Cover Page

Study title: A 24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3, 2-arm trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema
LEO Pharma number: LP0133-1528
NCT number: NCT05259722
Date: 29-Jun-2022

Title Page

Protocol Title:	A 24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3, 2-arm trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema
Brief Title:	A 24-week trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema
Acronym	DELTA FORCE
Compound:	Delgocitinib
Indication:	Chronic hand eczema
Trial Sponsor:	LEO Pharma A/S Industriparken 55, DK 2750 Ballerup, Denmark
Protocol Number:	LP0133-1528
Trial Phase:	Phase 3
Regulatory Agency Identifying Number:	EudraCT-2021-003543-16
Version:	Version 5.0
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Date and Version of Original Protocol:	30 Sep 2021; Version 1.0

Approval Statement for Sponsor Signatories:

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

PPD, MD
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Approval Statement for International Coordinating Investigator:
The international coordinating investigator approves the clinical trial protocol by manually signing the Investigator Agreement Page, which is provided as a separate document.

The following person has approved this clinical trial protocol:

PPD, MD
International coordinating investigator

Medical Monitor Name and Contact Information:

PPD

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY			
Document	**Amendment Scope; Region/Country Identifier (if applicable)**	**Protocol Version**	**Date**
Amendment 4	Global amendment	5.0	24 Jun 2022
Amendment 3	Global amendment	4.0	08 Apr 2022
Amendment 2	Country-specific; UK	3.0	25 Feb 2022
Amendment 1	Country-specific; CAN	2.0	21 Jan 2022
Original Protocol	Not Applicable	1.0	30 Sep 2021

Amendment 4 (24 Jun 2022)

Overall Rationale for the Amendment

The protocol was amended in order to add the patient reported outcomes PGI-S and PGI-C.

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (SoA) Section 8.1.3.7: Patient Global Impression of Severity (PGI-S) questionnaires Section 8.1.3.8: Patient Global Impression of Change (PGI-C) questionnaires Section 9.3.10: Analysis of PGI-S and PGI-C Appendix 5: COVID 19 Pandemic Contingency Plan Appendix 8**:** Abbreviations	Patient reported outcomes PGI-S and PGI-C were added to the trial.	To enable assessment of psychometric measurement properties of the HESD.
Section 6.8.3: Prohibited medications and procedures	Wash-out period for retinoids and vitamin A in Table 6-2 was corrected.	To avoid discrepancies.
Section 1.3: Schedule of Activities	Weight measurement was added at screening.	Weight is required at screening to calculate renal insufficiency (Cockcroft-Gault formula).
Throughout the document	Minor editorial revisions.	Minor, have therefore not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A 24-week, randomised, assessor-blinded, active-controlled, parallel-group, phase 3, 2-arm trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema

Brief Title: A 24-week trial to compare the efficacy and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules once-daily in adult participants with severe chronic hand eczema

Sponsor Protocol No.: LP0133-1528

Trial Phase: Phase 3

Sponsor: LEO Pharma A/S

Rationale: There is a clear unmet need for long-term treatment options for patients suffering from moderate to severe chronic hand eczema (CHE). Alitretinoin is the only approved product specifically indicated for treatment of CHE, but it is only indicated for severe CHE and only approved in few countries worldwide. Delgocitinib cream has the potential to become an effective, well-tolerated, and user-friendly treatment for CHE and thereby improve the everyday lives of affected patients. The purpose of this 24-week trial is to compare efficacy, health-related quality of life, and safety of delgocitinib cream and alitretinoin capsules in participants diagnosed with severe CHE.

Objectives and Endpoints and/or Estimands:

Primary Objective

Objectives	Estimand type and strategy	Endpoints
Primary objective: To compare the efficacy and health-related quality of life of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	**Primary**. 'Composite' strategy. **First supplementary**. 'Pandemic modified composite' strategy. **Second supplementary** (for endpoints at Week 12 and Week 24). 'Treatment policy' strategy.	**Primary endpoint:** • Change in HECSI score from baseline to Week 12. **Key secondary endpoints**: • HECSI-90 at Week 12. • IGA-CHE TS at Week 12. • Change in HESD itch score (weekly average) from baseline to Week 12. • Change in HESD pain score (weekly average) from baseline to Week 12. • AUC of HECSI-90 from baseline up to Week 24. • AUC of change from baseline in DLQI score up to Week 24. • Change in HECSI score from baseline to Week 24.

Abbreviations: AUC=area under the curve; CHE=chronic hand eczema; DLQI=Dermatology Life Quality Index; HECSI=Hand Eczema Severity Index; HECSI-90=at least 90% improvement in HECSI score from baseline; HESD=Hand Eczema Symptom Diary©; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS=IGA-CHE treatment success.

Secondary Objective

Objectives	Endpoints
Secondary objective: To compare the safety of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	**Secondary endpoints**: • Number of treatment-emergent AEs from baseline up to Week 26. • Number of treatment-emergent SAEs from baseline up to Week 26. • Number of AEs leading to IMP discontinuation up to Week 24.

Abbreviations: AE=adverse event; CHE=chronic hand eczema, IMP=investigational medicinal product, SAE=serious adverse event.

Exploratory objectives

Exploratory objectives are described in Section 3.

Overall Design:

- This is a phase 3, randomised, assessor-blinded, active-controlled, parallel-group, multi-site, 24-week trial.
- The trial population will consist of adult participants with severe CHE and with a documented inadequate response to treatment with topical corticosteroids (TCS) or for whom TCS are documented to be otherwise medically inadvisable. The trial will include a maximum of 20% of participants with hyperkeratotic subtype.
- Eligible participants will be randomised to receive topical administration of delgocitinib cream 20 mg/g, twice-daily, or oral administration of alitretinoin capsules 30 mg (with an option to reduce to 10 mg during trial conduct), once-daily. Randomisation will be stratified by subtype (hyperkeratotic/non-hyperkeratotic) and region (North America/Europe).
- Participants are not blinded to treatment assignment, but efficacy (Investigator's Global Assessment for chronic hand eczema© [IGA-CHE©, hereafter referred to IGA-CHE] and Hand Eczema Severity Index [HECSI]) will be evaluated by an assessor blinded to treatment assignment. Other assessments will be performed by an unblinded investigator and treatment decisions will be made by the unblinded investigator following the recommendation from the blinded assessor.
- Certain Contract Research Organisation (CRO) and sponsor staff will also be blinded to ensure the integrity of the trial.

Brief Summary:

The purpose of this trial is to compare the efficacy, health-related quality of life, and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules 30 mg (with an option to reduce to 10 mg during trial conduct) once-daily in adult patients with severe CHE. The trial duration will be up to 33 weeks. The treatment duration will be up to 24 weeks. The visit frequency will be weekly for the first 3 weeks of treatment and every 4 weeks from Week 4 to the end of treatment.

Number of Participants:

Approximately 510 participants will be randomly assigned to trial treatment in a 1:1 ratio, with 255 evaluable participants per treatment group. Approximately 660 participants will be screened to achieve this target.

Intervention Groups and Duration:

For each participant, the trial will last at least 25 weeks and up to 33 weeks, including:

- a screening period of 1 to 4 weeks (at least 1 visit)
- a treatment period of 24 weeks (9 visits)
- a safety follow-up period of 2 to 5 weeks (1 visit for all participants 2 weeks after the last investigational medicinal product [IMP] dose, plus a pregnancy follow-up visit for woman of childbearing potential [WOCBP] treated with alitretinoin 5 weeks after the last IMP dose)

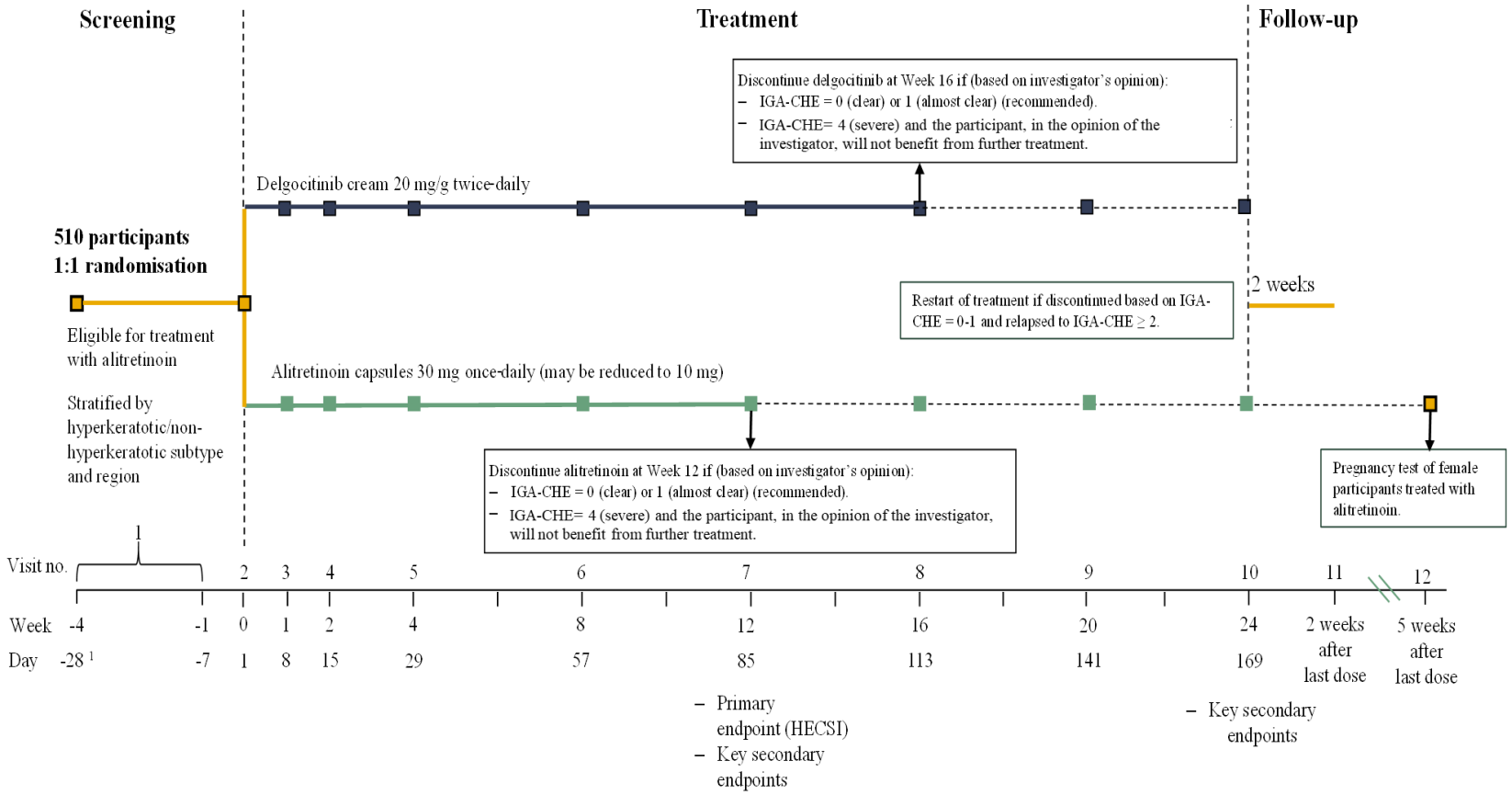
Eligible participants will be randomised in a 1:1 ratio to receive 1 of the following treatments:

- Topical administration of delgocitinib cream 20 mg/g, twice-daily until Week 16, which may continue up to Week 24 depending on clearance status (i.e. IGA-CHE score) and clinical benefit.
- Oral administration of alitretinoin capsules 30 mg (with an option to reduce to 10 mg during trial conduct), once-daily until Week 12, which may continue up to Week 24 depending on clearance status (i.e. IGA-CHE score) and clinical benefit.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1–1 Trial Design



1. For participants treated with medications requiring a 28-day washout period prior to baseline (see Table 6-2), the duration of the screening period may be extended up to 31 days to ensure appropriate washout.

Abbreviations: HECSI=Hand Eczema Severity Index; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©.

1.3 Schedule of Activities (SoA)

Table 1-1 Schedule of Activities (SoA)

	Screen-ing	Treatment period								EOT/ ET [1]	Follow-up [2]	Pregnancy follow-up [3]	Primary endpoint visit at Week 12, if applicable[4]	Nominal Week 24 visit, if applicable[4]	Unscheduled visit, if applicable [5]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**2 weeks after last dose**	**5 weeks after last dose**				
Day	**-28 [6] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**						
Visit window (days)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+6**				
Eligibility / baseline assessments																
Informed consent(s)	X															10.1.3
Participant eligibility	X	X														5.1, 5.2
Demographics	X															8
Fitzpatrick skin type	X															8, Table 8-1
Medical history (including CHE treatment history)	X															8
Classification of CHE (including patch test [7])	X														(X) [7]	8, Table 8-2
Height		X														8
Weight	X	X														8
Treatments and randomisation																
Randomisation		X														6.3
Instruction for use of IMP		X														6.2.1
Dispensing of IMP		X			X	X	(X)	(X)	(X)						(X)	6.1
Determination of affected area(s)		X													(X)	6.2.1
New CHE lesions			X	X	X	X	X	X	X	X			X	X	X	6.2.1

	Screen-ing	Treatment period								EOT/ ET [1]	Follow-up [2]	Pregnancy follow-up [3]	Primary endpoint visit at Week 12, if applicable[4]	Nominal Week 24 visit, if applicable[4]	Unscheduled visit, if applicable [5]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**2 weeks after last dose**	**5 weeks after last dose**				
Day	**-28 [6] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**						
Visit window (days)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+6**				
Delgocitinib cream topical application		Twice-daily for 16 weeks						Stop/restart as necessary								6.2.1.1
Alitretinoin capsules oral administration		Once-daily for 12 weeks					Stop/restart as necessary									6.2.1.2
Treatment compliance (eDiary)		Daily [8]														6.4
Return of treatment and accountability					X	X	X	(X)	(X)	(X)					(X)	6.4
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	X		X	X	X	6.8
Blinded assessor assessment of efficacy																
HECSI		X	X	X	X	X	X	X	X	X			X	X	(X)	8.1.1
IGA-CHE	X	X	X	X	X	X	X	X	X	X			X	X	(X)	8.1.2
Participant assessments of efficacy at home																
eDiary handout/training [8]	X															8.1.3.1
HESD	Daily [8]												Daily [8]	Daily [8]		8.1.3.1
Return of eDiary										X [9]				X [9]		8.1.3.1
Participant assessments of efficacy and health-related quality of life during trial visits																
HEIS		X	X	X	X	X	X	X	X	X			X	X		8.1.3.3
DLQI		X	X	X	X	X	X	X	X	X			X	X		8.1.3.2
EQ-5D-5L		X			X	X	X	X		X			X	X		8.1.3.4
TSQM					X		X			X			X	X		8.1.3.5
WPAI-CHE		X			X		X			X			X	X		8.1.3.6
PGI-S[10]		X		X	X	X	X									8.1.3.7

	Screen-ing	Treatment period								EOT/ ET [1]	Follow-up [2]	Pregnancy follow-up [3]	Primary endpoint visit at Week 12, if applicable[4]	Nominal Week 24 visit, if applicable[4]	Unscheduled visit, if applicable [5]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**2 weeks after last dose**	**5 weeks after last dose**				
Day	**-28 [6] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**						
Visit window (days)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+6**				
PGI-C[11]				X	X	X	X									8.1.3.8
Participant assessment of safety																
Participant assessment of local tolerability (delgocitinib group only)		Weekly while on treatment[12]								X						8.2.7.1
Unblinded investigator assessments of safety																
Physical examination	X									X					(X)	8.2.1
Vital signs	X	X								X					(X)	8.2.2
ECG	X		X							X					(X)	8.2.3
Fasting [13] triglycerides and cholesterol (central laboratory)	X	X			X	X	X	X	X	X	X				(X)	8.2.4, 10.2
Chemistry, haematology (central laboratory) [13]	X	X			X	X	X	X	X	X	X				(X)	8.2.4, 10.2
Serology, total IgE (central laboratory)	X															8.2.4, 10.2
Urinalysis (urine dipstick)	X	X				X	X	X		X					(X)	8.2.4, 10.2
Urine pregnancy test (WOCBP only)	X	X			X	X	X	X	X	X	X [14]	X [3]	X	X	(X)	8.2.5, 10.2
Check contraception compliance (alitretinoin group only)	X	X			X	X	X	X	X	X	X	X	X	X	(X)	8.2.5
Mental health interview[15]	X	X			X	X	X	X	X	X					(X)	8.2.6

	Screen-ing	Treatment period								EOT/ ET [1]	Follow-up [2]	Pregnancy follow-up [3]	Primary endpoint visit at Week 12, if applicable[4]	Nominal Week 24 visit, if applicable[4]	Unscheduled visit, if applicable [5]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**				
Week	**-4 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**2 weeks after last dose**	**5 weeks after last dose**				
Day	**-28 [6] to -7**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**						
Visit window (days)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+6**				
Local tolerability according to investigator (delgocitinib group only)			X	X	X	X	X	X	X	X					(X)	8.2.7.2
AEs	X	X	X	X	X	X	X	X	X	X	X		X	X	X	8.3, 10.3
Optional assessments (at selected sites only)																
Photography of both hands back and front including the wrist [16]		X					X	X		X						8.1.4
End of treatment/trial																
End-of-treatment form										X						8.10.1
End-of-trial form [17]										(X)	X	X		(X)	(X)	8.10.2

1. End-of-treatment assessments will be conducted at Week 24. Participants who permanently discontinue the IMP or who withdraw from the trial prior to Week 24 will be asked to return to the trial site for an ET visit as soon as possible after the last dose for completion of all trial procedures scheduled for the visit at Week 24.
2. All participants will be asked to return to the trial site approximately 2 weeks after the last dose of IMP for assessment of safety at a follow-up visit.
3. For WOCBP treated with alitretinoin, only.
4. Participants who permanently discontinue the IMP prior to Week 12 will be asked to return to the trial site at Week 12 for a primary endpoint visit and at Week 24 for a nominal Week 24 visit. Participants who permanently discontinue the IMP between Week 12 and Week 24 will be asked to return to the trial site for a nominal Week 24 visit.
5. Unscheduled visits occur if participants need to make a visit in between the scheduled visit dates, e.g. for reading of a patch test, due to an AE, or due to a significant change in their disease state. Assessments to be performed at unscheduled visits will be at the discretion of the unblinded investigator.
6. For participants treated with medications requiring a 28-day washout period prior to baseline (see Table 6-2), the duration of the screening period may be extended up to 31 days to ensure appropriate washout. For WOCBP the duration of the screening period may be extended up to 42 days to ensure compliance with contraceptive and pregnancy prevention programme requirements.
7. For participants who have not had a patch test within 3 years prior to screening, the patch test should be completed so results are available prior to baseline assessments (Day 1).

