Cover Page

Study title: A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3)
LEO Pharma number: LP0133-1403
NCT number: NCT04949841
Date: 03-Apr-2023

Clinical trial protocol

LP0133-1403

A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3)

Phase 3 – long-term safety

An open-label multi-site extension trial in subjects who completed the LP0133-1401 (DELTA 1) or LP0133-1402 (DELTA 2) trials

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:**	**LP0133-1403**
	Date:	**03-Apr-2023**
	EudraCT no:	**2020-002962-15**
	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:

[redacted], PhD
Vice president, Global Clinical Development

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

[redacted], MD
Medical lead, Global Clinical Development

[redacted], B.Sc. Chemistry
Clinical operations lead, Global Clinical Operations

Approval statement signatory investigator

The signatory investigator approves the clinical trial protocol by manually signing the signatory investigator clinical trial protocol approval form, which is a separate document appended to this document.

The following person has approved this clinical trial protocol:

[redacted], Prof, MD, DMSc
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 3 (non-substantial)	03-Apr-2023	Global
Amendment 2 (substantial)	23-Aug-2021	Global
Amendment 1 (non-substantial)	14-Jun-2021	Global
Original protocol	25-Mar-2021	NA

Amendment 3 (03-Apr-2023)

This amendment was considered to be non-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 because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

This amendment was mainly written to align this protocol to the parent trials' protocols regarding the reporting of adverse events occurring at baseline in this trial. Further, changes to the requirements for trial document retention in Canada were implemented. Finally, an analysis of time to IGA-CHE response after treatment re-initiation was added, and the data used for the definition of treatment status (on/off treatment) for the analysis of AEs was changed from eDiary data to IGA-CHE data.

Section no. and title	Description of change	Brief rationale
Approval statement LEO Pharma A/S	Update of sponsor's protocol approvers.	Changes in trial team.

Section no. and title	**Description of change**	**Brief rationale**
Section 5.2 Experience with investigational medicinal product	Minor edit to clarify that the mentioned preclinical studies were conducted in AD- and psoriasis-like models.	For completeness and clarity.
Section 6 Trial objectives and endpoints Section 14.3.6 Analysis of other/exploratory endpoints	An analysis of time to response (IGA-CHE 0 or 1) following treatment re-initiation after first off-treatment period for subjects treated with delgocitinib cream 20 mg/g twice daily in the parent trial was added.	To provide further insight into the long-term efficacy of as-needed treatment.
Section 9.2 Administration of investigational medicinal products	Clarified that subjects should return all IMP at each visit.	For clarity.
Section 9.10 Reporting product complaints Section 13.4.1 Investigator reporting responsibilities	Fax number of LEO Pharma global safety updated.	New fax number.
Section 11.3 eDiary assessments	Clarification that only HESD eDiary from parent trial starting 1 week prior to and until baseline will be rolled over to the extension trial, as these are the only parent trial eDiary data used for the LP0133-1403 CTR.	For completeness and clarity.

Section no. and title	Description of change	Brief rationale
Section 13.2 Collection of adverse event reports Throughout the document	AEs occurring at baseline in this extension trial (corresponding to the Week 16 visit in the parent trial) should be recorded as AEs in the parent trial instead of this trial. Therefore, only AEs occurring after the baseline visit or that worsen after the baseline visit should be recorded as AEs in this trial.	Alignment with procedure described in the parent trials' protocols.
Section 14.3.8.1 Adverse events	Data used for allocation of AEs according to treatment status (on/off treatment) was changed from eDiary treatment application data to IGA-CHE data.	To align the allocation of AEs to the definition of an on-treatment period defined in terms of the IGA-CHE score.
Section 14.3.8.3 Clinical laboratory evaluation	Clarified how laboratory data will be presented in the statistical analyses.	For clarity.
Appendix 4 Country-specific requirements	Update of a Canada-specific time to archive trial documents from 25 years to 15 years.	Updated as per new Canadian legislation.
Appendix 9 Assessments performed at baseline and screening in the parent trials	Removal of exception for performing patch test in Russia.	Stopping of trial activities in Russia.
Throughout the document	The term "on-treatment period" is introduced to differentiate the "treatment period", which covers the period from baseline to Week 36, from a period during which subjects apply delgocitinib cream 20 mg/g twice daily (now named "on-treatment period").	For clarity.

Section no. and title	Description of change	Brief rationale
Throughout the document	Minor editorial revisions.	Minor, have therefore not been summarised.

Table of contents

List of panels

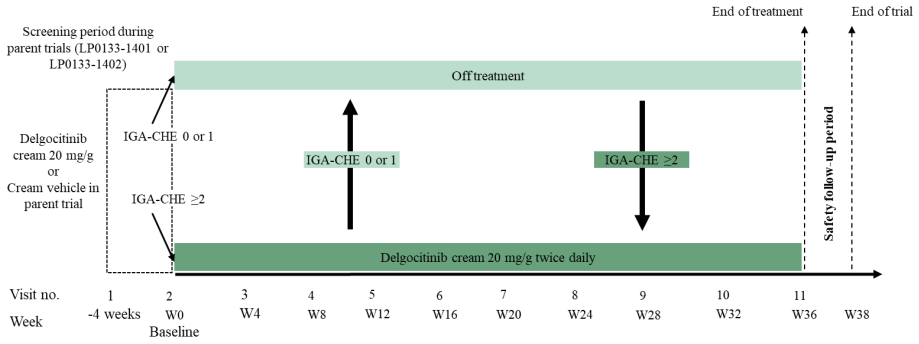
List of abbreviations

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDISC	Clinical Data Interchange Standards Consortium
CHE	chronic hand eczema
CMO	contract manufacturing organisation
COVID-19	coronavirus disease 2019
CRA	clinical research associate
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
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
HRQoL	Health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
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
LP0133-1401 / LP0133-1402	Parent trials. Randomised, double-blind, vehicle-controlled trials with delgocitinib cream 20 mg/g or cream vehicle treatment for 16 weeks
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PDAL	Proximal Daily Activity Limitations
PDE-4	phosphodiesterase-4
PGA	Physician's Global Assessment
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 Harmonisation Procedure
WPAI:CHE	Work Productivity and Activity Impairment: Chronic Hand Eczema

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td colspan="2">LP0133-1403
2020-002962-15</td></tr>
<tr><td>Title of trial</td><td colspan="2">A phase 3 extension trial of DELTA 1 and DELTA 2 to evaluate the long-term safety of a twice-daily treatment with delgocitinib cream 20 mg/g as needed for up to 36 weeks in adult subjects with chronic hand eczema (DELTA 3)</td></tr>
<tr><td>Short title of trial</td><td colspan="2">An open-label multi-site extension trial in subjects who completed the LP0133-1401 (DELTA 1) or LP0133-1402 (DELTA 2) trials</td></tr>
<tr><td rowspan="3">Main objectives and endpoints</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td>Primary objective:
To evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.</td><td>Primary endpoints:
• Number of treatment-emergent AEs from baseline up to Week 38.</td></tr>
<tr><td>Secondary objective:
To evaluate the long-term efficacy of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.</td><td>Secondary endpoints:
• IGA-CHE[1] score at each scheduled visit from baseline up to Week 36.
• IGA-CHE score of 0 (clear) or 1 (almost clear) at each scheduled visit from baseline up to Week 36.
• HECSI[2] score at each scheduled visit from baseline up to Week 36.
• HECSI-75 at each scheduled visit from baseline up to Week 36.
• HECSI-90 at each scheduled visit from baseline up to Week 36.</td></tr>
<tr><td colspan="2">1) The IGA-CHE is an instrument used in clinical trials to rate the severity of the subject's global chronic hand eczema (CHE) and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).
2) The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the 5 hand areas (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales.
Abbreviations: AE = adverse event; HECSI = Hand Eczema Severity Index; HECSI-75 = at least 75% improvement in HECSI score from baseline in parent trial; HECSI-90 = at least 90% improvement in HECSI score from baseline in parent trial; IGA-CHE = Investigator's Global Assessment for chronic hand eczema.</td></tr>
<tr><td>Final collection of data for the primary endpoint</td><td colspan="2">Week 38</td></tr>
<tr><td>Trial design</td><td colspan="2">Subjects who completed the treatment period in the parent trials (LP0133-1401 or LP0133-1402) will be offered the opportunity to participate in this extension trial. In the parent trials, subjects were treated either with delgocitinib cream 20 mg/g or cream vehicle twice daily for 16 weeks.</td></tr>
</table>

	The trial will include a screening period of about 4 weeks (during participation in the parent trial). The baseline visit in this extension trial will coincide with the Week 16 visit (end-of-treatment visit) in the parent trial. From baseline to Week 36, subjects will be treated on an as-needed basis with delgocitinib cream 20 mg/g twice daily, i.e. at any time during the trial, if a subject has an IGA-CHE score ≥2, the investigator will dispense delgocitinib cream 20 mg/g and instruct the subject to start treatment with twice-daily applications. When the subject achieves IGA-CHE score of 0 (clear) or 1 (almost clear) the investigator will instruct the subject to stop treatment. Between baseline and Week 36, subjects will attend site visits every 4 weeks. If the subject experiences worsening of CHE signs and symptoms between scheduled visits, an unscheduled visit should be planned as soon as possible in order to decide if treatment with delgocitinib cream 20 mg/g should be started. Similarly, once symptoms resolve, the subject should visit the site as soon as possible (either at a planned visit or unscheduled visit) so that the investigator can assess if treatment should be stopped. A follow-up phone visit will be conducted approximately 2 weeks after the end-of-treatment/early termination visit.  **Abbreviations:** IGA-CHE: Investigator's Global Assessment for chronic hand eczema. W: week.
Main assessments	**Safety assessments:** AE reporting, vital signs, physical examination, electrocardiogram (ECG), laboratory testing, subject and investigator assessment of local tolerability. **Efficacy assessments:** HECSI and IGA-CHE.
Criteria for inclusion	• Signed and dated informed consent has been obtained prior to any protocol-related procedures. • The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial. • Subjects must have met eligibility criteria at screening and baseline in the parent trial. • Subjects must have completed the treatment period in the parent trial (to be assessed at baseline visit in this extension trial). • Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator.

