Cover Page

Study title:	A 32-week Trial to Evaluate the Efficacy and Safety of Tralokinumab in Subjects With Moderate-to-severe Atopic Hand Eczema Who Are Candidates for Systemic Therapy
LEO Pharma number:	LP0162-2328
NCT number:	NCT05958407
Date:	13-Nov-2024

Updated clinical trial protocol

LP0162-2328

A phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy (ADHAND)

Approval statement, LEO Pharma A/S

The following persons have approved this CTP:

Name, academic degree	Role	Department
PPD , MD, MSc	PPD	Global Clinical Development
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PPD , MD, PhD	PPD	Medical Department
PPD , MSc Pharm	PPD	Global Clinical Operations
Benjamin David Ehst, MD PhD	Signatory investigator	External

Title page

Trial ID	LP0162-2328
Protocol title:	A phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy.
Brief title:	A 32-week trial to evaluate the efficacy and safety of tralokinumab in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy.
Acronym	ADHAND
Trial phase:	Phase 3b
Compound:	Tralokinumab
Indication:	Atopic dermatitis and moderate-to-severe atopic hand eczema.
Trial sponsor:	LEO Pharma A/S Industriparken 55, DK 2750 Ballerup, Denmark
Regulatory agency identifier numbers:	Universal trial number: U1111-1285-7014 IND number: 123797 EU CT number: 2022-502653-34 Japanese trial registration number: Not applicable.
Version:	6.0
Approval date:	13-Nov-2024

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP (1), and the applicable regulatory requirements.

Protocol amendment summary of changes

Document history

Document	Date	Type of protocol amendment
Amendment 6	13-Nov-2024	Country-specific (EU/EMA)
Amendment 5	08-May-2024	Country-specific (EU/EMA)
Amendment 4	12-Feb-2024	Global
Amendment 3	10-Oct-2023	Global
Amendment 2	09-Aug-2023	Global
Amendment 1/ KOR	07-Jul-2023	Country-specific (South Korea)
Original protocol	03-Mar-2023	Not applicable

Amendment 6 (13-Nov-2024)

This amendment is considered to be non-substantial based on guidance from RMS and the criteria set forth in Article 2(13) of Regulation 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

To fulfil the previous regulatory request, the protocol has been updated with the precise sample size calculated in the sample size recalculation interim analysis.

Section number and title	Description of change	Brief rationale
Section 9.3.2 Primary endpoint analysis	Correction that if the hypothesis is rejected, $\tilde{\mu}$ is not included in the confidence interval.	Correction of a mistake in the description of the method for constructing the 95% confidence interval.
Section 9.3.5.3 Clinical laboratory evaluation	Clarification that shift tables will not be presented for ALP and eGFR.	ALP and eGFR are only evaluated at screening.
Section 9.5 Sample size	The sample size, as calculated during the interim analysis for sample size recalculation has been included.	Per request from the reporting and other member states during the CTIS review process.
Section 10.7 Appendix 7 Protocol amendment history	Amendment 5 has been moved from the Protocol amendment summary of changes to Section 10.7	Administrative change
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

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List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AHE	atopic hand eczema
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	area score
AST	aspartate aminotransferase
BILI	bilirubin
CDISC	Clinical Data Interchange Standards Consortium
CHE	chronic hand eczema
CIQ	Classroom Impairment Questionnaire in atopic hand eczema
CMO	contract manufacturing organization
CRA	clinical research associate
CRO	contract research organization
CT	clinical trial
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
CTP	clinical trial protocol
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome
EU	European Union
FAS	full analysis set
FSH	follicle-stimulating hormone

GCP	Good Clinical Practice
HCP	healthcare professional
HECSI	Hand Eczema Severity Index
HEIS	Hand Eczema Impact Scale
HESD	Hand Eczema Symptom Diary
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IGA-AHE	Investigator's Global Assessment for Atopic Hand Eczema
IGA-CHE	Investigator's Global Assessment for Chronic Hand Eczema
IgE	immunoglobulin E
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	institutional review board
IRT	interactive response technology
JAK inhibitor	janus kinase inhibitor
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
PRO	patient-reported outcome
Q2W	every 2 weeks
SAE	serious adverse event
SAF	safety analysis set
SC	subcutaneous(ly)
SD	standard deviation
SFU	safety follow-up

SOC	system organ class
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential
WPAI	Work Productivity and Activity Impairment

1 Protocol summary

1.1 Protocol synopsis

Trial ID	LP0162-2328
Protocol title	A phase 3b, interventional, adaptive, clinical trial to evaluate the efficacy and safety of tralokinumab 300 mg every second week monotherapy compared with placebo in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy.
Brief title	A 32-week trial to evaluate the efficacy and safety of tralokinumab in subjects with moderate-to-severe atopic hand eczema who are candidates for systemic therapy.
Regulatory agency identifier numbers	Universal trial number: U1111-1285-7014 IND number: 123797 CT number: 2022-502653-34 Japanese trial registration number: Not applicable
Trial rationale	As the currently available treatment options either lack documented treatment effect or are limited by restrictions of long-term use due to safety concerns, there is a high unmet medical need for new treatments of AD with moderate-to-severe involvement of the hands and wrists that have high efficacy in combination with a good safety profile, especially for long-term use. New and better treatments would potentially improve HRQoL of patients with moderate-to-severe atopic hand eczema.
Ethical considerations	• This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and ICH GCP, and in compliance with the approved protocol and applicable regulatory requirements. • Participation in this trial is voluntary and subjects can withdraw at any time. The subjects will give informed consent. No vulnerable subject incapable of giving informed consent will be enrolled in this clinical trial. • To ensure subjects' safety, investigators are informed only to enroll subjects who are considered able to stop prohibited treatment during the screening period without experiencing intolerable worsening of AD and AHE symptoms. • Placebo control is considered to provide the best design for efficient assessment of both benefit and risk. • To mitigate the risk for worsening of AHE symptoms during the treatment and follow-up periods, rescue treatment may be prescribed to trial subjects at the discretion of the investigator. Subjects will be instructed to contact the investigator if their AD and/or AHE worsens significantly.

<table>
<tr><td></td><td>

- Qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial.

</td></tr>
<tr><td>Main objectives, estimands, and endpoints</td><td>

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary objective</td></tr>
<tr><td>To evaluate the efficacy of tralokinumab on severity and extent of atopic hand eczema compared with placebo in treatment of subjects with moderate-to-severe atopic hand eczema</td><td>

Primary endpoint

- IGA-AHE[a] score of 0 (clear) or 1 (almost clear) at Week 16.

Key secondary endpoints

- Having a decrease in HECSI[b] of at least 75% (HECSI-75) from baseline to Week 16.
- Having a decrease in HECSI of at least 50% (HECSI-50) from baseline to Week 16.
- Having a decrease in HECSI of at least 90% (HECSI-90) from baseline to Week 16.
- Percentage change in HECSI score from baseline to Week 16.

Secondary endpoints

- Having a ≥2-point reduction in IGA-AHE score from baseline to Week 16.

</td></tr>
<tr><td colspan="2">Secondary objective</td></tr>
<tr><td>To evaluate the efficacy of tralokinumab on severity, extent, itch, pain, sleep, and health-related quality of life compared with placebo in treatment of subjects with moderate-to-severe atopic hand eczema</td><td>

Key secondary endpoints

- Reduction in HESD[c] itch score (weekly average) of ≥4 points from baseline to Week 16.
- Reduction in HESD pain score (weekly average) of ≥4 points from baseline to Week 16[d].
- Percentage change in HEIS[e] score from baseline to Week 16.
- Percentage change in DLQI[f] score from baseline to Week 16.