8. Completion of the HESD component of the eDiary will be initiated at least 1 week prior to baseline (Day 1), but preferably from the date the participants receive the eDiary. Compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. Participants who permanently discontinue the IMP but remain in the trial will continue completing the eDiary until the nominal Week 24 visit.
9. Not applicable at the ET visit if the participant does not withdraw from the trial, as participants who discontinue IMP but remain in the trial will continue completing the eDiary until the nominal Week 24 visit.
10. Includes Itch PGI-S, Pain PGI-S, and HESD PGI-S.
11. Includes Itch PGI-C, Pain PGI-C, and HESD PGI-C.
12. While on treatment with delgocitinib cream 20 mg/g, local tolerability will be evaluated weekly by the participants in the eDiary from Day 7 onwards up to End of Treatment/Early Termination visit.
13. Participants should be fasting for at least 8 hours prior to collection of laboratory samples.
14. For WOCBP treated with delgocitinib, only.
15. After baseline, mental health interview is required only for the alitretinoin group.
16. Photography will require additional informed consent. If deemed necessary (e.g. in case of poor quality), photographs can be retaken at the next visit.
17. An end-of-trial form must be completed for all screened participants at the participant's last trial visit. For participants who discontinue IMP prematurely, the end-of-trial form will be completed at the nominal Week 24 visit, if this visit occurs after Visit 11 or Visit 12 (if applicable). For WOCBP treated with alitretinoin, the end-of-trial form must be completed at Visit 12 (pregnancy follow-up). For all other participants, the end-of-trial form must be completed at Visit 11 (follow-up).

Abbreviations: AE=adverse event; CHE=chronic hand eczema; DLQI=Dermatology Life Quality Index: ECG=electrocardiogram; eDiary=electronic diary; EQ-5D-5L=EuroQoL 5-Dimension Health Questionnaire 5-Level; EOT= end-of-treatment; ET=early termination; HECSI=Hand Eczema Severity Index; HEIS=Hand Eczema Impact Scale©; HESD=Hand Eczema Symptom Diary©; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IgE=immunoglobulin E; IMP=investigational medicinal product; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; TSQM=Treatment Satisfaction Questionnaire for Medicine; WOCBP=woman of childbearing potential; WPAI-CHE=Work Productivity and Activity Impairment – Chronic Hand Eczema.

2 Introduction

Delgocitinib is a pan-Janus kinase (JAK) inhibitor that is being developed as a cream for the treatment of inflammatory skin disorders, such as CHE.

2.1 Trial Rationale

There is a clear unmet need for new long-term treatment options for patients suffering from moderate to severe CHE. Alitretinoin is the only approved product specifically indicated for treatment of CHE, but it is only indicated for severe CHE and only approved in few countries worldwide.

Delgocitinib cream has the potential to become an effective, well-tolerated, and user-friendly treatment for CHE and thereby improve the everyday lives of affected patients.

The purpose of this 24-week trial is to compare efficacy, health-related quality of life, and safety of delgocitinib cream and alitretinoin capsules in participants diagnosed with severe CHE.

2.2 Background

2.2.1 Chronic Hand Eczema

CHE refers to hand eczema that persists for more than 3 months or returns twice or more often within 12 months (Diepgen et al, 2015).

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

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

Treatment of CHE involves different disease management strategies such as elimination of triggers, general skin care, and anti-inflammatory therapy in a step-wise approach. General skin care in terms of emollients is widely used and recommended by physicians, but evidence of efficacy is sparse (Diepgen et al, 2015). Elimination of triggers such as allergens and irritants can be effective and a necessary prerequisite for successful therapy on a longer term, but elimination may in many circumstances be difficult to achieve. Although lacking documented treatment

effect, TCS remain the mainstay of anti-inflammatory therapy for hand eczema. However, long-term use of TCS is restricted due to side effects such as skin atrophy and potential inhibition of skin barrier repair.

Whereas mild CHE to some extent may be managed by elimination of triggers and general skin care, management of moderate to severe CHE is more cumbersome. Alitretinoin is the only approved product specifically indicated for treatment of CHE, but it is only indicated for severe CHE and only approved in few countries worldwide. Significant safety precautions apply to alitretinoin. Alitretinoin is highly teratogenic and is strictly contraindicated in pregnant women and in women of childbearing potential unless all of the conditions of a Pregnancy Prevention Programme are met. Furthermore, alitretinoin is contraindicated in nursing mothers. Alitretinoin is also contraindicated in patients with hepatic insufficiency, severe or end-stage renal insufficiency, uncontrolled hypercholesterolemia, uncontrolled hypertriglyceridemia, uncontrolled hypothyroidism, and hypervitaminosis A. In addition, alitretinoin contains soya oil and sorbitol, and therefore patients who are allergic to peanut, soya, or with rare hereditary fructose intolerance should not use this product.

Considering the paucity of approved therapies for the treatment of CHE, other therapeutic options are limited to those approved for other skin diseases with an inflammatory pathophysiology. These applied treatments lack the clinical documentation for use in CHE and are restricted to short-term use, which is not suitable in a chronic disorder characterised by relapsing features often resulting in long-term treatment exposure.

As the currently available treatment options either lack documented treatment effect or are limited by restrictions of long-term use due to safety concerns (Diepgen et al, 2015; Christoffers et al, 2019), there is a high unmet medical need for new topical treatments of moderate to severe CHE with high efficacy in combination with a good safety profile especially for long-term use. New and better treatments would potentially improve the everyday lives of patients with moderate to severe CHE.

2.2.2 Delgocitinib Cream

Delgocitinib (LEO 124249) is a pan JAK inhibitor, which blocks various cytokine mediated signalling pathways and widely suppresses the activation of immune and inflammatory cells such as T cells, B cells, mast cells, and monocytes activated by these cytokines (Delgocitinib cream IB, 2022).

In nonclinical studies, topically administered delgocitinib inhibited inflammation in rat and mouse models of contact dermatitis and reduced IL-31-induced scratching in mice. Topical

administration of delgocitinib was also shown to improve the impaired skin barrier function in mouse models and in human skin (Amano et al, 2015).

The efficacy and safety of delgocitinib in CHE has been demonstrated in a phase 2a trial (LP0133-1180) with delgocitinib ointment 30 mg/g and in a phase 2b dose ranging trial (LP0133-1273) with delgocitinib cream (1, 3, 8, and 20 mg/g). In both trials, delgocitinib was well-tolerated, and a low systemic exposure to delgocitinib was observed. Two ongoing pivotal vehicle-controlled phase 3 trials (trial LP0133-1401 and trial LP0133-1402) are confirming the efficacy and evaluating the safety of delgocitinib cream 20 mg/g twice-daily for 16 weeks in patients with moderate to severe CHE (followed by 36-week safety evaluation in a long-term extension trial, trial LP0133-1403).

A detailed description of the chemistry, pharmacology, efficacy, and safety of delgocitinib is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of delgocitinib and alitretinoin may be found in the IB of delgocitinib cream and the local product information of alitretinoin.

2.3.1 Risk Assessment

Delgocitinib cream is a topically applied JAK inhibitor. Oral JAK inhibitors are associated with potential safety concerns of serious infections, all-cause mortalities, major adverse cardiovascular events, malignancies, thrombosis, lipid elevations and low blood cell counts. These risks are not considered relevant for delgocitinib cream due to the low systemic exposure observed in previous trials with topically applied delgocitinib in CHE patients.

No specific adverse drug reactions or important identified risks have been identified for delgocitinib cream during the nonclinical and clinical development to date. Nevertheless, as observed with other topical therapies, local skin reactions, such as pain (burning and stinging), sensitisation to IMP, allergic and irritant contact dermatitis, local immunosuppression, and skin infections, may occur. A detailed overview of nonclinical and clinical data on delgocitinib is available in the IB.

Table 2-1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Delgocitinib		
Lymphocytopenia	Lymphocytopenia was observed in oral nonclinical toxicity studies and is considered a potential clinical consequence of systemic levels of delgocitinib. Lymphocytopenia is therefore considered an important potential risk for delgocitinib cream (see IB Section 5.4 and Section 7.2.2).	Haematology parameters including WBC count (with differential count) will be monitored during the trial (see Section 8.2.4).
Local skin infection and acneiform eruptions	Potential risks that could arise from use of delgocitinib cream are local skin infection and acneiform eruptions, which have been reported in clinical trials, studying a different formulation (delgocitinib ointment) in atopic dermatitis (see IB Section 7.2.3).	Patients with clinically significant infections on the hands (exclusion criterion 5), a serious skin infection requiring parenteral antibiotics (exclusion criterion 7.b) will be excluded from the trial. During the trial, eczema herpeticum will be monitored as an AESI (see Section 8.3.6). Physical examination including whole body inspection of the skin will be performed at screening and the end of treatment and during any trial visit or unscheduled visits if necessary.
Use during pregnancy or lactation	No data are available about the use of delgocitinib cream in pregnant or breastfeeding women. In oral animal studies, delgocitinib was not teratogenic, but increased post-implantation loss was observed (see IB Section 5.6 and 7.4.6).	Women must agree to use highly effective contraception during the trial (inclusion criterion 6). Pregnant or breastfeeding women are excluded from the trial (exclusion criterion 30). Pregnancy tests will be performed for WOCBP prior to the first dose (screening and Day 1), every 4 weeks during the treatment period, and 2 weeks after the last dose of delgocitinib. Female participants will be instructed to discontinue the IMP immediately in case of pregnancy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Alitretinoin		
Teratogenicity	Alitretinoin is a powerful human teratogen inducing a high frequency of severe and life-threatening birth defects. It is strictly contraindicated in pregnant women and women of childbearing potential (unless specific pregnancy prevention program is followed). Refer to alitretinoin product information.	Women will be informed of the teratogenicity of alitretinoin and must agree to use highly effective contraception 1 month before treatment, throughout treatment period, including participants with amenorrhea. Contraception must additionally be used for 1 month after the end of treatment with alitretinoin (inclusion criterion 6). If local guidelines for contraception have stricter requirements, then local guidelines should be followed. Pregnant or breastfeeding women are excluded from the trial (exclusion criterion 30). Pregnancy tests will be performed prior to the first dose (screening and Day 1), every 4 weeks during the treatment period, and 5 weeks after the last dose of alitretinoin. Female participants will be instructed to discontinue the IMP immediately in case of pregnancy. Participants must not donate blood during and for 1 month after treatment with alitretinoin, as there is a potential risk to the foetus in pregnant women receiving such a blood transfusion. This will not be monitored in this trial, however, it will be stated in the ICF to ensure participant's consent to these instructions.
Phototoxicity	Refer to alitretinoin product information.	Participants will be instructed to avoid excessive exposure to sunlight or sunlamps and to use sun protection (see Section 5.3.1). The use of tanning bed and phototherapy is forbidden at least 28 days before the first dose and until the end of the trial (see Section 6.8.3).
Psychiatric disorders	Refer to alitretinoin product information.	Patients with psychiatric disorders within the last year or current self-reported depression or mood disturbance will be excluded from the trial (exclusion criterion 11). Mental health will be monitored during the treatment period (see Section 8.2.6) and a specific discontinuation criterion is defined in case of mental health issues (see Section 7.1).
Lipid metabolism	Refer to alitretinoin product information.	Participants with uncontrolled hypercholesterolemia and hypertriglyceridemia will not be enrolled in the trial. (exclusion criteria 6.c and 6.d) Fasting triglycerides and cholesterol parameters will be monitored every 4 weeks during treatment and 2 weeks after the last dose (see Section 8.2.4) and participants with increased lipids that cannot be controlled at an acceptable level are required to discontinue alitretinoin (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Male fertility	Based on non-clinical findings, the male fertility may be compromised by treatment with alitretinoin. No effects on male or female reproductive parameters were observed at the highest dose tested which reached similar plasma concentrations as those observed in humans. As with other retinoids, reversible effects on male reproductive organs were observed in experimental animals in the form of disturbed spermatogenesis and associated degenerative lesions of the testes. The safety margin in dogs with regard to the no-effect level of toxicity to male reproductive organs was 1-6 for a human dose of 30 mg	If a male is planning to reproduce during the treatment, he should be made aware that his fertility could potentially be reversibly compromised during the treatment period. The information should be given prior to enrolment and stated in the ICF.
Ability to drive and use machinery	Impaired night vision has been observed during treatment with alitretinoin and other retinoids.	Participants will be informed of this potential problem and urged to exercise appropriate caution when driving or operating machinery in the dark. These effects usually resolve after discontinuation of treatment.
Other risks related to alitretinoin	Refer to alitretinoin product information.	Participants with any contraindications to alitretinoin will be excluded from the trial (exclusion criterion 6) and participants with any symptoms requiring treatment discontinuation per local product information are required to discontinue alitretinoin (see Section 7.1). The most important risks will be stated in the ICF. For information on other side effects the participants should be informed according to the alitretinoin product information.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
COVID-19	Participation in clinical trials may currently be associated with increased risk and added challenges due to the COVID-19 pandemic caused by SARS-CoV-2. The proposed trial is not believed to put participants with CHE at an increased risk for viral infections including SARS-CoV-2. However, a risk of exposure to infected people cannot be excluded as the trial participants may enter public areas (e.g. commute to the trial site) and have additional human contact (e.g. with trial site staff). It is unknown whether treatment with delgocitinib cream 20 mg/g may predispose to COVID-19. Alitretinoin is not considered to increase the risk of COVID-19 infection.	Appropriate risk assessments and mitigation measures must be considered to protect the participants and trial site staff and to ensure the integrity of the trial data. If on-site visits are not possible, the affected site will postpone screening and randomisation of new participants until on-site visits can be conducted. For already randomised participants, post-baseline visits can be done remotely via phone or video (see Section 10.5 for details). During the trial, safety monitoring will ensure that all AEs are continuously monitored.
	The risk of the concomitant use of COVID-19 vaccine and delgocitinib was assessed and it is considered that, for topical delgocitinib, COVID-19 vaccination does not require pausing or discontinuing delgocitinib administration. Alitretinoin product information does not include any instruction or recommendation in relation to vaccination in general. Assessment of the benefit-risk of the concomitant use of COVID-19 vaccine and alitretinoin was performed and it was considered that, for oral alitretinoin, COVID-19 vaccination does not require pausing or discontinuing alitretinoin administration.	COVID-19 vaccines are allowed during the trial and should be recorded as a concomitant medication.

AESI=adverse event of special interest; COVID-19=coronavirus disease 2019; IB=Investigator's Brochure; ICF=informed consent form; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WBC=white blood cell; WOCBP=woman of childbearing potential.

2.3.2 Benefit Assessment

Participants randomised in the trial will receive either delgocitinib cream or alitretinoin capsules for the treatment of their severe CHE:

- The efficacy of delgocitinib in CHE was demonstrated in a phase 2a trial (LP0133-1180) with delgocitinib ointment 30 mg/g and in a phase 2b dose ranging trial (LP0133-1273) with delgocitinib cream (1, 3, 8, and 20 mg/g). In both trials, delgocitinib was well tolerated, and a low systemic exposure to delgocitinib was observed.
- Alitretinoin capsules are the only approved treatment for severe CHE.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimise risk for the trial participants, the potential risks identified in association with delgocitinib and alitretinoin are justified by the anticipated benefits that may be afforded to participants with severe CHE, and more generally the potential benefits to patients with moderate to severe CHE in the future.

3 Objectives and Endpoints

Table 3-1 Primary Objective and Estimands for Primary Endpoint and Key Secondary Endpoints

Objectives	Estimand type and strategy	Endpoints
Primary objective: To compare the efficacy and health-related quality of life of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	**Primary**. 'Composite' strategy. **First supplementary**. 'Pandemic modified composite' strategy. **Second supplementary** (for endpoints at Week 12 and Week 24). 'Treatment policy' strategy.	**Primary endpoint**: • Change in HECSI score from baseline to Week 12. **Key secondary endpoints**: • HECSI-90 at Week 12. • IGA-CHE TS at Week 12. • Change in HESD itch score (weekly average) from baseline to Week 12. • Change in HESD pain score (weekly average) from baseline to Week 12. • AUC of HECSI-90 from baseline up to Week 24. • AUC of change from baseline in DLQI score up to Week 24. • Change in HECSI score from baseline to Week 24.

Abbreviations: AUC=area under the curve; CHE=chronic hand eczema; DLQI=Dermatology Life Quality Index; HECSI=Hand Eczema Severity Index; HECSI-90=at least 90% improvement in HECSI score from baseline; HESD=Hand Eczema Symptom Diary©; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS=IGA-CHE treatment success.

Table 3-2 Secondary and Exploratory Objectives and Endpoints

Objectives	Endpoints
Secondary objective: To compare the safety of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	**Secondary endpoints**: • Number of treatment-emergent AEs from baseline up to Week 26. • Number of treatment-emergent SAEs from baseline up to Week 26. • Number of AEs leading to IMP discontinuation up to Week 24.
Exploratory objectives: To compare the efficacy and health-related quality of life of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	**Exploratory endpoints**: **Efficacy**: • IGA-CHE TS at Week 24. • HECSI-75 at Week 12 and Week 24. • HECSI-90 at Week 24. • Change in HESD itch score (weekly average) from baseline to Week 24. • Reduction of HESD itch score (weekly average) of ≥3 points [1] at Week 12 and Week 24 • AUC from baseline to Week 24 of reduction of HESD

Objectives	Endpoints
	itch score (weekly average) of ≥3 points [1]. • Reduction of HESD itch score (weekly average) of ≥4 points [2] at Week 12 and Week 24 • AUC from baseline to Week 24 of reduction of HESD itch score (weekly average) of ≥4 points [2]. • Change in HESD pain score (weekly average) from baseline to Week 24. • Reduction of HESD pain score (weekly average) of ≥3 points [3] at Week 12 and Week 24. • AUC from baseline to Week 24 of reduction of HESD pain score (weekly average) of ≥3 points [3]. • Reduction of HESD pain score (weekly average) of ≥4 points [4] at Week 12 and Week 24. • AUC from baseline to Week 24 of reduction of HESD pain score (weekly average) of ≥4 points [4]. • Change in HESD score (weekly average) from baseline to Week 12 and Week 24. • Reduction of HESD score (weekly average) of ≥3 points [5] at Week 12 and Week 24. • Reduction of HESD score (weekly average) of ≥4 points [6] at Week 12 and Week 24. **Health-related quality of life**: • Change in DLQI score from baseline to Week 12 and Week 24. • Reduction of DLQI score of ≥4 points [7] at Week 12 and Week 24. • DLQI score of 0 or 1 at Week 12 and Week 24. • Change in HEIS (individual domains and total score) from baseline to Week 12 and Week 24. • Change in EQ-5D-5L index score from baseline to Week 12 and Week 24. • Change in EQ-5D-5L visual analogue scale score from baseline to Week 12 and Week 24.
To evaluate the effect of twice-daily topical application of delgocitinib cream on treatment satisfaction and work productivity compared with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	• TSQM at Week 12 and at Week 24. • Change in WPAI-CHE (each individual domain) score from baseline to Week 12 and Week 24 [8].
To compare the safety of twice-daily topical application of delgocitinib cream with once-daily oral administration of alitretinoin capsules in the treatment of patients with severe CHE.	• Number of events of increased levels of triglycerides >3.42 mmol/L (fasted state) up to Week 26. • Number of AEs of hypertriglyceridaemia up to Week 26. • Number of events of increased levels of cholesterol >7.75 mmol/L (fasted state) up to Week 26. • Number of AEs of hypercholesterolaemia up to Week 26. • Number of AEs of headache up to Week 26.