	• A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the end-of-treatment/early termination visit.
Criteria for exclusion	• Subjects who prematurely discontinued treatment with the investigational medicinal product (IMP) or initiated rescue treatment in the parent trial. • Subjects who experienced any AE during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator. • Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial. • Current participation in any other interventional clinical trial, except for parent trials.
Investigational medicinal product	• Name of IMP: delgocitinib cream. • Active substance: delgocitinib. • Dosage form: cream. • Concentration: 20 mg/g and cream vehicle (only used for patch test). • Dose and method of administration: topical application twice daily as needed.
Duration of trial participation	The duration of trial participation will be up to 42 weeks, consisting of a screening period of up to 4 weeks (coinciding with the last 4 weeks of treatment in the parent trial), a treatment period of 36 weeks, and a safety follow-up period of 2 weeks.
Number of subjects	All eligible subjects who completed the treatment period in the parent trial will be offered the opportunity to participate in this extension trial. It is assumed that approximately 600 eligible subjects will roll over from the parent trials.
Number and distribution of trial sites	Approximately 110 sites in Europe and North America.
Statistical methods	**Primary endpoint:** Treatment-emergent AEs (AEs emerging from baseline in this extension trial up to Week 38) will be summarised for all enrolled subjects and will be presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class (SOC). AEs will be summarised in terms of the number and percentage of subjects with AEs, the number of AEs, and the rate of AEs (number of AEs per 100 person years of observation time). **Secondary endpoints:** IGA-CHE and HECSI scores will be summarised at each scheduled visit from baseline up to Week 36. The proportion of subjects with IGA-CHE score of 0 (clear) or 1 (almost clear) will be summarised at each scheduled visit from baseline up to Week 36.

	HECSI-75 and HECSI-90 will be summarised at each scheduled visit from baseline up to Week 36. For the calculation of HECSI-75 and HECSI-90, the baseline score from the parent trial will be used. If nothing else is stated, an observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit). For binary response tabulations, subjects experiencing discontinuation of IMP, initiation of rescue treatment, or withdrawal from trial, will be imputed as non-responders. Otherwise, missing values will not be imputed.
Signatory investigator	[redacted], Prof, MD, DMSc Department of Dermatology [redacted], Denmark
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

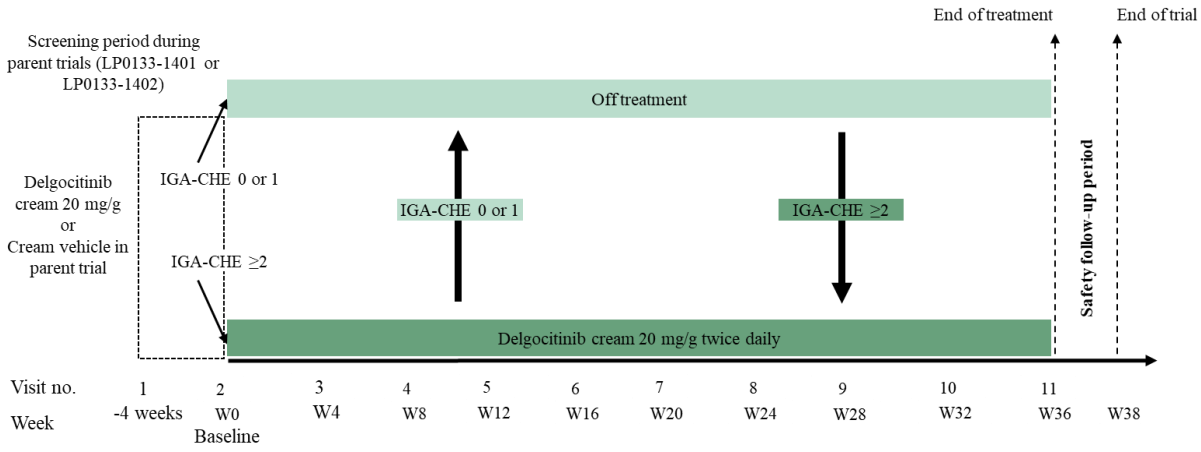
2 Trial identification

EudraCT number: 2020-002962-15

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

3 Schematic of trial design

Panel 1: Trial design



Abbreviations: IGA-CHE: Investigator's Global Assessment for chronic hand eczema. W: week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening[1]	Treatment period									End of treatment	Early termination, if applicable[2]	Safety follow-up[3]	Unscheduled visit (if applicable)[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**(12)**	**13**		
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**	**38**		
Day	**(-28 to 1)[1, 5]**	**1[1]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**	**267**		
Visit window (days)[5]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**		
Trial population and eligibility															
Informed consent[6]	X														Appendix 3B
Subject eligibility[7]	X	X													8.2 and 8.3
Investigator assessments at screening/baseline only															
Demographics[7]	X														11.2
Fitzpatrick skin type[7]	X														11.2
Medical history[7]		X[8]													11.2
Height and weight[7]	X														11.2
eDiary device update / training		X													11.3
Treatment															
Dispense IMP[9]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				(X)	9.2
Instruction for IMP application[10]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				(X)	9.2

	Screening[1]	Treatment period									End of treatment	Early termination, if applicable[2]	Safety follow-up[3]	Unscheduled visit (if applicable)[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**(12)**	**13**		
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**	**38**		
Day	**(-28 to 1)[1, 5]**	**1[1]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**	**267**		
Visit window (days)[5]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**		
Determination of treatment area(s)[10]		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)				(X)	11.2
Application of IMP		<=========Twice daily on an 'as-needed' basis[11]=========>													9.2
eDiary completion: 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)	(X)	(X)		(X)	9.8.3
Concomitant medication and concurrent procedures	X[7]	X[7]	X	X	X	X	X	X	X	X	X	X		(X)	9.6
Investigator assessments of efficacy															
IGA-CHE		X[7]	X	X	X	X	X	X	X	X	X	X		(X)	11.4.1
HECSI		X[7]	X	X	X	X	X	X	X	X	X	X			11.4.2
Subject assessments of efficacy – daily															
eDiary completion: HESD[7,14]		<========== Daily ==========>													11.4.3.2

	Screening[1]	Treatment period									End of treatment	Early termination, if applicable[2]	Safety follow-up[3]	Unscheduled visit (if applicable)[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**(12)**	**13**		
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**	**38**		
Day	**(-28 to 1)[1, 5]**	**1[1]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**	**267**		
Visit window (days)[5]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**		
Patient-reported outcomes – during trial visits															
HEIS		X[7]		X		X		X		X	X	X			11.8.1.2
DLQI		X[7]		X		X		X		X	X	X			11.8.1.3
EQ-5D-5L		X[7]		X		X		X		X	X	X			11.8.1.4
WPAI:CHE		X[7]		X		X		X		X	X	X			11.8.1.5
Subject assessments of safety															
Subject assessment of local tolerability[15]		<=======Daily while on treatment=======>									X	X			11.5.4
Investigator assessments of safety															
Vital signs		X[7]		X		X		X			X	X		(X)	11.5.1
Physical examination		X[7]									X	X		(X)	11.5.2
ECG		X[7]									X	X		(X)	11.5.3
Chemistry, haematology[16]	X[7]	X[7]		X		X		X			X	X		(X)	11.5.5
Urine pregnancy test[17]	X[7]	X[7]	X	X	X	X	X	X	X	X	X	X		(X)	11.5.5
Urinalysis (urine dipstick)[18]	X[7]	X[7]		X		X		X			X	X		(X)	11.5.5

	Screening[1]	Treatment period									End of treatment	Early termination, if applicable[2]	Safety follow-up[3]	Unscheduled visit (if applicable)[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**(12)**	**13**		
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**	**38**		
Day	**(-28 to 1)[1, 5]**	**1[1]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**	**267**		
Visit window (days)[5]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**		
AEs		X[7,8]	X	X	X	X	X	X	X	X	X	X	X	X	13
Investigator assessment of local tolerability[19]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	11.5.4
Scoring of suspected local skin reaction related to IMP (if applicable)[20]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	11.5.4
IMP-related patch test (if applicable)[20]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	11.5.4.1
Other assessments															
Photography of whole hands, including wrists (selected trial sites)[7,21]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X		(X)	11.8.2
New CHE lesions		X[7]	X	X	X	X	X	X	X	X	X	X		(X)	11.4.1
Return of eDiary device											X	X			11.3

	Screening[1]	Treatment period									End of treatment	Early termination, if applicable[2]	Safety follow-up[3]	Unscheduled visit (if applicable)[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**(12)**	**13**		
Week	**-4 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**-**	**38**		
Day	**(-28 to 1)[1, 5]**	**1[1]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**-**	**267**		
Visit window (days)[5]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**		
End of treatment/trial															
End-of-treatment form[22]											X	X			11.9
End-of-trial form[22]											X	X			11.9

1. The screening visit (Day -28) will ideally coincide with the Week 12 visit in the parent trials (LP0133-1401 or LP0133-1402) but can be conducted anytime between the Week 12 and Week 16 visits in those trials. If necessary, both the screening and baseline visits can be conducted at the Week 16 visit in the parent trial. The baseline visit (Day 1) in this extension trial will coincide with the end-of-treatment visit (Week 16) in the parent trials.
2. Subjects who permanently discontinue treatment prior to Week 36 or withdraw from trial will be asked to return to the trial site for an early termination visit as soon as possible for completion of all trial procedures scheduled for the visit at Week 36.
3. Safety follow-up will be performed as a phone visit (but can be performed as a site visit if needed) approximately 2 weeks after the end-of-treatment/early termination visit.
4. 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 change in disease state requiring start or stop of treatment with delgocitinib cream 20 mg/g or need of rescue treatment. Assessments to be performed at unscheduled visits will be at the discretion of the investigator. If the subject experiences a worsening of CHE signs and symptoms and a scheduled visit is not planned within a reasonable timeframe, an unscheduled visit should be conducted to determine if treatment should be started. If an IGA-CHE score of ≥2 is observed, the site will dispense delgocitinib cream 20 mg/g and the subject should start treatment with twice-daily applications. Once CHE signs and symptoms resolve, a new unscheduled visit should be scheduled if no scheduled visit is planned in a reasonable timeframe. At the first visit after symptoms resolve (scheduled or unscheduled visit), the investigator will assess whether IGA-CHE 0 or 1 is achieved, and if so, treatment will be stopped. An unscheduled visit at which a decision is taken to start treatment should at least comprise IGA-CHE assessment and collection of AEs. An unscheduled visit at which a decision is taken to stop treatment should at least comprise IGA-CHE assessment, collection of AEs, and investigator assessment of local tolerability. Subjects on treatment with delgocitinib cream 20 mg/g should bring all previously dispensed tubes to each visit (scheduled or unscheduled) in case a decision is made to stop treatment, in which case all tubes should be returned to the site.

