Dermatology
beyond the skin

Cover Page

Official title: A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical application of delgocitinib cream 1, 3, 8, and 20 mg/g for 16 weeks in adult subjects with mild to severe chronic hand eczema
LEO Pharma number: LP0133-1273
NCT number: NCT03683719
Date: 07-Dec-2018

Updated Clinical Trial Protocol

LP0133-1273

Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over a 16-week treatment period in adult subjects with chronic hand eczema

Phase 2b – dose-ranging trial

A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical application of delgocitinib cream 1, 3, 8, and 20 mg/g for 16 weeks in adult subjects with mild to severe chronic hand eczema

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:**	**LP0133-1273**
	Date:	**07-Dec-2018**
	EudraCT no:	**2018-000900-40**
	Version:	**3.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PDD , MSc Stat
Biostatistics Lead, Global Clinical Operations

PDD , MD
Vice President, Medical Sciences

PDD MA
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:

PDD , MD, PhD
Signatory investigator

Acknowledgement statement investigator(s)

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	Protocol version	Date	Type of protocol amendment
Amendment 2 (substantial)	3.0	07-Dec-2018	Global
Amendment 1 (substantial)	2.0	11-Jul-2018	Global
Original protocol	1.0	08-May-2018	Not applicable

Note that the protocol amendment summary of changes table for the previous amendment is provided in Appendix 6.

Amendment 2 (07-Dec-2018)

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

Overall rationale for the amendment

The main reason for the amendment is to address comments to the protocol received from the U.S. Food and Drug Administration. Miscellaneous other changes/updates have also been implemented.

The table below presents changes made in each section and a brief rationale for each change. Changes have been either summarised (written with plain text only) or marked as tracked changed (new text that has been added to the protocol is highlighted in **bold** and text that has been removed from the protocol is highlighted with ~~a line through the text~~).

Section no. and name	Description of change	Brief rationale
Section 1 Protocol synopsis	Change of treatment success abbreviation from IGA 0/1 to IGA TS. Patient Global Impression of Change (PGI-C) has been added to the list of subject assessments of efficacy and health-related quality of life; PROs. Subject assessment of local tolerability has been added as a safety assessment. Exclusion criterion slightly revised: "Concurrent skin diseases on the hands, **e.g. tinea manuum**". Exclusion criterion revised: "Tuberculosis requiring treatment within 12 months prior to screening **and/or subjects with a positive blood test for tuberculosis at screening*.** *** Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.**"	To reflect changes in the protocol.
Section 4 Schedule of trial procedures	Assessment of PGI-C added.	Added as a PRO anchor scale to generate a threshold for improvement that represents a meaningful amount of change in the

		target population.
	Tuberculosis test added.	To reflect that subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.
	Subject assessment of local tolerability added.	Added to have an active subject assessment of local tolerability in the trial.
	Assessment of new chronic hand eczema lesions added.	To reflect that the investigator will check for new chronic hand eczema lesions at the visits indicated in the schedule of trial procedures.
	Change to footnote on medical history: "Relevant medical history must be recorded from the subject's date of birth. **In case medical history is incomplete at screening visit, missing data will be retrieved at Day 1 (baseline).**"	To clarify that it is not the intention that full medical history is to be recorded both at screening and at baseline.

	Addition of footnote on WLQ: "**Only for subjects with a paid job**".	To clarify that only subjects with a paid job are to answer the WLQ.
Section 6 Trial objectives and endpoints	Change of treatment success abbreviations from IGA 0/1 to IGA TS and from PaGA 0/1 to PaGA TS.	To avoid misunderstandings between e.g. an IGA score of 0 (clear) or 1 (almost clear) and IGA treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement.
	Addition of text to 2 endpoints: "Change in Chronic Hand Eczema Symptom Diary (HESD) **(weekly average for each individual symptom)** from baseline to Week 16". "Change from baseline to each week from Week 1 to Week 15 in HESD **(weekly average for each individual symptom)".**	To clarify the endpoints.
Section 8.3 Exclusion criteria	Minor revision of exclusion criterion 1: "1. Concurrent skin diseases on the hands**, e.g. tinea manuum**".	To ensure exclusion of subjects with a diagnosis of tinea manuum.
	Revision of exclusion criterion 15: "15. Tuberculosis requiring treatment within 12 months prior to screening **and/or subjects with a positive blood test for tuberculosis at screening.*** *** Subjects with high risk of latent**	To further safeguard subjects in risk of (re)activation of latent tuberculosis.

	tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested".	
Section 9.6 Concomitant medication and concurrent procedures	The following sentence has been revised: "Normal bathing and washing is allowed **with the exceptions mentioned in the instructions for use**~~as generally performed~~. 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 not be changed during the trial."	To clarify subjects' usual skin care routines during the trial.
Section 9.7 Prohibited medication and procedures	Revision of text in Panel 5: "~~Use of systemic antibiotics or~~ ~~c~~Cutaneously applied antibiotics on the hands".	To allow treatment with systemic antibiotics throughout the trial, but not during screening.
Section 11.1 Overview	Panel 6 has been revised: "Investigator assessments" has been changed to "Efficacy assessments by the investigator". Box with text: "Baseline visit (Day 1) only: Check capping limits in IRT before randomization" has been deleted. "Safety and laboratory assessments" has been changed to "Safety assessments by the investigator".	 For clarification. Capping check will not be done in IRT but will be done by LEO Pharma A/S. For clarification.

	A new box after "Safety assessments by the investigator" has been added: "Subject assessment of local tolerability". "Other assessments" has been changed to "Laboratory and other assessments".	To reflect that subject assessment of local tolerability is added to the trial and that assessment should be performed after safety assessments by the investigator. For clarification.
Section 11.2.3 Medical history	Smoking history slightly revised: - During the past year: ~~- Less than 1 cigarette per day.~~ ~~- Less than 5 cigarettes per day.~~ **- 1 to 4 cigarettes per day.** - 5 to 10 cigarettes per day. - 11 to 20 cigarettes per day. - More than 20 cigarettes per day.	To simplify categories.
Section 11.4.4 Laboratory testing	In Panel 13 (Clinical laboratory tests), interferon gamma release test is added.	Added to test for tuberculosis in subjects with high risk of latent tuberculosis.
Section 11.4.5 Subject assessment of local tolerability	New section.	Added to have an active subject assessment of local tolerability (stinging/burning) in the trial.

Section 11.6.3 Skin biopsies and photographs (all sites, but optional)	The following sentence has been added: "**Biopsies will not be taken if the investigator considers the procedure unsuitable for the subject (e.g. subjects receiving anticoagulant therapy)".**	To clarify that biopsies are only to be taken if the procedure is suitable for the subject.
Section 11.7.1 Patient-reported outcomes (PROs)	PGI-C added to the list of PROs to be completed in the electronic device by the subjects. The number of PROs to be completed has changed from 6 to 7.	To reflect the addition of PGI-C assessment in the trial.
Section 11.7.1.4 Patient Global Impression of Change (PGI-C)	New section.	To reflect the addition of PGI-C assessment in the trial.
Section 11.7.1.8 Work Limitation Questionnaire (WLQ)	The following sentence has been revised: "The WLQ will be completed at the trial site **for subjects with a paid job** according to the schedule of trial procedures in Section 4".	To clarify that only subjects with a paid job are to answer the WLQ.
Section 13.6.1 Adverse events of special interest	New section.	To collect more information on events of eczema herpeticum in alignment with similar trials with delgocitinib cream in other indications than chronic hand eczema.
Section 14.3.1 Disposition of subjects	The following sentence has been revised: The reasons for permanent discontinuation of IMP **and**~~or~~ withdrawal from trial will be presented for all randomised subjects ~~by last visit attended and~~ by treatment group.	Reasons for permanent discontinuation of IMP or withdrawal will be presented by treatment group only.

Section 14.3.4 Testing strategy Section 14.3.5 Analysis of primary efficacy endpoint Section 14.3.6 Analysis of secondary efficacy endpoints	Change of treatment success abbreviation from IGA 0/1 to IGA TS.	To avoid misunderstandings between an IGA score of 0 (clear) or 1 (almost clear) and IGA treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement.
Section 14.3.7.1 Analysis of patient-reported outcomes	The following sentences have been revised: "The PROs HEIS, PaGA, DLQI, EQ-5D-5L, QOLHEQ, ~~and~~ WLQ**, and PGI-C** will be summarised by treatment group and visit using descriptive statistics. The summaries will be presented for the full analysis set." "…baseline weekly average will be defined by average of measurements from Day ~~-6~~**7** to Day -1 ~~(i.e., last 7x24 hours until day of baseline visit)~~, Week 1 weekly average will be defined by the average of measurements from Day ~~2~~**1** to Day ~~8~~**7**, Week 2 weekly average will be defined by the average of measurements from Day ~~9~~**8** to Day ~~15~~**14** and so on, until Week 15. Week 16 will be calculated based on the ~~last~~ 7 **days**~~x24 hours measurements before~~ **preceding** the ~~actual~~ Week 16 visit ~~day~~. "The change from baseline to Week 16 in HESD NRS **(weekly average for each**	To reflect the addition of PGI-C assessment in the trial. For clarification. The last time HEDSD is completed is in the evening before the Week 16 visit. Clarification of wording.

	individual symptom) ~~(weekly average), i.e., for each individual symptom~~, HEIS (for each individual **item**~~impact~~), DLQI, EQ-5D-5L, QOLHEQ, and WLQ will be summarised by treatment group and domain, where applicable, and analysed using the MMRM approach as described above for the analysis of the secondary continuous endpoint. Change of treatment success abbreviation from PaGA 0/1 to PaGA TS.	To avoid misunderstandings between a PaGA score of 0 (clear) or 1 (almost clear) and a PaGA treatment success defined as achieving: PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild) or PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) or 4 (severe).
Section 14.3.7.2 Efficacy over time	The following sentences have been revised: "Change from baseline to each week through Week 1 to 15 in HESD NRS **(weekly average for each individual symptom)** ~~(weekly average), i.e., for each individual symptom~~". Change from baseline to each scheduled	Clarification of wording.

	assessment until Week 14 in HEIS (for each individual **item~~impact~~**). Change of treatment success abbreviations from IGA 0/1 to IGA TS and from PaGA 0/1 to PaGA TS.	To avoid misunderstandings between e.g. an IGA score of 0 (clear) or 1 (almost clear) and IGA treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement.
Section 14.3.9.1 Adverse events	The following sentences have been added/revised: "**Adverse events of special interest will be tabulated by treatment group.** AEs leading to withdrawal from trial **and AEs leading to~~or~~** permanent discontinuation of IMP will be **tabulated by treatment group** ~~listed and a narrative for each will be given~~."	Adverse event of special interest was added to the trial. Tabulations are considered a more practical and informative way of presenting adverse events of special interest as well as AEs leading to withdrawal from trial and AEs leading to permanent discontinuation of IMP.
Section 14.3.9.4 Subject assessment of local tolerability	New section.	To describe statistical handling of the subject assessment of local tolerability.
Appendix 4 Short version of eligibility criteria	Minor revision of exclusion criterion 1: "Concurrent skin diseases on the hands**, e.g. tinea manuum**".	To ensure exclusion of subjects with a diagnosis of tinea manuum.

	Revision of exclusion criterion 15: Tuberculosis requiring treatment within 12 months prior to screening **and/or subjects with a positive blood test for tuberculosis at screening (subjects with high risk of latent tuberculosis must be tested).**	To further safeguard subjects in risk of (re)activation of latent tuberculosis.
Appendix 5 Contact list	List of protocol authors deleted.	To reflect changes in the LEO Pharma A/S internal procedure for protocol writing.
Appendix 6 Protocol amendment history	New appendix.	To list changes in the previous amendment.
Throughout	Minor editorial and document formatting changes.	Minor, have therefore not been summarised.

Table of contents

List of panels

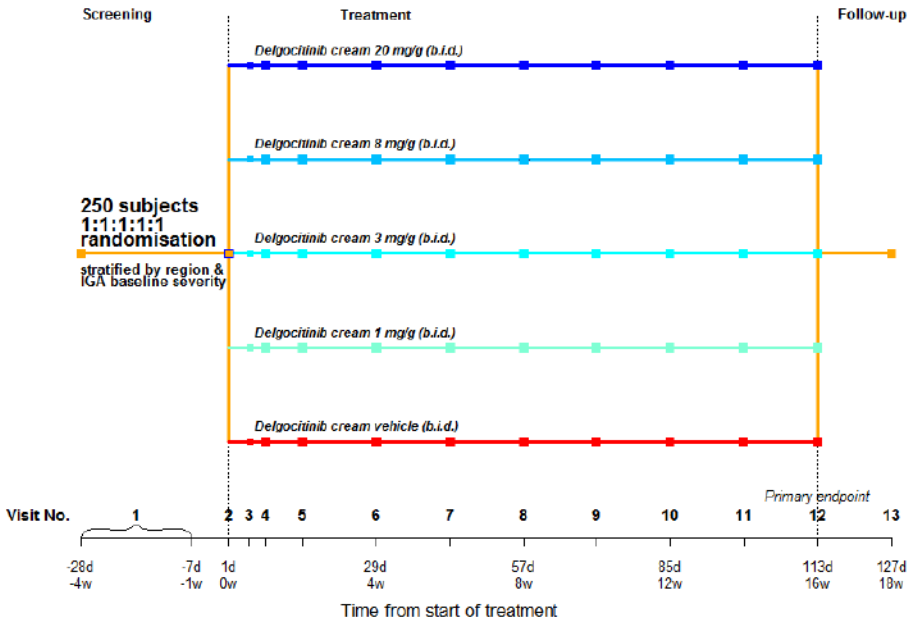
List of abbreviations

AE	adverse event
AS	area score
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMO	contract manufacturing organisation
CRA	clinical research associate
CRO	contract research organisation
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5-Dimension Health Questionnaire 5-Level
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HDL	high density lipoprotein
HECSI	Hand Eczema Severity Index
HEIS	Chronic Hand Eczema Impact Scale
HESD	Chronic Hand Eczema Symptom Diary
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC_{50}	half maximal inhibitory concentration
ID	identification number
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA TS	IGA treatment success, i.e. an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement
IgE	immunoglobulin E
IMP	investigational medicinal product

IND	investigational new drug
INN	international non-proprietary name
IRB	institutional review board
IRT	interactive response technology
JAK	janus kinase
LDL	low density lipoprotein
LEO	LEO Pharma A/S
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurement
NRS	numeric rating scale
PaGA	Patient's Global Assessment
PaGA TS	PaGA treatment success, i.e. a PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild), or a PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) or 4 (severe)
PDE-4	phosphodiesterase-4
PGI-C	Patient Global Impression of Change
PK	pharmacokinetics
PRO	patient-reported outcome
PT	preferred term
PUVA	psoralen and ultraviolet A
QOLHEQ	Quality of Life in Hand Eczema Questionnaire
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SOC	system organ class
SUSAR	serious and unexpected suspected adverse reaction
SS	severity score
STAT	signal transducer and activator
ULN	upper limit of normal range
UVB	ultraviolet B
WLQ	Work Limitation Questionnaire

1 Protocol synopsis

Trial ID EudraCT no. IND no. NCT no.	LP0133-1273 2018-000900-40 CCI [redacted] NCT03683719
Title of trial	A phase 2b, double-blind, randomised, 5-arm, vehicle-controlled, dose-ranging trial to evaluate the efficacy and safety of twice daily topical application of delgocitinib cream 1, 3, 8, and 20 mg/g for 16 weeks in adult subjects with mild to severe chronic hand eczema
Short title of trial	Phase 2b dose-ranging trial to evaluate delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle over a 16-week treatment period in adult subjects with chronic hand eczema
Main objectives	<u>Primary objective:</u> To establish the dose-response relationship of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g and delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema. <u>Other objectives:</u> To compare the safety of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g with delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema. To evaluate the health-related quality of life and efficacy of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema. To evaluate the effect of delgocitinib on *Staphylococcus aureus* colonisation of the skin, skin microbiome, skin barrier function, and skin inflammation.
Primary endpoint	• Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA treatment success [TS]) from baseline to Week 16.
Secondary endpoints	• Change in Hand Eczema Severity Index (HECSI) from baseline to Week 16. • Time to IGA TS.
Final collection of data for the primary endpoint	Week 16.
Trial design	The trial is designed as a double-blind, multi-centre, randomised, 5-arm, vehicle-controlled, parallel-group trial in which adult subjects with mild to severe chronic hand eczema will be treated with delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle for 16 weeks. The trial consists of a screening period, a treatment period, and a follow-up period.