Objectives	Endpoints
	• Number of AEs of liver toxicity up to Week 26. • Number of events of increased levels of ALT and/or AST >3×ULN (or >3×baseline if baseline was abnormal but <2×ULN) up to Week 26. • Number of events of increased levels of ALP >2.5×ULN up to Week 26. • Number of events of increased levels of bilirubin >1.5×ULN up to Week 26.

1. Among participants with a baseline HESD itch score (weekly average) ≥3 points.
2. Among participants with a baseline HESD itch score (weekly average) ≥4 points.
3. Among participants with a baseline HESD pain score (weekly average) ≥3 points.
4. Among participants with a baseline HESD pain score (weekly average) ≥4 points.
5. Among participants with a baseline HESD score (weekly average) ≥3 points.
6. Among participants with a baseline HESD score (weekly average) ≥4 points.
7. Among participants with a baseline DLQI score ≥4 points.
8. Among participants with paid work at baseline.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the curve; CHE=chronic hand eczema; DLQI=Dermatology Life Quality Index; EQ-5D-5L=EuroQol 5-Dimension Health Questionnaire 5 Level; HECSI=Hand Eczema Severity Index; HECSI-75=at least 75% improvement in HECSI score from baseline; HECSI-90=at least 90% improvement in HECSI score from baseline; HEIS=Hand Eczema Impact Scale©; HESD=Hand Eczema Symptom Diary©; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS=IGA-CHE treatment success; SAE=serious adverse event; TSQM=Treatment Satisfaction Questionnaire for Medicine; ULN=upper limit of normal; WPAI-CHE=Work Productivity and Activity Impairment – Chronic Hand Eczema.

4 Trial Design

4.1 Overall Design

This phase 3, randomised, assessor-blinded, active-controlled, parallel-group, multi-site, 24-week trial will compare the efficacy, health-related quality of life, and safety of delgocitinib cream 20 mg/g twice-daily with alitretinoin capsules 30 mg (with an option to reduce to 10 mg during trial conduct) once-daily in adult patients with severe CHE.

The trial will be conducted in approximately 80 sites in European countries and Canada.

For each participant, the trial will last at least 25 weeks and up to 33 weeks, including:

- a screening period of 1 to 4 weeks (at least 1 visit)
- a treatment period of 24 weeks (9 visits)
- a safety follow-up period of 2 to 5 weeks (1 visit for all participants 2 weeks after the last IMP dose, plus a pregnancy follow-up visit for WOCBP treated with alitretinoin 5 weeks after the last IMP dose)

Screening: During the screening visit, after checking eligibility criteria, participants will be dispensed with an eDiary and provided training and instructions to complete the eDiary at home. Participants will be asked to start completing the Hand Eczema Symptom Diary© (HESD©, hereafter referred to as HESD) component of eDiary at least 1 week prior to baseline (Day 1), but preferably from the date the participants receive the eDiary.

Treatment period: On Day 1, eligible participants will be randomised in a 1:1 ratio to receive 1 of the following treatments:

- Topical administration of delgocitinib cream 20 mg/g, twice-daily until Week 16, which may continue up to Week 24 depending on clearance status (i.e. IGA-CHE score) and clinical benefit.
- Oral administration of alitretinoin capsules 30 mg (with an option to reduce to 10 mg during trial conduct), once-daily until Week 12, which may continue up to Week 24 depending on clearance status (i.e. IGA-CHE score) and clinical benefit.

Randomisation will be stratified by subtype (hyperkeratotic/non-hyperkeratotic) and region (North America/Europe).

Efficacy (HECSI and IGA-CHE) will be evaluated by an assessor blinded to treatment assignment (hereinafter referred to as 'blinded assessor'). Based on the efficacy assessments, the blinded assessor will make recommendations for the following:

- Treatment discontinuation to initiate rescue medication due to lack of efficacy (Sections 6.8.2 and 7.1).
- To continue, stop or restart treatment from Week 12 and onwards for alitretinoin (Section 6.5.1).

Safety assessments, adverse events, and treatment decisions will be made by the unblinded investigator to allow for:

- Dose reductions for participants treated with alitretinoin (Section 6.5).
- Permanent IMP discontinuation (Section 7.1).
- Decisions to continue, stop or restart the IMP from Week 16 for delgocitinib or Week 12 for alitretinoin (Section 6.5.1).

Participants will stop the IMP if they achieve an IGA-CHE score of 0 (clear) or 1 (almost clear) after 16 weeks of delgocitinib treatment or 12 weeks of alitretinoin treatment. Participants who discontinued delgocitinib treatment due to IGA-CHE score of 0 or 1 must restart treatment if they relapse to an IGA-CHE score of ≥2. These participants will continue attending the treatment period visits as planned until Week 24.

Participants who permanently discontinue the IMP will attend an ET visit, they will stop attending the treatment period visits and will only be asked to return to the trial site at Week 12 for a primary endpoint visit and at Week 24 for a nominal Week 24 visit.

Follow-up period: Approximately 2 weeks after the last dose of IMP, participants will attend a follow-up visit for safety assessments. Women of childbearing potential treated with alitretinoin will attend an additional follow-up visit for a pregnancy test, 5 weeks after the last dose of alitretinoin.

Refer to Section 10.5 for coronavirus disease 2019 (COVID-19) pandemic contingency plan.

4.2 Scientific Rationale for Trial Design

This is a randomised, assessor-blinded, active-controlled, parallel-group, multi-site trial, which will be conducted in accordance with the protocol, International Council for Harmonisation of

Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

Patients with hand eczema represent a heterogeneous population as hand eczema is associated with different aetiologies and morphologies. To mitigate any potential difference in trial outcome based on baseline characteristics, the trial participants will be randomised in a stratified manner. The randomisation will minimise selection bias and minimise influence of confounding factors, and the stratification will ensure a balance of the treatment groups with respect to subtype (hyperkeratotic/non-hyperkeratotic) and region.

The trial will include a maximum of 20% of participants with hyperkeratotic subtype. Based on data from the phase 2b trial and the CARPE registry (Apfelbacher et al, 2014), the proportion of patients with hyperkeratotic subtype in the CHE background population is 20%, when calculated based on the aetiology of irritant and atopic CHE prevailing over the hyperkeratotic diagnosis. As there was a clear overrepresentation of participants with hyperkeratotic subtype in previous trials with alitretinoin (Ruzicka et al, 2008; Ruzicka et al, 2004), the rationale for limiting the proportion of participants with a hyperkeratotic subtype in this trial is to ensure a representative proportion of participants with this particular subtype.

As no topical treatment is approved for moderate to severe CHE, delgocitinib cream will be compared with alitretinoin capsules. Due to the different administration routes for delgocitinib and the active comparator (alitretinoin), participants and investigators will not be blinded to treatment assignment. However, the evaluation of efficacy (IGA-CHE and HECSI) will be performed by a blinded assessor (see Section 6.3). Certain CRO and sponsor staff will also be blinded to ensure the integrity of the trial.

Participants randomised to the alitretinoin arm will not receive delgocitinib vehicle cream because the vehicle cream may influence both the physician's clinical evaluation and patient-reported outcomes (PROs). Both arms are allowed to use their normal and preferred emollient throughout the trial in line with standard care of CHE.

Two ongoing pivotal vehicle-controlled phase 3 trials (trial LP0133-1401 and trial LP0133-1402) are confirming the efficacy and evaluating the safety of delgocitinib cream 20 mg/g twice-daily for 16 weeks in patients with moderate to severe CHE (plus 36-week safety evaluation in a long-term extension trial, trial LP0133-1403). The current trial enrols patients with severe CHE only, because alitretinoin is only approved for the treatment of severe CHE.

In the 2 vehicle-controlled trials, the primary endpoint is assessed at Week 16. However, the recommended continuous treatment with alitretinoin is 12 weeks with a label recommendation to

discontinue treatment in patients who have achieved an IGA-CHE score of 0 (clear) or 1 (almost clear) after 12 weeks and earlier than 24 weeks, and with an option to restart treatment in case of worsening. To ensure comparable evaluation in the 2 arms, the primary endpoint in this trial will be assessed at Week 12. After Week 12, alitretinoin will be used as per label with a recommendation to discontinue treatment if participants achieve an IGA-CHE score of 0 (clear) or 1 (almost clear) at the investigator's discretion. Delgocitinib treatment will be continuous until Week 16 as in the pivotal phase 3 trials and based on data from the phase 2b dose ranging trial LP0133-1273. After Week 16, it will be recommended to discontinue treatment with delgocitinib if the participants achieve an IGA-CHE score of 0 (clear) or 1 (almost clear), at the investigator's discretion, with an option to restart treatment in case of worsening.

Participants who stop treatment with delgocitinib or alitretinoin because they achieve an IGA-CHE score of 0 or 1 will continue to attend the treatment period visits as planned. The protocol requires that participants who relapse (defined as an IGA-CHE score of ≥2) after stopping treatment must restart treatment, as this is expected to mimic clinical practice.

The trial endpoints were selected to compare the efficacy of delgocitinib and alitretinoin in improving the extent and severity of CHE. Both the HECSI and the IGA-CHE will be used in this clinical trial as investigator-rated assessments of disease severity. The HECSI is an instrument used to score both the extent and the severity of the disease. The IGA-CHE is an assessment of the participant's global CHE severity at a given timepoint and is based on a 5-point scale ranging the severity of the disease from 0 (clear) to 4 (severe). The primary endpoint of the trial is change in HECSI score from baseline to Week 12.

The trial endpoints will also address the impact on health-related quality of life, work productivity, and treatment satisfaction.

AEs selected as exploratory endpoints (headache, hypertriglyceridaemia, hypercholesterolaemia, and liver toxicity) are based on the current knowledge of the safety profile of alitretinoin.

4.3 Justification for Dose

The strength of delgocitinib cream is selected based on results from the dose-ranging phase 2b trial LP0133-1273, where delgocitinib cream 20 mg/g was shown to be effective and well-tolerated in adults with mild to severe CHE.

4.4 End of Trial Definition

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

A participant is considered to have completed the trial if he/she has completed all periods of the trial including the last follow-up visit.

5 Trial Population

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

The trial population will consist of adult participants with severe CHE and with a documented inadequate response to treatment with TCS or for whom TCS are documented to be otherwise medically inadvisable. The trial will include a maximum of 20% of participants with hyperkeratotic subtype.

Participants must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:

Age

1. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of CHE defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months.
3. Disease severity graded as severe at screening and baseline according to IGA-CHE (i.e. an IGA-CHE score of 4).
4. Documented recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom TCS are documented to be otherwise medically inadvisable (e.g. due to important side effects or safety risks).

a. Inadequate response is defined as a history of failure to achieve and maintain a low disease activity state (comparable to an IGA-CHE score ≤2) despite treatment with a daily regimen of TCS of III-IV (potent to very potent) for the European Union (EU) and IV-I (medium potency to very/ultra-high potency) for Canada, applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter.

b. Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, and significant skin atrophy as assessed by the physician.

5. Participant is adherent to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.

Contraceptive/Barrier Requirements

6. Contraceptive use must be consistent with local regulations (if they are stricter than the protocol requirements) regarding the methods of contraception for those participating in clinical studies.

For female participants:

- A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and 1 of the following conditions applies:
  - Not a WOCBP as defined in Appendix 4.

    OR

  - Women of childbearing potential must use at least one highly reliable method of contraception (i.e., a user-independent method) or two complementary user-dependent methods of contraception (see Appendix 4). Contraception must be used 1 month before treatment and throughout treatment period, including participants with amenorrhea. Contraception must additionally be used for 1 month after the end of treatment with alitretinoin. If local guidelines for contraception have stricter requirements, then local guidelines should be followed.

Informed Consent

7. Participant is capable of giving signed informed consent as described in Appendix 1, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

Diagnostic Assessments

1. Concurrent skin diseases on the hands (e.g. tinea manuum).
2. Active atopic dermatitis requiring medical treatment in regions other than the hands and feet.
3. Active psoriasis on any part of the body.
4. Hyperkeratotic hand eczema in combination with a history of psoriasis on any part of the body.
5. Clinically significant infection (e.g. impetiginised hand eczema) on the hands.

Medical Conditions

6. Participants who cannot receive alitretinoin for any of the following reasons:
    a. Hepatic impairment, defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >2×ULN, and/or prothrombin international normalised ratio (INR) >1.5×ULN.
    b. Renal insufficiency, defined as creatinine clearance <60 mL/min calculated by use of the Cockcroft-Gault formula.
    c. Uncontrolled hypercholesterolemia, defined as fasting cholesterol >1.5×ULN and/or fasting low-density lipoprotein (LDL) cholesterol >1.5×ULN.
    d. Uncontrolled hypertriglyceridemia, defined as fasting triglyceridaemia 1.5×ULN.
    e. Uncontrolled hypothyroidism, defined as thyroid-stimulating hormone >1×ULN and/or thyroxine <1×lower limits of normal.
    f. Hypervitaminosis A, defined as retinol levels >1×ULN (e.g. due to the use of vitamin A supplements containing >2000 IU).
    g. Known or suspected hypersensitivity either to alitretinoin, to other retinoids or to any of the excipients listed in the applicable alitretinoin label, in particular allergies to peanut or soya, or intolerance to sorbitol or fructose.
    h. Any other contraindication to receive alitretinoin according to the investigator's judgement.

7. Clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator, may compromise the safety of the participant in the trial, interfere with the evaluation of the IMP, or reduce the participant's ability to participate in the trial. Clinically significant infections are defined as:
    a. A systemic infection.
    b. A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
8. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the participant taking antiretroviral medications as determined by medical history and/or participant's verbal report.
9. Major surgery within 8 weeks prior to baseline, or planned in-patient surgery or hospitalisation during the trial period.
10. History of cancer except the following:
    a. Participants 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 participant is in remission and curative therapy was completed at least 12 months prior to screening.
    b. Participants who have had other malignancies are eligible provided that the participant is in remission and curative therapy was completed at least 5 years prior to screening.
11. Psychiatric disorders within the last year (e.g. depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, suicidal ideation, suicide attempts) or current self-reported depression or mood disturbance.
12. Any disorder that is not stable and could:
    a. Affect the safety of the participant throughout the trial.
    b. Impede the participant's ability to complete the trial.

    Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, and immunological disorders, and major physical impairment.
13. Any abnormal finding that may:
    a. Put the participant at risk because of their participation in the trial.
    b. Influence the participant'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, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis.

14. Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody serology at screening.
15. Current or recent history of chronic alcohol or drug abuse or any condition associated with poor compliance as judged by the investigator.

Prior/Concomitant Therapy

16. Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), immunomodulating drugs, retinoids, potent CYP3A4 inducers (only for WOCBP who take hormonal contraceptives), or corticosteroids within 28 days prior to baseline (steroid eyedrops and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed).
17. Use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands within 28 days prior to baseline.
18. Previous or current treatment with JAK inhibitors (including delgocitinib/LEO 124249), systemic or topical.
19. Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands within 14 days prior to baseline.
20. Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 14 days prior to baseline.
21. Other transdermal and cutaneously applied therapy on the hands (except for the use of participant's own emollients) within 7 days prior to baseline.
22. Cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern, within 7 days prior to baseline.
23. Treatment with any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab), except vaccines:
    a. 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.
    b. Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
24. Treatment with CYP3A4 inhibitors (e.g. ketoconazole), potent CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone), or potent CYP2C8 inhibitors (e.g. gemfibrozil),

CYP2C8 substrates (e.g. amiodarone, paclitaxel, rosiglitazone, repaglinide), simvastatin, or tetracyclines within 7 days prior to screening. Topical treatment with CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone) on areas of the body other than hands is allowed.

25. Treatment with any marketed therapy that may interfere with the trial objective.

Prior/Concurrent Clinical Trial Experience

26. Previously used alitretinoin or participated in a clinical trial with alitretinoin or delgocitinib.
27. Treatment with any non-marketed drug substance (that is, an agent that has not yet been made available for clinical use following registration) within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.
28. Current participation in any other interventional clinical trial.

Other Exclusions

29. Known or suspected hypersensitivity to any component(s) of the IMPs, including allergies to peanut or soya.
30. Women who are pregnant or lactating.
31. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
32. Participants who are legally institutionalised.
33. Previously randomised in this clinical trial.

5.3 Lifestyle Considerations

5.3.1 Skin Care

- Participants should adhere to standard non-medicated skin care including avoidance of known and relevant irritants and allergens.
- Participants should not change their usual skin care routine of the hands regarding use of emollients during the trial. However, emollients should preferably not be used on the affected areas within 2 hours before and after application of delgocitinib. Furthermore, emollients must not be used on the hands and wrists in both treatment groups for at least 2 hours prior to trial visits. Participants are allowed to apply other skin treatments/products to other areas of the body for other skin conditions (including topical miconazole for foot dermatitis) during the trial, as long as this does not interfere with the trial (i.e. participants will need to wear disposable gloves, of a type recommended by the investigator, when applying treatment).
- If possible, normal bathing, washing of hands, and use of hand sanitisers should be avoided within 2 hours following application of delgocitinib.
- Use of cosmetic body care products (e.g. body lotion, shampoo, bath oil), which are routinely used by the participants, is allowed as per instructions for use, but the products should preferably not be changed during the trial and application should be avoided within 2 hours of delgocitinib application or alternatively performed using disposable gloves.
- Excessive exposure to sunlight and sunlamps should be avoided. Sunscreen products on the body and protective gloves on the hands are recommended when exposure cannot be avoided.