5. 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). Due to the 3-days window allowed for the Week 12 and Week 16 visits in the parent trial, screening in this extension trial can occur up to -34 days, as long as this overlaps with the dates of the respective visits in the parent trial.
6. The ICF must be signed prior to performing any protocol-related procedures. The ICF will be signed during participation in the parent trial.
7. To avoid duplicate data collection, any applicable data from the screening, baseline, Week 12, Week 16, and unscheduled visits between Week 12 and Week 16 from the parent trial will be transferred as screening or baseline data to the extension trial.
8. AEs occurring at or prior to baseline visit in this extension trial should be recorded in the parent trial. If ongoing at baseline visit for this extension trial, the AE will be recorded as medical history in the extension trial.
9. If the subject has IGA-CHE ≥2, delgocitinib 20 mg/g will be dispensed.
10. Before the first application of delgocitinib cream 20 mg/g and each time treatment is re-initiated, the subject will be instructed on how much cream to apply and which area(s) to treat.
11. If the subject has IGA-CHE ≥2, subject will apply delgocitinib cream 20 mg/g twice daily until IGA-CHE 0 (clear) or 1 (almost clear) is achieved.
12. Treatment application (yes/no) 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 delgocitinib cream 20 mg/g tubes will be weighed at site. Subjects must return all previously dispensed tubes of delgocitinib cream 20 mg/g to the site at all visits (scheduled and unscheduled).
14. HESD eDiary data from the parent trial starting from 1 week prior to and until Day 1 (baseline) in this extension trial will be transferred and considered as data for this extension trial.
15. While on treatment with delgocitinib cream 20 mg/g, local tolerability will be evaluated daily by the subject in the eDiary.
16. Subjects do not have to be fasting for safety laboratory samples.
17. For women of childbearing potential, a urine pregnancy test must be performed at each scheduled visit.
18. It will be at the investigator's discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.
19. Only to be performed if the subject is on treatment with delgocitinib cream 20 mg/g.
20. Only applicable if the subject is on treatment with delgocitinib cream 20 mg/g and if the investigator suspects contact dermatitis based on the initial inspection of the subject's hands and the subject's assessment of local tolerability (Section 11.5.4).
21. 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. Photographs of whole hands (front and back) including wrists, will be taken at visits (scheduled or unscheduled) at which a decision is taken to start or stop treatment, and at the end-of-treatment/early termination visit.
22. An end-of-trial form must be completed for all screened subjects, including subjects who discontinue treatment or withdraw from the trial, at their last trial visit. In addition, for all subject enrolled in the trial, an end-of-treatment form must be completed at their last trial visit (see Section 11.9).

Abbreviations: AE = adverse event; CHE = chronic hand eczema; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; HECSI = Hand Eczema Severity Index; HEIS = Chronic Hand Eczema Impact Scale; HESD = Chronic Hand Eczema Symptom Diary; ICF = informed consent form; IGA-CHE = Investigator's Global Assessment of chronic hand eczema; IMP = investigational medicinal product; WPAI:CHE = Work Productivity and Activity Impairment: Chronic Hand Eczema.

5 Introduction and trial rationale

5.1 Chronic hand eczema

Chronic hand eczema (CHE) is a serious inflammatory skin disorder located anywhere on the hands or wrists. In the acute stage, it is clinically characterised by erythema, infiltration, oedema, or vesicles, and in the chronic stage by scaling, fissures, and hyperkeratosis, and the condition may be exacerbated by bacterial infections. Important symptoms include itch and pain, and the disease is often characterised by 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 aetiology 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), however it is generally agreed that the most common subtypes of CHE are contact dermatitis (irritant and allergic), atopic hand eczema, and hyperkeratotic eczema (5). Other subtypes include acute recurrent vesicular hand eczema, and contact urticaria/protein contact dermatitis (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 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 atopic dermatitis (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 health-related quality of life (HRQoL), 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 (janus kinase/signal transducer and activator of transcription) 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 is a necessary prerequisite for successful therapy on a longer term. Topical corticosteroids (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 (24).

Whereas mild CHE to some extent may be managed by elimination of triggers, general skin care, and TCS, management of moderate to severe CHE is more cumbersome. Alitretinoin (25) is the only approved product specifically indicated for treatment of CHE but is only indicated for severe CHE unresponsive to treatment with potent TCS, and only approved in Europe and a few other countries worldwide.

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.

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, 26), 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 HRQoL of patients with moderate to severe CHE.

Delgocitinib has the potential to address the unmet medical need associated with this burdensome disease.

5.2 Experience with investigational medicinal product

Delgocitinib (LEO 124249) is a pan-JAK inhibitor, which blocks various cytokine-mediated signalling pathways and widely suppresses the activation of immune and inflammatory cells such as T-cells, B-cells, mast cells, and monocytes activated by these cytokines (27).

In nonclinical studies, topically administered delgocitinib inhibited inflammation in rat and mouse AD- and psoriasis-like 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 (28).

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: Physician's Global Assessment (PGA) treatment success at Week 8 (defined as achieving a PGA 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 Investigator's Global Assessment for CHE treatment success (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 Hand Eczema Severity Index (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 ($p<0.05$) (29).

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

This is a long-term extension trial to evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g in accordance with the ICH E1 guideline (30).

Subjects eligible for this trial will have received blinded treatment with either twice-daily delgocitinib cream 20 mg/g or cream vehicle and will have completed the 16-week treatment period in one of the 2 parent trials: LP0133-1401 or LP0133-1402.

The purpose of the parent trials is to confirm efficacy and evaluate safety of twice-daily delgocitinib cream 20 mg/g compared with cream vehicle for a treatment period of 16 weeks in adult subjects with moderate to severe CHE. Subjects transferring from the blinded parent trials will enter this extension trial without their individual treatment allocation being revealed, in order to maintain the blinding of the ongoing parent trial.

An open-label trial design is chosen as the aim of this trial is to evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g to mimic the anticipated use of delgocitinib cream in clinical practice. Further, a vehicle arm is not included since vehicle treatment beyond 16 weeks is not considered ethical.

Based on the available nonclinical and clinical data, delgocitinib cream has the potential to become an effective and well tolerated treatment for CHE and thereby improve HRQoL of affected patients.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (31), the ICH GCP (32) guidelines, 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 well-being of the trial subjects. All subjects will be treated with open-label delgocitinib cream 20 mg/g twice daily as needed. All subjects will have previously participated in one of the parent trials.

Subjects may initiate rescue treatment at the discretion of the investigator if medically necessary, in which case treatment with delgocitinib cream 20 mg/g will be discontinued immediately (see Section 9.5).

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.

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/contracted 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 severe CHE. Alitretinoin is only approved in Europe and a few countries worldwide.

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 nonclinical and clinical data on delgocitinib is available in the current investigator's brochure (33).

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 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.

The EMA (34), FDA (35), 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. Therefore, if and only if subjects are prevented from attending on-site visits due to local authority-issued preventive measures, a decision to start or stop treatment with delgocitinib 20 mg/g can be taken based on a phone or video visit. 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 patient-reported outcome (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 and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoint
To evaluate the long-term safety of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.	• Number of treatment-emergent AEs from baseline up to Week 38.
Secondary objective	Secondary endpoints
To evaluate the long-term efficacy of an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.	• IGA-CHE score at each scheduled visit from baseline up to Week 36. • IGA-CHE score of 0 (clear) or 1 (almost clear) at each scheduled visit from baseline up to Week 36. • HECSI score at each scheduled visit from baseline up to Week 36. • HECSI-75 at each scheduled visit from baseline up to Week 36.[1] • HECSI-90 at each scheduled visit from baseline up to Week 36.[1]
Other/exploratory objectives	Other/exploratory endpoints
To explore efficacy, health-related quality of life, and work productivity for an as-needed treatment with twice-daily applications of delgocitinib cream 20 mg/g.	*Efficacy* • Number of days on treatment with delgocitinib cream 20 mg/g from baseline up to Week 36. • Number of on-treatment periods[2] from baseline up to Week 36.