	<u>Screening period</u> The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks. At the screening visit, the subjects' eligibility to enter the trial will be checked. The subjects will receive training in completion of an electronic diary (eDiary). Furthermore, the subjects will be asked to fill out patient-reported outcomes (PROs). <u>Treatment period</u> At baseline (Day 1), subjects' eligibility to enter the trial will be confirmed and if still eligible and IGA baseline severity and regional capping have not been reached, the subjects will be randomised to 1 of the 5 treatment groups. The randomisation is stratified by the severity of chronic hand eczema according to IGA (mild, moderate, and severe) and region (Europe and North America). The first application of the investigational medicinal product (IMP) will occur at the trial site at baseline (Day 1). The subsequent IMP applications will be performed by the subjects at home twice daily for 16 weeks. During the treatment period, the subjects will be required to return to the trial site for the visits scheduled at Weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16. The last IMP application will occur before the subjects attend the visit scheduled at Week 16. <u>Follow-up period</u> All subjects will attend a follow-up visit approximately 2 weeks after the last IMP application for assessment of safety. 
Main assessments	<u>Investigator assessments of efficacy:</u> • IGA for assessment of disease severity. • HECSI for assessment of the clinical signs of chronic hand eczema. <u>Subject assessments of efficacy and health-related quality of life; PROs:</u>

	• Chronic Hand Eczema Symptom Diary (HESD). • Chronic Hand Eczema Impact Scale (HEIS). • Patient's Global Assessment (PaGA) of disease severity. • Patient Global Impression of Change (PGI-C) • Dermatology Life Quality Index (DLQI). • EuroQoL 5-dimension health questionnaire 5-level (EQ-5D-5L). • Quality of Life in Hand Eczema Questionnaire (QOLHEQ). • Work Limitation Questionnaire (WLQ). <u>Safety assessments:</u> • Vital signs, physical examinations, electrocardiograms, laboratory testing, subject assessment of local tolerability, and adverse event reporting.
Main criteria for inclusion	• Age 18 years or above. • Diagnosis of chronic hand eczema defined as hand eczema, which has persisted for more than 3 months or returned twice or more within the last 12 months. • Disease severity graded as mild to severe according to IGA (i.e., IGA $\geq$2). • Recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable. • Diagnostic patch testing performed within 3 years prior to the screening visit.
Main criteria for exclusion	• Concurrent skin diseases on the hands, e.g. tinea manuum. • Active atopic dermatitis in regions other than the hands or psoriasis requiring medical treatment. • Clinically significant infection (e.g., impetiginised hand eczema) on the hands. • Systemic treatment with immunosuppressive drugs (e.g., methotrexate, cyclosporine, azathioprine), immunomodulating drugs (e.g., janus kinase inhibitors), retinoids (e.g., alitretinoin), or corticosteroids within 4 weeks prior to baseline (inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for asthma or rhinitis may be used). • Psoralen ultraviolet A (PUVA) or ultraviolet B (UVB) therapy on the hands within 4 weeks prior to baseline. • Receipt of live attenuated vaccines 4 weeks prior to baseline. • Cutaneously applied treatment with immunomodulators (e.g., phosphodiesterase-4 (PDE-4) inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands within 2 weeks prior to baseline. • Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 2 weeks prior to baseline.

	• Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e., subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline. • Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 1 week prior to baseline. • Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 1 week prior to baseline. • Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab): o Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer. o Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline. • Clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as: o A systemic infection. o A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication. • Tuberculosis requiring treatment within 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening*. * Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested. • History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report. • Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb. • Any disorder, including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infections, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment, which is not stable in the opinion of the investigator and could: o Affect the safety of the subject throughout the trial. o Influence the findings of the trial or their interpretations. o Impede the subject's ability to complete the entire duration of the trial.

Investigational medicinal product (IMP)	Name of IMP: delgocitinib cream Active substance: delgocitinib Formulation: cream Formulation strength: 1, 3, 8, and 20 mg/g and vehicle Dose and method of administration: twice daily topical application
Duration of treatment	16 weeks.
Number of subjects	A total of 250 eligible subjects will be randomised in a 1:1:1:1:1 ratio to delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle. A lower limit of 20% and an upper limit of 30% will be imposed on the IGA baseline severity of subjects with mild and severe chronic hand eczema, respectively. Based on this capping, the overall number of subjects in each severity group can range between: • Mild: 50 to 75 subjects. • Moderate: 100 to 150 subjects. • Severe: 50 to 75 subjects.
Number and distribution of trial sites	Approximately 25 sites in Europe and North America.
Statistical methods	A dose-response modelling approach will be applied for the primary endpoint IGA TS at Week 16 and the secondary endpoint change in HECSI from baseline to Week 16. The dose-response relationship will be modelled by 3 identified candidate models selected based on the expected dose-response relationship for delgocitinib cream. In addition, for binary endpoints the difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test and continuous endpoints will be analysed using a repeated measurements model. For the primary and secondary endpoints, the selection of the dose-response model that fits data best will be controlled using a family-wise error rate of 5%. There will be no adjustment for the multiple testing of primary and secondary endpoints, all p-values will be considered nominal.
Signatory investigator	PDD , MD, PhD, Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Germany.
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

2 Trial identification

EudraCT number: 2018-000900-40

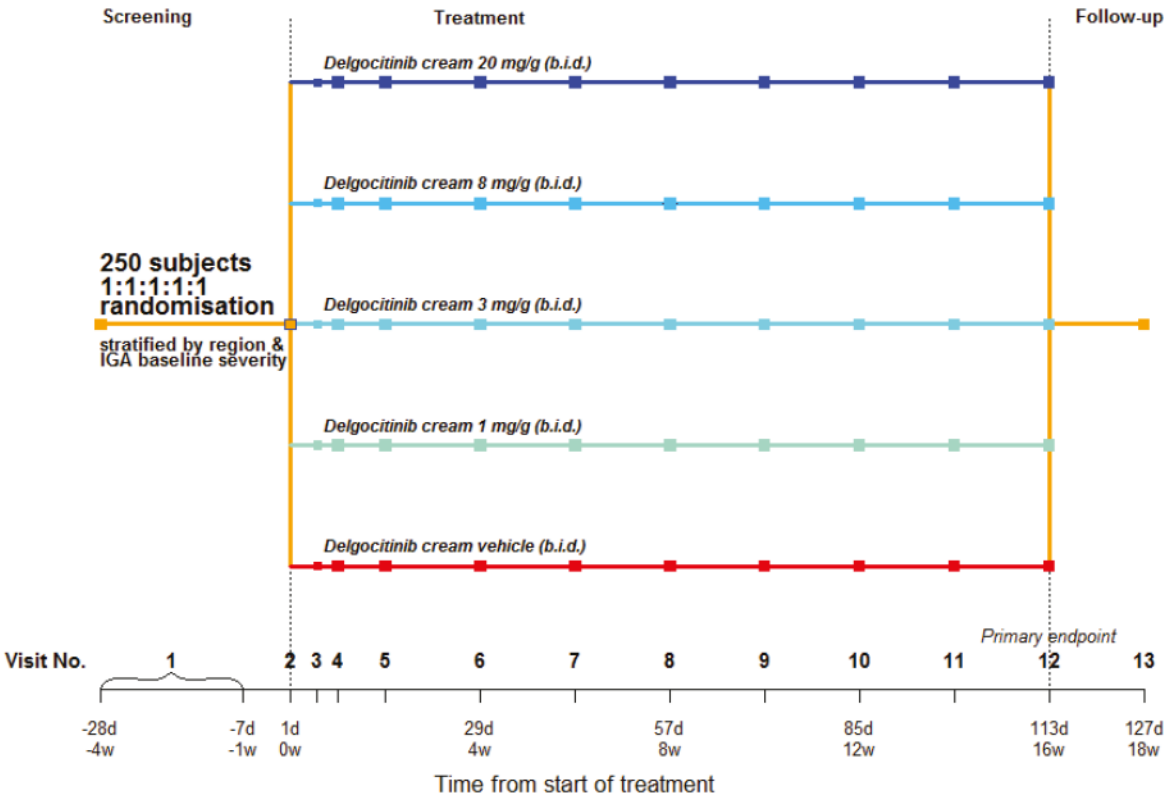
IND number: CCI

NCT number: NCT03683719

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, Investigator's Global Assessment; b.i.d (bis in die), twice a day; d, day; w, week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening	Treatment period										End of treatment/ early termination[3]	Follow-up[4]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	1	2	3[2]	4	5	6	7	8	9	10	11	12	13			
Week	-4 to -1	0		1	2	4	6	8	10	12	14	16	18			
Day	-28 to -7	1	4	8	15	29	43	57	71	85	99	113	127			
Visit window (days)[1]	-	-	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			
Trial population and eligibility																
Informed consent[7]	X															Appendix 3B
Subject eligibility	X	X														8.1, 8.2, 8.3
Trial products and randomisation																
Randomisation		X														9.3
Dispense IMP		X		X	X	X	X	X	X	X	X				(X)	9.2
Instruction on IMP application		X														9.2
Application of IMP		<=== twice daily ===>														9.2
Treatment compliance			X	X	X	X	X	X	X	X	X	X				9.8.3, 9.8.4
Return of IMP and accountability[8]				X	X	X	X	X	X	X	X	X				9.8.3, 10.3, 10.4
Concomitant medication, concurrent procedures[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	9.4, 9.5, 9.6, 9.7

	Screening	Treatment period										End of treatment/ early termination[3]	Follow-up[4]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3[2]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**			
Week	**-4 to -1**	**0**		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**			
Day	**-28 to -7**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**			
Visit window (days)[1]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Investigator assessments at screening/baseline only																
Demographics	X															11.2.1
Fitzpatrick skin type	X															11.2.2
Medical history[10]	X	X														11.2.3
Classification of chronic hand eczema	X															11.2.4
Height and weight		X														11.2.5
Determination of the treatment areas		X														11.2.6
eDiary hand out / training	X															7.1
Subject assessment of efficacy – daily																
eDiary completion: HESD[11]	<========== daily ==========>															11.7.1.1
Subject assessment of efficacy and health-related quality of life – during trial visits																
HEIS	X	X		X	X	X	X	X	X	X	X	X				11.7.1.2
PaGA	X	X		X	X	X	X	X	X	X	X	X		X		11.7.1.3
PGI-C						X		X				X				11.7.1.4
DLQI	X	X		X		X		X		X		X				11.7.1.5
EQ-5D-5L	X	X		X		X		X		X		X				11.7.1.6
QOLHEQ	X	X			X		X			X		X				11.7.1.7

	Screening	Treatment period										End of treatment/ early termination[3]	Follow-up[4]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	**1**	**2**	**3[2]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**			
Week	**-4 to -1**	**0**		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**			
Day	**-28 to -7**	**1**	**4**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**			
Visit window (days)[1]	-	-	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
WLQ[12]	X	X				X		X				X				11.7.1.8
Investigator assessments of efficacy																
IGA	X	X		X	X	X	X	X	X	X	X	X		X		11.3.1
HECSI	X	X		X	X	X	X	X	X	X	X	X		X		11.3.2
Investigator assessments of safety																
Vital signs	X	X										X			(X)	11.4.1
Physical examination	X	X										X			(X)	11.4.2
ECG	X	X										X			(X)	11.4.3
Chemistry, haematology[13]	X	X			X	X		X				X			(X)	11.4.4
Serology, total IgE, tuberculosis test[14]	X															11.4.4
Serum pregnancy test[15]	X														(X)	11.4.4
Urine pregnancy test[15]		X				X		X		X		X			(X)	11.4.4
Urinalysis - dipstick	X	X					X					X			(X)	11.4.4
AEs/SAEs	X	X	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	13
Subject assessment of local tolerability			X	X	X	X	X	X	X	X	X	X			X	11.4.5

	Screening	Treatment period										End of treatment/ early termination[3]	Follow-up[4]	Primary endpoint visit at Week 16, if applicable[5]	Unscheduled visit, if applicable[6]	References (protocol section)
Visit	1	2	3[2]	4	5	6	7	8	9	10	11	12	13			
Week	-4 to -1	0		1	2	4	6	8	10	12	14	16	18			
Day	-28 to -7	1	4	8	15	29	43	57	71	85	99	113	127			
Visit window (days)[1]	-	-	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			
Other assessments																
PK blood sample				X[17]												11.5.1
Skin swab/skin microbiome		X										X				11.6.2
Blood sample for filaggrin mutation status		X														11.6.4
Skin barrier function *(selected sites)*[18, 19]		X[19]			X	X		X		X		X				11.6.5
Skin biopsy and photography *(optional)*[19]		X[19]										X[20]				11.6.3
Check skin biopsy wound healing/suture removal				X									X			11.6.3
New chronic hand eczema lesions			X	X	X	X	X	X	X	X	X	X		X	X	9.2
Return of eDiary												X				
End of trial form[21]												X	X	X		10.3, 11.9

1) 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/randomisation at Day 1.
2) A visit at the trial site is not required on Day 4, a member of trial site personnel will call the subjects.
3) End of treatment assessments will be conducted at Week 16.
Early termination: subjects, who discontinue IMP treatment prior to Week 16 or withdraw from trial will be asked to return to the trial site for end of treatment assessments at an

early termination visit as soon as possible after the last IMP application for completion of all trial procedures scheduled for the visit at Week 16 (except for the skin biopsy, if the subject has consented to have skin biopsies obtained). They will also be asked to return at Week 16 (see footnote 5).

4) All subjects will be asked to return to the trial site approximately 2 weeks after the last IMP application for assessment of safety at a follow-up visit.
5) Subjects who discontinue IMP treatment prior to Week 16 will be asked to return to the trial site at Week 16 for a primary endpoint visit.
6) Unscheduled visits may occur if subjects need to make a visit in between the scheduled visit dates due to an AE, difficulty complying with the trial protocol requirements, or a significant change in their disease state.
7) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and alteration of ongoing treatments unless medically justified.
8) All returned IMP tubes will be weighed by the CMO.
9) Relevant prior/concomitant medication should be included from 6 months prior to Day 1 (baseline) until end of trial.
10) Relevant medical history must be recorded from the subject's date of birth. In case medical history is incomplete at screening visit, missing data will be retrieved at Day 1 (baseline).
11) Completion of the eDiary will be initiated at the latest 1 week prior to Day 1 (baseline).
12) Only for subjects with a paid job.
13) Subjects do not have to be fasting for safety laboratory samples.
14) Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.
15) For women of childbearing potential, a serum pregnancy test must be performed at the screening visit, and a urine pregnancy test at Day 1 (baseline), Weeks 4, 8, 12, and 16 (end of treatment).
16) If a subject reports an AE, it is up to the investigator's discretion to perform an unscheduled visit.
17) Collection of 1 PK plasma sample 2-6 hours after the morning application of IMP.
18) Skin barrier function will be measured using non-invasive or minimally invasive techniques at selected sites only.
19) The skin barrier function measurements, the skin biopsy sampling and the recommended photography scheduled at Day 1 (baseline) must be obtained prior to the first IMP application. This should be done both on lesional and corresponding non-lesional skin if possible.
20) The skin biopsy scheduled at Week 16 will be obtained 2-12 hours after the last IMP application. If a subject discontinues IMP treatment prematurely or withdraws from the trial, the skin biopsy scheduled at Week 16 does not have to be obtained.
21) An end of trial form must be completed for all subjects, including subjects who discontinue IMP treatment prematurely or withdraw from the trial, at their last trial visit (the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last).