5.3.2 Meals and Dietary Restrictions

- Participants should be fasting for at least 8 hours prior to collection of laboratory samples to allow for analysis of fasting values of triglycerides and cholesterol (LDL, HDL, and total cholesterol), at the visits specified in the SoA (Table 1-1).
- Alitretinoin capsules should be taken with a main meal, preferentially at the same time each day.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical trial is not subsequently randomly assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated

Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

As a minimum, the following data will be collected in the eCRF for screening failures:

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

In case of any SAEs, these must be followed up as described in Section 10.3.3.

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened. However, if the reason for screen failure is not due to the participant failing to meet the eligibility criteria but is administrative (e.g. delayed test results or temporary site closure due to the COVID-19 pandemic), re-screening may be permitted. This will require approval by the sponsor. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.4.1 Screening and Enrolment Log and Participant Identification Numbers

The investigator will maintain a log of all patients considered for screening, whether they have provided written informed consent or not (prescreening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated participant identification number. For patients not willing to consent, the main reason will be collected on the prescreening log (e.g. time constraint, due to side effect profile of alitretinoin, other safety concerns, number of blood samples).

Upon enrolment, each participant will receive a unique participant identification number. Participant numbers must not be re-used for different participants.

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

6 Trial Treatments and Concomitant Therapy

Trial treatment is defined as any investigational treatment or marketed product, intended to be administered to a trial participant according to the trial protocol.

6.1 Trial Treatments Administered

Table 6-1 Trial Treatments Administered

Treatment Name	Delgocitinib	Alitretinoin
Type	Drug	Drug
Dosage Formulation	Cream	Soft capsule
Unit Dose Strength(s)	20 mg/g	10[1] or 30 mg per capsule
Dosage Level(s)	1 application twice-daily	1 capsule per day
Route of Administration	Topical (application of a thin layer on affected areas)	Oral
Use	Experimental	Active Comparator
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labelling	Delgocitinib will be provided in a tube containing 30 g of cream. Each tube will be labelled as required per each country.	Alitretinoin will be provided in aluminium blisters, containing 30 capsules. Each blister will be labelled as required per each country.
Current/Former Name(s) or Alias(es)	LEO 124249	Toctino® (commercial name)

Abbreviations: IMP= investigational medicinal product; NIMP=non-investigational medicinal product.

1. 10 mg will only be used in participants with unacceptable adverse reactions after the dose of 30 mg (see Section 6.5).

6.2 Preparation, Handling, Storage, and Accountability

6.2.1 Administration of Trial Treatment

6.2.1.1 Delgocitinib Cream

Delgocitinib cream 20 mg/g will be applied as a twice-daily topical application for up to 24 weeks. The applications will be performed approximately 12 hours apart. Instructions for use will be provided.

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

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

The first application of delgocitinib will occur at the trial site under supervision of the unblinded investigator or delegate. Prior to the first application of delgocitinib cream, the participant will be instructed how much cream to apply and which area(s) to treat.

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

Only the affected area(s) on the hands, fingers, fingertips, and wrists will be treated. If new lesions occur on initially untreated area(s) of the hands, fingers, fingertips, and wrists, these new lesions will be treated with delgocitinib as well. The participants will be advised to contact the unblinded investigator before initiating treatment of new lesions.

Delgocitinib application on initially affected area(s) and new lesions will continue until Week 16 regardless of clearance status. Participants with an IGA-CHE score ≥2 may continue with treatment up until Week 24 if, in the opinion of the unblinded investigator, they may benefit from continued treatment. After Week 16, it is recommended to discontinue delgocitinib if IGA-CHE is 0 (clear) or 1 (almost clear). Participants who discontinued delgocitinib treatment due to IGA-CHE score of 0 or 1 must restart treatment if they relapse to an IGA-CHE score of ≥2. These participants will remain on continuous treatment until Week 24. Treatment with delgocitinib should be discontinued if participants still have an IGA-CHE score of 4 (severe) after the initial 16 weeks of treatment.

Prior to each trial visit, application of delgocitinib cream will occur at the participant's home at least 2 hours prior to the trial visit.

6.2.1.2 Alitretinoin Capsules

Alitretinoin capsules 30 mg will be taken once-daily for up to 24 weeks with an option to reduce to 10 mg during trial conduct (see Section 6.5).

Alitretinoin should be taken with a main meal, preferably at the same time each day. The capsules should be swallowed whole and not chewed. A missed dose should be taken as soon as

possible, unless it is close to the time for the next dose, in which case the missed dose should be skipped. It is not allowed to take a double dose to make up for a forgotten capsule.

The first dose of alitretinoin will be taken at the trial site with a meal, under the supervision of the unblinded investigator or delegate.

Treatment with alitretinoin will continue until Week 12 regardless of clearance status, according to the alitretinoin label, unless safety issues arise. After Week 12, it is up to the unblinded investigator's judgement whether the participant would benefit from continuing the treatment. Participants with an IGA-CHE score ≥2 may continue with treatment up until Week 24 if, in the opinion of the unblinded investigator, they may benefit from continued treatment. After Week 12, it is recommended to discontinue alitretinoin if IGA-CHE is 0 (clear) or 1 (almost clear). Participants who discontinued alitretinoin treatment due to IGA-CHE score of 0 or 1 must restart treatment if they relapse to an IGA-CHE score of ≥2. These participants will remain on continuous treatment until Week 24. It should be considered to discontinue treatment with alitretinoin for participants who still have an IGA-CHE score of 4 (severe) after the initial 12 weeks of treatment.

Local safety requirements for the use of alitretinoin should be followed, and educational material about alitretinoin should be discussed and handed out to the patients at inclusion (a sample of this information should be available in the trial master file [TMF] at each site).

Patients should stop alitretinoin if they develop depression, mood disturbance, psychosis, or aggression. Patients should be monitored until these symptoms resolve. Discontinuation of alitretinoin may be insufficient to alleviate symptoms and therefore further psychiatric evaluation may be necessary.

Alitretinoin capsules are approved in all countries participating in this trial. Alitretinoin is sourced from Almac UK (Toctino®). The UK SmPC for Toctino® has been chosen as the representative drug label for Canada and the UK. For the EU countries, the German SmPC for Toctino® has been chosen as the representative drug label to align with the requirements of EU legislation. The UK and German SmPC are equivalent. The sponsor will monitor the SmPC regulatory and inform agencies immediately should there be any divergence.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all IMPs received, and any discrepancies are reported and resolved before use of the IMP.

Only participants randomised in the trial may receive the IMP, and only authorised site staff may supply or administer the IMP. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (e.g. receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Investigator's Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

Due to the different administration routes for the 2 IMPs, participants are not blinded to treatment assignment. A double-dummy design is not considered feasible since addition of the cream vehicle to alitretinoin-treated participants may increase the clinical effect in the alitretinoin arm. To ensure unbiased clinical assessments, efficacy (IGA-CHE and HECSI) will be evaluated by a blinded assessor. Each site will have at least 1 dermatologist or allergist and 1 physician to allow for both an unblinded investigator and a blinded assessor. The sponsor will ensure appropriate measures are in place to keep information about treatment assignment segregated from the blinded assessor. Such measures will include training of site personnel and participants, as well as separate systems access and source documentation.

In addition, to minimise the risk of potential bias into final analyses, a blinding maintenance plan will be implemented by the sponsor and by the CRO to maintain the integrity of the trial data for the decision making at the final analyses. The details regarding access to blinded or unblinded data by the site, CRO and sponsor staff, as well as blinding procedures, will be outlined in the blinding maintenance plan. The blinding maintenance plan will be finalised prior to the first participant first visit. Although the trial is not double-blinded, the specific treatment to be taken by a participant will be randomly assigned using interactive response technology (IRT). The site will contact the IRT prior to the start of IMP administration for each participant. The site will record the treatment assignment on the applicable eCRF, if required.

Trial treatment will be administered/dispensed at the trial visits as summarised in the SoA (Table 1-1). Returned IMP should not be re-dispensed to the participants.

6.4 Trial Treatment Compliance

Treatment days will be recorded by the participants in the eDiary, the participant will be asked to confirm treatment administration once-daily.

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

At baseline, the date of first dose of IMP will be recorded in the eCRF.

Delgocitinib: The first application of delgocitinib cream will occur at the trial site with clear instructions from the site staff on which areas of the hands, fingers, fingertips, and wrists the cream must be applied and which amount of cream to be used per application. Returned, opened delgocitinib tubes will be weighed at the trial site to determine the amount of delgocitinib cream used. The weight of the returned tubes will be recorded in the individual drug accountability form and in the eCRF (in grams with 1 decimal).

Alitretinoin: Returned alitretinoin capsules will be counted to assess treatment compliance. The number of returned capsules will be recorded in the individual drug accountability form and in the eCRF.

6.5 Dose Modification

Delgocitinib: Dose modifications are not possible with the delgocitinib cream, but the amount of cream applied to the hands may be increased, if new lesions appear, at the discretion of the unblinded investigator (see Section 6.2.1.1).

Alitretinoin: The dose of alitretinoin may be reduced from 30 mg to 10 mg in participants with unacceptable adverse reactions. If the dose is decreased, it will not be permitted to increase the dose at a later point during the trial. Alitretinoin dose reductions and the reason for dose reduction will be reported in the eCRF.

6.5.1 Retreatment Criteria

For participants who achieve an IGA-CHE score of 0 or 1 after 16 weeks of delgocitinib treatment or 12 weeks of alitretinoin treatment, it is recommended to discontinue treatment.

However, these participants must restart treatment if they relapse to an IGA-CHE score of ≥2 and will remain on continuous treatment until Week 24.

6.6 Continued Access to Trial Treatment After the End of the Trial

After the end of the trial, participants will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

6.7 Treatment of Overdose

For this trial, the following will be considered an overdose:

- More than 1 alitretinoin capsule per day.

Alitretinoin: Alitretinoin has been administered in oncological clinical studies at dosages of more than 10-times of the therapeutic dosage given for CHE. The adverse effects observed were consistent with retinoid toxicity, and included severe headache, diarrhoea, facial flushing, hypertriglyceridemia. These effects were reversible.

In the event of an overdose, the investigator should:

- Closely monitor the participant for any AE/SAE or laboratory abnormalities.
- Report any clinically relevant findings.
- Use clinical judgement to treat any symptoms connected with an overdose.

6.8 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the trial must be recorded along with:

- Medication name or therapy.
- Primary indication.
- Whether the medication or therapy is a rescue treatment for CHE (yes, no), see Section 6.8.2.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration (oral, cutaneous, subcutaneous, transdermal, ophthalmic, intramuscular, respiratory [inhalation], intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other [if other, a specification must be provided]). For cutaneous treatments, the dosage form (cream, lotion, ointment, foam, other) will also be recorded.

- For cutaneous treatment, it must also be recorded if the treatment is within 5 cm (approximately 2 inches) of the borders of CHE lesions.

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

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Table 6-2. As described in Section 6.8.2, prohibited medications used as rescue treatment for intolerable CHE symptoms are allowed, but participants using rescue treatment must discontinue IMP immediately and will not be allowed to restart treatment with IMP. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prior and Concomitant Medications Review

The investigator or qualified designee will review prior medication use and record prior medications taken by the participant within 3 months prior to screening.

Previous treatments for CHE (name and type of treatment, rationale for discontinuation of treatment) will be collected. Note that for TCS, previous treatments will only be collected for the last 12 months and the following additional details will be recorded: strength, dose, and date(s) of treatment.

The following information will also be collected in the eCRF for prior CHE treatment history:

- Previous treatments for CHE (name and type of treatment, rationale for discontinuation of treatment). Note that for TCS, previous treatments will only be collected for the last 12 months, and the following additional details will be recorded: strength, dose, and date(s) of treatment.
- To support selection of trial participant specifically on inclusion criterion 4:
    - Has the participant fulfilled the trial inclusion criterion 4.a based on having inadequate response to treatment with TCS during the last 12 months? (yes, no).
    - Has the participant fulfilled the trial inclusion criterion 4.b based on TCS being medically inadvisable for the participant? (yes, no).
        - If yes: reason for TCS use being medically inadvisable.

The investigator or qualified designee will record medication, if any, taken by the participant during the trial through the last visit. Concomitant medications will be recorded for 14 days after the last dose of IMP (or longer if related to an SAE).

6.8.1 Background Treatment

No background treatment is required in this trial. Participants should adhere to standard non-medicated skin care, as described in Section 5.3.

Of note, emollients are not considered concomitant medication and should not be recorded as such.

6.8.2 Rescue Medication

If medically necessary (i.e. to control intolerable CHE symptoms), rescue treatment for CHE may be prescribed to the participant. Following the assessment of efficacy (IGA-CHE and HECSI), the blinded assessor will recommend whether rescue medication should be initiated. The unblinded investigator will select and initiate the rescue medication.

Alitretinoin cannot be used as rescue treatment. The investigator should make every attempt to ensure that efficacy and safety assessments (e.g. disease severity scores, safety laboratory assessments) are conducted immediately before administering any rescue treatment. If rescue treatment is initiated, the participant must stop the IMP immediately and will not be allowed to restart the IMP.

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

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.8.3 Prohibited Medications and Procedures

Medications and procedures listed in Table 6-2 are prohibited during the trial. All prohibited medications must be recorded as concomitant medication.

Table 6-2 Prohibited Medications and Procedures

Medication/procedure	Prohibited from	Prohibited to
Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, azathioprine), retinoids (other than the IMP), or corticosteroids (steroid eye drops [1] and inhaled or intranasal steroids corresponding to up to 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis are allowed).	28 days prior to baseline.	End of trial.
JAK inhibitors, systemic or topical (other than the IMP).	Participant's birth.	End of trial.
Tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands.	28 days prior to baseline.	End of trial.
Cutaneously applied treatment with immunomodulators (e.g. PDE-4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands.	14 days prior to baseline.	End of trial.
Cutaneously applied antibiotics on the hands.	14 days prior to baseline.	End of trial.
Other transdermal and cutaneously applied therapy on the hands (except for the IMP and the participant's own emollient).	7 days prior to baseline.	End of trial.
Cutaneously applied treatments in regions other than the hands that could interfere with clinical trial evaluations or pose a safety concern. [2]	7 days prior to baseline.	End of trial.
Any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, and dupilumab), except vaccines:		
• 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 that has not yet been made available for clinical use following registration).	28 days prior to baseline or 5 half-lives, whichever is longer.	End of trial.
CYP3A4 inhibitors (e.g. ketoconazole), potent CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone), or potent CYP2C8 inhibitors (e.g. gemfibrozil).	7 days prior to baseline	End of trial.
CYP2C8 substrates (e.g. amiodarone, paclitaxel, rosiglitazone, repaglinide).	7 days prior to baseline	End of trial.
Potent CYP3A4 inducers. [3]	28 days prior to baseline	End of trial.
Simvastatin.	7 days prior to baseline	End of trial.

Medication/procedure	Prohibited from	Prohibited to
Systemic tetracyclines.	7 days prior to baseline	End of trial.
Systemic vitamin A.	Baseline.	End of trial.

1. Steroid eyedrops should be recorded with the administration route 'ophthalmic', not 'cutaneous'
2. This allows for the treatment of foot eczema, as long as this does not interfere with the trial (i.e. the participants need to use gloves when applying treatment).
3. Only applies for WOCBP who take hormonal contraceptives.

Abbreviations: CYP=cytochrome P450; IgE=immunoglobulin E; IMP=investigational medicinal product; JAK=Janus kinase; PDE-4=phosphodiesterase-4; PUVA=psoralen ultraviolet A; TCS=topical corticosteroid; UVA1=ultraviolet A1; UVB=ultraviolet B; WOCBP=women of childbearing potential.

7 Discontinuation of Trial Treatment and Participant Discontinuation

Discontinuation of specific sites or of the trial as a whole are handled as part of the appendix on Governance, Appendix 1, Section 10.1.8.

7.1 Discontinuation of Trial Treatment

It may be necessary for a participant to permanently discontinue the IMP. If the IMP is permanently discontinued, the participant will remain in the trial and attend an early termination visit, a follow-up visit 2 weeks after the last administration of IMP, the primary endpoint visit at Week 12 (for participants who discontinue the IMP prior to Week 12), and the nominal Week 24 visit. Female participants on alitretinoin treatment should have a pregnancy test performed 5 weeks after the last IMP administration. See the SoA (Table 1-1) for data to be collected at the time of IMP discontinuation and follow-up and for any further evaluations that need to be completed.

IMP must be discontinued permanently in case of the following:

1. An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
2. Evidence of pregnancy.
3. Intolerable CHE symptoms requiring the initiation of rescue medication (see Section 6.8.2).
4. Symptoms or AEs requiring treatment with prohibited medication or procedure (see Section 6.8.3).
5. Clinically important laboratory abnormalities in liver chemistry (see Appendix 6):
    a. ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
    b. ALT and/or AST values >3×ULN with prothrombin INR >1.5×ULN.
    c. Confirmed ALT and/or AST values >5×ULN (for more than 2 weeks).
6. For alitretinoin only, if participant develops depression, mood disturbance, psychosis, or aggression. Participant should be referred immediately to a mental health care professional for further assessment.
7. For alitretinoin only, if participant develops any symptoms requiring treatment discontinuation per local product information (e.g. signs of benign intracranial hypertension, increased lipids that cannot be controlled at an acceptable level, symptoms of pancreatitis, severe diarrhoea).

Trial treatments should be discontinued permanently in case of the following:

8. An IGA-CHE score of 4 (severe) after receiving 12 weeks of alitretinoin treatment or 16 weeks of delgocitinib treatment.

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

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

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

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

7.2 Participant Discontinuation/Withdrawal from the Trial

A participant may withdraw from the trial at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. The participant will be permanently discontinued from the IMP and the trial at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1-1). Refer to the SoA for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Loss to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the trial site.