Objectives	Endpoints
	• Proportion[3] of response[4] days from baseline up to Week 36. • Mean duration of on-treatment periods per subject from baseline up to Week 36. • Time to first IGA-CHE score ≥2 in subjects previously treated with delgocitinib cream 20 mg/g in the parent trial and who achieved IGA-CHE TS at Week 16 in the parent trial. • Time to first response (IGA-CHE score of 0 [clear] or 1 [almost clear]) in subjects who did not achieve IGA-CHE TS at Week 16 in the parent trial. • Time to response (IGA-CHE score of 0 [clear] or 1 [almost clear]) following treatment re-initiation after first off-treatment period in subjects previously treated with delgocitinib cream 20 mg/g in the parent trial. • HESD score (weekly average) at each nominal week from baseline up to Week 36. • HESD itch, pain, cracking, redness, dryness, and flaking scores (weekly averages) at each nominal week from baseline up to Week 36. • Reduction of HESD score, HESD itch score, and HESD pain score, (weekly averages) of ≥4 points from parent baseline at each nominal week from baseline up to Week 36.[5] *Health-related quality of life* • HEIS score at each scheduled visit with assessment from baseline up to Week 36. • HEIS (each individual domain) score at each scheduled visit with assessment from baseline up to Week 36. • DLQI score at each scheduled visit with assessment from baseline up to Week 36. • EQ-5D-5L visual analogue score at each scheduled visit with assessment from baseline up to Week 36. • EQ-5D-5L index score at each scheduled visit with assessment from baseline up to Week 36. • WPAI:CHE domain scores at each scheduled visit with assessment from baseline up to Week 36. *Exposure and treatment compliance* • Total amount of delgocitinib cream 20 mg/g used during the trial. • Percentage of missed applications.

1. In the derivation of HECSI-75 and HECSI-90 the baseline score from the parent trials will be used.
2. An on-treatment period is defined from the day treatment is re-initiated (when IGA-CHE score ≥2 is observed by the investigator) to the day treatment is stopped (when IGA-CHE score of 0 [clear] or 1 [almost clear] is observed by the investigator).
3. Number of response days (days when a subject is not on treatment with delgocitinib cream 20 mg/g) divided by number of days between baseline and end of trial.

4. Response days are defined as the sum of days where the subject is in response periods. A response period is defined as the period from the day IGA-CHE score of 0 (clear) or 1 (almost clear) is observed by the investigator, to the day IGA-CHE score ≥2 is observed by the investigator.
5. Among subjects with a parent baseline HESD score, HESD itch score, and HESD pain score (weekly averages) ≥4 points, respectively

Abbreviations: AE = adverse event; 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; TS = treatment success; WPAI:CHE = Work Productivity and Activity Impairment: Chronic Hand Eczema.

7 Trial design

7.1 Overall trial design

This trial is a phase 3, open-label, multi-site, extension trial. The trial is designed to evaluate the long-term safety of twice-daily applications of delgocitinib cream 20 mg/g as needed in eligible subjects with CHE who completed one of the 2 pivotal phase 3 trials with delgocitinib cream 20 mg/g or cream vehicle (parent trials – LP0133-1401 or LP0133-1402). The trial will include a screening period of up to 4 weeks (Week -4 to Week 0) and a treatment period of 36 weeks during which subjects will be treated with delgocitinib cream 20 mg/g twice daily as needed. During the treatment period, subjects will attend site visits every 4 weeks; if needed, unscheduled visits will be performed to initiate or stop treatment with delgocitinib cream 20 mg/g twice daily. Subjects will attend an end-of-treatment visit at Week 36 and a safety follow-up will be performed by phone approximately 2 weeks after the end-of-treatment visit to assess any AEs. The trial design is illustrated in Panel 1.

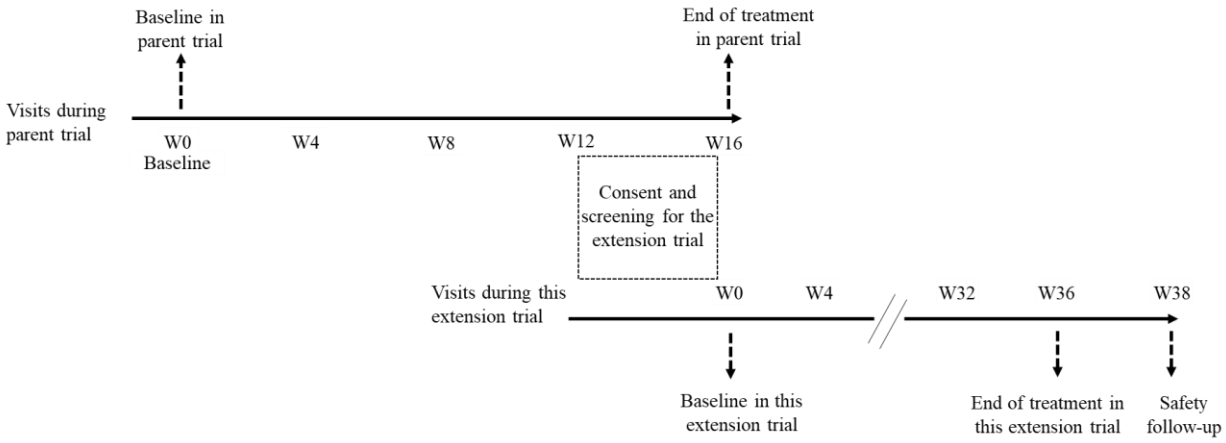
Screening period (Week -4 to Week 0)

Eligibility will be assessed at screening and at the baseline visit. Trial-specific measurements will be performed as outlined in Panel 2.

To facilitate a smooth transition between completing treatment in the parent trial and commencing participation in the extension trial, potentially eligible subjects will be offered participation in the extension trial preferably at the Week 12 visit (prior to the end-of-treatment visit at Week 16) in the parent trial. Hence, the screening period is expected to overlap with the last 4 weeks of the treatment period in the parent trial (see Panel 4). Any assessment from the Week 12 visit performed in the parent trials may be used to confirm eligibility for this extension trial. However, if for any reason, assessments from the Week 12 visit are not evaluable, the Week 16 assessments from the parent trials may be used as screening results for this trial, without precluding the initial enrolment of the subject in this extension trial. The end-of-treatment visit in the parent trial will coincide with the baseline visit of the extension trial. For subjects meeting the eligibility criteria (those which can be evaluated prior to the end-of-treatment visit [Week 16] in the parent trials), assessments performed at the end-of-treatment visit in the parent trial may be re-used without being repeated for this extension trial.

The subjects will have their eDiary from the parent trial updated to record PROs, treatment compliance, and local tolerability in this extension trial. Completion of the eDiary will be initiated from the baseline visit (Day 1).

Panel 4: Trial visits in the parent trials and extension trial



Treatment period (Week 0 up to Week 36)

Definition of terms:

Response is defined as IGA-CHE score of 0 (clear) or 1 (almost clear).

Treatment re-initiation is triggered by an IGA-CHE score of ≥2 after having achieved IGA-CHE 0 (clear) or 1 (almost clear) in this trial.

At baseline (Day 1), subjects will be evaluated by the investigator to determine the severity of their CHE. Subjects with IGA-CHE score of 0 (clear) or 1 (almost clear) will not be assigned treatment with delgocitinib cream 20 mg/g; they will however continue to use their routine skin care emollient, if applicable. Subjects with IGA-CHE score ≥2 will start treatment with twice-daily delgocitinib cream 20 mg/g. Treatment will continue until IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved.

If a subject experiences worsening of CHE signs and symptoms while off-treatment, the subject should contact the trial site. If a scheduled visit is not planned within a reasonable timeframe, an unscheduled visit should be planned as soon as possible. If an IGA-CHE score ≥2 is attested, the subject will be dispensed delgocitinib cream 20 mg/g and the investigator will instruct the subject to start treatment with twice-daily applications. The minimal set of assessments to be performed at an unscheduled visit to decide if treatment with delgocitinib cream 20 mg/g should be re-initiated is IGA-CHE and collection of AEs.

While on treatment with delgocitinib cream 20 mg/g, if the subject observes that CHE signs and symptoms are resolved, they should contact the trial site. If a scheduled visit is not planned within a reasonable timeframe, an unscheduled visit should be planned as soon as

possible. If IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved, the subject will be instructed to stop treatment and return all opened and unopened tubes to the site. The minimal set of assessments to be performed at an unscheduled visit to decide if treatment with delgocitinib cream 20 mg/g should be stopped is IGA-CHE, collection of AEs, and investigator's assessment of local tolerability.

For all subjects, regardless if on- or off-treatment, IGA-CHE will be evaluated by the investigator at visits to the trial site every 4 weeks from baseline up to Week 36.

If no improvement is observed after a continuous on-treatment period of 16 weeks with twice-daily delgocitinib cream 20 mg/g, it will be at the discretion of the investigator to evaluate if the subject will benefit from further treatment with delgocitinib cream 20 mg/g.

If CHE becomes 'intolerable', the subject should contact the investigator for an unscheduled visit. Rescue treatment for CHE may be provided to subjects at the discretion of the investigator. In this case, delgocitinib cream 20 mg/g will be discontinued immediately and the subject will be withdrawn from the trial (see Section 9.5).

At Week 36, subjects will attend an end-of-treatment visit. If treatment for CHE is required beyond the end-of-treatment visit, subjects will be referred to standard of care treatment at the discretion of the investigator.

Follow-up period (Week 36 to Week 38)

All subjects will complete a 2-week off-treatment follow-up period for the assessment of safety. The safety follow-up period will start after the Week 36 visit (end-of-treatment). Note that for subjects who permanently discontinue delgocitinib cream 20 mg/g, the 2-week follow-up period will start at the time of the early termination visit.

The safety follow-up visit will be performed via phone, but can be a site visit if needed.

Serious AEs (SAEs) will be followed up until a final outcome is established as described in Section 13.7.

7.2 Number of subjects needed

Sample size considerations are described in Section 14.1. Based on the expected drop-out rate in the parent trials, it is assumed that approximately 600 subjects will roll over to this extension trial.

The trial will be conducted at approximately 110 sites in Europe and North America. The number of subjects per site will depend on how many subjects in the parent trial meet the eligibility criteria and choose to participate in this extension trial.

7.3 End-of-trial definition

A subject is considered to have completed the trial if they completed the treatment period and the safety follow-up visit at Week 38.