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</table>

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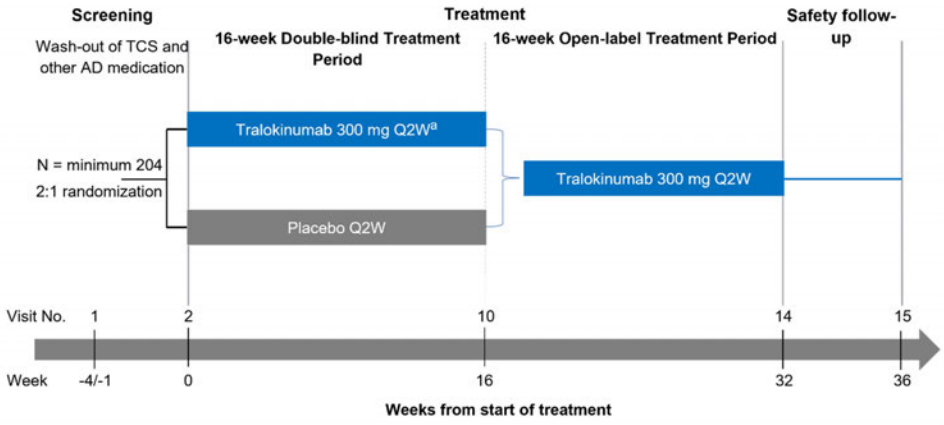
		Secondary endpoints • Percentage change in HESD itch score (weekly average) from baseline to Week 16. • Percentage change in HESD pain score (weekly average) from baseline to Week 16. • Change in WPAI+CIQ:AHE[g] domain scores from baseline to Week 16.
	To evaluate the safety and tolerability of tralokinumab in subjects with moderate-to-severe atopic hand eczema	**Secondary endpoint** • Number of treatment-emergent adverse events from baseline to Week 16.
	Other objective	
	To evaluate the efficacy on severity, extent, itch, pain, sleep, and health-related quality of life and the safety and tolerability of continued tralokinumab treatment in subjects with moderate-to-severe atopic hand eczema in the open-label treatment period (up to 32 weeks)	**Secondary endpoints** • IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 32. • Having a decrease in HECSI of at least 75% (HECSI-75) from baseline to Week 32. • Reduction in HESD itch score (weekly average) of ≥4 points from baseline to Week 32. • Reduction in HESD pain score (weekly average) of ≥4 points from baseline to Week 32[d]. • Percentage change in HEIS score from baseline to Week 32. • Percentage change in DLQI score from baseline to Week 32. • Change in WPAI+CIQ:AHE domain scores from baseline to Week 32. • Number of treatment-emergent adverse events during the open-label treatment period (Week 16 to Week 32).

a. IGA-AHE: The Investigator's Global Assessment for atopic hand eczema is an instrument developed by LEO Pharma to rate the severity of the subject's AHE and is based on a 5-point scale ranging from 0 (clear) to 4 (severe).

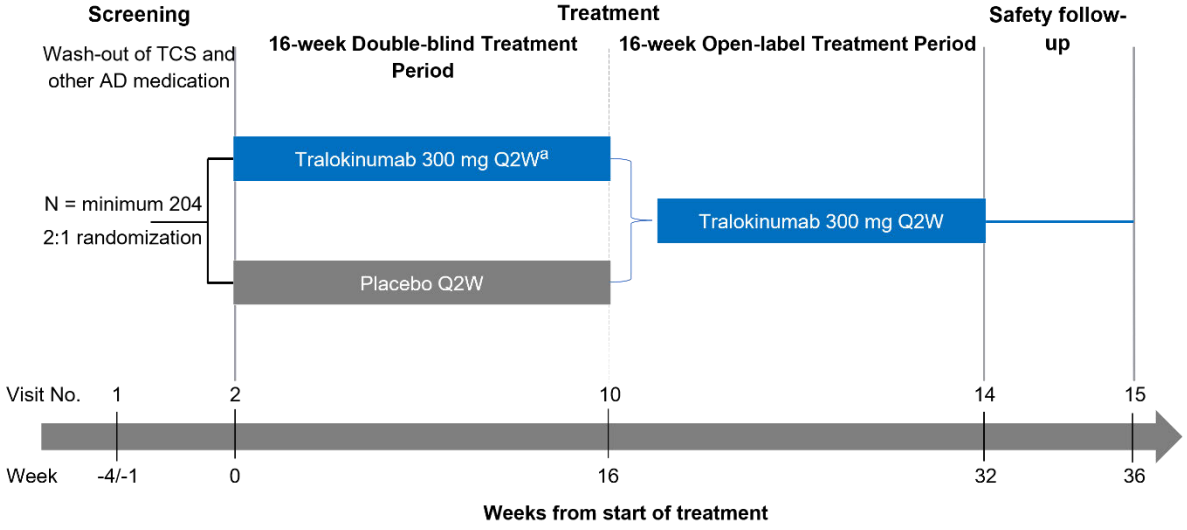
	b. HECSI: The Hand Eczema Severity Index (HECSI) is an instrument used in clinical trials to rate the severity of 6 clinical signs using a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) and the extent of the lesions on each of the 5 hand areas by assessing the percentage of the areas these lesions occupy and converting it to a score based on a 5-point scale. c. HESD: The Hand Eczema Symptom Diary (HESD) is a 6-item patient-reported outcome where the subject assesses the worst severity of 6 individual signs and symptoms of hand eczema over the past 24 hours using an 11-point numeric rating scale with anchors of 0 =‘no (symptom)’ and 10 =‘severe (symptom)’. Only the items on itch and pain will be completed. d. Among subjects with a baseline HESD pain score (weekly average) ≥4 points. e. HEIS: The Hand Eczema Impact Scale (HEIS) includes 9 items addressing the subject’s perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning over the past 7 days. Each item is scored on a 5-point scale (0=‘not at all’, 1=‘a little’, 2=‘moderately’, 3=‘a lot’, 4=‘extremely’). f. DLQI: The Dermatology Life Quality Index (DLQI) consists of 10 items addressing the subject’s perception of the impact of their skin disease on different aspects of their quality of life over the last week. 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’). g. WPAI+CIQ:AHE: The impact of AHE on the subject’s ability to work/school and perform regular activities will be assessed by WPAI+CIQ:AHE, which is an instrument to measure impairments in both paid work and unpaid work/school attendance. The WPAI+CIQ:AHE consists of 10 items, and scores can be calculated for 7 domains, each reflecting the percentage impairment due to AHE during the past 7 days, with higher numbers indicating greater impairment and less productivity/school attendance. The primary estimand for the primary endpoint will be the treatment difference in response rates of IGA-AHE after 16 weeks achieved without the use of rescue treatment or discontinuation of IMP due to lack of efficacy or adverse event in a hypothetical setting where discontinuation of IMP due to other reasons would not occur.
Trial design	This is a phase 3b, interventional, international, multi-center, randomized, 16-week, double-blind, placebo-controlled, parallel-group, adaptive clinical trial with a 16-week, open-label treatment period. The trial is designed to evaluate the efficacy and safety of 300 mg tralokinumab every 2 weeks compared to placebo for 16 weeks in subjects with moderate-to-severe atopic hand eczema. Following the 16-week,