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

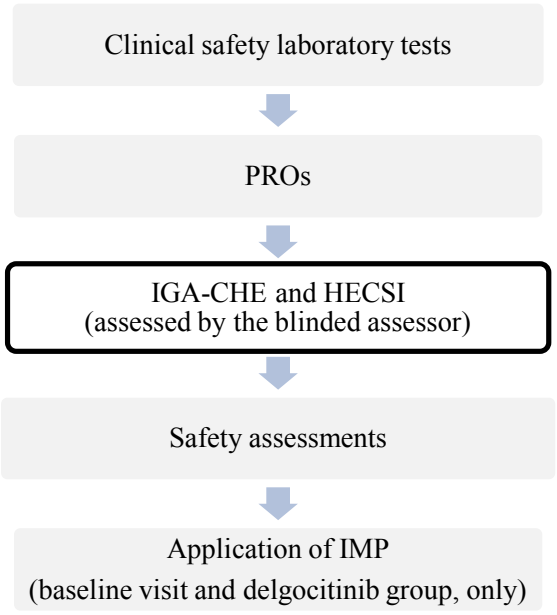
- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the trial.
- In cases in which the participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/CRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the trial.

8 Trial Assessments and Procedures

Trial procedures and their timing are summarised in the SoA (Table 1-1). Protocol waivers or exemptions are not allowed.

Assessments and procedures at each trial visit should be performed in the order shown in Figure 8–1.

Figure 8–1 Sequence of Assessments



Abbreviations: HECSI=Hand Eczema Severity Index; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IMP=investigational medicinal product; PRO=patient-reported outcome.

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

AEs must be assessed by a physician (Section 8.3).

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue the IMP.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each participant over the duration of the trial, including any extra assessments that may be required, will not exceed 180 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of treatment allocation/randomisation, site personnel will add the treatment/randomisation number to the participant identification card.

The participant identification card also contains information about the IMP.

Demographics

The following demographic data will be recorded:

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

Height and Weight

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

Fitzpatrick Skin Type

The participant's skin type will be recorded using the Fitzpatrick skin classification (Table 8-1).

Table 8-1 Fitzpatrick Skin Classification

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

Medical History

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

Relevant medical history also includes diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria (see Section 5.2).

Medical history related to CHE will include the following information:

- Date of diagnosis of CHE.
- Number and duration of flares experienced during the past year.

- Results of relevant previous diagnostic procedures other than diagnostic patch testing (e.g. prick test).
- Presence of atopy.
- Presence of atopy in the participant's family history.

The following exogenous risk factors for CHE will also be reported:

- Environmental trigger factors (yes, no, unknown).
    - If yes: Occupational relevance (yes, no, unknown).
    - If yes: Name of trigger (name or unknown).
    - If yes: Type of trigger (allergen, irritant, unknown).
    - If yes: Has the trigger been avoided (yes, no, not applicable).
    - If yes: Has it been possible to avoid the trigger (yes, no, not applicable).
- Onset and worsening of CHE symptoms during work (yes, no, unknown).
- Improvement of CHE symptoms when not at work (yes, no, unknown).
- Healing of CHE on vacations (yes, no, unknown).
- Recurrence of CHE symptoms upon returning to work (yes, no, unknown).
- Worsening of CHE symptoms when not at work (yes, no, unknown).
- Wet-work exposure (defined as skin exposed to liquids longer than 2 hours per day, using occlusive gloves longer than 2 hours per day, or more than 20 hand washes per day) (yes, no, unknown).
- Number of daily hand washes (0-10, 11-20, >20).
- Employment status during the past year (part-time employed, full-time employed, not employed). In case more than 1 option applies, the status that the participant had for the longest period during the past year should be captured.
    - If employed during the past year: Days home from work due to CHE during the last year (yes, no).
        - If yes: Total number of days home from work due to CHE during the last year (<7 days, 7-21 days, >21 days).
- Tobacco smoking history (Never smoked, previous smoker [non-smoker for more than 1 year], current smoker [smoker for the past year]).

- If current smoker: Type of tobacco (cigarettes, other).
- If current smoker: Average daily number of smoked cigarettes during the past year (1-4, 5-10, 11-20, >20). For tobacco types other than cigarettes, 1 g of tobacco will be considered equal to 1 cigarette.

Classification of CHE

The investigator will determine the CHE subtype(s) according to the definitions in Table 8-2.

Table 8-2 Definition of Subtypes of Hand Eczema

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

Reference: Adapted from Diepgen et al, 2015. Note that the terms eczema and dermatitis are used interchangeably in the referenced publication.

Abbreviations: IgE=immunoglobulin E.

The classification of CHE will be done according to standard clinical practice including mandatory diagnostic patch testing with at least a relevant baseline series including the most important contact allergens relevant to the locality of the site. For participants who have had a diagnostic patch test performed within 3 years prior to screening, the results from the most recent patch test will be used for the classification. For participants who have not had a patch test within 3 years prior to screening, a patch test will be performed. The patch test should be completed so results are available prior to baseline assessments (Day 1).

The diagnostic patch test is done by applying patches containing standardised samples of allergens to the participants' upper back. The patches will stay in place for approximately

48 hours under occlusion, after which they are removed during a visit at the trial site. The participants will return to the trial site for assessment of patch test reactions according to standard clinical practice at the trial site.

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

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1-1).

8.1.1 Hand Eczema Severity Index (HECSI)

The HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling, and oedema) and the extent of the lesions on each of the 5 hand regions (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales (Held et al, 2005).

For each hand region (total of both hands, e.g. 10 fingers), the investigator rates the average severity of each of the 6 clinical signs of hand eczema using a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) (Table 8-3). The investigator also rates the extent of the lesions by assessing the percentage of the hand regions these lesions occupy and converting it to a score based on a 5-point scale (the area score) (Table 8-3). For each of the hand regions, the region score will be calculated by adding up the severity scores for the 6 clinical signs of hand eczema and multiplying with the area score (Table 8-4). The HECSI score equals the sum of the region scores and will range from 0 (lowest possible score) to 360 (highest possible score).

The HECSI will be assessed according to the SoA (Table 1-1). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New CHE lesions will be included in the assessment. The HECSI score will be recorded in the eCRF.

Table 8-3 HECSI Severity Score Scale and Area Score Scale

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

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

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

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

Table 8-4 Calculation of the Total HECSI Score

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

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

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

The IGA-CHE is an instrument used in clinical trials to rate the severity of the participant's global disease and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Table 8-5). The IGA-CHE score will be assessed according to the SoA (Table 1-1). 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 will be included in the assessment. The IGA-CHE score will be recorded in the eCRF.

Table 8-5 Investigator's Global Assessment for Chronic Hand Eczema© (IGA-CHE)

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

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

8.1.3 Patient-reported Outcomes

8.1.3.1 eDiary Assessments

At the screening visit, participants will be dispensed with the eDiary device and will receive training on how to fill out the eDiary. Participants will complete the eDiary daily at home and will return the eDiary device to the trial site, as outlined in the SoA (Table 1-1).

Participants will complete the following assessments in the eDiary as outlined in the SoA (Table 1-1), in the listed order:

- Daily: HESD.
- Daily: treatment compliance (see Section 6.4).
- Weekly: Participant's assessment of local tolerability (see Section 8.2.7).

Hand Eczema Symptom Diary© (HESD)

The HESD is a 6-item PRO instrument designed to assess severity of CHE signs and symptoms. Participants will assess the worst severity of 6 signs and symptoms of CHE (itch, pain, cracking, redness, dryness, and flaking) over the past 24 hours using an 0-10 numeric rating scale with anchors of 0='no (symptom)' and 10='severe (symptom)'.

The HESD score is derived as an average of the 6 items.

8.1.3.2 Dermatology Life Quality Index (DLQI)

The DLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the participant's perception of the impact of their skin disease on different aspects of their quality of life over the last week, such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (Finlay et al, 1994). Each item is scored on a 4-point Likert scale (0='not at all/not relevant'; 1='a little'; 2='a lot'; 3='very much'). The DLQI score is the sum of the 10 items (score ranging from 0 to 30); a high score is indicative of a poor quality of life.

8.1.3.3 Hand Eczema Impact Scale© (HEIS)

The Hand Eczema Impact Scale© (HEIS©, hereafter referred to as HEIS) is an instrument that includes 9 items addressing the participant's perception over the past 7 days within the following domains: Proximal Daily Activity Limitations (PDAL), embarrassment with the appearance of the hands, frustration with CHE, sleep, work, and physical functioning.

Each item is scored on a 5-point scale (0='not at all', 1='a little', 2='moderately', 3='a lot', 4='extremely'). The HEIS score is the average of the 9 items. The highest possible score is 4, and a high score is indicative of a high impact. In addition, 6 domain scores can be calculated for HEIS: PDAL (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with CHE (1 item), sleep (1 item), work (1 item), and physical functioning (1 item).

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

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQoL Group, 1990). 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 participant using a 5-point scale ('no problems', 'slight problems', 'moderate problems', 'severe problems', and 'unable to/extreme problems'). The EQ-5D-5L index score is derived from the 5 dimensions and has been converted from the 5L system to the 3L system using the EQ-5D-5L crosswalk value set. The index score ranges from -0.594 to 1.0 (based on the UK country-specific value set), with a higher score indicating a better health status.

The second section consists of a vertical visual analogue scale anchored at 0 ('the worst health you can imagine') and 100 ('the best health you can imagine').

8.1.3.5 Treatment Satisfaction Questionnaire for Medicine (TSQM)

The TSQM v.II is a generic questionnaire assessing participant's satisfaction with the treatment (Atkinson et al, 2004).

The tool consists of 11 items addressing 4 domains (effectiveness, side effects, convenience and overall satisfaction):

- 7 items (in the domains of effectiveness, convenience and overall satisfaction) will be assessed by the participant using a 7-category scale (score) ('extremely dissatisfied'=1, 'very dissatisfied'=2, 'dissatisfied'=3, 'somewhat satisfied'=4, 'satisfied'=5, 'very satisfied'=6, and 'extremely satisfied'=7).
- 3 items (in the domain of side effects) will be assessed by the participants using a 6-category scale (score) ('extremely dissatisfied'=1, 'very dissatisfied'=2, 'somewhat dissatisfied'=3, 'slightly dissatisfied'=4, 'not at all dissatisfied'=5, 'not applicable'=5).
- 1 item (item 3 in the domain of side effects) will be assessed using a 2-category scale (score) ('yes'=1, 'no'=0).

The scores for each of the 4 domains ranges from 0 to 100 with higher scores indicating higher satisfaction.

The TSQM contains specific questions on side effects. If the participant answers 'yes' for item 3, and/or tick anything but 'not applicable' for items 4, 5 or 6, the investigator must follow-up with the participant to ensure AEs are appropriately recorded (see Section 8.3.2).

8.1.3.6 Work Productivity and Activity Impairment – Chronic Hand Eczema (WPAI-CHE)

The impact of CHE on the participant's ability to work and perform regular activities will be assessed by WPAI-CHE, which is an instrument to measure impairments in both paid work and unpaid work (Reilly et al, 1993). The WPAI-CHE consists of 6 items, and scores can be calculated for 4 domains, each reflecting the percentage impairment due to CHE during the past 7 days, with higher numbers indicating greater impairment and less productivity:

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

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

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

The participants will be asked to complete 3 PGI-S questionnaires, one each to assess itch (Itch PGI-S), pain (Pain PGI-S), and their overall impression of their chronic hand eczema (HESD PGI-S) (**Table 8-6**).

The PGI-S questionnaires will be completed at the trial site according to the schedule of trial procedures in Section 1.3.

Table 8-6 Patient Global Impression of Severity (PGI-S) questionnaires

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

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

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

The participants will be asked to complete 3 PGI-C questionnaires, one each to assess the change in itch (Itch PGI-C), pain (Pain PGI-C), and their overall impression of their chronic hand eczema (HESD PGI-C) (**Table 8-7**).

The PGI-C questionnaires will be completed at the trial site according to the schedule of trial procedures in Section 1.3.

Table 8-7 Patient Global Impression of Change (PGI-C) questionnaires

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

8.1.4 CHE Lesions Photography

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

Digital colour photographs will be taken of both hands-back and front, including wrist on both sides according the SoA (Table 1-1). It will be recorded in the eCRF if the photo(s) was taken; if not, a reason should be provided. If deemed necessary (e.g. in case of poor quality), photographs can be retaken at the next visit.

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

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

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

Depending on the participant's consent, LEO Pharma may use the photographs in publications, posters, and similar types of information material or media targeting patients and healthcare professionals. The photographs may also be part of training material used for training and educational purposes. Steps will be taken to ensure that the identity of the participant is protected to the extent possible.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1-1).

8.2.1 Physical Examinations

A complete physical examination of the participant including whole body inspection of the skin, auscultation of heart, lungs, and abdomen, palpation of the abdominal organs, and basic neurological status will be performed. Presence of foot dermatitis will be documented. The investigator should perform the same examinations as in clinical practice as a minimum.

If CHE is the only finding, the physical examination should be considered normal.

8.2.2 Vital Signs

Vital signs (resting blood pressure, pulse, and body temperature) will be assessed.

Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones).

Vital signs will consist of 1 pulse and 3 blood pressure measurements (after the participant has been sitting for 5 minutes, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

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

In case of clinically significant abnormality at screening, exclusion criterion 13 will be assessed at the discretion of the investigator.

It will be recorded in the eCRF if vital signs were measured; if not, a reason should be provided. Vital signs (resting blood pressure, pulse, and body temperature) will be recorded in the eCRF. Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE (see Section 10.3.3).

8.2.3 Electrocardiograms

Single 12-lead digital ECGs will be recorded as outlined in the SoA (Table 1-1), after at least 5 minutes of rest in a supine position.

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

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

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date. The investigator has the final decision on the clinical significance of any ECG abnormalities. The investigator will document the review of the ECG results by signing the ECG report at the trial site or in an electronic portal hosted by the ECG vendor.

In case of clinically significant abnormality at screening, exclusion criterion 13 will be assessed at the discretion of the investigator.

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.

8.2.4 Clinical Safety Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1-1) for the timing and frequency. All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual.

Central Laboratory

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

If a screening laboratory result is abnormal and clinically significant, it will be at the investigator's discretion to decide if the participant should be excluded from the trial per exclusion criterion 13. Participants should also be excluded if their screening laboratory results meet exclusion criteria 6.a, 6.b, 6.c, 6.d, 6.e, or 6.f.

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

Tests Performed at the Trial Site

Urine samples will be tested with a dipstick according to the SoA (Table 1-1). It will be at the investigator's discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.

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

It will be recorded in the eCRF if a urine dipstick test was performed and whether urinalysis is required for further assessment, as judged by the investigator. If so, a urine sample should be

sent to the central laboratory. If the urine sample was not tested with a dipstick, a reason will be provided. The investigator's assessment of the urine dipstick results ('normal', 'abnormal') will be recorded in the eCRF. In case urinalysis is performed, the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition will be reported as an AE. Any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE (see Section 10.3.3).

8.2.5 Pregnancy Testing

Alitretinoin is teratogenic, and there remains a risk of severe and serious malformation of the foetus in case of pregnancy even after stopping treatment. Thus, negative urine pregnancy test results must be obtained for WOCBP at screening and at baseline prior to randomisation, monthly during the trial, and 5 weeks after the last dose of alitretinoin, as shown in the SoA (Table 1-1).

For WOCBP randomised to alitretinoin, the investigator must confirm compliance to acceptable method(s) of contraception, as shown in the SoA (Table 1-1).

Similarly, for women treated with delgocitinib, negative urine pregnancy test results must be obtained for WOCBP at screening and at baseline prior to randomisation, monthly during the trial, but the last pregnancy test will occur 2 weeks after the last dose of delgocitinib, as shown in the SoA (Table 1-1).

If pregnancy occurs during the trial, treatment must be discontinued immediately, and participants treated with alitretinoin capsules should be referred to a physician specialised or experienced in teratology for evaluation and advice.

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

8.2.6 Mental Health Monitoring

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms, and very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with systemic retinoids, including alitretinoin.

All participants treated with alitretinoin should be monitored for signs of depression and referred for appropriate treatment if necessary.

Prior to initiation of alitretinoin and at each visit during treatment, participants should be asked about any psychiatric disorder, depression, or mood disturbance in a mental health interview, as outlined in the SoA (Table 1-1).

Participants should stop alitretinoin if they develop depression, mood disturbance, psychosis, or aggression, as described in Section 7.1. However, discontinuation of alitretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary. Awareness by family or friends may be useful to detect mental health deterioration.

8.2.7 Local Tolerability

For participants receiving delgocitinib cream only, an assessment of local tolerability will be provided by the participant and by the investigator, according to the SoA (Table 1-1).

8.2.7.1 Participant's Assessment of Local Tolerability

The participant will complete a weekly assessment of stinging/burning in connection with the delgocitinib cream applications in the eDiary. The participant will be asked to retrospectively assess the worst stinging/burning in connection with the delgocitinib cream application during the last week. In addition, the participant will be asked by the unblinded investigator at the End of Treatment/Early Termination visit to assess the local tolerability during the last week (see Section 1.3). The assessment will be done using the 4-point scale shown in Table 8-8.

Table 8-8 Participant's Assessment of Local Tolerability after Delgocitinib Cream Application

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

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

For the participant's assessment of local tolerability at the EOT/ET visit, the highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF.

8.2.7.2 Investigator's Assessment of Local Tolerability

The investigator will assess whether he/she suspects a local skin reaction related to application of the delgocitinib cream. If the investigator suspects a local skin reaction related to application of the delgocitinib cream, the skin reaction will be scored according to the Berger and Bowman scales in Table 8-9. The scoring should only assess skin signs suspected to be related to application of the delgocitinib cream and not signs or symptoms related to the participant's CHE.

Table 8-9 Berger and Bowman Scoring Scales if Investigator Suspects a Local Skin Reaction Related to Delgocitinib Application

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

Select the appropriate score (only 1 score) if a local skin reaction is suspected to be related to application of delgocitinib cream.

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

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

For the investigator's assessment of local tolerability, it will be reported in the eCRF if the investigator suspects a local skin reaction to be related to application of delgocitinib (yes, no). If the investigator suspects a local skin reaction to be related to application of delgocitinib, the scores in Table 8-9 (1 score for Scale 1; and 0, 1, or multiple scores for Scale 2) will be recorded in the eCRF.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs reported by the participants or observed by the investigator must be recorded on the AE form of the eCRF (see Section 8.3.2).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 8.3.3). The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the end of trial (defined as attending the last visit in the trial [the ET visit, the nominal Week 24 visit, or the last follow-up visit, whichever comes last]), at the timepoints specified in the SoA (Table 1-1).

It will be recorded in the eCRF if the AE started prior to first administration of IMP.