For an individual subject, end of trial is defined as attending the last visit (or phone visit) in the trial.

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

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 visits specified in Panel 2. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

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

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial.
3. Subjects must have met eligibility criteria at screening and baseline in the parent trial.
4. Subjects must have completed the treatment period in the parent trial (to be assessed at baseline visit in this extension trial).
5. Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator.
6. A woman of childbearing potential* must use an acceptable** method of birth control throughout the trial up until the end-of-treatment/early termination visit.

* 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. Subjects who prematurely discontinued treatment with IMP or initiated rescue treatment in the parent trial.
2. Subjects who experienced any adverse event (AE) during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator.
3. Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial.
4. Current participation in any other interventional clinical trial, except for parent trial.

8.4 Screening and screening failures

Subject identification number

Once informed consent is obtained, the subjects will be assigned the same subject identification number (ID) as for the parent trials in the central interactive response technology (IRT) system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the informed consent form was signed. To avoid duplicate data collection, any applicable data from the screening, baseline, Week 12, Week 16 (end-of-treatment), and unscheduled visits between Week 12 and Week 16 visits from the parent trial will be transferred to this extension trial. The subject ID will be used to identify the subject during the screening process and throughout trial participation. 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 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 (36) 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.
- 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.

Re-screening of screening failures is not allowed.

9 Treatments

9.1 Trial product description

Panel 5: Identification of investigational medicinal product - delgocitinib

Investigational medicinal product	Dosage form	Active ingredient and concentration	pH	Pack size	Manufacturer responsible for batch release
Delgocitinib cream 20 mg/g	Cream	Delgocitinib, 20 mg/g	[redacted]	15 g	LEO Pharma A/S

Panel 6: Identification of investigational medicinal product – challenge agent

Investigational medicinal product	Dosage form	Active ingredient and concentration	pH	Pack size	Manufacturer responsible for batch release
Cream vehicle (applicable only if IMP-related patch testing for suspected contact dermatitis needs to be performed)	Cream	Vehicle	[redacted]	15 g	LEO Pharma A/S

Panel 7: 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
Butylhydroxy anisole
Sodium hydroxide (may be used to adjust pH)

9.2 Administration of investigational medicinal products

Delgocitinib cream 20 mg/g will be administered as a twice-daily topical application, as needed (see Section 7.1). The applications will be performed approximately 12 hours apart. Instructions for use will also be provided.

Delgocitinib cream 20 mg/g will be applied to clean, dry hands, fingers, fingertips, and wrists in a thin layer covering the affected areas. The amount of delgocitinib cream 20 mg/g 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 the hands, fingers, fingertips, and wrists twice daily for 1 week; however, a few patients may need more (based on experience from the LP0133-1273 trial), which will be allowed at the discretion of the investigator.

Prior to the first application of delgocitinib cream 20 mg/g and each time treatment is re-initiated, 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 delgocitinib cream 20 mg/g as well.

At the scheduled trial visits, investigator assessments of efficacy should preferably be done at least 2 hours after application of delgocitinib cream 20 mg/g or emollient. Recommendations for bathing, washing, and hand sanitising in relation to delgocitinib cream 20 mg/g application are provided in Section 9.6.

Tubes of delgocitinib cream 20 mg/g will be dispensed by the investigational staff if it is decided during a visit (scheduled or unscheduled) that a subject should start treatment. After that, delgocitinib cream 20 mg/g tubes will be dispensed to the subject at each scheduled visit until it is decided that the subject should stop treatment. Application of delgocitinib cream 20 mg/g will be recorded by the subjects each day in the eDiary.

Returned opened tubes of delgocitinib cream 20 mg/g will be weighed at the trial site to determine the amount of cream used. Subjects must return all previously dispensed tubes of delgocitinib cream 20 mg/g to the site at all visits (scheduled and unscheduled). For details on handling of unopened tubes, see Section 9.8.3.

If no improvement is observed after a continuous on-treatment period of 16 weeks with twice-daily delgocitinib cream 20 mg/g, it will be at the discretion of the investigator to evaluate if the subject will benefit from further treatment with delgocitinib cream 20 mg/g.

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 fulfil any of the exclusion criteria will be rolled over to this extension trial. At baseline (Day 1), subjects with an IGA-CHE score of 0 (clear) or 1 (almost clear) will be taken off treatment whereas subjects with an IGA-CHE score ≥2 will be treated with twice-daily delgocitinib cream 20 mg/g until IGA-CHE score of 0 (clear) or 1 (almost clear) is achieved.

The IRT system will be used for IMP supply chain and expiry tracking.

9.3.2 Blinding

Not applicable.

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 delgocitinib cream 20 mg/g. The 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 signs and 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 safety and efficacy assessments (e.g. safety laboratory assessments, disease severity scores) immediately before administering any rescue treatment. If rescue treatment is initiated, the subject must discontinue treatment with delgocitinib cream 20 mg/g immediately and will not be allowed to restart treatment. Subjects who discontinue delgocitinib cream 20 mg/g will be asked to attend an early termination visit at the site. A follow-up visit (performed via phone, but can be a site visit if needed) will be performed approximately 2 weeks after the early termination visit. The subjects will then be withdrawn from the trial (see Section 10.3 for details).

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 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 within the treatment area.

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

As a rule, the subjects should not change their usual skin care routine for the hands if possible; however, emollients should not be used on the treatment areas within 2 hours before and after application of delgocitinib cream 20 mg/g. 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 delgocitinib cream 20 mg/g. 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 delgocitinib cream 20 mg/g 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 8 are prohibited during the trial from screening until end of trial for the individual subject as defined in Section 7.3.

Panel 8: Prohibited medications and procedures

Medication or procedure
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.
JAK inhibitors, systemic or topical (except for the use of IMP during the parent and extension trials).
Tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands.
Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands.
Cutaneously applied antibiotics on the hands.
Other transdermal or cutaneously applied therapy on the hands (except for the IMP and the subject's own emollient).
Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern.[2]
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. • Other biologics.
Any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration).

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.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

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

The labelling of IMP will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 (37), 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 IMP must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

The IMP must be stored below 25°C at the trial site. Do not freeze the IMP. 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 in order 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 IMP and should immediately contact their clinical research associate (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 IMP (including kits damaged upon receipt) are provided in the trial product handling manual.

9.8.3 Investigational medicinal product accountability

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

Dispensing 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.

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

The subject should bring all previously dispensed delgocitinib cream 20 mg/g tubes to all visits (scheduled and unscheduled). The subject will return used, partly used, and unused tubes (including packaging material) if a decision is taken to stop treatment.

Returned, opened delgocitinib cream 20 mg/g tubes will be weighed at the trial site to determine the amount of cream used. The weight of the returned tubes (in grams with 1 decimal) will be recorded in the drug accountability forms and transcribed to the eCRF.

Returned trial product (used, partly used, and unused IMP [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 contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO on an ongoing basis. Prior to return, the IMP must be weighed (only applicable for delgocitinib cream 20 mg/g tubes) and fully accounted for by the CRA with the help of site staff responsible for dispensing the IMP. Accountability must be documented on drug accountability forms and in the IRT system.

9.8.4 Treatment compliance

Treatment applications will be recorded by the subjects in an eDiary. The subject will be asked the following question once daily: ‘Did you apply trial cream today?’ (yes, no).

The investigator (or designee) should review the 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 delgocitinib cream 20 mg/g as prescribed.

Reporting in eCRF

For each time treatment with delgocitinib cream 20 mg/g is started or stopped as per the investigator's assessment, the date of first and last application of delgocitinib cream 20 mg/g 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 requirement.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

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

Critical complaints (defined as any defect, 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 complaint.

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

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

Fax number: +45 6910 2468

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

10 Discontinuation and withdrawal

10.1 General principles

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

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 discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- An AE that, in the judgement of the investigator or sponsor's medical expert, contraindicates further dosing.
- Evidence of pregnancy.
- Initiation of rescue treatment.
- Lack of efficacy.
- Clinically important laboratory abnormalities:
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3× upper limit of normal (ULN) with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome) – and at the discretion of the investigator.
    - Confirmed ALT and/or AST values >5×ULN (for more than 2 weeks).
- Positive reaction to IMP patch test.

It is not allowed to restart IMP treatment after permanent 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' or 'other' is selected, a specification must be provided in the eCRF. If 'adverse event' is selected, the AE in question will be linked to the discontinuation of IMP. If 'withdrawal by subject' is selected, it will be recorded whether the subject withdrew informed consent or not.

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

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP prior to Week 36 will be asked to attend the following visits:

- Early termination visit (as soon as possible).
- Safety follow-up visit (phone visit approximately 2 weeks after attending the early termination visit).

See the schedule of trial procedures (Section 4) for assessments to be done at these visits. The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

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 (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 11.9.

10.4 Lost to follow-up

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

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.

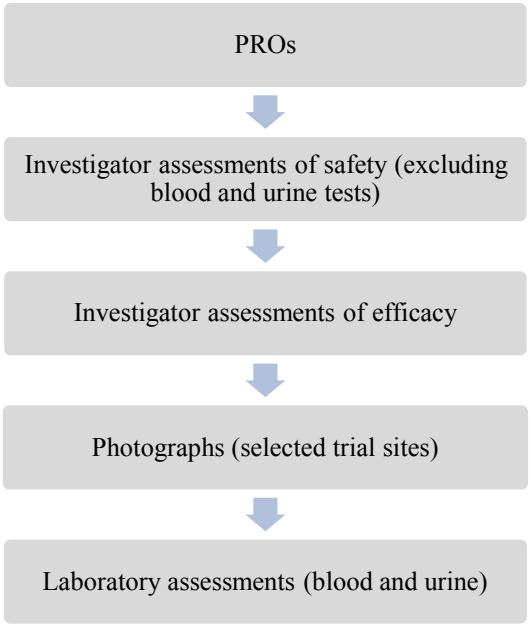
11 Trial assessments and procedures

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 as shown in Panel 9.