Abbreviations: AE, adverse event; CMO, contract manufacturing organisation; DLQI, Dermatology Life Quality Index: ECG, electrocardiogram; EQ-5D-5L, EuroQoL 5-Dimension Health Questionnaire 5-Level; HECSI, Hand Eczema Severity Index; HEIS, Chronic Hand Eczema Impact Scale; HESD, Chronic Hand Eczema Symptom Diary; IGA, Investigator Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; PaGA, Patient Global Assessment; PGI-C, Patient Global Impression of Change; PK, pharmacokinetics; QOLHEQ, Quality of Life in Hand Eczema Questionnaire; SAE, serious adverse event; WLQ, Work Limitation Questionnaire.

5 Introduction and trial rationale

5.1 Chronic hand eczema

Chronic hand eczema is an inflammatory skin disorder located anywhere on the hands and wrists. It is clinically characterised by erythema, infiltration, hyperkeratosis, oedema, and vesicles. Secondary signs include scaling, fissures, and erosions, and the condition may be exacerbated by bacterial infections. Important symptoms include itching and pain, and the disease is often characterised by chronic relapses and a poor prognosis. According to the guideline developed by the European Society of Contact Dermatitis (1), chronic hand eczema refers to hand eczema, which persists for more than 3 months or relapses twice or more often per year.

Hand eczema is usually multifactorial and there is no reliable connection between morphology and aetiology of the disease. Based on aetiology, eczema is commonly divided into exogenous or endogenous types. The most common aetiologies of hand eczema are found to be the exogenous types irritant contact dermatitis (35%) and allergic contact dermatitis (19%), and the endogenous type atopic hand dermatitis (22%) (2).

The severity of hand eczema varies from mild to severe and may cause significant pain and discomfort in daily life. General embarrassment is also associated with the disease due to its visible location (3). Hand eczema can result in impaired quality of life and decreased working capacity, imposing a great economic burden on patients and society. In Denmark, an 8-year follow-up study in a cohort of 274 people with hand eczema found that 12.4% had been on sick leave and 8.5% had changed jobs because of their hand eczema (4). Similarly, prolonged sick leave due to occupational hand eczema was reported in approximately 20% of patients in a study from 2005 (5). A US survey found that people with chronic hand eczema report worse quality of life and impaired activity and work performance compared with those without chronic hand eczema (3).

Treatment of chronic hand eczema involves different treatment 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). Nonetheless, elimination of triggers such as allergens and irritants is effective and a prerequisite for successful therapy on longer term but is in many circumstances difficult to achieve due to the occupational character of the exposure.

Alitretinoin is the only therapy approved in the EU for treatment of chronic hand eczema; no product is yet approved in the USA. Alitretinoin is however only approved for use in adults

with severe chronic hand eczema unresponsive to potent topical corticosteroids. Treatment with alitretinoin is associated with significant safety precautions. Pregnancy is an absolute contraindication due to the teratogenic properties of the product. In addition, the product can only be administered to women of childbearing potential if taking part in a detailed pregnancy prevention programme.

Other treatment options are limited to off-label use of products indicated for skin diseases with an inflammatory pathophysiology. These treatments lack the clinical documentation for use in chronic hand eczema and may only be used in the short-term, which is not suitable in treating a chronic disorder.

Topical corticosteroids, grouped by potency from very low to very high, are the most widely used treatment for chronic hand eczema. They are widely recognised to be effective. However, especially high-potency topical corticosteroids are also associated with a variety of safety concerns, including systemic effects of absorbed corticosteroids, local skin damage, atrophy, and impairment of the epidermal barrier function (in the long-term use). Non-steroid treatments include topical calcineurin inhibitors of which pimecrolimus has shown to lack effect when assessed in clinical trials addressing chronic hand eczema (6, 7). Other systemic anti-inflammatory therapies are off-label besides alitretinoin, e.g., cyclosporine and methotrexate have the potential to cause severe and systemic adverse events (AEs), which limit their use to strictly defined patient populations with severe chronic hand eczema that remains uncontrolled following use of treatment options having a more benign tolerability/safety profile. Non-pharmacological treatment options include Grenz rays and phototherapy, which may require multiple visits to the clinic per week and for this reason can be perceived as cumbersome for the patients. Long-term exposure to phototherapy and Grenz rays also raises concerns about possible increased risk for skin malignancies, especially with the concomitant use of topical calcineurin inhibitors.

Consequently, there is an unmet medical need for a new treatment option of chronic hand eczema with high efficacy in combination with an attractive safety profile. Such a treatment would potentially facilitate the everyday lives of patients with this skin disorder.

5.2 Experience with investigational medicinal product

Delgocitinib, recently assigned as the international non-proprietary name (INN) for LEO 124249, is a pan-janus kinase (JAK) inhibitor, which blocks various cytokine 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.

JAK is a family of intracellular tyrosine kinases consisting of 4 members, JAK1, JAK2, JAK3, and Tyk2, which can associate directly to the intracellular part of various cytokine receptors in various combinations (8, 9). After a cytokine binds to its cognate receptor, the relevant JAK members are autophosphorylated, which allow them to phosphorylate one or more signal transducer and activator (STAT) of proteins (STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6). The phosphorylated STAT proteins are in turn translocated to the nucleus where they initiate transcription leading to promotion of growth and activation of a variety of cells. The JAK family is thus essential for cytokines involved in the pathogenesis of various diseases with an immune-inflammatory component to exhibit their physiological activity. The immune mechanisms in chronic hand eczema are mostly driven by T cells, and JAK inhibitors inhibit signal transduction of many T cell-released cytokines.

In non-clinical studies, delgocitinib blocked JAK family members with half maximal inhibitory concentration (IC_{50}) values ranging from 2-60 nM in biochemical assays and inhibited activation of T cells, B cells, mast cells, and monocytes induced by various JAK cytokines in cellular assays. Topically administered delgocitinib inhibited inflammation in rat and mouse models of contact dermatitis, where T cells activated by various JAK-dependent cytokines were involved in the pathogenesis. Furthermore, delgocitinib improved the impaired skin barrier function, and reduced interleukin (IL)-31-induced scratching in mice. In a study by Amano et al, it was shown that IL-4 and IL-13 downregulated genes involved in keratinocyte differentiation, that STAT3 and STAT6 are involved in keratinocyte differentiation and chemokine production, respectively, and that topical application of delgocitinib suppressed STAT3 activation and improved skin barrier function (10).

Delgocitinib, formulated as an ointment for topical use, was effective in a clinical phase 2 trial (LP0133-1180) treating adults with mild to severe chronic hand eczema. The primary endpoint was treatment success according to the Physician's Global Assessment of disease severity at Week 8, with treatment success defined as subjects achieving 'clear' or 'almost clear' with at least a 2-step reduction from baseline, and the odds of achieving treatment success was statistically significantly higher in the delgocitinib 30 mg/g ointment group compared to the ointment vehicle group. The percentage of subjects achieving treatment success was numerically higher in the delgocitinib ointment 30 mg/g group than in the ointment vehicle group from Week 1 until end of the trial. The treatment was well-tolerated and had an acceptable safety profile. In addition, low systemic exposure of delgocitinib was observed in the trial, which is expected to limit the risk of AEs related to systemic exposure.

5.3 Trial rationale

The purpose of this phase 2b trial is to establish a dose-response signal and to evaluate the efficacy and safety of delgocitinib (1, 3, 8, and 20 mg/g), formulated as a cream for topical use, in the treatment of subjects with mild to severe chronic hand eczema. The results from this trial will support further development in phase 3 with regards to e.g., dose selection and treatment duration.

There is a clear unmet need for new treatment options in the treatment of patients suffering from chronic hand eczema. Based on currently available non-clinical and clinical data, delgocitinib has the potential to become a novel local-acting anti-inflammatory and immunosuppressive agent with skin barrier improving properties (10) for topical use in chronic hand eczema. There is a reasonable expectation that delgocitinib in a cream formulation will prove to be an effective and well-tolerated treatment based on the mechanism of action, and thereby facilitate the everyday lives of affected patients.

CCI

CCI

5.4 Justification for dose

CCI

CCI

CCI

CCI

5.5 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, in compliance with the approved protocol, and applicable regulatory requirements.

Risks associated with treatment in this clinical trial (risks of experiencing significant adverse reactions associated with dermal or systemic exposure to delgocitinib) are considered minimal.

The trial design chosen for this efficacy and safety trial with delgocitinib cream is regarded as ethically justified and adherent with ethical requirements. The efficacy and safety of delgocitinib cream will be evaluated in adults suffering from mild to severe chronic hand eczema who may benefit from treatment in the trial. Pregnant or breastfeeding women and women trying to become pregnant will not be enrolled in the trial. Women of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the trial.

Trial subjects will be informed at the screening visit that trial procedures prior to baseline (Day 1) may warrant an alteration of their ongoing concomitant treatments. As applicable for the entire trial, the subjects will be instructed to contact the investigator if their chronic hand eczema worsens significantly.

In accordance with the current version of the ICH-GCP guidelines, qualified medical personnel employed by LEO will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by Global Pharmacovigilance at LEO to ensure routine signal detection.

5.6 Benefit/risk assessment

There is an unmet medical need for new therapies for use in patients with mild to severe chronic hand eczema. Chronic hand eczema is a physically and psychologically challenging disease often accompanied by distress due to its visible location. Current treatment options are limited to only one approved therapeutic product (only in EU) with significant safety precautions, which is only appropriate for patients with severe chronic hand eczema. Other treatment options include topical steroids and calcineurin inhibitors, which lack a valid benefit/risk evaluation by competent regulatory authorities (as further described in Section 5.1).

No important identified risks have been documented during the overall non-clinical and clinical development of delgocitinib to date. A detailed overview of non-clinical and clinical data on delgocitinib is available in the current Investigator's Brochure.

To ensure the safety and wellbeing of subjects participating in this clinical trial, safety monitoring will be evaluated as described in Section 11.4. The risks associated with the following invasive trial procedures are considered minimal. Blood samples can be considered a low risk procedure. Skin biopsies are optional to the subject. The size of the skin biopsies should not necessitate suturing, but suturing can be performed at the investigator's discretion. The risk associated with a skin biopsy, including secondary infection, is considered low. Skin barrier function is measured using non-invasive or minimally invasive techniques, and the risk associated with these techniques is considered low.

Altogether, the risks associated with participating in this clinical trial are considered very low and outweighed by the benefit of a potential future treatment option for chronic hand eczema. There is an opportunity for a positive treatment effect for the subjects participating in this clinical trial based on the currently available clinical data.

6 Trial objectives and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary and secondary endpoints
To establish the dose-response relationship of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g and delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema.	*Primary endpoint* • Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA TS) from baseline to Week 16. *Secondary endpoints* • Change in Hand Eczema Severity Index (HECSI) from baseline to Week 16. • Time to IGA TS.
Other objectives	Other endpoints
To compare the safety of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g with delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema. To evaluate the health-related quality of life and efficacy of twice daily applications of delgocitinib cream 1, 3, 8, and 20 mg/g compared to delgocitinib cream vehicle for 16 weeks in the treatment of subjects with mild to severe chronic hand eczema.	*Safety and tolerability* • Number of adverse events (AEs). *Health-related quality of life and efficacy* • Change in Chronic Hand Eczema Symptom Diary (HESD) (weekly average for each individual symptom) from baseline to Week 16. o Reduction in worst pruritus ("itch" – one of the symptoms captured in HESD) (weekly average) of ≥4 points from baseline to Week 16 among subjects with baseline worst pruritus (weekly average) ≥4. • Change in Chronic Hand Eczema Impact Scale (HEIS) from baseline to Week 16. • Patient's Global Assessment (PaGA) TS at Week 16. PaGA TS refers to achieving: PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild), or PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) or 4 (severe). • Time to PaGA TS.

Objectives	Endpoints
	• Reduction in Dermatology Life Quality Index (DLQI) of ≥4 points from baseline to Week 16 among subjects with baseline DLQI ≥4. • Change in DLQI score from baseline to Week 16. • Change in EuroQoL 5-dimension 5-level questionnaire (EQ-5D-5L) from baseline to Week 16. • Change in Quality of Life in Hand Eczema Questionnaire (QOLHEQ) from baseline to Week 16. • Change in Work Limitation Questionnaire (WLQ) from baseline to Week 16. *Efficacy over time* • IGA TS at each scheduled assessment until and including Week 14. • PaGA TS at each scheduled assessment until and including Week 14. • Change from baseline to each week from Week 1 to Week 15 in HESD (weekly average for each individual symptom). ○ Reduction of worst pruritus (weekly average) of ≥4 points from baseline to each week from Week 1 to Week 15 among subjects with baseline worst pruritus (weekly average) ≥4. • Change from baseline to each scheduled assessment until Week 14 in HEIS. • Change in DLQI score from baseline to each scheduled assessment until Week 14. • Reduction of DLQI of at least 4 points from baseline to each scheduled assessment until Week 14.
To evaluate the effect of delgocitinib on *Staphylococcus aureus* colonisation of the skin, skin microbiome, skin barrier function, and skin inflammation.	*Biomarkers* • Change in *Staphylococcus aureus* colonisation from baseline to Week 16. • Change in microbiome composition from baseline to Week 16. • Change in skin barrier function, measured as transepidermal water loss, capacitance, skin pH, and content of natural moisturising factors, from baseline to Week 16. • Change in expression of skin barrier proteins and in extent of immune cells in skin biopsies from baseline to Week 16.

7 Trial design

7.1 Overall trial design

This is a phase 2b, double-blind, multi-centre, randomised, 5-arm, vehicle-controlled, parallel-group trial. The trial is designed to establish a dose-response signal and to investigate the efficacy and safety of delgocitinib cream in the treatment of adult subjects with mild to severe chronic hand eczema. The trial design is illustrated in Panel 1.

The trial consists of a screening period, a treatment period, and a follow-up period.

Screening period: between 1 and 4 weeks prior to the baseline visit (Day 1)
The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks.

At the screening visit, the subjects' eligibility to enter the trial will be checked. Trial-specific measurements will be performed as described in Section 11.

The subjects will receive training in completion of an electronic diary (eDiary) at the screening visit and will be given an electronic device to record certain patient-reported outcomes (PROs). Furthermore, to complete training of the eDiary and as an opportunity to fill out PROs before the treatment period, subjects will be asked to complete PROs at the screening visit. Completion of the eDiary will be initiated at the latest 1 week prior to the baseline visit (Day 1).

Treatment period: 16 weeks
At baseline (Day 1), subjects' eligibility to enter the trial will be confirmed and if still eligible and Investigator's Global Assessment (IGA) baseline severity and regional capping have not been reached, the subjects will be randomised to one of the following 5 treatment groups in a 1:1:1:1:1 ratio: delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle.

The subjects will apply the investigational medicinal product (IMP) (delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle) twice daily for 16 weeks. The first application of the IMP will occur at the trial site on Day 1 when all baseline assessments have been carried out. The subsequent IMP applications will be performed by the subjects at home.