All SAEs will be recorded and reported to the sponsor immediately without undue delay but no later than within 24 hours of awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on new AEs or SAEs after the conclusion of trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

At all visits, participants will be asked a non-leading question by the investigator about AEs, e.g.: ‘How have you felt since I saw you last?’. Participant-reported local tolerability will be

queried specifically (see Section 8.2.7.1) and reported as AE(s) if deemed relevant by the investigator.

When completing the TSQM PRO questionnaire, participants will be asked direct questions about side effects. If the participant answers 'yes' for item 3, and/or tick anything but 'not applicable' for items 4, 5 or 6 (see Section 8.1.3.5), the investigator must follow-up with the participant to ensure AEs are appropriately recorded.

If the AE qualifies as an SAE, expedited reporting is required (see Section 10.3.4). It is important that the investigator also observes the participant for any changes not reported by the participant and records these changes.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow-up with the participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilisation, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, see Appendix 3) by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a trial treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators.

An investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the IB of delgocitinib cream and the product information of alitretinoin capsules, and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs that occur during the trial, and all SAEs occurring until the safety follow-up visit, whether considered to be associated with the IMP or not, must be reported to the sponsor on the (paper) SAE form immediately, without undue delay and no later than within 24 hours of obtaining knowledge. The completed SAE forms must be faxed or scanned and e-mailed to

Global Safety at LEO Pharma. Contact details are given as described in Appendix 3 (Section 10.3.4).

Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

8.3.5 Pregnancy

Details of all pregnancies in female participants will be collected after the start of IMP and until 2 weeks after the last dose of delgocitinib or 5 weeks after the last dose of alitretinoin.

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

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Appendix 3 (Section 10.3.4).

Pregnant participants must immediately discontinue IMP permanently (see Section 7.1).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.

Any post-trial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

Any woman who becomes pregnant while participating in the trial will discontinue the IMP immediately and participants treated with alitretinoin capsules should be referred to a physician specialised or experienced in teratology for evaluation and advice.

8.3.6 Other Events

8.3.6.1 AEs of Special Interest

The events listed in Table 8-10 are considered AEs of special interest (AESIs) in this trial and will require additional details to be recorded. The sponsor may request that the investigator forward additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting via the SAE form as described in Section 8.3.4 in addition to the requirements specified in Table 8-10.

Table 8-10 Adverse Events of Special Interest

Adverse event of special interest	Additional data to be recorded
Eczema herpeticum	**Skin findings**: • Lesion type (papules, vesicles, crusts, eroded pits, other) • Disseminated/localised • Location (face, scalp, back, chest, upper limb, lower limb, genitals) • Present in an area with visible eczema/no visible eczema/present in areas with and without eczema • Monomorphic/polymorphic • Confirmation of herpes simplex virus (not confirmed, polymerase chain reaction [PCR], viral culture, Tzanck, other)
Deep vein thrombosis / Pulmonary embolism	**Risk factors**: • Previous thromboembolism (record as medical history) • Family history of deep vein thrombosis/pulmonary embolism or other cardiovascular/blood-clotting disorders • Genetic disorders that might increase the risk for thrombosis (record as medical history) • History of cancer (record as medical history) • Recent venous catheter placement (record as medical history) • Current smoker (record as tobacco smoking history) • Hormonal contraception/hormonal replacement therapy (record as concomitant medication) • Trauma or surgery (record as per protocol) • Immobilisation (e.g. prolonged bed rest or sitting for long periods) **Method of verification**: • Clinical evaluation • Image-verified • Laboratory test(s)

8.3.6.2 Medication Errors

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

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

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

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

Treatment non-compliance (including missed doses) where no clinical consequence occurred or could have occurred should not be recorded as medication errors. See Section 6.4 for recording of treatment compliance.

Medication error must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (see Section 10.3.4).

8.3.6.3 Misuse or Abuse

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

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

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

Misuse and abuse must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of misuse or abuse must be recorded as separate AEs on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (see Section 10.3.4).

8.3.7 Handling of Urgent Safety Measures

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 participants, the sponsor and the investigator shall take appropriate

urgent safety measures to protect the participants against any immediate hazard." (EU Directive 2001/20/EC).

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

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

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

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this trial.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.6 Genetics

Genetics are not evaluated in this trial.

8.7 Biomarkers

Biomarkers are not evaluated in this trial.

8.8 Immunogenicity Assessments

Immunogenicity is not evaluated in this trial.

8.9 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics parameters are not evaluated in this trial.

8.10 End-of-trial Assessments

8.10.1 End-of-treatment Form

An end-of-treatment form will be completed in the eCRF for all randomised participants exposed to IMP when they have had their last administration of IMP. This form will also be completed for participants who permanently discontinue IMP prior to Week 24 and participants who withdraw from trial, unless they were never exposed to IMP (see Section 7).

The date of last administration of IMP will be recorded on the end-of-treatment form. It will also be recorded if the participant completed the treatment (i.e. did not discontinue IMP prior to Week 24, unless they achieved good clearance), and, if not, whether the reason for not completing the treatment period was related to COVID-19. If the participant did not complete the treatment, the primary reason for permanent discontinuation of IMP must be recorded (see Section 7.1).

8.10.2 End-of-trial Form

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

- Date of last contact.
- Did the participant complete the trial? Refer to Section 4.4 for a definition of trial completion.
- Primary reason for not completing the trial based on the following categories: death, AE, lack of efficacy, lost to follow-up, withdrawal by participant, screen failure (failure to meet eligibility criteria), or other.
- Whether the reason for not completing the trial was related to COVID-19.

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

9 Statistical Considerations

The statistical analysis plan (SAP) will be finalised prior to first participant's first visit and if revisions are necessary the revised SAP will be finalised prior to database lock (DBL). The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

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

9.1 Statistical Hypotheses

For the primary and key secondary endpoints, confirmatory 1-sided (superiority) hypotheses will be tested for delgocitinib cream versus alitretinoin capsules, except for the key secondary endpoint 'change in HECSI score from baseline to Week 24' that will initially be evaluated for non-inferiority (at margin M) and subsequently for superiority.

Let the treatment effect be defined as μ=(delgocitinib cream minus alitretinoin capsules), then:

- For binary endpoints or area under the curve (AUC): $H_0: \mu \leq 0$ against $H_a: \mu > 0$.
- For continuous endpoints (superiority): $H_0: \mu \geq 0$ against $H_a: \mu < 0$.
- For continuous endpoints (non-inferiority): $H_0: \mu \geq M$ against $H_a: \mu < M$.

9.1.1 Multiplicity Adjustment

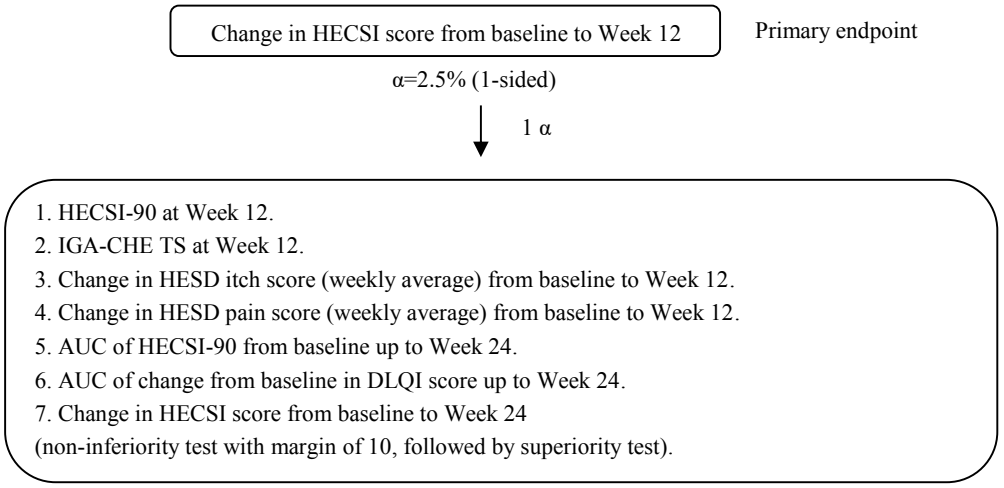
A closed testing procedure with hierarchical tests will be used to control the overall type I error at a nominal 1-sided 2.5% level. The statistical testing strategy is built on the principle that superiority of change in HECSI score from baseline to Week 12 will have to be established before testing for additional benefits (key secondary endpoints) related to efficacy and health-related quality of life.

The first hypothesis to be tested is superiority of delgocitinib cream in terms of change in HECSI score from baseline to Week 12. It will be tested at the overall 1-sided significance level of 2.5%.

The endpoints will be tested according to the fixed sequence specified in Figure 9–1. If a test is significant, the significance level will be reallocated to the next hypothesis. Each of the following hypotheses will be tested at a significance level of 2.5%. This process will be repeated until no further tests are significant.

The last hypothesis to be tested is the non-inferiority of delgocitinib cream in terms of change in HECSI score from baseline to Week 24 using a non-inferiority margin of 10 (i.e. M=10). The margin is based on a conservative choice (<½ minimal important difference) of what was found to be the minimal important difference between groups obtained from psychometric analyses of HECSI based on data from the moderate-to-severe population in the LP0133-1273 trial. If non-inferiority is statistically significant, superiority is then evaluated.

Figure 9–1 Graphical Display of Closed Testing Procedure for Primary and Key Secondary Endpoints



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

9.2 Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Table 9-1 Participant Analysis Sets

Participant Analysis Set	Description
Full analysis set	All randomised participants. Participants will be included in the analyses according to randomised treatment allocation. Exclusions from the FAS can be considered in special cases, as described in Section 5.2.1 (Full Analysis Set) of ICH E9 guidelines. If a participant is excluded from the FAS, a justification per ICH E9 guidelines will be given.
Safety analysis set	All participants who are exposed to the IMP. Participants will be analysed according to the treatment they actually received.

Abbreviations: FAS=full analysis set; IMP=investigational medicinal product.

The full analysis set (FAS) is used to analyse endpoints related to the efficacy objectives and the safety analysis set is used to analyse the endpoints and assessments related to safety.

The decisions regarding inclusion/exclusion of participants or participant data from the analysis sets will be documented in the analysis set definition document before DBL.

9.3 Statistical Analyses

9.3.1 General Considerations

Significance tests will be 1-sided using the 2.5% significance level. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified.

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

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

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

The statistical analyses were performed using SAS software (SAS Institute, Cary NC), version 9.3 or later.

9.3.2 Aspects Related to the COVID-19 Pandemic

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

A supplementary estimand, 'pandemic modified composite', is introduced for analysis of the primary and key secondary endpoints. This estimand addresses permanent discontinuation of IMP related to the COVID-19 pandemic as an intercurrent event (IE). Details are described in Section 9.3.6.

Interruption of IMP during the treatment period is not expected as per protocol and hence not considered as an IE. This is supported by the assumption that LEO Pharma will secure availability of IMP at all times. In addition, as the IMP supply is secured, the IE initiation of rescue medication will be considered independent of the COVID-19 pandemic (see Section 10.5).

The causal relationship of permanent discontinuation of IMP related to the COVID-19 pandemic will be recorded in the eCRF (see Section 10.5).

Missing or 'treated as missing' data related to the COVID-19 pandemic

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

Observed data after permanent discontinuation of IMP related to the COVID-19 pandemic will be 'treated as missing' and imputed assuming missing at random (MAR). Missing data related to the COVID-19 pandemic will be imputed assuming MAR (Section 9.3.6).

It should be noted that a participant may have missing data related to the COVID-19 pandemic, even though the participant has not experienced an IE related to the COVID-19 pandemic.

An overview of how observed and missing data will be handled according to the IEs and their relatedness to the COVID-19 pandemic is presented in Table 9-2 for the primary analysis for estimands. Details of the analysis are described in Section 9.3.6.

9.3.3 Disposition of Participants

The reasons for permanent discontinuation of IMP and for not completing the trial will be presented for all randomised participants and by treatment group.

An overall summary of participant disposition will be presented for all randomised participants. The disposition summary will include information on the number of randomised, exposed, included in the FAS, permanently discontinuing IMP, restarting after response, and not completing the trial by treatment group and overall.

9.3.4 Demographics and Other Baseline Characteristics

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

Demographics include age, sex, ethnicity, and race. Other baseline characteristics include height, weight, body mass index, region, country, total IgE, Fitzpatrick skin type, CHE history, CHE treatment history, exogenous risk factors for CHE, past and current medical history, and prior and concomitant medication. In addition, the baseline assessment for the primary and key secondary endpoints will be presented.

9.3.5 Exposure and Treatment Compliance

The duration of exposure to treatment in a specific week interval will be calculated as the number of days from date of first administration of IMP in that period to the date of last administration 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.

For delgocitinib only, the average weekly and total amount of IMP used will be presented for the safety analysis set for each visit interval and for the total treatment period.

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

9.3.6 Estimand Strategy

9.3.6.1 General Considerations

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

The following primary and supplementary estimands will be defined for binary, continuous, and AUC endpoints (primary and key secondary endpoints):

- The primary estimand will use a 'composite' strategy to handle IEs. With a 'composite' strategy, the occurrence of an IEs is a component of the endpoint. The occurrence of any IE will lead to assume failure of the randomised treatment. For continuous endpoints, observed data after the IEs will be imputed as non-response by using WOCF (including baseline value) which is considered an extremely unfavourable value.
- A first supplementary estimand will use a 'pandemic modified composite' strategy. The strategy follows a 'composite' strategy for IEs independent of the COVID-19 pandemic. However, data collected after the IE related to the COVID-19 pandemic will be 'treated as missing' and imputed assuming MAR.
- A second supplementary estimand will use a 'treatment policy' strategy which attempts to quantify the effect of the randomised treatment, ignoring the occurrence of IEs. This policy reflects the intention-to-treat (ITT) principle and is intended to measure the effectiveness of the treatment under conditions closer to 'real world' conditions where patients will not adhere perfectly to the protocol when taking medication. Data collected for the endpoint of interest are used regardless of whether an IE occurred, except for the occurrence permanent discontinuation of IMP related to the COVID-19 pandemic data which will be assumed MAR and imputed.

  To support the 'treatment policy' strategy, participants who experience IEs prior to Week 12 will be asked to attend the primary endpoint visit at Week 12 and nominal visit at Week 24 for collection of data. Participants who experience IEs between Week 12 and Week 24 will be asked to attend the nominal visit at Week 24 for collection of data.

For primary and key secondary endpoints only, pre-specified sensitivity analyses will also be conducted for selected combinations of endpoints and estimands to assess the robustness of the results with respect to the handling of missing data.

Analysis to summarise and assess the effect of patterns of missing data related to the COVID-19 pandemic will be specified in the SAP prior to DBL.

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

- **Initiation of rescue treatment:** This IE occurs when a participant initiates rescue treatment. This IE can occur at the discretion of the investigator. If rescue treatment is initiated, regardless of relatedness to the COVID-19 pandemic, the participant must stop treatment with the IMP immediately and will not be allowed to restart treatment with the IMP (refer to Sections 6.8.2 and 7.1 for details). This IE is handled without assessing relatedness to the COVID-19 pandemic.
- **Permanent discontinuation of IMP independent of the COVID-19 pandemic:** This IE occurs when a participant permanently discontinues the IMP independent of the COVID-19 pandemic. This IE can occur at the participant's own initiative, at the discretion of the investigator or the sponsor, or if the participant is lost to follow-up.
- **Permanent discontinuation of IMP related to the COVID-19 pandemic**: This IE occurs when a participant permanently discontinues the IMP due to circumstances related to the COVID-19 pandemic; not attributed to lack of efficacy or randomised treatment features considered unacceptable by the participant.

The occurrence of IEs will be listed and summarised by treatment group. Table 9-2 presents an overview of how observed and missing data will be handled according to the IEs for the primary analysis for estimands.

Table 9-2 Handling of Observed and Missing Data According to the Intercurrent Events for the Primary Analysis for Estimands

		Estimand strategy for binary endpoints			Estimand strategy for continuous endpoints		
Intercurrent event	**Data observed or missing**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**	**Composite (Primary)**	**Pandemic modified composite (First supplementary)**	**Treatment policy (Second supplementary)**
Initiation of rescue treatment	Observed	Non-response	Non-response	Value will be used as observed	WOCF	WOCF	Value will be used as observed
	Missing	Non-response	Non-response	MI (MAR)	WOCF	WOCF	MI (MAR)
Permanent discontinuation of IMP independent of the COVID-19 pandemic	Observed	Non-response	Non-response	Value will be used as observed	WOCF	WOCF	Value will be used as observed
	Missing	Non-response	Non-response	MI (MAR)	WOCF	WOCF	MI (MAR)
Permanent discontinuation of IMP related to the COVID-19 pandemic	Observed	Non-response	MI (MAR)	MI (MAR)	WOCF	MI (MAR)	MI (MAR)
	Missing	Non-response	MI (MAR)	MI (MAR)	WOCF	MI (MAR)	MI (MAR)
No intercurrent events	Observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed	Value will be used as observed
	Missing independent of the COVID-19 pandemic	Non-response	Non-response	MI (MAR)	WOCF	WOCF	MI (MAR)
	Missing related to the COVID-19 pandemic	Non-response	MI (MAR)	MI (MAR)	WOCF	MI (MAR)	MI (MAR)

IMP=investigational medicinal product; MAR=missing at random; MI=multiple imputation; WOCF=worst observation carried forward (including baseline value).

9.3.6.2 Estimand Strategy for Continuous Endpoints

The population level summary will be the difference in mean change (or percentage change) from baseline to the endpoint of interest between delgocitinib cream and alitretinoin capsules.

The change (or percentage change) from baseline to the endpoint of interest will be analysed using an analysis of covariance (ANCOVA) model with effects of treatment group, region, hyperkeratotic/non-hyperkeratotic subtype, and baseline value (of the measure of interest).

When analyses require multiple imputation (MI) procedures of data, 100 complete datasets will be sampled. For each dataset, the ANCOVA model will be fitted. The estimates and standard errors from the analyses will be combined using Rubin's rule to provide the estimate and associated standard error.

Primary Estimand: 'Composite' Strategy

For the primary analysis, observed and missing data will be handled according to the IEs, as described in Table 9-2.

For the sensitivity analysis, which is rather conservative against the delgocitinib group, missing data at the endpoint of interest, for participants who did not experience IEs prior to that, will be handled as follows:

- For participants in the delgocitinib cream group, missing data will be imputed as WOCF (including baseline value).
- For participants in the alitretinoin capsules group, missing data will be imputed using MI assuming MAR.