	double-blind period, subjects will receive open-label, 300 mg tralokinumab every 2 weeks for 16 weeks.  a. Subjects will receive a loading dose of tralokinumab 600 mg on Day 1.
Brief summary	• The purpose of this trial is to compare the efficacy and safety of 300 mg tralokinumab every 2 weeks with placebo in subjects with moderate-to-severe hand eczema. • The objective of the primary endpoint is to demonstrate that tralokinumab is superior to placebo in achieving a higher response rate of IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16. • The subjects have had atopic dermatitis for at least 1 year with atopic hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months prior to screening with avoidance of any known and relevant irritants and allergens. • Subjects must not enter the trial if they have subtypes of hand eczema other than atopic hand eczema.
Number of subjects	229 subjects will be randomized 2:1 to tralokinumab or placebo.
Treatment groups and duration	For each subject, the trial will last at least 37 weeks and up to 40 weeks, including: ○ a 1-to 4-week screening period ○ a 16-week double-blind treatment period ○ a 16-week open-label treatment period ○ a 4-week safety follow-up period. • At Baseline (Visit 2, Day 1), subjects will be randomized 2:1 to receive either tralokinumab or placebo: ○ Tralokinumab 300 mg Q2W: tralokinumab 600 mg (4 mL) at baseline, then tralokinumab 300 mg (2 mL) Q2W. ○ Placebo Q2W: placebo (4 mL) at baseline, then placebo (2 mL) Q2W. • After the initial 16 weeks, all subjects will receive tralokinumab every 2 weeks for an additional 16 weeks.

	• Tralokinumab and placebo will be given as subcutaneous injections in the upper arm, anterior thigh, or abdomen. • The visit frequency will be every 2 weeks for the first 18 weeks, then a visit after 6 weeks (Week 24), followed by visits every 4 weeks; the Week 18, Week 28, and Week 36 visits are remote. IMP will be administered at home by the subject at Weeks 18, 20, 22, 26, 28, and 30.
DMC / Other Committee	Not applicable.

1.2 Schematic of trial design

Panel 1: Trial design



a. Subjects will receive a loading dose of tralokinumab 600 mg on Day 1.

Abbreviations: AD = atopic dermatitis; N = number of subjects; Q2W = every 2 weeks; TCS = topical corticosteroids.

1.3 Schedule of activities

Panel 2: Schedule of activities – Double-blind treatment period

	Screening	Double-blind treatment period									Notes (protocol section number)
Visit	**1**	**2**[1]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	1. Baseline.
Week	**-4**[2]**/-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**[3]	2. For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period (4.1 and 5.2).
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	3. Primary endpoint.
Visit window (days)[4]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
Administrative and baseline procedures											
Informed consent(s)	X										The ICF(s) must be signed prior to performing any protocol related procedures, including screening evaluations and wash-out (10.1.3).
Subject eligibility	X	X									(5.1 and 5.2)
Demographics	X										(8.1.1)
Medical history	X	X									(8.1.2)
Body measurements		X									(8.1.3)
eDiary handout/training	X										(8.7.1)
Treatments and randomization											
Randomization		X									(6.3.1)
IMP dispensation		X	X	X	X	X	X	X	X	X	The IRT system will assign the required kit numbers for each subject at each dispensing visit (6.2.1).

	Screening	Double-blind treatment period									Notes (protocol section number)
Visit	**1**	**2**[1]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	1. Baseline.
Week	**-4**[2]**/-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**[3]	2. For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period (4.1 and 5.2).
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	3. Primary endpoint.
Visit window (days)[4]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
IMP administration		X	X	X	X	X	X	X	X	X[5,6]	IMP administration on site must be performed by a qualified, unblinded health care professional (6.2.1). 5. Training in home dosing and hand-out of the instruction for use document (6.2.1). 6. IMP will be open-label tralokinumab.
IMP dispensation for home use										X	Subject will receive IMP for home administration.
IMP compliance		X	X	X	X	X	X	X	X	X	(6.4)
Prior and concomitant medication and concurrent procedures	X	X	X	X	X	X	X	X	X	X	Any prior/concomitant medication should be included from 3 months prior to screening (Visit 1) until end of trial (Week 36) (6.7).
Assessments of efficacy											
IGA-AHE	X	X	X	X		X		X		X	(8.2.1)
HECSI		X	X	X		X		X		X	(8.2.2)
EASI		X				X				X	(8.2.3)
Assessments of safety											
Vital signs	X	X								X	(8.3.1)
Physical examination	X										(8.3.2)

	Screening	Double-blind treatment period								
Visit	**1**	**2**[1]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-4**[2]**/-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**[3]
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**
Visit window (days)[4]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adverse events		X[7]	X	X	X	X	X	X	X	X
Laboratory tests										
Chemistry, hematology, and serology (central laboratory)	X					X				X
Serum pregnancy test (central laboratory)	X									
Urine pregnancy test		X		X		X		X		X
PROs										
eDiary completion: HESD itch and pain	Daily									
PGI-S		X	X	X		X		X		X
PGI-C			X	X		X		X		X

Notes (protocol section number)

1. Baseline.
2. For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period (4.1 and 5.2).
3. Primary endpoint.
4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
7. Only report AEs with onset from the day of the baseline visit. However, medical occurrences with onset between informed consent and baseline visit need to be recorded, if applicable, as medical history in the eCRF (8.4 and 10.2).
8. Serology performed only at screening (8.3.3).

Completion of HESD itch and pain will be initiated at least 1 week prior to baseline (Visit 2), but preferably from the date the subjects receive the eDiary. Compliance with the eDiary completion will be reviewed by the site staff throughout the trial (8.2.4). For subjects who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met (5.1).

Includes Itch PGI-S and Pain PGI-S (8.7.1.1).

Includes Itch PGI-C and Pain PGI-C (8.7.1.2).

	Screening	Double-blind treatment period								
Visit	**1**	**2**[1]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-4**[2]**/-1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**[3]
Visit type	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**	**Site**
Visit window (days)[4]	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
HEIS		X	X	X		X		X		X
DLQI		X	X	X		X		X		X
WPAI+CIQ:AHE		X	X	X		X		X		X
Other assessments										
Photography of hand eczema		X		X		X		X		X

Notes (protocol section number)

1. Baseline.
2. For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period (4.1 and 5.2).
3. Primary endpoint.
4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).

(8.7.1.3)

(8.7.1.4).

(8.7.1.5)

Optional (8.7.2).

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-AHE = Investigator's Global Assessment for Atopic Hand Eczema; IMP = investigational medicinal product; NA = not applicable; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; WPAI+CIQ:AHE = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire in atopic hand eczema.