During the 16-week treatment period, the subjects will return to the trial sites for the visits scheduled at Weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16. On Day 4, a member of trial site personnel will call the subjects for an unsolicited questioning of AEs, and to enquire about compliance with treatment and eDiary completion. The last IMP application will occur before

the subjects attend the visit scheduled at Week 16. Efficacy and safety assessments during the treatment period will be performed as described in Section 11.

Follow-up period: 2 weeks
All randomised subjects will attend a follow-up visit approximately 2 weeks after the last IMP application for assessment of safety. This visit will mark the end of trial participation for subjects who have completed the entire trial. For subjects who discontinue trial treatment prematurely or withdraw from the trial, please refer to Section 10.3.

7.2 Number of subjects needed

This trial will be conducted at approximately 25 sites in Europe and North America. The anticipated minimum number of randomised subjects per trial site is 6 and the maximum number of subjects per trial site is 30.

Assuming a screening failure rate of 35%, approximately 385 subjects will be screened and approximately 250 subjects will be randomly assigned to a treatment group in the trial (50 subjects in each of the 5 treatment groups: delgocitinib cream 1, 3, 8, and 20 mg/g and delgocitinib cream vehicle). The statistical power considerations for this sample size are described in Section 14.1.

The randomisation is stratified by the severity of chronic hand eczema according to IGA (IGA score of 2 [mild], 3 [moderate], or 4 [severe]) and region (Europe and North America).

A lower limit of 20% and an upper limit of 30% will be imposed on the IGA baseline severity of subjects with mild and severe chronic hand eczema, respectively. Based on this capping, the overall number of subjects in each severity group can range between:

- Mild: 50 to 75 subjects.
- Moderate: 100 to 150 subjects.
- Severe: 50 to 75 subjects.

A maximum of 50 subjects will be randomised in the North American region.

7.3 End of trial definition

A subject is considered to have completed the trial if he/she has completed all periods (i.e., screening, treatment, and follow-up period).

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

Final collection of data for the primary endpoint occurs at Week 16.

7.4 Software

Clinical Data Interchange Standards Consortium (CDISC) controlled terminology version 30-Mar-2018 or newer was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. Study Data Tabulation Model (SDTM) version 1.4 will be used for data tabulations and SDTM Implementation Guide version 3.2 will be adhered to.

Dose-response modelling will be done using the package DoseFinding implemented in R statistical software version 3.5.0 or newer. All other analysis will be performed using SAS® statistical software version 9.4.

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 institutional review boards (IRBs) / independent ethics committees (IECs), as applicable.

8.2 Inclusion criteria

For inclusion into this trial, subjects must fulfil all of the following criteria:

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. Age 18 years or above.
3. Diagnosis of chronic hand eczema defined as hand eczema, which has persisted for more than 3 months or returned twice or more within the last 12 months.
4. Disease severity graded as mild to severe according to Investigator's Global Assessment (i.e., an IGA score of 2 or more).
5. Recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable.
6. Diagnostic patch testing performed within 3 years prior to the screening visit.
7. A woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and for at least 2 weeks after last application of IMP.

   * 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).

**A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device, intrauterine hormone-releasing system, combined (estrogen 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), sexual abstinence (when this is in line with the preferred and usual life style of the subject), vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

Subjects must not enter the trial if any of the following exclusion criteria are fulfilled:

1. Concurrent skin diseases on the hands, e.g. tinea manuum.
2. Active atopic dermatitis in regions other than the hands or psoriasis requiring medical treatment.
3. Clinically significant infection (e.g., impetiginised hand eczema) on the hands.
4. Systemic treatment with immunosuppressive drugs (e.g., methotrexate, cyclosporine, azathioprine), immunomodulating drugs (e.g., janus kinase inhibitors), retinoids (e.g., alitretinoin), or corticosteroids within 4 weeks prior to baseline (inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for asthma or rhinitis may be used).
5. Psoralen ultraviolet A (PUVA) or ultraviolet B (UVB) therapy on the hands within 4 weeks prior to baseline.
6. Receipt of live attenuated vaccines 4 weeks prior to baseline.
7. Cutaneously applied treatment with immunomodulators (e.g., phosphodiesterase-4 (PDE-4) inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands within 2 weeks prior to baseline.
8. Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 2 weeks prior to baseline.
9. Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e., subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline.
10. Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 1 week prior to baseline.

11. Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 1 week prior to baseline.
12. Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab):
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to baseline, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
13. Treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within the last 4 weeks prior to baseline or 5 half-lives whichever is the longest.
14. Clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
15. Tuberculosis requiring treatment within 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening*.
    * Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.
16. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
17. Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.

18. History of cancer:
    - Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to screening.
    - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to screening.
19. Any disorder, including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infections, endocrine, metabolic, haematological, immunological, psychiatric, or major physical impairment, which is not stable in the opinion of the investigator and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial or their interpretations.
    - Impede the subject's ability to complete the entire duration of the trial.
20. Any abnormal finding which may:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis.
21. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
22. Alanine aminotransferase or aspartate aminotransferase level ≥2.0 times the upper limit of normal range (ULN) at screening.
23. Known or suspected hypersensitivity to any component(s) of the IMP.
24. Current participation in any other interventional clinical trial.
25. Previously randomised in this clinical trial.

26. Previously participated in a clinical trial with delgocitinib (LEO 124249).
27. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
28. Employed at the trial site or directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
29. Legally institutionalised.
30. Pregnant or lactating.

8.4 Screening and screening failures

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central interactive response technology (IRT) system and the screening evaluations to assess eligibility may begin. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects, who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects.

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

Screening failures
Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (12) and to respond to queries from regulatory authorities. Individuals who do not meet the criteria for participation in the trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative e.g., delayed test results and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted. Individuals who are re-screened will get a new subject ID. The following data will be collected in the eCRF for screening failures:

- Date of informed consent.
- Demographics (date of birth, age, sex, ethnicity, race).
- Reason for screening failure:
  - Failure to meet eligibility criteria (specify which).
  - Withdrawal by subject.
  - Capping limitation in IGA baseline severity.
  - Other (specification is required).
- Date of screening failure.
- Any AEs and serious AEs (SAEs).

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

9 Treatments

9.1 Trial product description

Delgocitinib is a pan-JAK inhibitor, which is presented in this trial in a cream formulation for cutaneous application. Refer to Panel 4 for further details.

Panel 4: Identification of IMPs

Investigational medicinal product	Formulation	Active ingredient and formulation strength	Pack size	Source
Delgocitinib cream 1 mg/g	Cream	Delgocitinib 1 mg/g	15 g	CCI [redacted]
Delgocitinib cream 3 mg/g	Cream	Delgocitinib 3 mg/g	15 g	CCI [redacted]
Delgocitinib cream 8 mg/g	Cream	Delgocitinib 8 mg/g	15 g	CCI [redacted]
Delgocitinib cream 20 mg/g	Cream	Delgocitinib 20 mg/g	15 g	CCI [redacted]
Delgocitinib cream vehicle	Cream	Vehicle	15 g	CCI [redacted]

9.2 Administration of IMP

The IMP (delgocitinib cream 1, 3, 8, or 20 mg/g or delgocitinib cream vehicle) will be administered as a twice daily cutaneous application for 16 weeks. The applications will be performed approximately 12 hours apart. Instructions for use will be provided.

A thin layer of delgocitinib cream covering the affected areas on the hands will be applied. The maximum use depends on the size of the affected area and the size of the hands. One tube of 15 g delgocitinib cream is considered maximum for treatment of the whole surface of both hands twice daily for 1 week.

The first application of the IMP will occur at the trial site. Prior to the first IMP application, the subject will be instructed how much cream to be applied and which area(s) to be treated. Only the affected area(s) on the hand(s) will be treated. If new lesions occur on initially untreated area(s) of the hand(s), these new lesions will be treated with IMP as well. The subjects will be advised to contact the investigator before initiating treatment of new lesions. The IMP application on initially affected areas and new lesions will continue until Week 16

regardless of clearance status. The last IMP application will occur at the subject's home before the subject attends the visit scheduled at Week 16.

The IMP will be dispensed by the investigational staff at the visits scheduled in Section 4. The IRT will assign the required kit number(s) for each subject at each dispensing visit.

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

9.3 Treatment assignment

Subjects who have been found to meet all the inclusion criteria and not to fulfil any of the exclusion criteria will be randomised at baseline (Day 1) to receive treatment with either delgocitinib cream (1, 3, 8, or 20 mg/g) or delgocitinib cream vehicle. The treatment assignment occurs on the basis of a computer-generated randomisation scheme in a 1:1:1:1:1 ratio.

Subjects eligible on selection criteria at baseline may be prevented from being randomised into the trial due to the applied capping limitation in IGA baseline severity and regional enrolment (as described in Section 7.2). Due to this capping, the sponsor will actively monitor the subjects in the screening period to minimise the number of subjects that may be excluded from the trial prior to randomisation.

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

9.3.1 Blinding

The packaging and labelling of the IMPs will contain no evidence of their identity. It will not be possible to differentiate between the IMPs solely by sensory evaluation.

9.3.2 Emergency unblinding of individual subject treatment

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

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment in the IRT. For a requester who is not a member of the trial staff and who does not have access to the

IRT (e.g., a physician at an emergency room), a local contact number for the emergency unblinding contract research organisation (CRO) is provided on the subject card (see Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the subject's treatment allocation.

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation. Should the requester wish to discuss whether unblinding is necessary, the emergency unblinding CRO will provide the requester with the LEO 24/7 contact which will be diverted to the medical cover.

9.4 Background treatment (emollients)

The subjects should not change their usual skin care routine regarding use of emollients. However, the emollient must not be used within 2 hours before and after application of the IMP. Use of concomitant treatment is further described in Section 9.6.

9.5 Rescue treatment

If medically necessary (i.e., to control intolerable chronic hand eczema symptoms), rescue treatment for chronic hand eczema may be provided to the subjects at the discretion of the investigator. The investigators should make every attempt to conduct efficacy and safety assessments (for example disease severity scores, safety labs) immediately before administering any rescue treatment.

If rescue treatment is initiated, the subject must stop treatment with IMP immediately and must not re-start treatment with IMP. It must be stated in the eCRF that the subject receives rescue medication. For the purpose of the primary efficacy analyses, subjects receiving rescue treatment during the IMP treatment period will be considered as non-responders.

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 6 months prior to baseline (if relevant) through follow-up period must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name.
- Indication.

- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose, unit, and frequency.
- Route of administration.
- For topical treatment, the body location must be recorded; it must also be recorded if the treatment is within 5 cm (approximately 2 inches) of the treatment area.

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded:

- Procedure.
- Body location.
- Diagnosis.
- Start and stop date (it will also be recorded if the procedure is ongoing).
- For topical treatments, it must also be recorded if the procedure is inside the treatment area.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. Use of emollients is described in Section 9.4.

As a rule, the subjects should not change their usual skin care routine if possible. The subjects will be asked to wear vinyl gloves when applying any other skin treatments/products to other areas of the body for other skin conditions during the trial. Normal bathing and washing is allowed with the exceptions mentioned in the instructions for use. 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 not be changed during the trial.

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.

9.7 Prohibited medication and procedures

The medications listed in Panel 5 are prohibited during the trial. In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication.

Panel 5: Prohibited medication

Medication	Prohibited from	Prohibited to
Systemic treatment with immunosuppressive drugs (e.g., methotrexate, cyclosporine, azathioprine), immunomodulating drugs (e.g., janus kinase inhibitors), retinoids (e.g., alitretinoin), or corticosteroids (inhaled or intranasal steroids corresponding to up to 1 mg prednisone for asthma or rhinitis may be used).	4 weeks prior to baseline.	End of trial.
Phototherapy e.g., PUVA or UVB therapy.	4 weeks prior to baseline.	End of trial.
Live attenuated vaccines.	4 weeks prior to baseline.	End of trial.
Cutaneously applied treatment with immunomodulators (e.g., PDE-4 inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands.	2 weeks prior to baseline.	End of trial.
Cutaneously applied antibiotics on the hands.	2 weeks prior to baseline.	End of trial.
Change in systemic antihistamine therapy.	2 weeks prior to baseline.	End of trial.
Other cutaneously applied therapy on the hands (except for the use of subject's own emollient).	1 week prior to baseline.	End of trial.
Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern.	1 week prior to baseline.	End of trial.
Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab):		
• Any cell-depleting agents including but not limited to rituximab.	6 months prior to baseline or until lymphocyte count returns to normal, whichever is longer.	End of trial.
• Other biologics.	3 months or 5 half-lives, whichever is longer, prior to baseline.	End of trial.
Any non-marketed drug substance (i.e., an agent which has not yet been made available for clinical use following registration).	4 weeks prior to baseline or 5 half-lives whichever is the longest.	End of trial.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

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

The labelling of IMPs will be in accordance with Annex 13, local regulations and trial requirements. Label text will be translated into local languages, as required.

9.8.2 Storage of trial products

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

The IMPs must be stored at 2-8°C (36-46°F). Do not freeze. The temperature during storage at the trial site should be monitored by a calibrated, stationary, and continuous electronic recording system with alarm and back-up of data. If no alarm is triggered, a log must be printed, reviewed, signed and dated each month. If the alarm is triggered, the log must be immediately printed, reviewed, signed and dated, and appropriate follow-up action will be taken in accordance with the trial product handling manual.

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

Storage of the IMPs may be delegated, e.g., to a hospital pharmacy, as locally applicable.

In the situations listed below, site staff should not use the affected IMPs 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 IMPs should be documented in the IRT and reported as a product complaint to Global Pharmacovigilance, LEO (see Section 9.10). Damaged IMPs may not be used.

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

9.8.3 Drug accountability

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

Dispensing of IMPs may be delegated, e.g., to a hospital pharmacy, as locally applicable.

An individual drug accountability form must be kept of the IMP administered to and returned by each subject randomised in the trial. This individual drug accountability form must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMP. Drug accountability information will be entered in the IRT, where also inventory status of all IMP at the trial site will be maintained.

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

Returned trial products (used and unused IMPs (including packaging material)) can be stored at room temperature and must be stored separately from non-allocated trial products.

All IMPs (including packaging material) supplied by the contract manufacturing organisation (CMO) on behalf of LEO will be returned to the CMO on an ongoing basis. Prior to return, the IMPs must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMPs.

All tubes returned to the CMO will be weighed to determine the amount of IMPs used.

Reporting in eCRF
The kit/tube number, date of dispensation and return, and number of tubes dispensed and returned will be recorded in the eCRF.

9.8.4 Treatment compliance

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

At the phone call scheduled on Day 4 and at each visit scheduled in the treatment period (see Section 4), the subject will be asked if they have used the IMP as prescribed. If a subject is found to be non-compliant, the investigator must remind the subject of the importance of following the instructions given, including applying the IMP as prescribed. Compliance or

non-compliance, i.e., number of missed IMP applications and the reason for it, must be recorded in the eCRF.

9.8.5 Trial product destruction

Used and unused IMPs will be destroyed by the CMO according to approved procedures and/or local requirements.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

Any defects or issues with the IMP (e.g., strange colour or consistency, inadequate labelling) must be reported to Global Pharmacovigilance at LEO 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 for the subject [e.g., SAE]) must be reported to Global Pharmacovigilance, LEO within 24 hours.

Complaint forms should contain a detailed description of the defect, 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.

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 Pharmacovigilance, LEO contact information for reporting product complaints:

Fax number: +45 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (i.e., withdraw from treatment and protocol-defined interventions) or permanently discontinue trial treatment (i.e., stop treatment only, but agree to continued protocol-defined interventions) at any time (prior to first dose or during the treatment period) if the subject, the investigator, or LEO considers that it is not in the subject's best interest to continue.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the subject's source documentation.