Panel 9: Sequence of assessments



Abbreviations: 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 and have documented experience and/or 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

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process.

Any applicable data from the screening or baseline visits in the parent trial, and relevant results from the assessments performed at the Week 12 visit and the end-of-treatment visit (Week 16) from parent trial will be transferred as screening or baseline results in this extension trial. Refer to Appendix 9 for a description of assessments performed at screening and baseline in the parent trials.

11.3 eDiary assessments

Subjects participating in this extension trial will have their eDiary set up for the extension trial by the trial site staff. Daily completion of the eDiary will continue in this extension trial.

At the baseline visit, the subjects will have their eDiary device updated. The eDiary will be open for entry from 4 pm until midnight. HESD eDiary data from the parent trial starting from 1 week prior to and until Day 1 (baseline) in this extension trial will be rolled over. The Hand Eczema Symptom Diary (HESD) must be completed in the eDiary every evening until Week 36. Treatment application (daily) and subject assessment of local tolerability (daily while on treatment) 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.

Update, training, and return of the eDiary are outlined in the schedule of trial procedures (Section 4).

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 application (see Section 9.8.4).
- Daily while on treatment: subject assessment of local tolerability (see Section 11.5.4).

11.4 Efficacy assessments

11.4.1 Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE)

The IGA-CHE is an instrument used in the phase 2b trial with delgocitinib (LP0133-1273) and has been further revised for use in the parent trials and this extension 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 10). The IGA-CHE score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit or in the parent trial. New lesions that occurred on previously untreated areas will be included in the assessment. The IGA-CHE score will be recorded in the eCRF.

Panel 10: Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE)

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 score scales (38).

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

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

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

Panel 11: HECSI severity score scale and area score scale

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

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

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

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

Panel 12: Calculation of the total HECSI score

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

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

11.4.3 Patient-reported outcomes

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 efficacy assessment in this trial. HESD will be completed by subjects at home in the eDiary.

Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. The eDiary should be returned to the trial site as outlined in the schedule of trial procedures (Section 4).

The PROs will be completed in the order specified in Section 11.8.1.1.

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 use in the parent trials and this extension trial. The HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Subjects will assess the worst severity of 6 individual signs and symptoms of CHE (itch, pain, cracking, redness, dryness, and flaking) over the past 24 hours using an 11-point numeric rating scale with anchors of 0=‘no (symptom)’ and 10=‘severe (symptom)’. The HESD score is derived as an average of the 6 items. Subjects will complete the HESD as an eDiary each evening from Week 0 until Week 36 (see 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.

Vital signs results from the Week 16 visit in the parent trial will be used as baseline results in this extension trial.

If an abnormal vital sign at baseline is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be included in the trial.

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. Any new clinically significant abnormal finding at the baseline visit will be recorded as an AE in the parent trial. Any clinically significant deterioration of a pre-existing condition recorded in the parent trial, as well as any new clinically significant sign, symptom, or illness occurring after the baseline visit will be recorded 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.

Physical examination results from the Week 16 visit in the parent trial will be used as baseline results in this extension trial.

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.

Any new clinically significant abnormal finding at the baseline visit will be recorded as an AE in the parent trial. Any clinically significant deterioration of a pre-existing condition recorded in the parent trial, as well as any new clinically significant sign, symptom, or illness occurring after the baseline visit will be recorded as an AE in accordance with Section 13.3.

11.5.3 Electrocardiography

A single 12-lead resting digital electrocardiogram (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).

ECG results from the Week 16 visit in the parent trial will be used as baseline results in this extension trial.

An evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. As 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 baseline is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be included in the trial.

The collection and transmission of ECG data will be described in a separate ECG manual.

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.

Any new clinically significant abnormal finding at the baseline visit will be recorded as an AE in the parent trial. Any clinically significant deterioration of a pre-existing condition recorded in the parent trial, as well as any new clinically significant sign, symptom, or illness occurring after the baseline visit will be recorded as an AE in accordance with Section 13.3.

11.5.4 Assessment of local tolerability

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

While on treatment, the subject will complete a daily assessment of stinging/burning in connection with the IMP applications in the eDiary. The subject will be asked to retrospectively assess the worst stinging/burning in connection with the IMP application during the day. The assessment will be done using the 4-point scale shown in Panel 13.

Panel 13: Subject assessment of local tolerability after IMP application

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

Abbreviation: IMP = investigational medicinal product.

While the subject is on treatment, 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 14. 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 11.5.4.1. 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 the 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 14 (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 reaction to IMP patch test, see Section 11.5.4.1], or other [specify]) will be captured in the eCRF and the final diagnosis will be captured as an AE.

Panel 14 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

11.5.4.1 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 11.5.4. The subject's own dispensed delgocitinib cream 20 mg/g as well

as cream vehicle control will be used for the patch test. To avoid contamination, approximately 1 cm of delgocitinib cream should be squeezed out of the tube before performing the IMP patch test. If this is not possible, a new tube of delgocitinib cream will be used (dispensed at the given visit) for the procedure. The trial site staff will apply a small amount of delgocitinib cream and vehicle control to the patch test chambers 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 two readings of any apparent patch test reaction 3-4 days and again 5-7 days after applying the patch. The positive patch test reaction will be documented by photography and scored (Panel 15) according to guidelines (39). 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 any positive patch test reactions will be provided in the laboratory manual.

Panel 15: 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, from Johansen et al. (39).

Reporting in the 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.

11.5.5 Laboratory testing

11.5.5.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4). Laboratory results from the Week 12 and Week 16 visit in the parent trial will be used as screening and baseline results, respectively, in this extension trial.

The evaluations shown in Panel 16 will be performed by the central laboratory.

Panel 16: Clinical laboratory tests performed by the central laboratory

Chemistry	Haematology	Urinalysis[2]
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	Protein Glucose Ketones Occult blood Leukocytes Nitrite

1. If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2. Urine samples will be tested for the listed analytes at trial site (dipstick). It will be at the investigator's discretion to decide whether a urine sample will 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).

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; RBC = red blood cells; WBC = white blood cells

11.5.5.2 Investigator evaluation of laboratory samples

Central laboratory

Chemistry, haematology, and urinalysis (if applicable) 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 included in the trial.

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 each scheduled visit, as shown in the schedule of trial procedures in Section 4.

Reporting in eCRF

At the visits indicated in the schedule of trial procedures (Section 4), 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 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 the baseline visit, any clinically significant deterioration of a pre-existing condition will be reported as an AE in the parent trial. Any new clinically significant sign, symptom, or illness occurring after baseline will be reported as an AE in accordance with Section 13.3.

11.6 Pharmacokinetic assessments

Not applicable.

11.7 Pharmacodynamics assessments

Not applicable.

11.8 Other assessments

11.8.1 Patient reported outcomes

11.8.1.1 Overview

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

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:

- HEIS
- DLQI
- EQ-5D-5L
- WPAI:CHE

PROs completed at the Week 16 visit in the parent trial will be used as baseline scores in this extension trial.

11.8.1.2 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 9 items addressing the subject's perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning 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 9 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: Proximal Daily Activity Limitations (PDAL) (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with CHE (1 item), sleep (1 item), work (1 item), and physical functioning

(1 item). The HEIS will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.8.1.3 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 (40). Each item is scored on a 4-point Likert scale (0 = 'not at all/not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (score range 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.

11.8.1.4 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 (41). 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.

11.8.1.5 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 (42). 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.

11.8.2 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 to

capture disease status over time.

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.

11.9 End of trial

End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all subjects who were enrolled in the trial. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (see Section 10.3 for early termination assessments).

The date of last application of delgocitinib cream 20 mg/g will be recorded on the end-of-treatment form. It will also be recorded if the subject completed the treatment (i.e. did not permanently discontinue IMP prior to the Week 36 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 in the 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?

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.

11.10 Estimate of total blood volume collected

Blood samples will be drawn for haematology and biochemistry. The total volume of blood to be drawn is approximately 40 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).

11.11 Storage of biological samples

The blood and urine samples for laboratory testing (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.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This trial is designed as an open-label trial with as-needed treatment to reflect the expected clinical practice regarding the use of delgocitinib cream 20 mg/g. The absence of a control arm using cream vehicle is justified by the long trial duration. Administering cream vehicle to subjects beyond 16 weeks is not considered ethical.

The eligibility criteria are chosen to ensure that subjects from the parent trial can safely be included in this long-term extension trial.

The trial will be conducted at multiple trial sites participating in the parent trials (LP0133-1401 or LP0133-1402) that are located in Europe and North America. High-quality trial sites with shared standards of practice will be selected.

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, patient insights support that topical treatment for CHE is preferred over systemic treatment from a patient point of view.

The trial endpoints have been selected to evaluate the safety of delgocitinib. The primary endpoint of the trial is the number of treatment-emergent AEs from baseline up to 38 weeks. Long-term safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, ECG, vital signs, and clinical laboratory measurements.

The dose of delgocitinib cream is 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 warrants 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.

In this extension trial, subjects will receive treatment with twice-daily delgocitinib cream 20 mg/g as needed over a 36-week period.

The benefit of treatment with twice-daily delgocitinib cream 20 mg/g as needed will be assessed using IGA-CHE and HECSI. IGA-CHE is a scale to assess the overall disease severity at a given time point and is based on a 5-point scale describing the severity of the disease from ‘clear’ to ‘severe’. HECSI is an instrument used to score both the extent and the intensity of the disease.

The clinical efficacy of twice-daily delgocitinib cream 20 mg/g as needed treatment will also be assessed using PROs.

12.2 Appropriateness of assessments

The safety of delgocitinib cream will be assessed using standard clinical methods such as AE reporting, ECG, vital signs, and clinical laboratory measurements.