Panel 3: Schedule of activities – Open-label treatment period and safety follow-up, unscheduled, and early termination visits

	Open-label treatment period				SFU[1] (6 weeks after last dose of IMP)	Un-scheduled visit[2]	Early term. (if applicable)[3]	Notes (protocol section number)
Visit	**11**	**12**	**13**	**14**	**15**			1. SFU may be performed as on-site visit if needed. 2. Assessments to be performed at unscheduled visits will be at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment as outlined in Section 6.7.2. 3. All subjects will have a SFU visit 6 weeks after last administration of IMP. 4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
Week	**18**	**24**	**28**	**32**	**36**			
Visit type	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Site**	
Visit window (days)[4]	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	
Treatments								
IMP dispensation		X				X		
IMP administration	X	X	X			X		IMP administration will be performed by the subject at home at Weeks 18, 20, 22, 26, 28, and 30 (6.2.1). IMP administration on site (Week 24) should preferably be performed by the subject or alternatively by a qualified unblinded health care professional (6.2.1).
IMP dispensation for home use		X				X		Subject will receive IMP for home administration.
IMP compliance	X	X	X	X		X	X	(6.4)
Prior and concomitant medication and concurrent procedures	X	X	X	X		X	X	Any prior/concomitant medication should be included from 3 months prior to baseline (Day 1) until end of trial (Week 36) (6.7).
Assessments of efficacy								
IGA-AHE		X		X		X	X	(8.2.1)
HECSI		X		X		X	X	(8.2.2)

	Open-label treatment period				SFU[1] (6 weeks after last dose of IMP)	Un-scheduled visit[2]	Early term. (if applicable)[3]	Notes (protocol section number)
Visit	**11**	**12**	**13**	**14**	**15**			1. SFU may be performed as on-site visit if needed. 2. Assessments to be performed at unscheduled visits will be at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment as outlined in Section 6.7.2. 3. All subjects will have a SFU visit 6 weeks after last administration of IMP. 4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
Week	**18**	**24**	**28**	**32**	**36**			
Visit type	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Site**	
Visit window (days)[4]	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	
EASI		X		X		X	X	(8.2.3)
Assessments of safety								
Vital signs				X		X	X	(8.3.1)
Adverse events	X	X	X	X	X	X	X	(8.4 and 10.2)
Chemistry, hematology (central laboratory)				X		X	X	(8.3.3)
Urine pregnancy test		X		X		X	X	Only women of childbearing potential (8.3.3 and 10.4).
PROs								
eDiary completion: HESD itch and pain	Daily							Compliance with the eDiary completion will be reviewed by the site staff throughout the trial (8.2.4).
PGI-S						X		Includes Itch PGI-S and Pain PGI-S (8.7.1.1).
PGI-C						X		Includes Itch PGI-C and Pain PGI-C (8.7.1.2).
HEIS		X		X		X	X	(8.7.1.3).
DLQI		X		X		X	X	(8.7.1.4).
WPAI+CIQ:AHE		X		X		X	X	(8.7.1.5)

	Open-label treatment period				SFU[1] (6 weeks after last dose of IMP)	Un-scheduled visit[2]	Early term. (if applicable)[3]	Notes (protocol section number)
Visit	**11**	**12**	**13**	**14**	**15**			1. SFU may be performed as on-site visit if needed. 2. Assessments to be performed at unscheduled visits will be at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment as outlined in Section 6.7.2. 3. All subjects will have a SFU visit 6 weeks after last administration of IMP. 4. If a visit does not conform to the protocol, subsequent visits should be planned to maintain the visit schedule relative to Week 0 (Visit 2).
Week	**18**	**24**	**28**	**32**	**36**			
Visit type	**Phone**	**Site**	**Phone**	**Site**	**Phone**	**Site**	**Site**	
Visit window (days)[4]	**±3**	**±3**	**±3**	**±3**	**±3**	**NA**	**NA**	
Other assessments								
Photography of hand eczema		X		X		X	X	Optional (8.7.2).
Other procedures								
Return of eDiary				X			X	(8.7.1)
End of trial								
End of treatment				X			X	(8.8)
End of trial					X		X	(8.8)

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-AHE = Investigator's Global Assessment for Atopic Hand Eczema; IMP = investigational medicinal product; NA = not applicable; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; SFU = safety follow-up; WPAI+CIQ:AHE = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire in atopic hand eczema.

2 Introduction and trial rationale

2.1 Atopic dermatitis and moderate-to-severe atopic hand eczema

AD is a chronic inflammatory skin disease that may affect up to 20% of children and up to 10% of adults (2, 3). In its moderate and severe form, AD is characterized by widespread skin lesions, intractable itch, as well as enhanced susceptibility to bacterial, viral, and fungal skin infections. AD is associated with a substantial patient burden that typically includes poor quality of life and sleep disturbance (4).

The majority of patients with AD also present with involvement of their hands (atopic hand eczema [AHE]) (5, 6). AHE occurs in individuals with a previous or current medical history of atopic dermatitis and with no documented irritant exposure and/or relevant contact allergen likely to cause eczema (7). AHE is among the most frequently reported subtypes of HE (8), alone or in combination with other subtypes (9).

The association between AD and HE is strongest in patients with severe AD, in patients with AD since childhood, and in patients with persistent AD on other parts of the body (10-12). Furthermore, patients with AHE have more severe HE (13, 14) and resolution of AHE is less likely than other subtypes of HE (12).

There is often no apparent link between the etiologic and morphologic picture of HE, and the morphology of lesions, and even the cause often change over time in affected patients (15, 16). Among the primary acute lesions that may be observed are erythema, oedema, oozing, crusting, papules, and vesicles/bullae. Secondary chronic lesions include lichenification, hyperkeratosis, scaling, and fissures. Pruritus is the most common symptom in all types of eczema, whereas skin pain, burning, and stinging are increasingly appreciated as important symptoms as well (17).

Due to the severity and location on the body, hand eczema has the potential to dramatically impact quality of life by affecting social functioning and the ability to perform activities of daily living. There are no studies of the impact of AHE specifically on the patients' quality of life. However, CHE, which is defined as hand eczema which persists for more than 3 months or returns twice or more within 12 months (7), is associated with increased sick leave (18, 19) as well as job loss and change in jobs (8, 20, 21). Overall, HE has a significant detrimental effect on HRQoL, work productivity, daily activities, and health care costs (22). Capucci et al. (23) reported that the lives of patients with AD and CHE can be as strenuous as those of patients living with other diseases, such as cancer or type 2 diabetes, and compared with most other chronic conditions, moderate-to-severe AD and CHE have a bigger impact on HRQoL.

HE often has a chronic relapsing course which is generally difficult to treat and presents with periods of flares and periods of remissions, and, in HE as well as in AHE, long-term treatment is needed. AHE is treated the same way as AD on other parts of the body (5), that is, general skin care and anti-inflammatory therapy in a step wise approach. Treatment recommendations for AD include topical therapies, the main being TCS. Unfortunately, TCS and TCIs of mild to moderate potency have limited efficacy, while ultrapotent TCS are associated with side effects, including atrophy, with long-term use. TCS and non-biologic systemic therapies (e.g., cyclosporine A, azathioprine) are all associated with toxicities with long-term use (25-27). The biological agent dupilumab has shown preliminary effect in CHE (28), suggesting there may be similarities in the pathophysiology of atopic dermatitis and hand dermatitis.

Tralokinumab has demonstrated good efficacy in the treatment of moderate-to-severe AD and has an established favourable benefit-risk profile, also in long-term use.

2.2 Experience with investigational medicinal product

A total of 4,908 subjects have received at least one dose of tralokinumab in a clinical trial setting (cut-off date 18-Aug-2022). The majority of the tralokinumab exposure was from trials within AD and asthma. A clinical development program continues in subjects with AD. All doses studied thus far have had an acceptable benefit-risk profile and no major safety concerns have been identified.

Possible risks associated with the use of tralokinumab are summarized in Section 2.5.1.

Further details can be found in the IB for tralokinumab (29).