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

Data to be recorded in the eCRF
The primary reasons for withdrawal from the trial, discontinuation of IMP, and not attending the primary endpoint visit at Week 16, if applicable, must be recorded in the medical records and on the end of trial form in the eCRF where the following options are available:

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

If 'adverse event' or 'other' is selected, a specification must be provided in the eCRF with a clear link to the specific AE if applicable.

10.2 IMP discontinuation rules

10.2.1 Reasons for discontinuation of IMP

Subjects will discontinue IMP in the event of:

- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.

- Evidence of pregnancy.
- Initiation of rescue medication.
- Clinically important laboratory abnormalities:
  - Alanine aminotransferase and/or aspartate aminotransferase values >3xULN with total bilirubin >2xULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
  - Confirmed aspartate aminotransferase and/or alanine aminotransferase >5xULN (for more than 2 weeks).

It is not allowed to re-start IMP treatment after discontinuation of IMP.

10.3 Early termination assessments

An end of trial form must be completed for all subjects, including subjects who withdraw from the trial or discontinue IMP treatment, at their last trial visit (the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last).

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

Discontinuation of IMP
Subjects, who discontinue IMP prior to Week 16 will be asked to attend an early termination visit as soon as possible after last IMP application and return to the trial site for 2 additional visits as indicated below. See the schedule of trial procedures (Section 4) for data to be collected at these visits.

Subjects, who discontinue IMP prior to Week 16 will be asked to attend:

- Early termination visit (as soon as possible after the last IMP application).
- Safety follow-up visit (2 weeks after the last IMP application).
- Primary endpoint visit (16 weeks after the first IMP application).

10.4 Lost to follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails 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 to retrieve eDiary and unused IMP and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not 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. Should the subject continue to be unreachable, he/she will be considered as withdrawn from the trial with a primary reason of lost to follow-up.

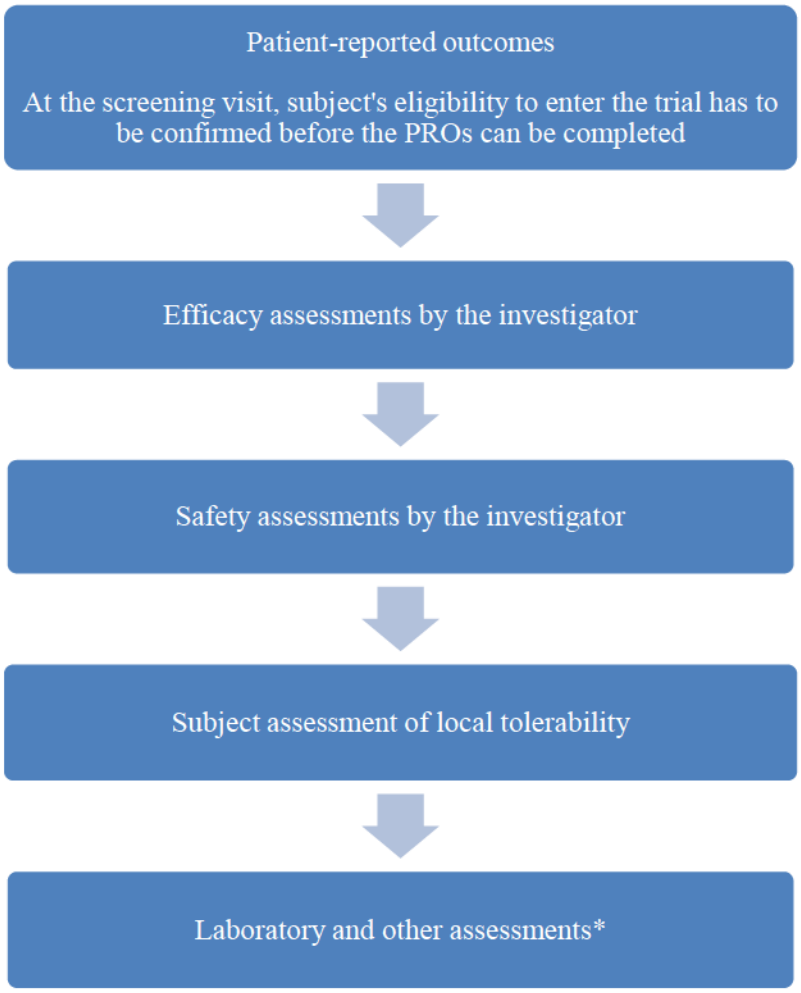
11 Trial assessments and procedures

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 should be performed in the following order as shown in Panel 6:

Panel 6: Sequence of assessments



* Blood sampling for PK and filaggrin mutational status, skin swabs, skin barrier function assessments (selected sites), skin biopsies (optional) and photography of biopsied areas (recommended).

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 chronic hand eczema and have documented experience and/or training in use of the assessments required by the protocol and must be either a physician, certified physician's assistant, or advanced registered nurse practitioner.

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

AEs must be assessed by medically qualified personnel (i.e., adequately trained medical doctors) (Section 13.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Date of birth. If full date of birth is not allowed to be recorded, month and year of birth should be collected together with the subject's age.
- Sex: female, male.
- Race: American Indian or Alaska native, Asian, black or African American, native Hawaiian or other Pacific islander, white, other (requires a specification to be provided).
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.

11.2.2 Fitzpatrick skin type

The subject's skin type will be recorded using the Fitzpatrick skin classification (Panel 7).

Panel 7: 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 exposures, 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 light complected black individuals, those of Indian descent.
VI	Individuals who have the heaviest constitutive pigmentation, especially dark skinned black individuals.

11.2.3 Medical history

Relevant medical history from the subject's date of birth must be recorded.

To support selection of trial subjects specifically on inclusion criterion 5 (either one or both of the following):

1. Has the subject fulfilled the trial inclusion criterion 5 based on being uncontrolled on topical corticosteroid treatment during the last 12 months? Yes/No
    - Record medication name of previous treatment with topical corticosteroid, time point of exposure, and rationale for discontinuing the treatment.
2. Has the subject fulfilled the trial inclusion criterion 5 based on topical corticosteroids being medically inadvisable for the subject? Yes/No
    - Record reason why topical corticosteroid use is not advisable, medication name of previous treatment with topical corticosteroid, time point of exposure, and rationale for discontinuing the treatment.

Chronic hand eczema history:

- Diagnosis of chronic hand eczema:
  - Onset of chronic hand eczema disease.
  - Previous treatments for chronic hand eczema except the use of topical corticosteroids (name or type of treatment, time point of exposure, rationale for discontinuing previous hand eczema treatments).
  - History of foot dermatitis.
  - Result of diagnostic patch testing performed within 3 years (Positive/ Negative).
    If positive, was the identified allergen considered relevant for the chronic hand eczema (Yes/No).
  - Results of other relevant previous diagnostic procedures (e.g., prick test).
- Predictive factors relevant for chronic hand eczema:
  - Previous or current atopic dermatitis.
  - Allergic asthma or allergic rhinitis.
  - Presence of atopy in the subject's family history.
- Exposures relevant for chronic hand eczema:
  - Occupational or environmental trigger factors (Yes/No/Do not know).
  - Onset and worsening of chronic hand eczema symptoms during work (Yes/No/Do not know).
  - Improvement of chronic hand eczema symptoms on the weekends (Yes/No/Do not know).
  - Healing of chronic hand eczema on vacations (Yes/No/Do not know).
  - Recurrence of chronic hand eczema symptoms upon returning to work (Yes/No/Do not know).
  - Worsening of chronic hand eczema symptoms when not at work (Yes/No/Do not know).
  - Wet-work exposure (Yes/No/Do not know).
  - Number of daily hand washes.

- Smoking history, defined as:
  - Never smoked.
  - Non-smoker for more than 1 year.
  - During the past year:
    - 1 to 4 cigarettes per day.
    - 5 to 10 cigarettes per day.
    - 11 to 20 cigarettes per day.
    - More than 20 cigarettes per day.

Other medical history:

- Skin disease history: all past and current skin disease history (including history of atopic dermatitis) will be collected. For each diagnosis, the start date and the stop date will be recorded. It will be recorded if the diagnosis is ongoing and if the disease is/has been present in the hands.
- Other medical and surgical history including concurrent diagnoses within the previous 12 months. For each condition, diagnosis or surgical procedure, the start date and stop date or whether it is ongoing will be recorded.

Relevant medical history also includes diseases that are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

11.2.4 Classification of chronic hand eczema

Based on medical history (including history of diagnostic patch testing within 3 years) and morphology of the present lesions, the investigator will determine the subtype(s) according to the definitions in Panel 8. The subtype(s) of the subject's chronic hand eczema will be recorded as main diagnosis and additional diagnoses, if applicable.

Panel 8: 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.
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: Diepgen et al. 2015 (1).

11.2.5 Height and weight

The subject's height (without shoes) will be measured; the subject's weight (in indoor clothing and without shoes) will be measured.

11.2.6 Determination of treatment area

Prior to the first IMP application, 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.

11.3 Efficacy assessments

11.3.1 Investigator's Global Assessment (IGA)

The IGA is an instrument used in clinical trials to rate the severity of the subject's global disease stage and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 9). The severity of each sign or symptom is described in Panel 10. The IGA score will be assessed at time points according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New lesions that occurred on previously untreated areas will be included in the assessment.

Panel 9: Investigator's Global Assessment (IGA)

IGA severity	IGA score	Sign/symptom	Intensity
Clear	0	Erythema, scaling, hyperkeratosis/lichenification Vesiculation, oedema, fissures	Absent Absent
Almost clear	1	Erythema Scaling, hyperkeratosis/lichenification, vesiculation, oedema, fissures	Mild Absent
Mild	2	Erythema, scaling, hyperkeratosis/lichenification Vesiculation, oedema, fissures	At least one mild At least one mild
Moderate	3	Erythema, scaling, hyperkeratosis/lichenification Vesiculation, oedema, fissures	At least one mild or moderate At least one moderate
Severe	4	Erythema, scaling, hyperkeratosis/lichenification Vesiculation, oedema, fissures	At least one moderate or severe At least one severe

IGA V2.0. Inspired by Ruzicka et al, 2008 (11) and JF Fowler (personal communication, 09 May 2017). The term Physician Global Assessment was used by Ruzicka/Fowler, but IGA will be used in this trial.

Panel 10: Description of the severity of each IGA sign or symptom

Sign/symptom	Severity	Description of severity
Erythema	Mild	Faint erythema
	Moderate	Prominent redness
	Severe	Deep intense red colour
Scaling	Mild	Slight flaking, mostly fine scales
	Moderate	Flaking, thicker scales
	Severe	Desquamation with thick scales
Lichenification / hyperkeratosis	Mild	Mild thickening with exaggerated skin lines
	Moderate	Palpable thickening
	Severe	Prominent thickening with exaggeration of normal skin markings
Vesiculation	Mild	Scattered vesicles, without erosion
	Moderate	Clustered vesicles, without visible erosion or excoriation
	Severe	High density of vesicles, or with erosion or excoriation
Oedema	Mild	Slight dermal swelling
	Moderate	Definite dermal swelling
	Severe	Dermal swelling with skin induration
Fissures	Mild	Superficial fissures
	Moderate	Definite fissures
	Severe	One or more deep fissures with/without bleeding

Inspired by Ruzicka et al (11) and Fowler JF (personal communication, 09 May 2017). The term Physician Global Assessment was used by Ruzicka/Fowler, but IGA will be used in this trial.

11.3.2 Hand Eczema Severity Index (HECSI)

The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema [E], infiltration/papulation [I], vesicles [V], fissures [F], scaling [S], oedema [O]) 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 (13).

For each hand area (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 areas these lesions occupy, and converting it to a

score based on a 5-point scale (the affected area score [AS]) (Panel 11). For each of the hand areas, the grades for 6 selected clinical signs of hand eczema are totalled (E + I + V + F + S + O = total grade) and this total grade will be multiplied by the converted affected AS based on the area of both hands (Panel 12). The highest possible HECSI score is 360.

The HECSI will be assessed at time points according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New lesions that occurred 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-steps (0.5, 1.5, 2.5) are not allowed.

Area score (AS) scale (based on the 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-steps (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)	x AS	
Fingers (except fingertips)	(SS +	SS +	SS +	SS +	SS +	SS)	x AS	
Palm of hands	(SS +	SS +	SS +	SS +	SS +	SS)	x AS	
Back of hands	(SS +	SS +	SS +	SS +	SS +	SS)	x AS	
Wrists	(SS +	SS +	SS +	SS +	SS +	SS)	x AS	
The total HECSI score equals the sum of the 5 above region scores:								_____

AS, area score; SS, severity score.

11.4 Safety assessments

11.4.1 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) will be assessed according to the schedule of trial procedures (Section 4). Vital signs will be measured in a supine position following at least 5 minutes of rest.

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator whether the subject should be randomised into the trial (respecting exclusion criterion no. 20).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with the subject resting in a supine position 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. If the third measurement confirms the first measurement (abnormal), the second measurement will be considered false. Only the last value measured and considered correct will be recorded in the eCRF.

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

11.4.2 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin, auscultation of heart, lungs, and abdomen, palpation of the abdominal organs, and basic neurological status must be performed according to the schedule of trial procedures (Section 4). Presence of foot dermatitis will be documented. The investigator should perform the same examinations as in clinical practice as a minimum.

If the screening physical examination results in a finding, which is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criterion no. 20).

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

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

11.4.3 ECG

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

A preliminary evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. As a minimum, the date of ECG collection will be recorded in the source documents.

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 ECG abnormalities.

If the screening ECG results in a finding, which is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criterion no. 20).

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

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

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

11.4.4 Laboratory testing

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4). See Panel 13 for an overview of the individual clinical laboratory parameters to be assessed in this trial.

Central laboratory
Chemistry, haematology, urinalysis (if applicable), serology, and serum pregnancy tests will be analysed by a central laboratory, which will provide results to the trial sites. The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date. The signed and dated version will be filed with the investigator's trial documentation. Clinically significant abnormal tests must be repeated to confirm the abnormality.

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criteria no. 16, 20, 21, 22, and 30).

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 at the trial site with a dipstick; if abnormal, a urine sample will be sent to the central laboratory for further analysis.

Women of childbearing potential will have urine pregnancy tests performed at the trial site at the visits indicated in the schedule of trial procedures in Section 4.

Panel 13: Clinical laboratory tests

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils, neutrophils/total cells Lymphocytes, lymphocytes/total cells Monocytes, monocytes/total cells Eosinophils, eosinophils/total cells Basophils, basophils/total cells Thrombocytes
	Serology[2]
	Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody Immunoglobulin E
	Tuberculosis test[2,3]
	Interferon gamma release test
Urinalysis[4]	**Serum pregnancy test[2,5]**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Choriogonadotropin beta

1) If bilirubin is above ULN, direct and indirect bilirubin will also be measured.
2) Measured at screening only.
3) Subjects with high risk of latent tuberculosis (e.g. prior residence in or travel to countries with high prevalence of tuberculosis, close contact with a person with active tuberculosis, or a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed) must be tested.
4) Urine samples will be tested at the trial site (dipstick). In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts).
5) Only women of childbearing potential. In addition, urine pregnancy tests will be performed at the trial site.

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

Reporting in eCRF

The site staff will record in the eCRF if a sample was taken and the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant').

The date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

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

11.4.5 Subject assessment of local tolerability

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

The subject will retrospectively be asked by the investigator to assess stinging/burning in connection with the IMP applications since their last visit. The highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF by use of the 4-point scale shown in Panel 14.

Panel 14: Subject assessment of local tolerability after IMP application

Grade	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.

Subject assessment of local tolerability will be performed after safety assessments by the investigator (Panel 6). Local tolerability reactions are not reported as AEs; however, if they qualify as an SAE, they will be reported as described in Section 13.4.1.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of systemic concentration of delgocitinib

One blood sample from each subject will be collected for PK assessments 2-6 hours after the morning application of IMP as specified in the schedule of trial procedures in Section 4.