First Supplementary Estimand: 'Pandemic Modified Composite' Strategy

Observed and missing data will be handled according to the IE, as described in Table 9-2.

All missing or 'treated as missing' data will be imputed using MI assuming MAR within treatment groups. The WOCF imputation of relevant data points not affected by the COVID-19 pandemic will be applied.

Second Supplementary Estimand: 'Treatment Policy' Strategy

Observed data and missing data will be handled according to the IEs, as described in Table 9-2.

Missing data at Week 12 and Week 24, independent of the COVID-19 pandemic, will be imputed using MI assuming MAR within 4 groups defined according to treatment group and whether the participant has experienced an IE (independent of the COVID-19 pandemic). For imputation purposes, data available from all participants will be used.

For the endpoint of interest, missing data or 'treated as missing' data due to the COVID-19 pandemic will be imputed using MI assuming MAR within treatment group using data from participants who have not experienced an IE.

9.3.6.3 Estimand Strategy for Binary Endpoints

The population level summary will be the difference in response rates between delgocitinib cream and alitretinoin capsules.

The difference in response rates between the 2 treatment groups with the 95% CI will be calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by region and hyperkeratotic/non-hyperkeratotic subtype.

When analyses require MI procedures of data, 100 complete datasets will be sampled. For each dataset, the difference in response rates will be analysed using the CMH test stratified by region and hyperkeratotic/non-hyperkeratotic subtype. The results of the analyses will be combined using Rubin's rule to provide the estimated treatment difference and associated standard error, and the 95% CI for the treatment difference will be calculated.

Primary Estimand: 'Composite' Strategy

For the primary analysis, observed data and missing data will be handled according to the IEs, as described in Table 9-2.

For the sensitivity analysis, which is rather conservative against the delgocitinib group, missing data at the endpoint of interest for participants who did not experience IEs prior to that will be handled as follows:

- For participants in the delgocitinib cream group, missing data will be imputed as non-response.
- For participants in the alitretinoin capsules group, missing data will be imputed using MI (100 iterations) assuming MAR. Binary response/non-response will be determined after imputation of the original raw continuous values when binary variable is obtained by derivation (e.g. for the HECSI-90 from baseline up to Week 24, the percentage of reduction from baseline will be derived from imputed values).

First Supplementary Estimand: 'Pandemic Modified Composite' Strategy

Observed data and missing data will be handled according to the IEs, as described in Table 9-2.

All missing or 'treated as missing' data will be imputed using MI assuming MAR within treatment groups. Once the 100 complete data sets have been generated by MI, non-responder imputation of relevant data points not affected by the COVID-19 pandemic will be applied.

Second Supplementary Estimand: 'Treatment Policy' Strategy

For the primary analysis, observed data and missing data will be handled according to the IEs, as described in Table 9-2.

Missing data at Week 12 and Week 24 independent of the COVID-19 pandemic will be imputed using MI assuming MAR within 4 groups defined according to treatment group and whether the participant has experienced an IE (independent of the COVID-19 pandemic).

Missing data or 'treated as missing' data at Week 12 and Week 24 due to the COVID-19 pandemic will be imputed using MI assuming MAR within treatment group using data from participants who have not experienced an IE.

For the sensitivity analysis, missing data at Week 12 and Week 24 will be imputed as non-response, unless data is missing or 'treated as missing' due to the COVID-19 pandemic in which case it will be imputed using MI assuming MAR within treatment group using data from participants who have not experienced an IE.

9.3.6.4 Estimand Strategy for AUC Endpoints

The population level summary will be the difference in estimated mean AUC from baseline to the endpoint of interest between delgocitinib cream and alitretinoin capsules. The AUC endpoints are based on curves that will be fitted on values determined for the corresponding continuous and binary endpoints, as presented in Table 9-2.

Once points have been identified in accordance with estimands strategies, a piecewise line function will be drawn to connects points ($f(t)$, where t is the time in days from baseline). Baseline value will be set at 0 (zero). For each participant, the area under piecewise line will be determined integrating $f(t)$, as follows:

$$AUC = \int_{t=0}^{t=Week\ 24} f(t)\Delta t$$

The integral will be approximated by the trapezoidal rule.

The differences between treatment group will be analysed using robust ANCOVA model with the AUC or related transformation as dependent variable, and treatment, region, hyperkeratotic/non-hyperkeratotic subtype and baseline value (of the measure of interest), as covariates. Details on robust ANCOVA model will be described in the SAP.

The AUC at participant level (to be implemented as dependent variable in the ANCOVA model) will be determined in accordance with nature of the endpoint of interest, as follows:

- **AUC derived from binary endpoints**, such as the AUC of HECSI-90 from baseline up to Week 24: 1 will be assigned when response is observed and 0 otherwise. The AUC is interpreted as number of days with 90% reduction in HECSI score until Week 24.
- **AUC derived from continuous endpoints**, such as the AUC of change from baseline in DLQI score up to Week 24: For the sake of interpretability, differences will be analysed with opposite sign to interpret positive area as improvement in scores and negative area as worsening.

When analyses require MI procedures of data, 100 complete datasets will be sampled. For each dataset, piecewise line function will be drawn to connects points and the AUC will be determined. ANCOVA model will be fitted for each dataset with treatment, region, hyperkeratotic/non-hyperkeratotic subtype as covariates. The estimates and standard errors from the analyses will be combined using Rubin's rule to provide the estimate and associated standard error.

Primary Estimand: 'Composite' Strategy

For the primary analysis, observed data and missing data will be handled according to the IEs, as described in Table 9-2.

First Supplementary Estimand: 'Pandemic Modified Composite' Strategy

Observed data and missing data of the corresponding continuous or binary endpoint will be handled according to the IEs, as described in Table 9-2.

All missing or 'treated as missing' data will be imputed using MI assuming MAR within treatment groups. The WOCF or non-response imputation of relevant data points not affected by the COVID-19 pandemic will be applied.

Second Supplementary Estimand: 'Treatment Policy' Strategy

Observed data and missing data of the corresponding continuous or binary endpoint will be handled according to the IEs, as described in Table 9-2.

Missing data at Week 12 and Week 24, independent of the COVID-19 pandemic, will be imputed using MI assuming MAR within 4 groups defined according to treatment group and whether the participant has experienced an IE (independent of the COVID-19 pandemic). For imputation purposes, data available from all participants will be used.

For the endpoint of interest, missing data or 'treated as missing' data due to the COVID-19 pandemic will be imputed using MI assuming MAR within treatment group using data from participants who have not experienced an IE.

9.3.7 Primary Endpoint(s) Analysis

The primary endpoint will be analysed following the estimands strategy for continuous endpoints described in Section 9.3.6.2. The confirmatory 1-sided (superiority) hypothesis, described in Section 9.1, will be tested for delgocitinib cream versus alitretinoin capsules based on the primary analysis for the primary estimand.

9.3.8 Secondary Endpoint(s) Analysis

The confirmatory hypotheses for key secondary endpoints, presented in Section 9.1. will be tested based on the primary analyses for the primary estimand strategies described in Sections 9.3.6.2, 9.3.6.3, and 9.3.6.4.

Table 9-3 provides an overview of the primary statistical analysis of the key secondary efficacy endpoints related to the primary and supplementary estimands. For further details, including sensitivity analysis, refer to Section 9.3.6.

Table 9-3 Overview of the Primary Statistical Analysis of the Key Secondary Efficacy Endpoints Related to the Primary and Supplementary Estimands

Key secondary endpoints	Type of endpoint	Primary estimand		First Supplementary estimand		Second Supplementary estimand	
		Strategy to handle IEs	Handling of missing data and data collected after IE	Strategy to handle IEs	Handling of missing data	Strategy to handle IEs	Handling of missing data
HECSI-90 at Week 12	Binary	Composite	Non-response imputation	Pandemic modified composite	Independent of the COVID-19 pandemic: non-response imputation Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
IGA-CHE TS at Week 12							
AUC of HECSI-90 from baseline up to Week 24	AUC (derived from binary)						
Change in HECSI score from baseline to Week 24	Continuous	Composite	WOCF (including baseline value)	Pandemic modified composite	Independent of the COVID-19 pandemic: WOCF (including baseline value) Related to the COVID-19 pandemic: MI assuming MAR within treatment group	Treatment policy	Independent of the COVID-19 pandemic: MI assuming MAR within treatment group and occurrence of IEs Related to the COVID-19 pandemic: MI assuming MAR within treatment group
Change in HESD itch score (weekly average) from baseline to Week 12							
Change in HESD pain score (weekly average) from baseline to Week 12							
AUC of change from baseline in DLQI score up to Week 24	AUC (derived from continuous)						

AUC=area under the curve; COVID-19=coronavirus disease 2019; DLQI=Dermatology Life Quality Index; HECSI=Hand Eczema Severity Index; HECSI-90=at least 90% improvement in HECSI from baseline; HESD=Hand Eczema Symptom Diary©; IE=intercurrent event; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS=IGA-CHE treatment success, i.e. an IGA-CHE score of 0 (clear) or 1 (almost clear) with a ≥2 step improvement from baseline; MAR=missing at random; MI=multiple imputation; TS=treatment success; WOCF=worst observation carried forward (including baseline value).

9.3.9 Exploratory Endpoints Analysis

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

The analysis of exploratory endpoints will resemble the primary analysis for the primary estimand related to a specific endpoint type: binary, continuous, or AUC. For details refer to Section 9.3.6.

Table 9-4 provides an overview of the statistical analysis of the exploratory endpoints.

Table 9-4 Overview of the Statistical Analysis of Exploratory Endpoints

Endpoints	Type of endpoint	Primary estimand	
		Strategy to handle IEs	Handling of missing data and data collected after IE
Efficacy			
IGA-CHE TS at Week 24.	Binary	Composite	Non-response imputation
HECSI-75 at Week 12 and Week 24.			
HECSI-90 at Week 24.			
Reduction of HESD itch score (weekly average) of ≥3 points [1] at Week 12 and Week 24.			
Reduction of HESD itch score (weekly average) of ≥4 points [2] at Week 12 and Week 24.			
Reduction of HESD pain score (weekly average) of ≥3 points [3] at Week 12 and Week 24.			
Reduction of HESD pain score (weekly average) of ≥4 points [4] at Week 12 and Week 24.			
Reduction of HESD score (weekly average) of ≥3 points [5] at Week 12 and Week 24.			
Reduction of HESD score (weekly average) of ≥4 points [6] at Week 12 and Week 24.			
Change in HESD itch score (weekly average) from baseline to Week 24.	Continuous	Composite	WOCF (including baseline value)
Change in HESD pain score (weekly average) from baseline to Week 24.			
Change in HESD score (weekly average) from baseline to Week 12 and Week 24.			
AUC from baseline to Week 24 of reduction of HESD itch score (weekly average) of ≥3 points [1]	AUC (derived from binary)	Composite	Non-response imputation
AUC from baseline to Week 24 of reduction of HESD itch score (weekly average) of ≥4 points [2]			
AUC from baseline to Week 24 of reduction of HESD pain score (weekly average) of ≥3 points [3]			
AUC from baseline to Week 24 of reduction of HESD pain score (weekly average) of ≥4 points [4]			
Health-related quality of life			
Change in DLQI score from baseline to Week 12 and Week 24.	Continuous	Composite	WOCF (including baseline value)
Change in HEIS (individual domains and total score) from baseline to Week 12 and Week 24.			
Change in EQ-5D-5L index score from baseline to Week 12 and Week 24.			
Change in EQ-5D-5L visual analogue scale score from baseline to Week 12 and Week 24.			

Endpoints	Type of endpoint	Primary estimand	
		Strategy to handle IEs	Handling of missing data and data collected after IE
Reduction of DLQI score of ≥4 points[7] at Week 12 and Week 24.	Binary	Composite	Non-response imputation
DLQI score of 0 or 1 at Week 12 and Week 24.			
Treatment satisfaction and work productivity			
Change in WPAI-CHE (each individual domain) score from baseline to Week 12 and Week 24.	Continuous	Composite	WOCF (including baseline value)
TSQM at Week 12 and at Week 24.			WOCF

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

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CHE=chronic hand eczema; DLQI=Dermatology Life Quality Index; EQ-5D-5L=EuroQol 5-Dimension Health Questionnaire 5 Level; HECSI=Hand Eczema Severity Index; HECSI-75=at least 75% improvement in HECSI score from baseline; HECSI-90=at least 90% improvement in HECSI score from baseline; HEIS=Hand Eczema Impact Scale©; HESD=Hand Eczema Symptom Diary©; IGA-CHE=Investigator's Global Assessment for chronic hand eczema©; IGA-CHE TS=IGA-CHE treatment success; SAE=serious adverse event; TSQM=Treatment Satisfaction Questionnaire for Medicine; ULN=upper limit of normal; WOCF=Worst Observation Carried Forward; WPAI-CHE=Work Productivity and Activity Impairment – Chronic Hand Eczema.

9.3.10 Analysis of PGI-S and PGI-C

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

9.3.11 Safety Analyses

All safety analyses will be made on the safety analysis set.

9.3.11.1 Adverse Events

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

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in participant data listings. An event will be considered

treatment-emergent if it started after the first administration of IMP or if it started before the first administration of IMP and worsened in severity after the first administration of IMP. The tabulations described in the following will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

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

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

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

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

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

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

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

Specific summaries presenting AEs of hypertriglyceridaemia, hypercholesterolaemia, headache, liver toxicity will be prepared. The MedDRA search terms for these AEs will provided in the SAP.

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

9.3.11.2 Vital Signs and Physical Examination

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

9.3.11.3 Clinical Laboratory Evaluation

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

A shift table will be produced for relevant parameters showing the categories at baseline against those at each post-baseline visit.

For participants with post-baseline values, the number of events reported up to Week 26 will be summarised. For the following laboratory abnormalities endpoints, binary estimand strategy will be applied, as described in Section 9.3.6.3:

- Increased levels of triglycerides >3.42 mmol/L (fasted state).
- Increased levels of cholesterol >7.75 mmol/L (fasted state).
- Increased levels of ALT and/or AST >3×ULN (or >3×baseline if baseline was abnormal but <2×ULN).
- Increased levels of ALP >2.5×ULN.
- Increased levels of bilirubin >1.5×ULN up to Week 26.

9.3.11.4 Participant's and Investigator's Assessment of Local Tolerability

Participant's and investigator's assessment of local tolerability for delgocitinib cream will be summarised by visit.

9.4 Interim Analyses

No interim analysis is planned during the trial.

9.5 Sample Size Determination

Approximately 510 participants will be randomly assigned to trial treatment in a 1:1 ratio, with 255 evaluable participants per treatment group. Approximately 660 participants will be screened to achieve this target.

With 510 participants randomised, the trial will provide 80% power to establish superiority of delgocitinib cream with regard to change from baseline to Week 12 in HECSI based on a 1-sided hypothesis test at a 2.5% significance level, assuming a difference in the mean change from baseline to Week 12 in HECSI of 7.5 (with a standard deviation of 30) between the 2 treatment arms (Ruzicka et al, 2008). Since there is limited published data on alitretinoin in terms of HECSI, anticipated treatment difference between delgocitinib and alitretinoin has been set using IGA scales as a surrogate endpoint (LP0133-1273 trial). Expected standard deviation is based on data observed in LP0133-1273 trial.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.

The investigator will be responsible for the following:

- 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/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Overall conduct of the trial at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor 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 trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The ICF(s) must be signed prior to performing any protocol related procedures, including but not limited to screening evaluations and initiation of wash-out for treatments listed as exclusion criteria.

The investigator or their representative will explain the nature of the trial, including the risks and benefits, to the participant and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the trial.

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

Participants who are rescreened are required to sign a new ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all participants subsequently enrolled in the trial as well as those currently enrolled in the trial.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Trial Data

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

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

Results of this clinical trial will be posted on leopharmatrials.com in accordance with our Position on Public Access to Clinical Trial Information within approximately 12 months of trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu, and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

10.1.6 Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and Regulatory Agency inspections and provide direct access to source data documents.

Monitoring details describing strategies, including definition of trial critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g. contract research organisations).

Records and documents, including signed ICF, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless otherwise required by local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

All data generated by the site personnel will be captured electronically at each trial site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data site, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the trial site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to trial sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.6.1 Quality Tolerance Limits

Quality Tolerance Limits will be defined in the Data Surveillance Plan.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and 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.

10.1.8 Trial and Site Start and Closure

First Act of Recruitment

The trial start date is the date on which the clinical trial will be open for recruitment of participants.

The first act of recruitment is the first participant's first visit and will be the trial start date.

Trial/Site Termination

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. 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.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further IMP development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

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

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

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

The sponsor may give researchers outside LEO Pharma access to anonymised data from this trial for further research according to the principles outlined by the European Federation of

Pharmaceutical Industries and Associations (EFPIA) (48). In that case, the researchers are obliged to attempt publication of the results obtained from their analyses.

The sponsor complies with Good Publication Practice (GPP3) standards and the recommendations from ICMJE.

10.1.10 Protocol Approval and Amendment

Before the start of the trial, the trial protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the trial.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

The sponsor will take out reasonable third-party liability insurance cover in accordance with all legal requirements. The civil liability of the investigator, the persons instructed by him or her and the hospital, practice, or institute in which they are employed and the liability of the sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this trial are governed by the applicable law.

The sponsor will arrange for patients participating in this trial to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the trial.