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). The IGA-CHE was used in the phase 2b trial (LP0133-1273) and has been further revised for use in the parent trials and this extension trial. HECSI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of CHE (38).

By using validated PROs, this trial will also address the subjects’ perception of disease severity and the impact on HRQoL.

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 informed consent form (ICF) until end of trial (as defined in Section 7.3). To avoid duplicate reporting of AEs for subjects rolling over from a parent trial, any AE with onset prior to or at the baseline visit in the extension trial should be recorded as an AE in the parent trial. If ongoing at the baseline visit for this extension trial, the AE will be transferred to the extension trial as part of the subject's medical history. If such an ongoing AE worsens after the baseline visit in this extension trial, the AE should be recorded as a new AE in the extension trial. An AE with onset after the baseline visit in this extension trial and until end of trial for the individual subject (defined as attending the last visit in the trial) will be recorded as an AE in the extension trial.

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 11.5.4) 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 11.5.4.1) 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.

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.

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 obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

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

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

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

Global Safety at LEO Pharma

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

Fax number: +45 6910 2468

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

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

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

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported 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 (33).

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.

The following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma (32), and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, 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 17 are considered adverse events of special interest (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 17.

Panel 17: 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 (including 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 intended.

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

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

Misuse and abuse must be recorded in the eCRF on the other event involving IMP form. 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 the area which is normally not affected by CHE.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP until the safety follow-up visit or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome after the subject leaves the trial. The safety follow-up will be performed as a phone visit and may be delegated to site staff as per the signature and designation of responsibility log, provided the personnel is trained in AE reporting.

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

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

13.8 Handling of an urgent safety measure

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

The expected sample size for this trial is approximately 600 subjects. No formal sample size has been calculated, as the primary objective for the trial is to evaluate safety, which is reflected by the open-label trial design. No comparative analyses are performed in this trial. The expected sample size is based on the population size of the parent trials (920 subjects) and assumptions regarding completion rates in the parent trials.

The aim is to have sufficient exposure for an adequate safety evaluation of long-term treatment according to the ICH E1 guideline. The target is a minimum of 300 subjects completing 6 months and 100 subjects completing 12 months of treatment with delgocitinib, respectively. Six months of treatment is defined as 16 weeks of twice-daily delgocitinib cream 20 mg/g plus 10 weeks with twice-daily delgocitinib cream 20 mg/g as needed treatment, or cream vehicle (in the parent trial) plus 26 weeks with twice-daily delgocitinib cream 20 mg/g as needed treatment. Similarly, 12 months of treatment is defined as 16 weeks of twice-daily delgocitinib cream 20 mg/g plus 36 weeks with twice-daily delgocitinib cream 20 mg/g as needed treatment.

14.2 Trial analysis sets

All screened subjects will be accounted for in the clinical trial report (CTR).

In this open-label safety trial with an as-needed treatment regimen, all eligible subjects could potentially receive treatment with twice-daily delgocitinib cream 20 mg/g. Therefore, only the safety analysis set is defined and used as the basis for the analysis of all endpoints.

The safety analysis set is defined as all enrolled subjects.

The decisions regarding inclusion/exclusion of subjects or subject data from the safety analysis set will be documented in the analysis set definition document.

14.3 Statistical analysis

14.3.1 Disposition of subjects

The reasons for permanent discontinuation of IMP and withdrawal from trial will be presented for all subjects in the safety analysis set.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects in the safety analysis set.

Demographics include age, sex, ethnicity, and race. Other baseline characteristics include height, weight, body mass index, Fitzpatrick skin type, duration and classification of CHE, age at diagnosis of CHE, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, number of flares in the past 12 months, previous chronic hand eczema treatments, and IGA-CHE and HECSI scores at baseline in the parent trial.

14.3.3 Exposure and treatment compliance

Based on the attended visits data, exposure to treatment will be presented for the safety analysis set as days of exposure during the trial.

The total amount of IMP used during the trial will be summarised for the safety analysis set.

Treatment compliance will be presented for the safety analysis set as the percentages of missed applications during on-treatment periods, derived from the eDiary.

14.3.4 Analysis of primary endpoint

The analysis of the primary endpoint, number of treatment-emergent AEs from baseline up to Week 38 is described in Section 14.3.8.1.

14.3.5 Analysis of secondary endpoints

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

IGA-CHE and HECSI scores will be summarised at each scheduled visit from baseline up to Week 36 based on observed data.

In addition, the proportion of the subjects achieving IGA-CHE score of 0 (clear) or 1 (almost clear), HECSI-75 and HECSI-90 will be summarised at each scheduled visit from baseline up to Week 36, where subjects who discontinue treatment with IMP prior to Week 36, initiate rescue treatment, or withdraw from the trial, whichever comes first, will be imputed as non-responders.

In the derivation of HECSI-75 and HECSI-90 the baseline score from the parent trials will be used.

14.3.6 Analysis of other/exploratory endpoints

All analyses are based on safety analysis set.

The number of on-treatment days from baseline up to Week 36 will be summarised.

The number of on-treatment periods from baseline up to Week 36 and the rates per 100 person years of observation time will be presented.

The proportion of response days (days with IGA-CHE 0 or 1) from baseline up to Week 36 will be summarised. Mean duration of on-treatment periods per subject from baseline up to Week 36 will be summarised.

Time to first IGA-CHE score ≥2, initiation of rescue treatment, or discontinuation of IMP, whichever occurs first, will be presented for the subjects in the safety analysis set who were previously treated with delgocitinib cream 20 mg/g twice daily in the parent trial and achieved IGA-CHE TS at Week 16 in the parent trial. Kaplan-Meier curve and estimates will be presented. Subjects will be censored at the date of the last assessment visit in case of no events. Follow-up time to first IGA-CHE score ≥2 starts from the baseline visit.

Time to first response (IGA-CHE 0 or 1) will be presented for the subjects in the safety analysis set who did not achieve IGA-CHE TS at Week 16 in the parent trial, by treatment group assigned in the parent trial (delgocitinib cream 20 mg/g or cream vehicle respectively). Kaplan-Meier curves and estimates will be presented. Subjects will be censored at the date of the last assessment visit, initiation of rescue treatment, or discontinuation of IMP, whichever occurs first. Follow-up time to first response will be derived from the baseline visit.

Time to response (IGA-CHE 0 or 1) following treatment re-initiation after first off-treatment period will be presented for subjects in the safety analysis set who were treated with delgocitinib cream 20 mg/g twice daily in the parent trial. Kaplan-Meier curves and estimates will be presented. Subjects will be censored at the date of the last assessment visit, initiation of rescue treatment, or discontinuation of IMP, whichever occurs first. Follow-up time to response will be derived from the visit of treatment re-initiation after first off-treatment period.

14.3.7 Analysis of patient-reported outcomes

HESD score (weekly average) and HESD scores for itch, pain, cracking, redness, dryness, flaking (weekly average) will be summarised at each nominal week from baseline up to Week 36.

A ≥4-point reduction from parent baseline of HESD score (weekly average), HESD scores for itch and pain (weekly average) respectively, will be summarised at each nominal week. Subjects who discontinue treatment with IMP prior to Week 36, initiate rescue treatment, or withdraw from the trial, whichever comes first, will be imputed as non-responders-.

HEIS score, HEIS (each individual domain) score, DLQI score, EQ-5D-5L visual analogue score, EQ-5D-5L index score, and WPAI:CHE (each individual domain) score, will be summarised at the scheduled visits where the assessments are performed from baseline up to Week 36.

14.3.8 Analysis of safety

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

14.3.8.1 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).

AEs with onset after baseline visit will be considered treatment-emergent. AEs reported as ongoing at baseline in this trial will be reported as medical history. Any worsening of an ongoing AE after baseline visit will be recorded as a new AE in this trial. In each of the tabulations, AEs will be defined by MedDRA preferred terms within primary SOC. New AEs recorded after end of trial will be presented in a listing.

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, premature discontinuations from IMP and/or withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be given.

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 and pregnancy occurrences will be evaluated separately, and a narrative will be given.

AESIs will be listed. 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, if the subject was on treatment with IMP 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.

AEs will be summarised by treatment status (on/off treatment) at the time of onset. Treatment status will be derived from IGA-CHE data..

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

14.3.8.2 Vital signs and physical examination

For vital signs (resting blood pressure, pulse, and body temperature), the absolute values at baseline and Week 8, 16, 24, and 36 as well as the changes from baseline to Week 8, 16, 24, and 36 will be summarised as mean, standard deviation (SD), median, minimum, and maximum values.

Subjects with abnormal, clinically significant physical findings will be listed.

14.3.8.3 Clinical laboratory evaluation

For laboratory parameters, the absolute values at baseline and Week 8, 16, 24, and 36 as well as the changes from baseline to Week 8, 16, 24, and 36 will be summarised as mean, SD, median, minimum, and maximum values.

For selected liver, kidney, lipid, and haematology parameters, guideline or literature-defined thresholds will be used for producing shift tables and categorical threshold tables. The remaining laboratory parameters will be classified as ‘low’, ‘normal’, or ‘high’, depending on whether the value is below, within, or above the reference range and these categories will be used for producing shift tables. Shift tables will be either from baseline to end-of-treatment,

from baseline to maximum post-baseline value, or from baseline to minimum post-baseline value.

Subjects with laboratory parameters outside the reference range will be listed.

14.3.9 Subject assessment of local tolerability

Subject assessment of local tolerability will be summarised by nominal week.

14.3.10 Interim analysis

No interim analysis is planned.

14.3.11 Analysis of data to support submission for marketing authorisation approval

To support submission for marketing approval, analyses of data will be performed once sufficient exposure (defined in section 14.1) is available to evaluate the long-term safety of delgocitinib cream 20 mg/g. Results of these analyses will be included in a preliminary clinical trial report.

14.3.12 General principles

If nothing else is stated, an observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit).