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

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

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

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

11.6 Pharmacodynamics and pharmacogenomics

11.6.1 Overview

A hallmark of chronic hand eczema is an impaired skin barrier function leading to dry skin, excoriations, and superinfection by *Staphylococcus aureus*. Based on its mechanism of action and on findings in a previous clinical trial (10), delgocitinib is believed to be able to improve the skin barrier in people with eczema. It is the purpose to investigate this further in a selected subject group in this trial by demonstrating improved skin barrier on the back of the hand by non-invasive methods combined with histology. The skin barrier function will be compared to filaggrin mutation status of the subjects. Mutations in filaggrin lead to decreased skin barrier function and may thus be linked to a higher disease prevalence as well as to a lesser improvement of skin barrier function in response to treatment.

Little is known about the skin microbiome and *Staphylococcus aureus* in chronic hand eczema. Due to the similarity of the pathophysiology of chronic hand eczema and atopic dermatitis it is highly likely that there will be similarities to atopic dermatitis, which is associated with increased skin colonisation with *Staphylococcus aureus* accompanied by decreased colonisation with many commensal bacterial species. To investigate the effect of

treatment with delgocitinib on the skin microbiome in general and on colonisation with *Staphylococcus aureus*, skin swabs will be taken.

Finally, treatment with delgocitinib is supposed to lead to a reduction of immune cells and inflammation in the skin and a normalisation of the epidermis, which will be further explored in this trial.

The following parameters will be assessed:

- *Staphylococcus aureus* colonisation in skin swabs measured by qPCR.
- Microbiome diversity in a subset of skin swabs investigated by use of next generation sequencing methods.
- Epidermal thickness and inflammatory infiltrate in the skin by histology.
- Expression of proteins involved in skin barrier integrity and skin matrix modulation including but not limited to filaggrin and loricrin by immunohistochemistry.
- Expression of disease markers of chronic hand eczema and markers of immune cells including but not limited to CD3 and CD45.
- Filaggrin gene mutation status.
- Change in skin barrier function measured as transepidermal water loss, skin pH, and content of natural moisturising factors in tape strips. These measurements will be carried out only at selected sites, which have the needed expertise and equipment.

Since the skin structure, microbiome, and impact of contamination are profoundly different between the dorsal side and the palm, only the wrist or dorsal aspect of the hand and fingers will be used for investigation of the above parameters. Subjects who do not have any disease involvement of these locations will not take part in any of these assessments.

A summary of the results will be included in the clinical trial report (CTR) if they are available in time for this. The full pharmacodynamics / biomarker results will be reported in an addendum report to the CTR.

11.6.2 Skin swabs

A total of 4 skin swabs for microbiome and *Staphylococcus aureus* measurements will be taken at the time points specified in the schedule of trial procedures (Section 4).

At baseline (Day 1), 2 skin swabs are to be taken:

- 1 skin swab from a representative lesional area from the dorsal side of the hand or fingers or from the wrist.
- 1 skin swab from a non-lesional area at an anatomically similar site to the lesional skin swab.

At Week 16 (end of treatment), 2 skin swabs will be taken at the same locations as the baseline skin swabs.

If biopsies are to be taken (see Section 11.6.3), the baseline biopsies should be taken from the same area as the skin swabs, so the sites selected for skin swabs must then also be appropriate for biopsying.

It will be recorded in the eCRF if the skin swabs were taken and from which location (dorsal hand, dorsal or volar wrist, finger); if skin swabs were not taken, a comment will be provided.

Subjects will be instructed not to wash their hands or apply disinfectants/hand sanitizers for at least 1 hour prior to the baseline visit and Week 16 visit.

Further instructions for collection, handling and shipment for skin swabs are provided in a laboratory manual.

11.6.3 Skin biopsies and photographs (all sites, but optional)

Subjects, who have lesions at a location suitable for biopsying (i.e., dorsal hand, fingers, or wrist) will be asked to participate in an exploratory component involving skin biopsies. Participation in this component of the trial requires that the subject provides additional informed consent and is NOT mandatory for participation in the trial. Biopsies will not be taken if the investigator considers the procedure unsuitable for the subject (e.g. subjects receiving anticoagulant therapy).

It is expected that approximately half of eligible subjects will accept to participate in this exploratory component of the trial. If biopsies are obtained from less than 10% of subjects, analysis may not be carried out as the number of biopsies may be too low to allow for a meaningful analysis. A final decision will be made after unblinding. Once biopsies have been obtained from 100 subjects (40% of trial population), no further biopsies will be taken as inclusion of further biopsies are not believed to improve the quality of results significantly. If at least 10% of subjects have consented to biopsies, filaggrin expression and epidermal

thickness will be measured in all biopsies. Loricrin, CD45, CD3 and potentially other disease markers will be measured in a subset of biopsies selected after unblinding. This subset will include biopsies from 10-12 vehicle-treated subjects and 30-40 subjects treated with delgocitinib selected from the highest formulation strengths. If biopsies are obtained from less than 50 subjects, these markers will be measured in all biopsies.

A total of 3 skin biopsies (3 mm punch biopsies) for histology/immunohistochemistry will be taken at the time points specified in the schedule of trial procedures (Section 4).

At baseline (Day 1), 2 biopsies are to be taken from the same areas and according to the same criteria as the skin swabs (see Section 11.6.2):

- 1 biopsy from a representative lesional area, from the dorsal side of the hand, wrist, or finger.
- 1 biopsy from a non-lesional area at an anatomically similar site to the lesional biopsy. If an anatomically similar non-lesional area cannot be found, this biopsy may be omitted.

The third biopsy should be taken at Week 16. The area from which the third biopsy will be taken is to be specified at baseline. This must be at an anatomically similar site and of similar baseline lesion severity to the baseline lesional biopsy.

It will be recorded in the eCRF if the biopsies were taken and from which location (dorsal hand, dorsal wrist, or finger); if biopsies were not taken and the subject has given consent to biopsies, a comment will be provided.

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the next trial visit as specified in the schedule of trial procedures (Section 4).

The biopsies will be submerged in 10% formalin immediately after acquisition and shipped to the central laboratory for further processing. Further instructions for collection, handling, and shipment for skin biopsy samples are provided in a laboratory manual.

It is recommended to document the biopsied areas with photographs taken before biopsying and immediately after, both at baseline and at Week 16, using digital photography assessments. This will serve both as a documentation of the biopsy site and to show disease progression over time. This photography component for the skin biopsies is recommended and not mandatory.

The trial sites participating in this photography component will be expected to use their own equipment to take the photographs. Instructions and specifications for photography will be provided in a photography manual.

The photographs will have no other subject identifier than the subject ID and visit number and will be transmitted electronically using a secure file transfer protocol.

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

LEO may at its discretion 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 to the extent possible.

11.6.4 Filaggrin mutations

A blood sample will be collected at baseline (Day 1) for measurement of filaggrin mutational status.

11.6.5 Non-invasive measurements of skin barrier function (selected trial sites)

The skin barrier function will be measured using non-invasive or minimally invasive techniques at selected sites only. The sites participating in these measurements will be defined prior to trial start. Thus, the below measurements are not mandatory, but will be included only as agreed with individual sites.

Transepidermal water loss, skin capacitance, skin pH, and natural moisturising factors will be measured at the time points specified in the schedule of trial procedures (Section 4) from a representative lesional area from the dorsal side of the hand or fingers or from the wrist.

The same measurements will be performed both on the site of the lesional biopsy and on a non-lesional area which is anatomically similar to the lesional biopsy site. If possible, the same area selected for swabs should also be used for these measurements. If an anatomically similar non-lesional area cannot be found on the hands, the volar forearm may be used instead.

The measurements will be repeated on both the lesional and non-lesional areas at the time points specified in the schedule of trial procedures (Section 4).

Subjects will be instructed not to apply any emollients on their hands and wrists for at least 12 hours prior to the visits, and not to wash their hands or use disinfectants / hand sanitizer for at least 1 hour prior to the visits at which these measurements will be taken. The time from last IMP application to skin barrier measurement will be recorded. Further instructions for these measurements are provided in a laboratory manual.

11.7 Other assessments

11.7.1 Patient-reported outcomes (PROs)

Each subject must make individual assessments relating to their perception of their disease and quality of life. These will be performed prior to the investigator performing his/her efficacy assessments. At the screening visit, the subject's eligibility needs to be established before the PROs can be completed.

The subjects will receive an eDiary device and eDiary training, as well complete all of the PROs, at the screening visit (minimum 7 days before baseline [Day 1]) and start completing the eDiary.

One PRO will be assessed daily using an eDiary:

- Chronic Hand Eczema Symptom Diary (HESD)

The subjects must complete the HESD each day in the evening, and compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial.

In addition, 7 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:

- Chronic Hand Eczema Impact Scale (HEIS)
- Patient's Global Assessment (PaGA)
- Patient Global Impression of Change (PGI-C)
- Dermatology Life Quality Index (DLQI)
- EuroQoL 5-dimension health questionnaire 5-level (EQ-5D-5L)
- Quality of Life in Hand Eczema Questionnaire (QOLHEQ)

- Work Limitation Questionnaire (WLQ)

11.7.1.1 Chronic Hand Eczema Symptom Diary (HESD)

Subjects will assess the worst severity of 11 symptoms of chronic hand eczema (itch, burning feeling, pain, cracking, redness, dryness, swelling, bleeding, thickening, flaking, oozing/weeping) over the past 24 hours using an 11-point NRS with 0 indicating e.g., 'no itch' and 10 indicating 'severe itch'/'worst itch imaginable'. Subjects will complete the HESD as an eDiary each evening at the latest from Week -1 until Week 16 (see Section 4).

11.7.1.2 Chronic Hand Eczema Impact Scale (HEIS)

The HEIS includes 9 items addressing the subject's perception of the impact of hand eczema on their daily activities, emotional wellbeing, sleep, and work 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 total score is the sum of the 9 items. The highest possible score is 36 and a high score is indicative of a high impact. Domain scores can be calculated for daily activities (4 items), emotional wellbeing (3 items), sleep (1 item), and work (1 item). The HEIS will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.3 Patient's Global Assessment (PaGA)

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

11.7.1.4 Patient Global Impression of Change (PGI-C)

The PGI-C is a 1-item questionnaire designed to assess the subject's impression of changes (21). The subjects have to select the one response from the response options ('much better', 'a little better', 'no change', 'a little worse', or 'much worse') that best describes the overall change in their chronic hand eczema since they started IMP treatment. The PGI-C will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.5 Dermatology Life Quality Index (DLQI)

DLQI is a validated questionnaire with content specific to those with dermatological 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. These include dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (14). Each item is scored on a 4-point 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. The highest possible score is 30 and a high score is indicative of a poor quality of life. The DLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.6 EuroQoL 5-dimension health questionnaire 5-level (EQ-5D-5L)

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

11.7.1.7 Quality of Life in Hand Eczema Questionnaire (QOLHEQ)

QOLHEQ is a validated questionnaire used to assess disease-specific health-related quality of life in subjects with hand eczema (16, 17, 18, 19). It consists of 30 items and assesses disease-related impairment over the last 7 days within 4 domains: (i) symptoms, (ii) emotions, (iii) functioning, and (iv) treatment/prevention. Each item is scored on a 5-point scale ('never', 'rarely', 'sometimes', 'often', 'all the time'). The total score as well as summary scores for each domain is calculated. A high score is indicative of a high impact on health-related quality of life. The QOLHEQ will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.8 Work Limitation Questionnaire (WLQ)

WLQ is a validated questionnaire to measure the degree to which health problems interfere with specific aspects of job performance and the productivity impact of these work

limitations (20). It asks subjects to rate their level of difficulty or ability to perform 25 specific job demands in the last 2 weeks. Responses to the 25 items are combined into 4 work limitation scales: time management, physical demands, mental/interpersonal, and output demands. These capture the multidimensionality of job roles and also reflect an important characteristic of many chronic illnesses, in that they may result in limitations in performing some activities but not others. Scale score range from 0 ('limited none of the time') to 100 ('limited all the time'). The WLQ will be completed at the trial site for subjects with a paid job according to the schedule of trial procedures in Section 4.

11.8 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK, filaggrin, and pregnancy test. The total volume of blood to be drawn in the trial is approximately 40 mL.

11.9 End of trial

An end of trial form must be completed in the eCRF for all randomised subjects (including subjects who permanently discontinue IMP and subjects who withdraw from trial). The following data will be collected:

- Whether the subject completed the trial.
- Last trial site visit or contact for which data is recorded.
- Date and time of last application of IMP.
- Primary reasons for discontinuation of IMP, withdrawal from trial, and not attending primary endpoint visit, if applicable (lack of efficacy, AE, withdrawal by subject, lost to follow-up, pregnancy, death, other).

The end of trial form will be completed when the subjects have had their last visit (at the early termination visit, the safety follow-up visit, or the primary endpoint visit, whichever comes last).

11.10 Storage of biological samples

Filaggrin and PK samples (blood) and skin biopsies will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR unless specific additional consent has been obtained that allows storage for future research (see below).

Biobank

This protocol includes the collection and analysis of different biological samples. If consent is given by the subject, LEO will store skin biopsies collected in a biobank established by LEO and hosted by BioStorage Technologies GmbH. The residual biological samples will be used for future research performed by LEO or may be given to academic partners to be used for future research in chronic hand eczema and related diseases. Donation of the samples for future research is voluntary and subjects must give their separate written consent to confirm donation and storage and the terms associated herewith. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and the sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples from this trial will be stored in the biobank for up to 10 years after the end of the trial and will then be destroyed.

12 Scientific rationale for trial design and appropriateness of assessments

This is a multi-centre, randomised, vehicle-controlled, double-blind, parallel-group trial, which will be conducted in accordance with the protocol, ICH-GCP, and applicable regulatory requirements.

The trial will be conducted at multiple trial sites located both in Europe and in North America. High-quality trial sites with shared standards of practice and values will be selected; all trial sites follow the globally accepted guidelines for diagnosis, prevention, and treatment of hand eczema (1).

Patients with hand eczema represent a heterogeneous patient population as hand eczema is associated with different aetiologies and morphologies and the severity may range from mild to severe. To mitigate any potential difference in trial outcome based on baseline characteristics, the trial subjects will be randomised in stratified manner as described in Section 9.3. The randomisation will minimise selection bias and minimise influence of (intrinsic) confounding factors and the stratification will ensure a certain balance of the treatment groups with respect to disease severity and region. The enrolment is controlled by disease severity to allow for assessment of co-variability in patients with mild, moderate, and severe disease state.

The inclusion of 4 active treatment groups with 1, 3, 8, and 20 mg/g of delgocitinib cream and a vehicle control group is considered enough to establish a dose-response signal. The vehicle control group will serve as reference and has been added to establish the efficacy and safety of delgocitinib cream in a blinded trial design.

The trial endpoints have been selected to evaluate the efficacy of delgocitinib in improving the severity and extent of chronic hand eczema. Both IGA and HECSI will be used in this clinical trial as investigator-rated assessments of disease severity. The IGA is an assessment of 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”. The HECSI is an instrument used to score both the extent and the intensity of the disease. The primary endpoint of the trial is to evaluate the percentage of subjects achieving treatment success defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement from baseline to Week 16. The trial endpoints will also address subject’s perception of disease severity and the impact on sleep, daily activity, and health-related quality of life.

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

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form until completion of the clinical trial for the individual subject.

AEs must be assessed by medically qualified personnel.

