Valk PG, Anema JR. Economic evaluation of an integrated care programme for patients with hand dermatitis. Contact Dermatitis. 2013;69(3):144-152.

17. Cvetkovski RS, Rothman KJ, Olsen J, Mathiesen B, Iversen L, Johansen JD, Agner T. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. Br J Dermatol. 2005;152(1):93-98.

18. Lerbaek A, Kyvik KO, Ravn H, Menne T, Agner T. Clinical characteristics and consequences of hand eczema - an 8-year follow-up study of a population-based twin cohort. Contact Dermatitis. 2008;58(4)**:**210-216.

19. Cazzaniga S, Apfelbacher C, Diepgen T, Ofenloch RF, Weisshaar E, Molin S, Bauer A, Mahler V, Elsner P, Schmitt J, et al. Patterns of chronic hand eczema: a semantic map analysis of the CARPE registry data. Br J Dermatol. 2018;178(1)**:**229-237.

20. Herschel S, Schmitt J, Bauer A. Satisfaction with medical treatment in patients with hand dermatitis - a cross-sectional study. J Dtsch Dermatol Ges. 2013;11(10)**:**1007-1013.

21. Pedersen MB, Skov L, Menne T, Johansen JD, Olsen J. Gene expression time course in the human skin during elicitation of allergic contact dermatitis. J Invest Dermatol. 2007;127(11)**:**2585-2595.

22. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139(4S)**:**S65-S76.

23. Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. Journal of Allergy and Clinical Immunology. 2013;131(2)**:**300-313.

24. Stiefel. Toctino. Summary of Product Characteristics (SmPC). 2020.

25. Christoffers WA, Coenraads PJ, Svensson Å, Diepgen TL, Dickinson-Blok JL, Xia J, Williams HC. Interventions for hand eczema. Cochrane Database of Systematic Reviews. 2019;(4).

26. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov. 2017;16(12)**:**843-862.

27. Amano W, Nakajima S, Kunugi H, Numata Y, Kitoh A, Egawa G, Dainichi T, Honda T, Otsuka A, Kimoto Y, et al. The Janus kinase inhibitor JTE-052 improves skin

barrier function through suppressing signal transducer and activator of transcription 3 signaling. J Allergy Clin Immunol. 2015;136(3):667-677.e667.

28. LEO Pharma. Clinical Trial Report (CTR) - LP0133-1273: Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over a 16-week treatment period in adult subjects with chronic hand eczema. 2020.

29. WMA. World Medical Association. Declaration of Helsinki – ethical principles for medical research involving human subjects. Amended by the 64th WMA General Assembly, Fortaleza, Brazil. 2013.

30. ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): Guideline for good clinical practice E6(R2). 2016.

31. LEO Pharma. Delgocitinib cream Investigator's Brochure (IB) Edition 4.0. 2021.

32. EMA. European Medicines Agency. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic. Version 3. 2020.

33. FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. 2020.

34. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med. 2010;8:18.

35. European Commission. EudraLex: The Rules Governing Medicinal Products in the European Union. Guidelines for good manufacturing practices for medicinal products for human and veterinary use. 2010;Volume 4.

36. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2):302-307.

37. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez-Arnau A, Gonçalo M, Goossens A, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015;73(4)**:**195-221.

38. FDA. Food and Drug Administration. Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. Attachment to Discussion Document for Patient-Focused Drug Development Public Workshop on Guidance 3. 2018.

39. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3)**:**210-216.

40. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3)**:**199-208.

41. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5)**:**353-365.

42. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152(2)**:**302-307.

43. European Parliament Union, European CoT. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.

44. ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Clinical Safety Data Management. Definitions and Standards for Expected Reporting (E2A), Step 4; 27-Oct. 1994.

45. CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. Council for International Organizations of Medical Sciences. 4th. Geneva. 2016.

46. EFPIA. European Federation of Pharmaceutical Industries and Associations. Principles for Responsible Clinical Trial Data Sharing. 2013.

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 (44).

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 11.5.4.2).

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 in-patient 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 concern 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 severity change, should be recorded. However, if an AE with onset prior to initiation of IMP worsens after administration of IMP, 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.

Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
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.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
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 (29) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (45).
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines (30).
- 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 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 process

Subjects 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 will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated informed consent to participate in the clinical trial 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 informed consent must also sign the ICF.

Subjects will be re-consented to the most current version of the ICF(s) during their participation in the trial, if required.

A copy of the ICF(s) must be provided to the subject.

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 consent 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 might keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research.

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. 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.

Subjects must be asked to consent to 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.

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 generated by the site should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site from which the data will be transcribed into the eCRF. 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 physicians.

The date and time of 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 major 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 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 30-Mar-2018 or newer was used for definition of controlled terminology used 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 (30). 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 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 on leopharmatrials.com in accordance with our Position on Public Access to Clinical Trial Information within approximately 12 months of 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

A publication can be a journal manuscript, an abstract, a poster/presentation for a congress, or any openly accessible material.

A primary publication including the primary results of the trial (i.e. the results of the primary endpoint[s]) will be submitted for peer-reviewed publication within 12 months of database lock. LEO Pharma is responsible for this publication. All authors (trial responsible employees and/or applicable investigators and advisors) must fulfill the criteria for authorship from the International Committee of Medical Journal Editors (ICMJE).

The investigators may reach out to LEO Pharma to publish results that are not included in the primary publication. The investigator and LEO Pharma should agree on terms for data sharing and collaboration on such publications, as well as timing for release of the publication(s). In all cases, LEO Pharma retains the right to review and comment on the draft publication in due time before submission, but the investigator is not required to revise the draft accordingly, unless it discloses company confidential information or protected personal information, or may compromise intellectual property rights of LEO Pharma.

LEO Pharma may give researchers outside LEO Pharma access to anonymised data from this trial for further research according to the principles outlined by the European Federation of Pharmaceutical Industries and Associations (EFPIA) (46). In that case, the researchers are obliged to attempt publication of the results obtained from their analyses.

LEO Pharma complies with Good Publication Practice (GPP3) standards and the recommendations from ICMJE.

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 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: 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 3I: 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

Canada

As per Health Canada standards, all essential trial documents and source documents will be archived for 25 years.

Appendix 5: Short version of eligibility criteria

	Inclusion criteria
No.	**Short version**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2	Age 18 years or above at screening.
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	HESD itch score (weekly average) of ≥4 points at baseline.
6	Subjects who have a documented recent history of inadequate response to treatment with TCS or TCS treatment being medically inadvisable.
7	Subjects adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.
8	A woman of childbearing potential must use an acceptable form of birth control throughout the trial up until the last application of IMP.

	Exclusion criteria
No.	**Short version**
1	Concurrent skin diseases on the hands, e.g. tinea manuum.
2	Active AD requiring medical treatment in regions other than the hands and feet.
3	Active psoriasis on any part of the body.
4	Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
5	Clinically significant infection (e.g. impetiginised hand eczema) on the hands.
6	Systemic treatment with immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids within 28 days prior to baseline.
7	Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.
8	Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical.

9	Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.
10	Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.
11	Other transdermal or cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 7 days prior to baseline.
12	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.
13	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.
14	Treatment with any non-marketed drug substance within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.
15	Clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 28 days prior to baseline.
16	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications.
17	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
18	History of cancer.
19	Any disorder which is not stable and could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial.
20	Any abnormal finding which may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial.
21	Positive hepatitis B surface antigen or hepatitis C virus antibody serology at screening.
22	ALT or AST level 2.0 times the ULN or more at screening.
23	Known or suspected hypersensitivity to any component(s) of the IMP.
24	Current participation in any other interventional clinical trial.
25	Previously randomised in this clinical trial.
26	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, appointed 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

International coordinating investigator

Sibylle Schliemann, PD Dr. med.
Department of Dermatology
University Hospital Jena UHJ
Erfurter Straße 35
D-07743 Jena, Germany

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 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).
- PROs (HEIS, PaGA, DLQI, EQ-5D-5L, WPAI:CHE). The subjects will receive a link to complete the PROs in a web browser from their own device.
- 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 will 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.