Baseline measurements will be defined as the latest available observation at or prior to the baseline visit (Day 1), unless otherwise specified (e.g. baseline of the parent trial will be used for responder's definition of HECSI-75/90).

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, median, quartiles, SD, minimum, and maximum values.

Data will be presented for the total cohort of subjects, as well as the combination between randomised treatment in the parent trial (delgocitinib 20 mg/g or cream vehicle) and IGA-CHE TS status at baseline (IGA-CHE 0/1 or ≥2), when appropriate.

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, depending on the type of change.

All statistical analysis will be based on the safety analysis set.

14.3.13 Handling of missing values

For binary response tabulations, subjects experiencing discontinuation of IMP, initiation of rescue treatment, or withdrawal from trial, will be imputed as non-responders. Otherwise, missing values will not be imputed.

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (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 11.5.5.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation*.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/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, including skin malignancies, should be reported as SAEs.

Definition of adverse events of special interest

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

AESIs are described in Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement. If the AE worsens in severity, the new severity, including date of worsening, should be recorded. However, if an AE with onset prior to 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 Clinical Data Interchange Standards Consortium (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 (31) 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 (32).
- 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.

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 IMP 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.
- The fact that the subject is participating in a clinical trial in CHE including treatment with twice-daily delgocitinib cream 20 mg/g as needed for 36 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 electronic CRF (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.
The investigator must verify the correctness of the data entered by the site by electronically dating and signing the eCRF. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require re-signature by the investigator. The person making the change to the data, and the date, time, and reason for the change will be identified in the audit trail.

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

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

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

During the conduct of the study, 2 database locks will be performed to support submission for marketing approval.

Transmissions of data are documented in more detail in the 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 (32). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

For archiving purposes, each investigator will be supplied with an electronic copy of the eCRFs and ePRO data for all screened subjects at the trial site. This is done after completion of the trial and before access to the eCRF/ePRO is revoked. Audit trail information will be included. eCRFs and ePRO data must be available for inspection by authorised representatives from LEO Pharma, from regulatory authorities and/or IRBs/ IECs.

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

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

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

Results of this clinical trial will be posted 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

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.

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

France

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

Section 8.3 Exclusion criteria

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

5. **Subjects not affiliated with or not a beneficiary of a social security scheme.**

Canada

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

Appendix 5: Short version of eligibility criteria

Inclusion criteria	
No.	**Short version**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2	The baseline visit in this extension trial must coincide with the Week 16 (end-of-treatment) visit in the parent trial.
3	Subjects must have met eligibility criteria at screening and baseline in the parent trial (LP0133-1401 or LP0133-1402).
4	Subjects must have completed the treatment period in the parent trial (to be assessed at baseline visit in this extension trial).
5	Subjects must have complied with the clinical trial protocol in the parent trial to the satisfaction of the investigator.
6	A woman of childbearing potential must use an acceptable method of birth control throughout the trial up until the end-of-treatment/early termination visit.

Exclusion criteria	
No.	**Short version**
1	Subjects who prematurely discontinued treatment with IMP or initiated rescue treatment in the parent trial (LP0133-1401 or LP0133-1402).
2	Subjects who experienced any AE during participation in the parent trial, which precludes further treatment with delgocitinib cream 20 mg/g in the judgement of the investigator.
3	Any medical or psychiatric condition that could put the subject at undue risk by participating in the trial, or which, by the investigator's judgment, makes the subject inappropriate for the trial.
4	Current participation in any other interventional clinical trial, except for parent trial.

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

Coordinating investigator

[redacted], Prof, MD, DMSc
Department of Dermatology
[redacted], Denmark

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 safety and efficacy 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 enrolment of subjects (Week 12 and Week 16 in the parent trials) until on-site visits can be conducted. For already enrolled subjects, post-baseline visits can be done remotely via phone or video. At phone/video visits, no investigator assessments of efficacy can be done. Decisions to start or stop treatment with delgocitinib cream 20 mg/g will be at the investigator's discretion based on the outcome of the phone/video visit and the decision will be documented on a separate eCRF page. This option can only be used in case of local authority-issued preventive measures related to COVID-19 that would prevent the subjects from attending an on-site visit. The following data will be collected remotely (according to the schedule of trial procedures in Section 4):

- AE reporting.
- Treatment application (daily completion in the eDiary).
- Concomitant medication and concurrent procedures.
- Subject assessment of local tolerability (daily completion in the eDiary while on treatment).
- HESD (daily completion in the eDiary).
- PROs (HEIS, DLQI, EQ-5D-5L, WPAI-CHE). The subjects will receive a link to the PROs in a web browser and will complete them from their own computer.
- New CHE lesions.
- Urine pregnancy test. Women of childbearing potential will receive 1 extra urine pregnancy test at the baseline visit to keep at home in case on-site visits become impossible during the trial. The subject will take 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.

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.

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.

Appendix 9: Assessments performed at baseline and screening in the parent trials

Demographics

The following demographic data will be recorded:

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

Fitzpatrick skin type

The subject's skin type will be recorded using the Fitzpatrick skin classification (Panel 18).

Panel 18: 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.

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.

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.

Classification of chronic hand eczema

The investigator will determine the CHE subtype(s) according to the definitions in Panel 19. 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. 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 19: 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.

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.

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.

Appendix 10: Protocol amendment history

The Protocol amendment summary of changes table for the current amendment is located directly before the table of contents.

Amendment 2 (23-Aug-2021)

This amendment was 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, to accommodate for the conduct of the trial in Russia, to add photography of hands at certain visits, and to proceed with administrative and editorial changes.

Section no. and title	Description of change	Brief rationale
Section 4 Schedule of trial procedures	Determination of treatment area moved to the "treatment" section. Addition of photography.	This procedure was incorrectly listed under the section "Investigator assessments at screening/ baseline only". To provide guidance as to when photographs should be taken during the trial.
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 5.5 Benefit/risk assessment	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.	As per VHP request during assessment of the parent trials protocols (LP0133-1401 and LP0133-1402).
Section 8.3 exclusion criteria	Modified the introductory wording: the word "violate" was changed to "fulfil".	For clarity and to avoid misinterpretation.

Section no. and title	Description of change	Brief rationale
Section 8.4 Screening and screening failures	Addition of a screening log.	As per regulation requirement.
Section 9.6 Concomitant medication and concurrent procedures	Guidance regarding COVID-19 vaccines added. COVID-19 vaccines can be administered to subjects without the need to pause or discontinue IMP.	As per MHRA request during assessment of the parent trials protocols.
Section 10.2 Reasons for discontinuation of IMP	Positive reaction to IMP patch test added as reason for discontinuation of IMP.	For consistency with Section 11.5.4.1.
Section 11.1 Overview	Modification of the sequence of assessments: laboratory assessments (blood and urine) were included as the last assessments to be performed. Addition of photographs to the sequence of assessments.	Performing invasive procedures such as lab draws could be a cause of anxiety to some subjects that could lead to skin flushing, including that of the hands, thereby affecting efficacy assessments. Moving them after efficacy assessments will prevent the risk of influencing the efficacy endpoints. To provide guidance as to when photographs should be taken during a visit.
Section 11.1 Overview Section 13.2 Collection of adverse event 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 11.5.1 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 no. and title	Description of change	Brief rationale
Section 11.5.4.1 IMP patch test procedure	Clarified that photography of IMP patch test reaction should only be taken if there is a positive reaction.	For clarity.
Section 11.8.2 Photography (selected trial sites)	New section added to describe that photographs of hands will be taken to capture disease status at selected trial sites.	In the parent trial LP0133-1402, selected sites offer the possibility for subjects to consent to their hands being photographed to capture disease status during the trial. LEO Pharma wishes to continue capturing disease status in these subjects throughout this long-term extension trial.
Section 11.9 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 13.2 Collection of adverse event reports	Clarified that at baseline, an ongoing AE from the parent trial will be transferred to the extension trial as medical history.	For clarity and to avoid duplicate reporting of AEs.
Section 13.3 Reporting of adverse events	The sentence “In addition, it will be recorded if the AE started prior to first administration of IMP.” was deleted.	Recording if an AE started prior the first IMP application is not relevant with the trial design. Subjects will be treated with IMP for 16 weeks in the parent trial, and the first IMP administration in this extension trial will depend on the IGA-CHE at baseline. In the statistical analysis, AEs will be classified as occurring during a treatment period, or during a period without treatment.

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 13.6.1 Adverse events of special interest	The categories “none” and “other” were removed as risk factors in Panel 17.	For clarity.
Section 14.1 Sample size	Expected sample size of the parent trials increased to 920 subjects.	Due to the addition of Russia in trial LP0133-1401.
Section 14.3.8.1 Adverse events	The text on the analysis of other events was simplified.	The excessive detailed description of outputs was not appropriate for the protocol.
Appendix 1 Definitions of adverse events and serious adverse events	Hospitalisation definition clarified.	For clarity.
Appendix 3D Record keeping, quality control, and data handling	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 Country-specific requirements	The text was simplified to only show the added exclusion criterion.	For clarity.

Section no. and title	Description of change	Brief rationale
Appendix 9 Assessments performed at baseline and screening in the parent trials	Wording that does not mandate diagnostic patch testing for Russia implemented.	Russia added as country in the parent trial LP0133-1401 and in this extension trial.
Appendix 9 Assessments performed at baseline and screening in the parent trials	Asian - Chinese added as race.	To support a potential future submission in China.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarised.

Amendment 1 (14-Jun-2021)

This amendment was considered to be non-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 because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

This amendment was written to comply with requests from Health Canada.

Section no. and title	Description of change	Brief rationale
Section 5.5 Benefit/risk assessment	Clarification of text in relation to COVID-19	As per Health Canada preference
Appendix 4 Country-specific requirements	Addition of a Canada-specific requirement to archive trial documents for 25 years	Clarification of the requirement as per Health Canada standards