At all visits/phone call, the subject will be asked a non-leading question by the investigator about AEs, for example: "How have you felt since I saw you last?" No specific symptoms should be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes. If a subject reports an AE during the phone call on Day 4, it is up to the investigator's discretion to perform an unscheduled visit.

Refer to Sections 11.4.1 to 11.4.4 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 (for example '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 the following terminology:

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

The *duration* of the AE must be reported by the start date and stop date of the event (it will also be recorded if the event is ongoing). In addition, it will be recorded if the AE started prior to start of IMP.

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

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

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

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

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 on the (paper) SAE form within 24 hours of first knowledge. This report should contain 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.

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

Global Pharmacovigilance at LEO

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

Fax number: +45 7226 3287

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

Additionally, Global Pharmacovigilance at LEO may request further information in order to fully assess the SAE. The investigator must forward such information to LEO 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 collected. However, such events should be reported to Global Pharmacovigilance at LEO (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO reporting responsibilities

Global Pharmacovigilance at LEO is responsible for assessing whether or not an SAE is expected. The relevant reference safety information document for this clinical trial is:

For the IMP, the Investigator's Brochure, edition 1 and subsequent updates must be used.

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

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

For all non-US countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP **by either the investigator or LEO** (ICH E2A Guideline), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions [SUSARs]), are subject to expedited reporting to regulatory authorities and IEC(s)/IRB(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

For the US, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP **by LEO** (Guidance for Industry and Investigators - Safety Reporting Requirements for INDs and BA/BE Studies; Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection) and which are unexpected (Serious and Unexpected Suspected Adverse Reactions [IND safety report]) are subject to expedited reporting to regulatory authorities and IRB(s). 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 during the clinical trial must be reported to LEO within 24 hours of first knowledge using the (paper) Pregnancy Form (Part I). All pregnancies must be followed up until delivery or termination and final 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 Pharmacovigilance at LEO. Contact details are given in Section 13.4.1.

Pregnant subjects must immediately discontinue IMP permanently (Sections 10.2.1 and 10.3).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The event listed in Panel 15 is considered an adverse event of special interest in this trial and will require that the investigator provides additional details to be recorded in the eCRF. An adverse event of special interest may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 15: Adverse event of special interest

Adverse event of special interest	Additional information to be provided
Eczema herpeticum	Skin findings: • Lesion type. • Disseminated/localised. • Location. • Present in area with visible eczema/no visible eczema/present in areas with and without eczema. • Monomorphic/polymorphic. Confirmation of herpes simplex virus.

13.6.2 Overdose

An overdose is defined as a subject using more than double the recommended quantity of IMP specified in this protocol in Section 9.2. An overdose is either accidental or intentional.

The term ‘overdose’ including a specification of why it occurred (accidental or intentional) must be documented on the AE form of the eCRF. In addition, AEs originating from an overdose must be documented on a separate line. If the AE originating from the overdose qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.3 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP while in the control of the investigator or subject. Broadly, medication errors fall into 4 categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration, or wrong subject.

The medication error category must be documented on the AE form in the eCRF. In addition, AEs originating from a medication error must be documented on a separate line. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.4 Misuse

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

The term ‘misuse’ must be documented on the AE form in the eCRF. In addition, AEs originating from misuse must be documented on a separate line. If the AE originating from misuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.5 Abuse

Abuse relates to the sporadic or persistent, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects.

The term ‘abuse’ must be documented on the AE form in the eCRF. In addition, AEs originating from abuse must be documented on a separate line. If the AE originating from abuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.6 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.

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 of possibly/probably relationship to the IMP for 14 days or until the final outcome is determined, whichever comes first. 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 cannot be expected to resolve during the trial or the safety follow-up periods, for example chronic or stabilised conditions, 'not resolved' is accepted as a final outcome and a statement that the SAE has stabilised or is chronic should be added to the narrative in the SAE form.

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."* (22).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO, regulatory authorities, or IRBs/IECs.

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

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

14 Statistical methods

14.1 Sample size

A total of 250 subjects will be divided into 5 treatment groups and randomised 1:1:1:1:1 to one of each dose level of delgocitinib cream (1, 3, 8, or 20 mg/g) or delgocitinib cream vehicle.

The sample size is based on the following pairwise consideration, even though the primary objective of the trial is to establish the dose-response relationship. With a significance level of 5% when comparing 2 treatment groups and assuming treatment success rates (according to IGA) of 45% and 15%, respectively of the investigative treatment group (delgocitinib cream) and delgocitinib cream vehicle, then 50 subjects per treatment group will provide a power slightly above 90% for finding significantly different success rates between treatment groups.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All randomised subjects will be included in the full analysis set and will be analysed for efficacy parameters up to Week 16. Exclusions from the full analysis set can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a randomised subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set will be defined by excluding subjects from the full analysis set who fulfil any of the following criteria:

- Did not receive treatment with the IMP.
- Did not provide IGA or HECSI data following start of treatment.
- Are known to have taken the wrong IMP throughout the treatment period of the trial.
- Did not fulfil the disease defining inclusion criteria (that is, inclusion criteria 3, 4, and 5).
- Did not apply IMP at least 80% of the time in the period from date of first application of IMP to date of last application of IMP.

A safety analysis set will be defined by excluding subjects from the full analysis set who receive no treatment with IMP.

Based on the above rules, the decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the analysis set definition document before breaking the randomisation code.

14.3 Statistical analysis

14.3.1 Disposition of subjects

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

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects by treatment group. Presentations of demographics, baseline disease severity, and proportion of subjects with baseline worst pruritus (weekly average) above/below 4 on the numeric rating scale (NRS), i.e., one of the symptoms captured in the HESD, will also be given by region and baseline disease severity.

Demographics include age, sex, ethnicity, and race. Other baseline characteristics include vital signs, height, weight, body mass index, total IgE, Fitzpatrick skin type, duration and classification of chronic hand eczema, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, and previous chronic hand eczema treatments.

14.3.3 Exposure and treatment compliance

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

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

Drug accountability data will be calculated by subtracting the weight of the used tubes from the mean normal weight of full tubes. Average weekly/bi-weekly and total usage will be presented per treatment group, respectively, both for time intervals between visits (1 or 2-week periods depending on the time between site visits) and total period.

Adherence to treatment regimen will be recorded in the eCRF. If any complications or deviations in administration are observed, these will be described as protocol deviations.

Adherence will be presented for the safety analysis set for each treatment group via the percentage of applications missed.

14.3.4 Testing strategy

This is a dose-ranging trial with the primary objective to establish the dose-response relationship. For the primary endpoint IGA TS and the secondary endpoint change in HECSI from baseline to Week 16, the selection of the dose-response model that fits data best will be controlled using a family-wise error rate of 5%. There will be no adjustment for the multiple testing of primary and secondary endpoints, all p-values will be considered nominal.

14.3.5 Analysis of primary efficacy endpoint

The primary endpoint IGA TS at Week 16 will be analysed for the full analysis set and for the per protocol analysis set. The per protocol analysis is regarded as supportive.

IGA TS refers to IGA score of 0 (clear) or 1 (almost clear) with ≥2-step improvement from baseline.

For the analysis of the primary endpoint, subjects who initiate rescue medication before Week 16 or withdraw from the trial and have no retrieved data at Week 16, will all be considered non-responders.

The Multiple Comparison Procedure – Modelling (MCP-Mod) approach (see e.g., EMA Qualification Opinion of MCP-Mod [23] or Bretz et al [24] for further details of the framework) will be used to guide dose selection. The dose-response relationship for the binary endpoint IGA TS will be modelled by the following 3 identified candidate models. These candidate models are selected based on the expected dose-response.

Linear in log: $E_0 + \delta \times \log(d + c)$,

E_{max}: $E_0 + E_{max} \times d / (ED_{50} + d)$,

Sigmoid E_{max}: $E_0 + E_{max} \times d^h / (ED_{50}^h + d^h)$,

where d is the dose (incl. vehicle), E_0 is the efficacy offset (anticipated vehicle effect), E_{max} is the asymptotic maximum effect, ED_{50} is the half-life value of E_{max}, h is the steepness at ED_{50}, δ is the slope parameter, and c is a fixed offset parameter.

The models will be adjusted for the stratification variables region and baseline IGA. The model parameters (ED_{50}, h) will be prespecified a priori by suitable guesses based on data from Japan Tobacco's dose-ranging trial QBA2-1 (25). Akaike's Information Criteria will be

used as the goodness-of-fit criterion that will drive the selection of the dose-response model that fits data best while controlling the family-wise error rate at 5%. Based on the selected model, the dose-response relationship will be estimated and presented with 2-sided 95% CI. If none of the candidate models converge, other possibilities of models and goodness-of-fit criteria will be explored. The dose-response modelling will be performed on both the total population and subjects having a baseline IGA of 3 or 4, in order to further explore heterogeneity in the disease population.

In addition to the dose-response modelling approach, the difference in response rates between the delgocitinib doses and vehicle will be analysed separately for each of the dose groups using the Cochran-Mantel-Haenszel test stratified by region (Europe and North America) and disease severity (baseline IGA of 2, 3, and 4). The null hypothesis of no difference in response rates between delgocitinib and vehicle will be tested against the 2-sided alternative that there is a difference.

Sensitivity analysis will be performed as applicable in order to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 16, use of rescue medication, and assumptions regarding missing data. This will be described in further detail in the statistical analysis plan.

14.3.6 Analysis of secondary efficacy endpoints

The secondary endpoints change from baseline to Week 16 in HECSI and time to IGA TS will be analysed for the full analysis set and for the per protocol analysis set. The per protocol analysis is regarded as supportive.

For the analysis of the change from baseline to Week 16 in HECSI, data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis. Missing data at Week 16 will be imputed using the mixed model for repeated measurements (MMRM) predicted values from the below specified model for repeated measurements.

The dose-response modelling approach suggested for the primary endpoint will also be applied for the continuous endpoint change from baseline to Week 16 in HECSI.

In addition to the dose-response modelling approach, the continuous endpoint will be analysed using a MMRM on the post baseline responses up to Week 16 with an unstructured

covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows:

Change from baseline in HECSI

$$= \text{treatment} \times \text{visit} + \text{baseline HECSI} \times \text{visit} + \text{region} + \text{baseline IGA}$$

The estimates will be presented with nominal p-values and 95% CI at each visit. The primary comparison between each delgocitinib dose and vehicle will be at Week 16.

Time to IGA TS response is defined as the time from baseline to first assessment of an IGA TS. Subjects will be censored at the date of the last assessment visit or at initiation of rescue medication, whichever occurs first. Kaplan-Meier curves of time to IGA TS will be estimated and presented by treatment for the full analysis set. Treatment groups will be compared using a 2-sided log-rank test stratified by region and baseline IGA.

Sensitivity analysis will be performed as applicable in order to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 16 and assumptions regarding missing data. This will be described in further detail in the statistical analysis plan.

14.3.7 Analysis of other endpoints

14.3.7.1 Analysis of patient-reported outcomes

The PROs HEIS, PaGA, DLQI, EQ-5D-5L, QOLHEQ, WLQ, and PGI-C will be summarised by treatment group and visit using descriptive statistics. The summaries will be presented for the full analysis set.

The HESD collected in the eDiaries on a daily basis (all individual symptoms) will be summarised over time by treatment group using descriptive statistics. The summaries will be presented for the full analysis set.

The daily diary recordings of the HESD NRS scores will be derived into discrete weekly endpoints based on calendar time (with the exception of Week 16) from baseline visit i.e., the endpoints represent the nominal week and are not directly related to the actual visit in contrast to other visit based assessments. The algorithm for deriving the endpoints at each time point is described as follows: baseline weekly average will be defined by average of measurements from Day -7 to Day -1, Week 1 weekly average will be defined by the average of measurements from Day 1 to Day 7, Week 2 weekly average will be defined by the average of measurements from Day 8 to Day 14 and so on, until Week 15. Week 16 will be calculated

based on the 7 days preceding the Week 16 visit. A minimum of 4 HESD NRS scores out of the 7 days are required to calculate the average score. This will be derived for each symptom, respectively.

In the subgroup of subjects with a baseline worst pruritus (weekly average) – one of the symptoms captured in the HESD – score of at least 4, the proportion of subjects with reduction in worst pruritus (weekly average) of at least 4 from baseline to Week 16 will be summarised by treatment group and analysed using the Cochran-Mantel-Haenszel approach as described for the analysis of the primary endpoint.

PaGA TS refers to achieving:

- PaGA score of 0 (clear) when classified at baseline as 1 (almost clear) or 2 (mild)

or

- PaGA score of 0 (clear) or 1 (almost clear) when classified at baseline as 3 (moderate) or 4 (severe).

The proportion of subjects achieving PaGA TS at Week 16 will be summarised by treatment group and analysed using the Cochran-Mantel-Haenszel approach as described for the analysis of the primary endpoint.

The time to PaGA TS will be summarised by treatment group and analysed as described for the primary analysis of the secondary time to event endpoint.

In the subgroup of subjects with a baseline DLQI score of at least 4, the proportion of subjects with a reduction in DLQI score of at least 4 at Week 16 will be summarised by treatment group and analysed using the Cochran-Mantel-Haenszel approach as described for the analysis of the primary endpoint.

The change from baseline to Week 16 in HESD NRS (weekly average for each individual symptom), HEIS (for each individual item), DLQI, EQ-5D-5L, QOLHEQ, and WLQ will be summarised by treatment group and domain, where applicable, and analysed using the MMRM approach as described above for the analysis of the secondary continuous endpoint.

14.3.7.2 Efficacy over time

To further explore possible early onset of effect and general efficacy over time, the following endpoints will be evaluated at each scheduled assessment up to Week 14 or each week up to Week 15:

- IGA TS at each scheduled assessment until Week 14.
- PaGA TS at each scheduled assessment until Week 14.
- Change from baseline to each week through Week 1 to 15 in HESD NRS (weekly average for each individual symptom).
    - Reduction of worst pruritus (weekly average) – one of the symptoms captured in the HESD – of at least 4 from baseline to each week through Week 1 to 15 among subjects with baseline worst pruritus (weekly average) of at least 4.
- Change from baseline to each scheduled assessment until Week 14 in HEIS (for each individual item).
- Change in DLQI score from baseline to each scheduled assessment until Week 14.
- Reduction of DLQI of at least 4 from baseline to each scheduled assessment until Week 14.

For the binary endpoints, the same Cochran-Mantel-Haenszel test as for the Week 16 assessment will be applied. For the continuous endpoints, the repeated measurements model already described previously for the Week 16 assessments facilitates that the p-values, treatment differences and 95% CIs can be derived for each visit up to Week 14 (or Week 15 for the change in HESD NRS (weekly average)).

14.3.7.3 Exploratory analyses

Treatment effect within each subtype of chronic hand eczema in terms of disease aetiology will be explored for the primary and secondary endpoints using the same analysis methods as described previously.

14.3.8 Analysis of pharmacodynamics and pharmacogenomics

Exploratory analyses of biomarkers will be performed for the total population as well as for subtype of chronic hand eczema and by disease severity.

A summary of the results will be included in the CTR if it is available in time for this. The full set of biomarker results will be reported in an addendum report to the CTR.

14.3.9 Analysis of safety

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

14.3.9.1 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 terms and primary system organ class (SOC).

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

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

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

The severity for each type of AE will be tabulated by treatment group. Where there are several recordings of severity for a given type of AE, severity will be taken as the most severe recording for that AE.

The causal relationship to IMP for each type of AE will be tabulated by treatment group. Where there are several recordings of causal relationship to the IMP for a given type of AE, causal relationship will be taken as the most-related recording from the last report of that AE, since that is when the investigator will be in possession of most information and so best able to judge causal relationship.

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

SAEs will be evaluated separately and a narrative for each will be given.

Adverse events of special interest will be tabulated by treatment group.