10.1.11.1 Access to Source Data

During the trial, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the trial is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the trial. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the sponsor, and Parexel if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by a central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Haematology	Thrombocytes Erythrocytes Haemoglobin Haematocrit Erythrocyte indices: • Erythrocyte mean corpuscular volume (MCV) • Erythrocyte mean corpuscular haemoglobin (MCH) • % Reticulocytes	Leukocytes with differential count: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical chemistry	Urea nitrogen Potassium Creatinine Sodium Glucose fasting [1] Calcium Cholesterol (LDL, HDL total) fasting [1] Triglycerides fasting [1]	AST/SGOT [2] Total and direct bilirubin [2] ALT/SGPT [2] Prothrombin INR [2] Protein Alkaline phosphatase [3] Gamma glutamyl transferase Lactate dehydrogenase Albumin

Laboratory Tests	Parameters
Routine urinalysis	Specific gravity Glucose, protein, occult blood, ketones, nitrite, leukocytes by dipstick Urine samples will be tested at the trial site (dipstick). It will be at the investigator's discretion to decide whether a urine sample should be sent to the central laboratory for microscopic examination (WBC; RBC; epithelial cells, squamous; epithelial cells, transitional; epithelial cells, renal tubular; hyaline casts; WBC casts; RBC casts; waxy casts; granular casts; calcium oxalate crystals; uric acid crystals; triphosphate crystals; yeast; and bacteria).
Pregnancy testing (WOCBP only)	Highly sensitive urine hCG pregnancy test (as needed for women of childbearing potential) at timepoints detailed in Section 8.3.5. [4]
Other screening tests	Follicle-stimulating hormone and oestradiol (as needed in women of non-childbearing potential only) Serology (HIV-1 antibody, HIV-2 antibody, HBsAg, HCV antibody) Immunoglobulin E Thyroid-stimulating hormone, thyroxine Retinol

1. Participants should be fasting for at least 8 hours prior to the collection of samples for analysis of fasting values of triglycerides, cholesterol, and glucose. Participants will be reminded of fasting requirement the day before the visit. If they do not follow fasting requirements on the visit day, they will be asked to return to the site in fasting conditions (within the visit time window), so fasting blood samples can be collected.
2. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1 and Appendix 6. All events of concurrent measurements of ALT and/or AST ≥3×ULN with total bilirubin ≥2×ULN or prothrombin INR >1.5, which may indicate severe liver injury (possible Hy's Law), should be reported as an SAE without undue delay and no later than within 24 hours (see Section 10.3.4 for reporting of SAEs).
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC. The test should have a minimum sensitivity of 25 mIU/mL.

Abbreviations: ALT= alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; HBsAg=hepatitis B virus surface antigen hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL=high-density lipoprotein; IEC=independent ethics committee; INR=international normalised ratio; IRB=institutional review board; LDL=low-density lipoprotein; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell; WOCBP=woman of childbearing potential.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant 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 E2A guidelines).

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 participant 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 8.2.4).

10.3.2 Definition of SAE

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).

- Requires in-patient hospitalisation or prolongation of existing hospitalisation.

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

- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.

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

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording
AEs must be assessed by a physician.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

AEs reported by the participant 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 participant). Whenever possible, a specific diagnosis should be stated (e.g. 'allergic contact dermatitis').

For cutaneous AEs, the location must be part of the AE description and may be described as (e.g. the face, scalp, back, chest, arm, leg, trunk, or limb). Additionally, for participants treated with delgocitinib cream, 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 border of lesion(s) treated with IMP).

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

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

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

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

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

Assessment of Severity
The severity of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement. If the AE worsens in severity, the new severity including

date of worsening, should be recorded. However, if an AE with onset prior to IMP initiation worsens after IMP administration, a new AE should be recorded:

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

The investigator will also consult the delgocitinib IB or the SmPC for alitretinoin (Toctino®) in their assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report in the EDC tool. However, **it is very important**

that the investigator always make an assessment of causality for every event before the initial recording of the SAE data in the EDC tool.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following decision choices will be used by the investigator to describe the causality assessment:

Probably related:
- Follows a reasonable temporal sequence from administration of the IMP.
- Could not be reasonably explained by the participant's clinical state, environmental or toxic factors, or other therapies administered to the participant.
- 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 participant's clinical state, environmental or toxic factors, or other therapies administered to the participant.
- 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 participant's clinical state, environmental or toxic factors, or other therapies administered to the participant.
- Does not reappear or worsen upon re-challenge.
- Does not follow a known pattern of response to the IMP.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of 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 participant is clearly recovering from an event. The event is not yet completely resolved.

Not recovered/ not resolved: Event is still ongoing.

Recovered/ resolved with sequelae: The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.
The stop date of the event must be recorded. In case of an SAE, the sequelae should be specified.

Fatal: The participant 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. participant lost to follow-up.

The sponsor's definitions versus Clinical Data Interchange Standards Consortium (CDISC) definitions: Note that as per the above definition, the sponsor 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 sponsor's 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, the sponsor 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 the sponsor with the outcome 'recovered/resolved with sequelae' could have been classified with the outcome 'recovered/resolved' according to the CDISC definition.

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

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include

additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the trial or during a recognised follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed form.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAE

Investigator Reporting Responsibilities
Any SAE must be reported to the sponsor on the (paper) SAE form immediately, without undue delay but not later than within 24 hours of obtaining knowledge. This report should contain among others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form. By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE. The actual reporter, if not the investigator, should also sign and date the SAE form. The completed SAE form must be faxed or scanned and e-mailed to Global Safety at LEO Pharma using the e-mail address or fax number below: Global Safety at LEO Pharma E-mail address: drug.safety@leo-pharma.com Fax number: +45 6910 2468 If relevant, the investigator will enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

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

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

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

Sponsor Reporting Responsibilities

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

- For delgocitinib, the IB Section 7.3 for delgocitinib cream, edition 5.0 (Delgocitinib cream IB, 2022) and subsequent updates must be used.
- For alitretinoin (Toctino®), the latest version of the SmPC must be used (Toctino® SmPC, UK).

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

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

The following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or the sponsor, and which are unexpected (i.e. 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.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)
Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

    - A postmenopausal state is defined as no menses for 24 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 24 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before randomisation.
    - Permanent sterilisation methods (for the purpose of this trial) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial entry.

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

    - If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)
Women in the following categories are considered WONCBP:

1. Premenopausal woman with permanent infertility due to 1 of the following:
    a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

d. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal woman

   a. A postmenopausal state is defined as no menses for 24 months without an alternative medical cause.

      i. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 24 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

      ii. Women on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before randomisation.

10.4.2 Contraception Guidance

Women of childbearing potential must use at least one highly reliable method of contraception (i.e., a user-independent method) or two complementary user-dependent methods of contraception. Contraception must be used 1 month before treatment and throughout the treatment period, including participants with amenorrhea. Contraception must additionally be used for 1 month after the end of treatment with alitretinoin. If local guidelines have stricter requirements, then local guidelines should be followed.

CONTRACEPTIVES [a] ALLOWED DURING THE TRIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of < 1% per year when used consistently and correctly.
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c].
Intrauterine device (IUD).
Intrauterine hormone-releasing system (IUS)[c].
Bilateral tubal occlusion.
Azoospermic partner (vasectomised or due to a to medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant)
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

10.5 Appendix 5: COVID-19 Pandemic Contingency Plan

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

If on-site visits are not possible due to local authority-issued preventive measures, the affected site will postpone screening and randomisation of new participants until on-site visits can be conducted. For already randomised participants, post-baseline visits can be done remotely via phone or video. At phone/video visits, no investigator assessments of efficacy can be done, but the following data will be collected remotely, according to the SoA (Table 1-1):

- AE reporting.
- Treatment compliance (daily completion in the eDiary).
- Concomitant medication and concurrent procedures.
- HESD (daily completion in the eDiary).
- Participant assessment of local tolerability (weekly completion in the eDiary).
- PROs (DLQI, HEIS, EQ-5D-5L, TSQM, WPAI-CHE, PGI-S, and PGI-C). The participants will receive a link to complete the PROs in a web browser from their own device.
- New CHE lesions.
- Urine pregnancy test. Women of childbearing potential will receive 1 extra urine pregnancy test at the randomisation visit to keep at home in case on-site visits become impossible during the trial. The participant will perform the test at home and inform the investigator about the result via phone and to send a picture of the test to the site or show it via video. Additional urine pregnancy tests can be shipped to the participant's home together with IMP (see below) if needed.
- For participants treated with alitretinoin:
    - Serum cholesterol and serum triglycerides (fasting values) should continue to be monitored by a local laboratory, at the timepoints outlined in the SoA (Table 1-1).
    - Remote consultation to allow for adequate monitoring of mental health should be maintained at the timepoints outlined in the SoA (Table 1-1). The potential for psychiatric disorders may be increased by COVID-19 isolation measures and this may complicate the clinical picture.

In the eCRF, it will be recorded whether a visit or a given assessment was done remotely or not done. If not done, it will be recorded if this was due to the COVID-19 pandemic.

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

Contingency plans due to COVID-19 must follow the authorities' COVID-19 guidelines and local requirements. Written procedures describing the contingency plan must be in place at site and depot. To ensure availability of IMP, the trial sites will dispense additional IMP if considered relevant (i.e. if local authority-issued preventive measures are to be expected at the given trial site). This will allow participants to continue IMP although they are not able to go to the trial site. If a participant will not be able to attend on-site visits due to the COVID-19 pandemic before running out of IMP, the trial site will ensure shipping of IMP to the participant's home. As the participants' IMP supply is secured, the IE of initiation of rescue treatment will be considered independent of the COVID-19 pandemic in the statistical analysis.

If a participant is tested positive for COVID-19, the investigator will evaluate whether this is an AE that contraindicates further dosing, in which case the participant will permanently discontinue IMP as described in Section 7.1.

10.6 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

10.6.1 Liver Chemistry Monitoring and Reporting

In case of an increase of ALT and/or AST ≥5×ULN, re-sampling for ALP, ALT, AST, bilirubin, and prothrombin INR should be done immediately, without undue delay and no later than within 72 hours from initial sampling time to confirm abnormalities. Re-sampling may be relevant at lower levels at the discretion of the investigator. Participant should be monitored weekly until liver chemistry test abnormalities resolve, stabilise, or return to baseline.

In case of abnormal liver function tests of concurrent measurements of ALT and/or AST ≥3×ULN with total bilirubin ≥2×ULN or prothrombin INR ≥1.5×ULN, re-sampling for ALP, ALT, AST, bilirubin, and prothrombin INR should be done immediately, without undue delay and no later than within 24 hours from initial sampling time and the abnormality should be should be reported as an SAE (see Section 10.3.4 for reporting of SAEs). Participants should be monitored twice weekly until liver function test abnormalities resolve, stabilise, or return to baseline.

10.6.2 Discontinuation of IMP

As described in Section 7.1, the IMP should be discontinued permanently in case of:

- ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
- ALT and/or AST values >3×ULN with prothrombinINR >1.5×ULN.
- Confirmed ALT and/or AST values >5×ULN (for more than 2 weeks).

10.6.3 Recommended Follow-up Assessments

- Viral hepatitis serology, including hepatitis A immunoglobulin M (IgM) antibody; HBsAg and hepatitis C core antibody (HBcAb); hepatitis C ribonucleic acid (RNA); cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at trial entry (identified by positive HBsAg) quantitative hepatitis B desoxyribonucleic acid (DNA) and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) (Le Gal et al, 2005).
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin > 2×ULN

- Complete blood count with differential to assess eosinophilia
- Record the following:
  - Appearance or worsening of clinical symptoms of liver injury, or hypersensitivity.
  - Use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications).
  - Alcohol use.
- If ALT and/or AST > 3×ULN and total bilirubin > 2×ULN or prothrombin INR > 1.5, the following assessments may be obtained (in addition to the assessments listed above):
  - Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.
  - Serum acetaminophen adduct, when available, assay to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week.
  - Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.
  - Liver biopsy may be discussed with local specialist if available, for instance:
    - In participants when serology raises the possibility of autoimmune hepatitis (AIH).
    - In participants when suspected drug-induced liver injury (DILI) progresses or fails to resolve on withdrawal of trial intervention.
    - In participants with acute or chronic atypical presentation: hepatic vascular disorder, chronic hepatitis fibrosis, micro vesicular steatosis.

10.7 Appendix 7 Country-specific requirements

France

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

Section 5.2 Exclusion criteria

Participants are excluded from the trial if any of the following criteria apply:

34. Participants not affiliated with or not a beneficiary of a social security scheme.

10.8 Appendix 8: Abbreviations

Abbreviation	Description
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	area score
AST	aspartate aminotransferase
AUC	area under the curve
BfArM	Federal Institute for Drugs and Medical Devices
CDISC	Clinical Data Interchange Standards Consortium
CHE	chronic hand eczema
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this trial)
CRO	Contract Research Organisation
DBL	database lock
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data collection
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis C core antibody
HCV	hepatitis C virus
HDL	high-density lipoprotein
HECSI	Hand Eczema Severity Index

HEIS / HEIS©	Hand Eczema Impact Scale©
HESD / HESD©	Hand Eczema Symptom Diary©
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IE	intercurrent event
IEC	Independent Ethics Committee
IGA-CHE / IGA-CHE©	Investigator's Global Assessment for chronic hand eczema©
IgE	immunoglobulin E
IMP	investigational medicinal product
INR	international normalised ratio
IRB	Institutional Review Board
IRT	interactive response technology
JAK	Janus kinase
LDL	low-density lipoprotein
MAR	missing at random
MI	multiple imputation
PCR	polymerase chain reaction
PDAL	Proximal Daily Activity Limitations
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PRO	patient-reported outcome
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase

SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TCS	topical corticosteroid(s)
TMF	trial master file
WBC	white blood cell
WOCBP	woman of childbearing potential
WOCF	worst observation carried forward

10.9 Appendix 9: Amendments

Amendment 3 (08 Apr 2022)

Overall Rationale for the Amendment

The protocol was amended in order to implement changes from local amendments (UK and Canada).

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (SoA)	Table 1-1 was updated to include the check of contraception compliance in the alitretinoin group only at all study visits (except at Day 8 and Day 15). A typo was corrected in footnote number 13. Sub header "Participant assessment of safety" was added. "Weekly" changed to "Weekly while on treatment" as many participants will not be on Delgocitinib treatment at visit 9 and 10. Footnote added to clarify this difference.	This was updated to address questions from Health Canada.

Section # and Name	Description of Change	Brief Rationale
Section 1.3: Schedule of Activities (SoA) Section 8.2.7.1: Pregnancy Testing	Assessment added under sub-header "Participant assessments of efficacy and health-related quality of life during trial visits" to indicate an additional local tolerability assessment during visits. Addition of Participant assessment of local tolerability at End of Treatment and Early Termination visit.	Only weekly assessment of local tolerability is collected in the eDiary. Participant assessment of local tolerability is added to the End of Treatment and Early Termination visit in eCRF to ensure that participant assessment of local tolerability data is collected at these visits.
Section 1.3: Schedule of Activities (SoA) Section 2.3.1: Risk Assessment (Table 2-1) Section 5.1: Inclusion Criteria Section 10.4.2: Contraception Guidance	Additional information for footnote 6 to accommodate for the extension of the screening period for WOCBP on contraception. Text amended to clarify contraception requirements.	To ensure compliance with pregnancy prevention program for WOCBP.
Section 1.3: Schedule of Activities (SoA)	The text "alitretinoin group only" removed from mental health interview. Footnote added to Table 1-1 for clarification.	To clarify that the metal health interview is applicable for both treatment groups at Screening and Baseline.
Section 2.3.1: Risk Assessment	Text was added to report on the safety concerns for oral JAK inhibitors.	This was updated according to the latest edition of the IB.
Section 5.2: Exclusion Criteria	Exclusion criterion number 16 was updated to include potent CYP3A4 inducers to the list of drugs.	This was updated to address questions from Health Canada.
Section 6.2.1.2: Alitretinoin Capsules Section 10.3.4: Reporting of SAE	Text added to specify the representative drug label to be used for Canada, the UK and EU countries.	Added as per request from BfArM.

Section # and Name	Description of Change	Brief Rationale
Section 6.8.3: Prohibited Medications and Procedures	Table 6-2 was updated to include the prohibition period for potent CYP3A4 inducers (from 28 days prior to baseline to end of the trial). Footnote added to Table 6-2 for clarification.	This was updated to address questions from Health Canada.
Section 8: Trial Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the trial was changed from 100 mL to 180 mL.	It was identified that the previously indicated blood volume was lower than the amount required for the sampling specified in the protocol.
Section 8.1.1: Hand Eczema Severity Index (HECSI) Section 8.1.2: Investigator's Global Assessment for Chronic Hand Eczema© (IGA-CHE)	Text amended to clarify the assessment of new lesions by blinded assessor.	This was updated to address the comments of the Italian Regulatory Authority.
Section 8.2.5: Pregnancy Testing	A statement was added to mention that for women of childbearing potential randomized to alitretinoin, the investigator must confirm compliance to acceptable method(s) of contraception, as shown in the schedule of activities.	This was updated to address questions from Health Canada.
Section 10.9: Appendix 9: Amendments	Addition of previous amendments under Appendix 9.	Included to reflect the different amendments of the document.
Section 11: References	Reference added for the German Toctino® Summary of Product Characteristics (SmPC).	Added as per request from BfArM.
Throughout the document	Addition of BfArM in the abbreviations list. Updating IB edition and year.	Minor editorial and document formatting revisions.

Amendment 2 (25 Feb 2022)

Overall Rational for the Amendment

The protocol was amended in order to address feedback from the Federal Institute for Drugs and Medical Devices (BfArM) while allowing for a factual correction relating to blood sample volume that was identified in review.

Section # and Name	Description of Change	Brief Rationale
Section 5.1: Inclusion Criteria Section 10.4.2: Contraception Guidance	Text amended to clarify contraception requirements.	Added as per request from BfArM.
Section 8: Trial Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the trial was changed from 100 mL to 180 mL.	It was identified that the previously indicated blood volume was lower than the amount required for the sampling specified in the protocol.

Amendment 1 (21 Jan 2022)

Overall Rationale for the Amendment:

The protocol was amended in order to address feedback from Health Canada while allowing for a factual correction relating to blood sample volume that was identified in review.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Table 1-1 was updated to include the check of contraception compliance in the alitretinoin group only at all study visits (except at Day 8 and Day 15). A typo was corrected in footnote number 13.	This was updated to address questions from Health Canada.
Section 5.2 Exclusion Criteria	Exclusion criterion number 16 was updated to include potent CYP3A4 inducers to the list of drugs.	This was updated to address questions from Health Canada.
Section 6.8.3 Prohibited Medications and Procedures	Table 6-2 was updated to include the prohibition period for potent CYP3A4 inducers (from 28 days prior to baseline to end of the trial).	This was updated to align with the change done to the exclusion criterion number 16.
Section 8 Trial Assessments and Procedures	The maximum amount of blood collected from each participant over the duration of the trial was changed from 100 mL to 180 mL.	It was identified that the previously indicated blood volume was lower than the amount required for the sampling specified in the protocol.
Section 8.2.5 Pregnancy Testing	A statement was added to mention that for women of childbearing potential randomized to alitretinoin, the investigator must confirm compliance to acceptable method(s) of contraception, as shown in the schedule of activities.	This was updated to align with the change done to the schedule of activities.

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Toctino® SmPC, UK
Summary of Product Characteristics for alitretinoin (Toctino®) – Stiefel – UK.

Toctino® SmPC, Germany
Summary of Product Characteristics for alitretinoin (Toctino®) – Germany.