2.3 Trial rationale

As the currently available treatment options either lack documented treatment effect or are limited by restrictions of long-term use due to safety concerns (7, 30), there is a high unmet medical need for new treatments of AD with moderate-to-severe involvement of the hands and wrists that have high efficacy in combination with a good safety profile, especially for long-term use. New and better treatments would potentially improve HRQoL of patients with AD and moderate-to-severe AHE.

The type 2 cytokine IL-13 is one of the key drivers of the underlying inflammation in AD (31, 32), implicated in skin barrier disruption, skin inflammation, increased risk of skin infections, itch signalling, and epidermal hyperplasia (33), with levels of IL-13 in lesional skin correlating with AD severity (34, 35).

The biological agent dupilumab, which inhibits both IL-4 and IL-13, has shown preliminary effect in CHE (28), suggesting there may be similarities in the pathophysiology of atopic dermatitis and hand dermatitis.

Tralokinumab, a fully human immunoglobulin G4 monoclonal antibody, specifically binds with high affinity to IL-13 alone, preventing its interaction with its receptor and subsequent downstream signalling (36). The favourable benefit-risk profile of tralokinumab in the treatment of moderate-to-severe AD has been established and tralokinumab thus has the potential to address the unmet medical need associated with moderate-to-severe AHE.

2.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (37) and ICH GCP (1), and in compliance with the approved protocol and applicable regulatory requirements.

Participation in this trial is voluntary and subjects can withdraw at any time. The subjects will give informed consent. No vulnerable subject incapable of giving informed consent will be enrolled in this clinical trial.

Female subjects who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled. Female subjects of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the investigational medicinal product (IMP). In addition, all female subjects of childbearing potential will have a pregnancy test performed before, during and at end of treatment to ensure no foetal exposure to the IMP.

Trial subjects will be informed at the screening visit that trial procedures prior to baseline may warrant an alteration of their ongoing concomitant treatments. To ensure subjects' safety, investigators are informed only to enroll subjects who are considered able to stop prohibited treatment during the screening period without experiencing intolerable worsening of AD and AHE symptoms.

Placebo control is considered to provide the best design for efficient assessment of both benefit and risk. After the initial 16 weeks of double-blind treatment, all subjects will receive tralokinumab.

To mitigate the risk for worsening of AHE symptoms during the treatment and follow-up periods, rescue treatment may be prescribed to trial subjects at the discretion of the

investigator. Subjects will be instructed to contact the investigator if their AD and/or AHE worsens significantly.

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

In accordance with the current version of ICH GCP, qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial.

2.5 Benefit/risk assessment

2.5.1 Risk assessment

The overall incidence of AEs for tralokinumab has been comparable to that for placebo in controlled clinical trials. Injection site reactions have generally been mild, and ADA have been detected in very few subjects exposed to tralokinumab for up to 1 year.

The incidence of conjunctivitis was higher with tralokinumab than with placebo in the clinical development programme, however, the risk of conjunctivitis remains to be fully characterized. Conjunctivitis is therefore considered an adverse event of special interest and additional data will be collected for these events (Section 8.4.7.1).

Treatment with other therapies will be withheld from the subjects for the duration of the trial (up to 36 weeks) and the subject's AD and AHE symptoms are likely to worsen as a result. Also, subjects receiving placebo may experience a worsening of their AD and AHE symptoms. To mitigate the risk for worsening of AHE symptoms during the treatment and follow-up periods, rescue treatment may be prescribed to trial subjects regardless of their treatment allocation at the discretion of the investigator. However, the use of rescue treatment on hands and wrists during the initial 8 weeks of the double-blind treatment period will lead to permanent discontinuation of IMP. Subjects will be instructed to contact the investigator if their AD and/or AHE worsens significantly.

2.5.2 Benefit assessment

The efficacy of tralokinumab as monotherapy in subjects with moderate-to-severe AD was demonstrated consistently in the replicate pivotal phase 3 trials (ECZTRA 1 and 2) for all primary and multiplicity-adjusted secondary endpoints. Likewise, in the combination trial (ECZTRA 3), the efficacy of tralokinumab administered in combination with TCS was consistently demonstrated for all primary and multiplicity-adjusted secondary endpoints.

Across the trials, significant and clinically meaningful benefits were obtained. This was combined with a favourable safety profile, without any important risks identified.

Within the 52-week duration of treatment in the completed clinical trials and in the ongoing long-term ECZTEND trial, no safety issues related to the duration of treatment have been identified. Also, there was no indication of loss of therapeutic effect over time. Both parameters are critical for a chronic disease like AD and AHE.

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of tralokinumab may be found in the IB, participant information leaflet and informed consent form(s), and instruction for use.

2.5.3 Overall benefit/risk conclusion

Tralokinumab is a new biological therapy approved and marketed for the treatment of moderate-to-severe AD in adult and adolescent patients in the EU, UK, and Canada, and in adult patients also in the US, Japan, and other countries.

The AE profile for tralokinumab has been comparable to that for placebo in controlled clinical trials. Injection site reactions have generally been mild, and ADA have been detected in very few subjects exposed to tralokinumab for up to 1 year. Measures are in place in this trial to protect participating subjects.

In conclusion, previous clinical experience with tralokinumab shows no major safety or tolerability concerns, and appropriate measures have been instituted in this trial to protect subjects from potential risks that have been previously identified and to sufficiently monitor each subject. The current benefit-risk profile is considered favourable and supports the administration of tralokinumab for the purposes of achieving the objectives of this trial.

3 Trial objectives, endpoints, and estimands

Panel 4: Objectives and Endpoints

Objectives	Endpoints
Primary objective	
To evaluate the efficacy of tralokinumab on severity and extent of atopic hand eczema compared with placebo in treatment of subjects with moderate-to-severe atopic hand eczema	**Primary endpoint** • IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16. **Key secondary endpoints** • Having a decrease in HECSI of at least 75% (HECSI-75) from baseline to Week 16. • Having a decrease in HECSI of at least 50% (HECSI-50) from baseline to Week 16. • Having a decrease in HECSI of at least 90% (HECSI-90) from baseline to Week 16. • Percentage change in HECSI score from baseline to Week 16. **Secondary endpoints** • Having a ≥2-point reduction in IGA-AHE score from baseline to Week 16.
Secondary objective	
To evaluate the efficacy of tralokinumab on severity, extent, itch, pain, sleep, and health-related quality of life compared with placebo in treatment of subjects with moderate-to-severe atopic hand eczema	**Key secondary endpoints** • Reduction in HESD itch score (weekly average) of ≥4 points from baseline to Week 16. • Reduction in HESD pain score (weekly average) of ≥4 points from baseline to Week 16[a]. • Percentage change in HEIS score from baseline to Week 16. • Percentage change in DLQI score from baseline to Week 16. **Secondary endpoints** • Percentage change in HESD itch score (weekly average) from baseline to Week 16. • Percentage change in HESD pain score (weekly average) from baseline to Week 16. • Change in WPAI+CIQ:AHE domain scores from baseline to Week 16. **Other/exploratory endpoints** • Reduction in HESD itch score (weekly average) of ≥3 points from baseline to Week 16. • Reduction in HESD pain score (weekly average) of ≥3 points from baseline to Week 16[b]. • Percentage change in HEIS sleep score (weekly average) from baseline to Week 16.