AEs leading to withdrawal from trial and AEs leading to permanent discontinuation of IMP will be tabulated by treatment group.

14.3.9.2 Vital signs

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

14.3.9.3 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to each visit will be summarised by visit and treatment group as mean, standard deviation, median, minimum, and maximum values.

Laboratory parameters will be classified as 'low', 'normal' or 'high', depending on whether the value is below, within or above the reference range, respectively. A shift table will be produced showing the categories at baseline against those at end of treatment. Subjects with laboratory parameters outside the reference range will be listed.

14.3.9.4 Subject assessment of local tolerability

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

14.3.10 Pharmacokinetics

A separate report will be written by the respective bioanalytical CRO and added as an addendum to the CTR.

Plasma concentrations of delgocitinib will be listed and plotted versus time since last IMP application by treatment group.

14.3.11 Interim analysis

No interim analysis is planned.

14.3.12 General principles

Unless otherwise stated, all significance tests will be 2-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence.

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

Categorical data will be summarised using the number and percentage of subjects in each category and treatment group. Continuous data will be summarised using the mean, median, standard deviation, minimum, and maximum values.

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

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

14.3.13 Handling of missing values

Procedures for handling of missing values are included under the sections describing the individual analyses.

15 References

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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. (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

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 unless these were planned before the subject consented to trial participation.
- 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 11.4.4).

Serious adverse event definition

An SAE is any untoward medical occurrence that

- Results in death.
- Is life-threatening.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

or

- 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 broncospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

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.

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.

If the severity of an AE worsens, a new AE should be recorded.

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. The categories are defined below.

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 a 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.

Note that as per the above definition, LEO uses “RECOVERED/RESOLVED” only if an event has actually stopped. According to the CDISC definition, the category “RECOVERED/RESOLVED” also includes events which have improved. However, following the LEO 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 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 with the outcome “RECOVERED/RESOLVED WITH SEQUELAE” could have been classified with the outcome “RECOVERED/RESOLVED” according to the CDISC definition.

For SAEs which have stabilised and cannot be expected to resolve during study or safety follow-up periods, for example chronic illnesses, ‘not resolved’ is accepted as the final outcome and a statement that the SAE has stabilised or is chronic should be added to the narrative in the SAE form.

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 (26) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (27).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (28).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authorities 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 leaflet, informed consent forms, 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 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 (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the informed consent form.

Subjects will be re-consented to the most current version of the informed consent form during their participation in the trial, if applicable.

A copy of the informed consent form(s) must be provided to the subject.

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

Appendix 3C: Subject and data confidentiality

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

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

Trial subjects will be assigned a unique identifier (subject ID) by LEO. Any subject's records or datasets that are transferred to LEO 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 and consent to that their personal trial-related data will be used by LEO 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, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Processing of personal data
This protocol specifies the personal data on trial subjects (for example race, age, gender, 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 and third parties acting on behalf of LEO.

Processing of personal data on behalf of LEO requires a written agreement between LEO 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 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 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
For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be 1 source defined at any time for any data elements.

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

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:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Subject ID.
- The fact that the subject is participating in a clinical trial in chronic hand eczema including treatment with delgocitinib cream (1, 3, 8, or 20 mg/g) or delgocitinib cream vehicle for 16 weeks of treatment plus 2 weeks of follow-up.
- Other relevant medical information.

Trial monitoring

During the course of the trial, CRA(s) will visit the trial site. These visits have the following objectives: (i) to continually verify source data to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; (ii) to confirm that the safety and rights of subjects are being protected; and (iii) to confirm that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP, and all applicable regulatory requirements.

The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH-GCP.

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 and major 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 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 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 must be notified immediately.

Risk assessment
In this trial, the risks to critical trial processes and data have been evaluated.

Risk mitigation activities for endpoints include:

- Ensuring consistent data with respect to assessments of efficacy (IGA and HECSI), all assessors will receive training and whenever possible, the efficacy assessments will be made by the same investigator at each visit for a given subject to reduce inter-rater variability.
- Ensuring subjects and investigational staff are well instructed and trained about the use of the eDiary and the eDevice which will be used to collect the PROs (HESD, HEIS, PaGA, DLQI, EQ-5D-5L, QOLHEQ, WLQ, PGI-C).
- Ensuring investigational staff are well instructed and trained in collecting biomarker samples.
- Ensuring administration of IMP is controlled and documented at the site. This will be done by providing training and clear instructions to trial sites.
- Ensuring that trial sites are well trained in safety procedures such as collection and reporting of AEs.

- Ensuring investigational staff are well instructed and trained in informing subjects about the capping limits i.e., the risk of not being randomised in spite of meeting eligibility criteria.

Throughout the trial, data quality review meetings will be held to ensure that data collection can be improved, and mistakes prevented. During monitoring visits to the trial sites, the CRAs will verify that investigators work according to the protocol.

Data handling

Data will be collected by means of electronic data capture unless transmitted to LEO or designee electronically (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs (eCRFs). Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

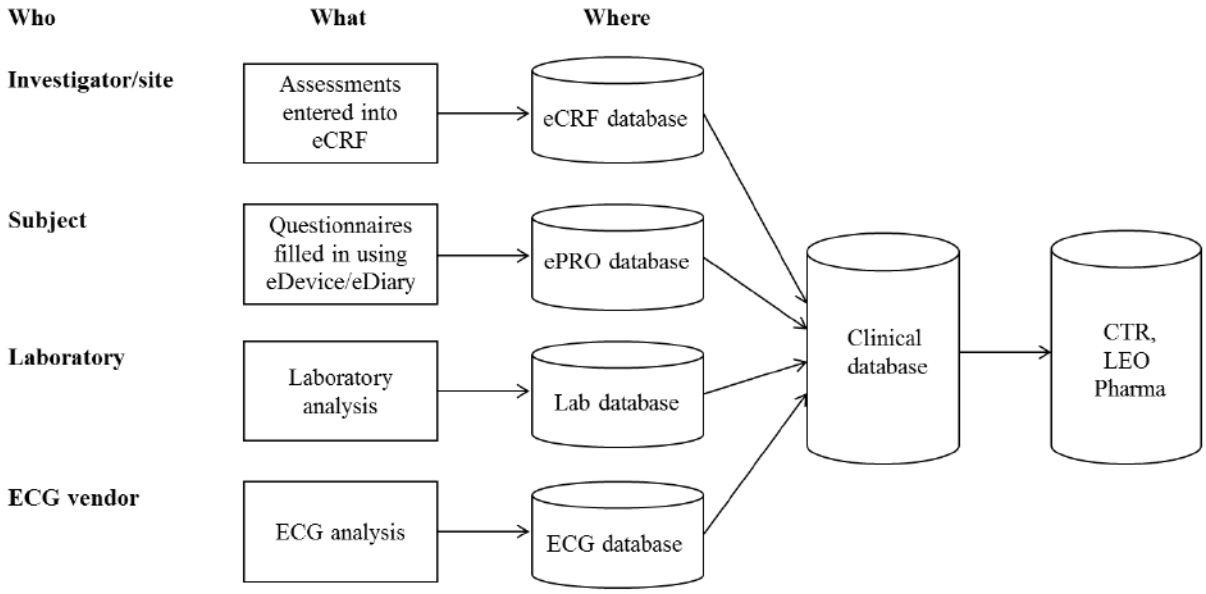
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original 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 or data transmission and available for monitors and site personnel, including the investigator, with read 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 will be transmitted and handled via a secure file transfer protocol site. Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 16.

Panel 16: Transmission of electronic data



Abbreviations: CTR, clinical trial report; ECG, electrocardiogram; eCRF, electronic case report form; ePRO, electronic patient-reported outcome

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (28). Essential trial documents must be stored until LEO 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 (for example 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. No documents may be transferred to another location or party without written acceptance from LEO.

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 and randomised subjects enrolled 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, from regulatory authorities and/or IRBs/ IECs.

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

LEO 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 the corporate website of LEO in accordance with our Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

LEO may also provide researchers access to anonymised patient level data for further research. Publication and access will be in accordance with the Position on Public Access to Clinical Trials which can be found on the LEO website.

Publications

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

A multi-centre publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-centre publication is made public, or if no multi-centre publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

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

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

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

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

LEO complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO also follows the CONSORT reporting guidelines (12).

Appendix 3F: Insurance

LEO 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 with sufficient, accurate financial information as requested to allow LEO 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 site closure

Premature termination of trial or trial site

LEO, the investigator, the IRB/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 must promptly inform IRB/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 early closure of a trial site by LEO 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 procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

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

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

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

Appendix 3I: Responsibilities

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

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a National Coordinating Investigator Agreement.

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

Appendix 4: Short version of eligibility criteria

This appendix provides a short form (maximum 200 characters) of each of the eligibility criteria to be used when data are submitted to regulatory authorities in CDISC format.

Inclusion criteria	
No.	
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2	Age 18 years or above.
3	Diagnosis of chronic hand eczema defined as hand eczema, which has persisted for more than 3 months or returned twice or more within the last 12 months.
4	Disease severity graded as mild to severe according to IGA (i.e., an IGA score of 2 or more).
5	Recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable.
6	Diagnostic patch testing performed within 3 years prior to the screening visit.
7	A woman of childbearing potential must use a highly effective form of birth control throughout the trial and at least for 2 weeks after last application of IMP.

Exclusion criteria	
No.	
1	Concurrent skin diseases on the hands, e.g. tinea manuum.
2	Active atopic dermatitis in regions other than the hands or psoriasis requiring medical treatment.
3	Clinically significant infection (e.g., impetiginised hand eczema) on the hands.
4	Systemic treatment with immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids within 4 weeks prior to baseline.
5	Psoralen ultraviolet A (PUVA) or ultraviolet B (UVB) therapy on the hands within 4 weeks prior to baseline.
6	Receipt of live attenuated vaccines 4 weeks prior to baseline.
7	Cutaneously applied treatment with immunomodulators (e.g., PDE-4 inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands within 2 weeks prior to baseline.
8	Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 2 weeks prior to baseline.
9	Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e., subjects must not start antihistamine treatment or change the current dosage regime within 2 weeks prior to baseline.
10	Other cutaneously applied therapy on the hands (except for the use of subject's own emollients) within 1 week prior to baseline.
11	Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern within 1 week prior to baseline.
12	Receipt of any marketed or investigational biologic agents within 6 months or 5 half-lives prior to baseline or until cells counts returns to normal, whichever is longer.

13	Received treatment with any non-marketed drug substance within the last 4 weeks prior to baseline or 5 half-lives whichever is the longest.
14	Clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to baseline.
15	Tuberculosis requiring treatment within 12 months prior to screening and/or subjects with a positive blood test for tuberculosis at screening (subjects with high risk of latent tuberculosis must be tested).
16	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications.
17	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
18	History of cancer.
19	Any disorder which is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial.
20	Any abnormal finding which in the investigator's opinion may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial.
21	Positive HBsAg, HBsAb, HBcAb, or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
22	Alanine aminotransferase or aspartate aminotransferase level 2.0 times the ULN range or more at screening.
23	Known or suspected hypersensitivity to any component(s) of the IMP.
24	Current participation in any other interventional clinical trial.
25	Previously randomised in this clinical trial.
26	Previously participated in a clinical trial with delgocitinib (LEO 124249).
27	History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
28	Employed at the trial site or directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
29	Legally institutionalised.
30	Pregnant or lactating.

Abbreviations: anti-HCV, hepatitis C virus antibody; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; PDE-4, phosphodiesterase-4; ULN, upper limit of normal.

Appendix 5: Contact list

Contact details for the clinical project manager (CPM), 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' 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

Appendix 6: Protocol amendment history

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

Amendment 1 (11-Jul-2018)

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

Overall rationale for the amendment

The main reason for the amendment is to add an exclusion criterion to ensure that subjects who previously participated in a clinical trial with delgocitinib (LEO 124249) are not allowed to participate in this trial. In addition, the amendment includes other changes, as presented in the table below.

The table below presents changes made in each section and a brief rationale for each change. Changes have either been summarised (written with plain text only) or marked as tracked changes (new text that has been added to the protocol is highlighted in **bold** and text that has been removed from the protocol is highlighted with ~~a line through the text~~).

Section no. and name	Description of change	Brief rationale
Section 4 Schedule of trial procedures	The 'X' at Week 1 and at Week 12 for the WLQ questionnaire in the schedule of trial procedures have been removed.	The WLQ will be assessed less frequently to reduce the burden on the trial subjects.
Section 8.3 Exclusion criteria, Appendix 4: Short version of eligibility criteria	A new exclusion criterion has been added: **Previously participated in a clinical trial with delgocitinib (LEO 124249).**	To avoid recruitment of subjects who have been evaluated in previous delgocitinib trials.

Section no. and name	Description of change	Brief rationale
Section 8.3 Exclusion criteria, Appendix 4: Short version of eligibility criteria	Exclusion criterion 25 has been changed to: Previously **randomised** ~~screened~~ in this clinical trial.	This has been changed to allow for re-screening in case of administrative reasons.
Section 8.4 Screening and screening failures	The text in this section has been changed to: ~~Re-screening of screening failures is not allowed.~~ **Individuals who do not meet the criteria for participation in the trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative e.g., delayed test results and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted. Individuals who are re-screened will get a new subject ID.**	This has been changed to allow for re-screening in case of administrative reasons.
Section 9.2 Administration of IMP	The following sentence has been added: **The subjects will be advised to contact the investigator before initiating treatment of new lesions.**	This has been added to describe that the determination of new lesions should be considered by the investigator.
Section 9.8.2 Storage of trial products	The following sentence has been changed to: The IMPs must be stored at 2-8°C **(36-46°F). Do not freeze.**	This has been added to further clarify the storage condition of the IMP.

Section no. and name	**Description of change**	**Brief rationale**
Section 10.1 General principles	The text in this section has been changed to: The primary reasons for withdrawal from the trial, ~~and~~ discontinuation of IMP, **and not attending the primary endpoint visit at Week 16, if applicable,** must be recorded in the medical records and on the end of trial form in the eCRF where the following options are available:	This sentence has been changed for consistency with other sections in the protocol.
Section 11.4.4 Laboratory testing	The text in this section has been changed to: If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criteria no. 16, 20, 21, ~~and~~ 22**, and 30**).	This sentence has been changed to clarify that the pregnancy testing should also be considered to determine if a subject is eligible.
Section 11.5.1 Blood sampling for analysis of systemic concentration of delgocitinib	The following sentence has been added in the last paragraph: Samples from delgocitinib cream vehicle-treated subjects will not be analysed. **Written procedures are in place to avoid unblinding of the trial and any trial subjects in relation to analysis of the PK samples.**	This sentence has been added to clarify that written procedures are in place to avoid potential unblinding.
Section 11.6.1 Overview	The last sentence in the 2nd bullet point has been deleted:	This sentence has been deleted to allow for flexibility and not

Section no. and name	Description of change	Brief rationale
	Microbiome diversity in a subset of skin swabs investigated by use of next generation sequencing methods. ~~The subset will be selected after unblinding from subjects from the highest dose group and from the vehicle-controlled group.~~	restrict this subset to the highest delgocitinib dose group.
Section 11.6.5 Non-invasive measurements of skin barrier function (selected trial sites)	The following sentence has been added: **The time from last IMP application to skin barrier measurement will be recorded.**	This sentence has been added to allow for assessing whether there is any correlation between the time from last IMP application and the measured values of skin barrier function.
Section 11.10 Storage of biological samples	The following sentence in the section describing the biobank has been changed to: The residual biological samples will be used for future research performed by LEO **or may be given to academic partners to be used for future research in chronic hand eczema and related diseases**.	This has been added to clarify that collaboration partners may be involved in future research of the samples.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

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