Objectives	Endpoints
	• Reduction in DLQI score of ≥4 points from baseline to Week 16[c].
To evaluate the safety and tolerability of tralokinumab in subjects with moderate-to-severe atopic hand eczema	**Secondary endpoint** • Number of treatment-emergent[d] adverse events from baseline to Week 16.
Other objectives	
To evaluate the efficacy of tralokinumab on severity and extent of AD compared with placebo in subjects with moderate-to-severe atopic hand eczema	**Other/exploratory endpoints** • Percentage change in EASI score from baseline to Week 16. • Change in EASI score from baseline to Week 16.
To evaluate the efficacy on severity, extent, itch, pain, sleep, and health-related quality of life and the safety and tolerability of continued tralokinumab treatment in subjects with moderate-to-severe atopic hand eczema in the open-label treatment period (up to 32 weeks)	**Secondary endpoints** • IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 32. • Having a decrease in HECSI of at least 75% (HECSI-75) from baseline to at Week 32. • Reduction in HESD itch score (weekly average) of ≥4 points from baseline to Week 32. • Reduction in HESD pain score (weekly average) of ≥4 points from baseline to Week 32[a]. • Percentage change in HEIS score from baseline to Week 32. • Percentage change in DLQI score from baseline to Week 32. • Change in WPAI+CIQ:AHE domain scores from baseline to Week 32. • Number of treatment-emergent[d] adverse events during the open-label treatment period (Week 16 to Week 32).

Abbreviations: AD = Atopic dermatitis; AE = adverse event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; HECSI = Hand Eczema Severity Index; HEIS = Hand Eczema Impact Scale; HESD = Hand Eczema Symptom Diary; IGA-AHE = IGA for Atopic Hand Eczema; WPAI+CIQ:AHE = Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire in atopic hand eczema.

a. Among subjects with a baseline HESD pain score (weekly average) ≥4 points.
b. Among subjects with a baseline HESD pain score (weekly average) ≥3 points.
c. Among subjects with a baseline DLQI score ≥4 points.
d. An event will be considered treatment-emergent if started after the first administration of IMP or, if started before the first administration of IMP and worsened in severity after first dose of IMP.

Primary estimand for binary endpoints

The clinical question of interest for the primary estimand for binary endpoints is: What is the treatment difference in response rates at the endpoint of interest in subjects with moderate-to-severe AHE treated with tralokinumab versus placebo without initiation of rescue treatment for AHE or permanent discontinuation of IMP due to AE or lack of efficacy on AHE in a hypothetical setting where all subjects remain on treatment except those permanently discontinuing due to lack of efficacy on AHE or the occurrence of an AE?

The estimand is described by the following attributes:

- Population: Subjects with moderate-to-severe AHE as defined through eligibility criteria in Sections 5.1 and 5.2.
- Endpoint attribute: Achievement of endpoint of interest at Week 16 without initiation of rescue treatment for AHE or permanent discontinuation of IMP due to lack of efficacy on AHE or adverse events (composite strategy) in a hypothetical setting where permanent discontinuation of IMP due to other reasons would not occur (hypothetical strategy).
- Treatment condition: The IMP.
- Remaining ICEs: The ICEs 'permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event' 'permanent discontinuation of IMP not related to lack of efficacy on AHE or adverse event', and 'initiation of rescue treatment for AHE' are addressed by the endpoint attribute of interest. There are no remaining ICEs anticipated at this time.
- Population-level summary: Difference in response rates between tralokinumab 300 mg Q2W and placebo.

Rationale for estimand: Since initiation of rescue treatment for AHE or permanent discontinuation of IMP due to lack of efficacy on AHE or occurrence of an AE indicates failure of randomized treatment, a composite strategy is chosen were the initiation of rescue treatment for AHE/permanent discontinuation of IMP is a part of the endpoint (i.e., subjects initiating rescue treatment for AHE or permanently discontinuing IMP due to lack of efficacy on AHE or adverse event prior to Week 16 will be considered as non-responders to treatment at Week 16). The estimand targets the treatment difference in a scenario where permanent discontinuation of IMP due to other reasons would not occur.

Primary estimand for continuous endpoints

The clinical question of interest for the primary estimand for continuous endpoints: What is the difference in mean change/percentage change from baseline to the endpoint of interest in subjects with moderate-to-severe AHE treated with tralokinumab versus placebo in a hypothetical setting where subjects would not permanently discontinue IMP or use rescue treatment for AHE?

The estimand is described by the following attributes:

- Population: Subjects with moderate-to-severe AHE.

- Endpoint attribute: Change from baseline in endpoint of interest in a hypothetical setting where permanent discontinuation of IMP or use of rescue treatment for AHE would not occur (hypothetical strategy).
- Treatment condition: The IMP.
- Remaining ICEs: The ICEs ‘permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event’, ‘permanent discontinuation of IMP not related to lack of efficacy on AHE or adverse event’, and ‘initiation of rescue treatment for AHE’ are addressed by the endpoint attribute of interest. There are no remaining ICEs anticipated at this time.
- Population-level summary: Difference in mean change/percentage change between tralokinumab and placebo.

Rationale for estimand: The estimand aims at assessing the treatment effect if all the subjects adhered to the treatment regimen in the sense that they did not permanently discontinue IMP and no rescue treatment for AHE was used.

Note: For endpoints using DLQI and EASI, the ICEs will be modified to reflect that the scores evaluate skin disease or AD on the whole body, and thus the ICEs included will be treatment initiated for AD (instead of rescue treatment for AHE), permanent discontinuation of IMP due to lack of efficacy on AD or adverse event, and permanent discontinuation of IMP not due to lack of efficacy on AD or adverse event. The handling of the ICEs will be the same as for the other endpoints, just with the modified ICEs.

4 Trial design

4.1 Overall trial design

This is a phase 3b, interventional, international, multi-center, randomized, 16-week, double-blind, placebo-controlled, parallel-group, adaptive clinical trial with a 16-week, open-label treatment period. The trial is designed to evaluate the efficacy and safety of 300 mg tralokinumab Q2W compared to placebo in subjects with moderate-to-severe atopic hand eczema. The primary endpoint is assessed at Week 16, and the final efficacy assessments will be conducted at Week 32.

The trial design is illustrated in Panel 1. For each subject, the trial will last at least 37 weeks and up 40 weeks, including:

- a 1-to 4-week screening period
- a 16-week double-blind treatment period
- a 16-week open-label treatment period
- a 4-week safety follow-up period.

The trial design includes a sample size re-evaluation, see Section 9.4.

Screening period (Week -4/-1 to Week 0)

The screening period has a minimum duration of 1 week and a maximum duration of 4 weeks depending on the need for wash-out (i.e., the screening visit should take place between Week -4 and Week -1). For subjects using treatments that are listed as exclusion criteria, the duration of the screening period will depend on the required wash-out period as defined in Section 5.2.

Eligibility will be assessed at the screening visit and at baseline prior to start of treatment. Trial-specific measurements will be performed as outlined in the schedule of activities (Section 1.3). Subjects will receive an eDiary device, eDiary training, and start completion of HESD itch and pain in the eDiary. Completion of the eDiary will be initiated preferably from the date the subjects receive the eDiary, and at the latest 7 days prior to the baseline visit on Day 1. Data entered into the eDiary during the 7 days immediately preceding the baseline visit (Day -7 to Day -1) will be used to calculate baseline values of the PROs.

Double-blind treatment period (Week 0 to Week 16)

Following the screening period, a minimum of 204 subjects will be randomized 2:1 to the following groups stratified by region (Europe, North America, and Asia) and baseline disease severity (IGA-AHE of 3 or 4):

- Tralokinumab 600 mg (4 mL) at Day 1 (hereinafter ‘baseline’), then 300 mg (2 mL) Q2W.

- Placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

During the 16-week double-blind treatment period, subjects will attend site visits for IMP administration and efficacy and safety assessments as listed in Panel 2 and described in Section 8.

Open-label treatment period (Week 16 to Week 32)

After completion of the double-blind treatment period, all subjects will roll-over to open-label tralokinumab treatment 300 mg Q2W for 16 weeks with optional mild (US class ≥6 or Europe class 1) potency TCS and/or TCI on hands and wrists.

After adequate training by site staff at Week 16, subjects will self-inject tralokinumab in their home at Weeks 18, 20, 22, 26, 28, and 30.

During the 16-week open-label treatment period, subjects will attend site visits for IMP administration and efficacy and safety assessments as listed in Panel 3 and described in Section 8.

Safety follow-up period (Week 32 to Week 36)

All subjects who complete the open-label treatment period (Week 32) will attend a safety follow-up visit (performed via phone, but can be performed as a site visit if needed) 6 weeks after the last IMP administration for assessment of safety. Note that for subjects who prematurely permanently discontinue IMP, the 4-week safety follow-up period will start 2 weeks after the last IMP injection.

During the safety follow-up period, subjects will be allowed to receive standard of AD care (excluding biologic therapies other than commercially available tralokinumab) at the discretion of the investigator (Panel 7).

4.2 Scientific rationale for trial design

The trial is designed to evaluate the efficacy and safety of tralokinumab versus placebo in subjects with moderate-to-severe AHE. The trial endpoints have been selected to evaluate the efficacy of tralokinumab in improving the severity and extent of AHE, including both objective signs of disease and subjective symptoms (e.g., itch) as well as HRQoL.

The planned trial design is considered appropriate for evaluating the trial objectives, as the double-blind conditions regarding the subject's treatment (tralokinumab or placebo) are maintained and the possible observer bias regarding treatment effects are minimized.

In the double-blind treatment period, a placebo-controlled, parallel-group design has been added to investigate superiority of tralokinumab to placebo. The randomization ratio of 2:1 allows the majority of subjects to receive active treatment with tralokinumab. Subjects who have intolerable AHE symptoms may receive rescue treatment if needed. However, the use of rescue treatment on hands and wrists during the initial 8 weeks of the double-blind treatment period will lead to permanent discontinuation of IMP.

The treatment duration of 16 weeks in the double-blind period was chosen to ensure that all subjects had ample time to benefit from the active treatment. The treatment duration of tralokinumab is based on data from the two similar monotherapy trials of 52 weeks' duration in adults with moderate-to-severe AD (38), demonstrating superiority of tralokinumab Q2W over placebo at Week 16 with a similar overall incidence and rate of adverse events during the initial 16 weeks of treatment with tralokinumab and placebo.

The open-label treatment period ensures generation of additional efficacy and safety data without treating subjects with placebo for a prolonged period of time. In the open-label treatment period, the visit schedule will be similar to standard practice for home use by introducing home dosing to decrease the burden of frequent site visits. Mandatory telephone visits in between site visits ensures close safety monitoring of the subjects. Subjects will also have the possibility to use tralokinumab both with and without mild TCS (US class ≥6 or Europe class 1) and/or TCI, reflecting the intended use of tralokinumab in real clinical practice.

4.2.1 Choice of control group

The placebo control group will serve as a reference and is considered to provide the best design for efficient assessment of both benefit and risk.

4.2.2 Appropriateness of measurements

The clinical efficacy of tralokinumab in the treatment of AHE will be assessed by IGA-AHE and HECSI:

- IGA-AHE is an instrument to rate the severity of the subject's AHE based on a modification of the IGA-CHE developed by LEO Pharma.
- HECSI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of HE signs (39).

The clinical efficacy of tralokinumab treatment will also be assessed using validated PROs to assess the subjects' perception of disease severity and impact on HRQoL including assessment of itch, pain, and sleep quality:

- HESD is a 6-item PRO developed by LEO Pharma to assess severity of hand eczema signs and symptoms. Only 2 items (itch and pain) will be included and will be used to assess worst itch and skin pain from AHE.

- HEIS is a validated 9-item PRO instrument developed by LEO Pharma to assess the subject's perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning.
- DLQI is a validated and widely used questionnaire designed to measure the quality of life of dermatological patients (40).
- WPAI+CIQ:AHE is a validated PRO instrument to assess work productivity and activity impairment plus classroom impairment in patients with AHE (41, 42).

In addition, the clinical efficacy of tralokinumab in the treatment of AD in patients with AD and moderate-to-severe AHE will be assessed using EASI:

- EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of global AD (43).

Safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, vital signs, and clinical laboratory measurements.

4.2.3 Suitability of the trial population

The trial population is selected to reflect the general adult population with AHE to ensure that the trial results will be generalisable to the target population. No upper age limit is included, and the eligibility criteria are designed to comply with standard safety precautions and to avoid confounding diagnoses or subtypes of hand eczema than AHE which may interfere with the trial results. The target population consists of subjects with moderate-to-severe AHE based on the pronounced unmet medical need for this population, whereas subjects with mild AHE are generally well managed by elimination of trigger factors, general skin care, and TCS treatment.

The most important eligibility criteria for entry into the trial are:

- A diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD (see Appendix 5, Section 10.5) at screening and a history of AD for at least 12 months, to ensure correct diagnosis and rule out differential diagnosis. A prerequisite for inclusion into the trial is a documented history of topical AHE treatment failure (due to inadequate response or for whom topical treatments are otherwise medically inadvisable), to ensure that the subject is candidate for systemic treatment (inclusion criteria 4, 5, and 11).
- The presence of AHE that has persisted for more than 3 months or returned twice or more within the last 12 months (inclusion criteria 6 and 7) and not predominantly due to other subtypes of hand eczema than AHE (exclusion criterion 1).

4.2.4 Patient input to trial design

Previously obtained patient input to similar tralokinumab trial designs has been considered for this trial and new input has thus not been collected for this trial.

4.3 Justification for dose

The tralokinumab dose investigated is the same as that approved for the treatment of patients with moderate-to-severe AD (an initial 600 mg loading dose followed by 300 mg Q2W), a dose with an established favourable benefit-risk profile.

In the double-blind treatment period, all subjects randomized to receive treatment with tralokinumab will get an initial loading dose of 600 mg on Day 1 (baseline). The administration of the loading dose of tralokinumab will allow systemic concentrations to reach steady state faster, and potentially reduce the time to onset of clinical effect. The serum concentrations of tralokinumab after the 600 mg loading dose will not exceed the serum tralokinumab concentrations at steady state for the 300 mg Q2W.

To maintain the blinding, all subjects rolled-over to open-label tralokinumab treatment will be treated with 300 mg tralokinumab Q2W. Consequently, subjects who have received placebo in the double-blind treatment period, will reach the 300 mg tralokinumab Q2W steady state 2–4 weeks later than subjects who are already at steady state after treatment with 300 mg tralokinumab Q2W in the double-blind treatment period.

4.4 End of trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial, including the safety follow-up visit at Week 36.

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

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

5 Trial population

5.1 Inclusion criteria

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

Informed consent

1. Signed and dated informed consent as described in Appendix 1, Section 10.1.3 has been obtained prior to any protocol-related procedures.

Age

2. Age 18 years or above at screening.

Compliance

3. Willingness to comply with the clinical trial protocol.

Type of subject and disease characteristics

4. Diagnosis of AD as defined by the Hanifin and Rajka (44) criteria for AD (Appendix 5, Section 10.5).
5. History of AD for at least 12 months prior to screening.
6. Presence of AHE that has persisted for more than 3 months or returned twice or more within the last 12 months (7), with avoidance of any known and relevant irritants and allergens.
7. Disease severity graded as moderate-to-severe at screening and baseline according to IGA-AHE (i.e., an IGA-AHE score of 3 or 4).
8. AD involvement of at least one body location other than the hands and wrists at screening.
9. Subjects must adhere to standard non-medicated skin care including avoidance of known and relevant allergens and irritants from screening through end of treatment (Week 32).
10. A HESD itch score (weekly average) score of ≥4 at baseline. The baseline weekly average will be calculated from daily assessments of itch severity during the 7 days immediately preceding the baseline visit (Day -7 to Day -1). A minimum of 4 scores out of the 7 days is required to calculate the baseline average score.
    - For subjects who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met.
11. Subjects who have a documented recent history (within 12 months before the screening visit) of inadequate response to treatment of AHE with topical prescription medications or for whom topical treatments are otherwise medically inadvisable (e.g., due to important side effects or safety risks).

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA-AHE score of ≤2) despite treatment with a daily regimen of TCS of US class ≤4 (medium to very/ultra-high potency) and Europe class ≥3 (potent to very potent) (with or without TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super potent TCS), whichever is shorter.
- Subjects with documented systemic treatment for AHE in the past year are also considered as inadequate responders to topical treatments and are potentially eligible for enrollment after appropriate wash-out.
- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.

Sex and contraceptive/barrier requirements

12. A WOCBP* must use a highly effective** form of birth control throughout the trial and for at least 16 weeks (5 half-lives) after last administration of IMP.

    * A WOCBP is defined as a female subject aged ≥12 years who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

    **A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject and not just being without a current partner), same-sex partner, or vasectomized partner (given that the subject is monogamous).

5.2 Exclusion criteria

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

Medical conditions

1. Subjects must not enter the trial if they have active subtypes of hand eczema other than AHE that are considered to be the predominant cause of the current hand eczema including[a]:
   - Active irritant contact dermatitis where a relevant exposure to irritants is considered as the predominant cause of the current hand eczema.
   - Active allergic contact dermatitis where a relevant exposure to allergens is considered as the predominant cause of the current hand eczema; this includes subjects with a positive patch test reaction[b] within 3 years prior to screening that is deemed to be clinically relevant as the predominant cause of the current hand eczema.
   - Active protein contact dermatitis/contact urticaria where a relevant exposure to proteins is considered as the predominant cause of the current hand eczema.
   - Active hyperkeratotic hand eczema considered as the predominant cause of the current hand eczema.
   - Active vesicular hand eczema (pompholyx) considered as the predominant cause of the current hand eczema.

   a. Further guidance on classification of hand eczema is provided in Appendix 6 (Section 10.6).
   b. Patch testing is not a requirement.
2. Active dermatologic condition on any part of the body, including the hands and wrists, that may confound the diagnosis of AD or AHE, or that would interfere with the assessment of treatment (such as seborrheic dermatitis, active skin infection, scabies, cutaneous T cell lymphoma, or psoriasis).
3. Clinically significant infection on the hands or wrists, e.g., impetiginized hand eczema.
4. History of a clinically significant infection within 28 days prior to baseline which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial, interfere with the evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
   - a systemic infection.
   - a serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
5. A helminth parasitic infection within 6 months prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.

6. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
7. Known or suspected hypersensitivity to any component(s) of the IMPs.
8. History of anaphylaxis following any biological therapy.
9. History of immune complex disease.
10. History of cancer:
    - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
    - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.
11. History of any known primary immunodeficiency disorder including a positive HIV test at screening.
12. Current or recent chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
13. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, immunological, psychiatric, or major physical impairment that is not stable, in the opinion of the investigator, and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial or their interpretations.
    - Impede the subject's ability to complete the entire duration of trial.
14. Any clinically significant abnormal findings in physical examination, vital signs, hematology, or clinical chemistry during the screening period, which in the opinion of the investigator, may put the subject at risk because of his/her participation in the trial, or may influence the results of the trial, or the subject's ability to complete the entire duration of the trial.
15. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), or hepatitis B core antibody (anti-HBc), or hepatitis C virus antibody serology at screening. Subjects with positive anti-HBs are eligible provided that they have a negative HBsAg and negative anti-HBc (blood pattern in vaccinated subjects).
16. Women who are pregnant or lactating.

Prior/concomitant therapy and procedures

17. Treatment with the following medications within 28 days prior to baseline:
    - Systemic immunosuppressive/immunomodulating drugs (e.g., methotrexate, cyclosporin A, azathioprine, mycophenolate mofetil, JAK inhibitors, retinoids [e.g., alitretinoin]).
    - Systemic corticosteroid use (excludes topical, inhaled, ophthalmic, or intranasal delivery).
18. Use of tanning beds, phototherapy (e.g., UVB, UVA1, PUVA), or Grenz ray therapy on the hands or wrists within 28 days prior to baseline or use of bleach baths on the hands or wrists within 7 days prior to baseline.
19. Treatment with the following medications within 7 days prior to baseline:
    - TCS*.
    - TCI*.
    - Topical PDE-4 inhibitors.
    - Topical JAK inhibitors.

    * Mild-to-moderate TCS (US class ≥4 or Europe class ≤3) or TCI related to AD treatment on other areas of the body than the hands and wrists are allowed as long as it does not interfere with the trial (i.e., the subjects must use disposable gloves when applying treatment or have it applied by someone other than self).
20. Use of cutaneously applied antibiotics or other transdermal or cutaneously applied therapy on the hands or wrists (except for the use of subject's own emollients) within 7 days prior to baseline.
21. Receipt of any biological therapy (including immunoglobulin and anti-IgE):
    - 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 the longest.
    - Dupilumab[a]: within 3 months prior to baseline.
    - Tralokinumab[b]: within 3 months prior to baseline.
    - Other biologics: within 3 months prior to baseline or 5 half-lives, whichever is the longest.

    a. Subjects who have discontinued treatment with dupilumab due to lack of efficacy must not enter the trial.

    b. Subjects who have discontinued treatment with tralokinumab due to lack of efficacy or due to a safety concern and for whom continued tralokinumab treatment may present an unreasonable safety risk, must not enter the trial.

22. Subjects who have received treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within the last 28 days prior to baseline or 5 half-lives, whichever is the longest.
23. Receipt of live (attenuated) vaccines within 28 days prior to baseline and during the trial, including the safety follow-up period.
    - Receipt of inactive/killed vaccinations (e.g., inactive influenza and inactive COVID-19 vaccines) is allowed.
24. Receipt of blood products within 28 days prior to screening.

Prior/concurrent clinical trial experience

25. Current participation in any other interventional clinical trial.
26. Previously randomized in this clinical trial.

Other exclusion criteria

27. Planned in-patient surgery or hospitalization during the trial period.
28. 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.
29. Subjects who are legally institutionalised.

5.3 Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 1, Section 10.1.3 for details on the informed consent process. Once informed consent is obtained, a subject ID will be assigned by a IRT system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the informed consent form was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given informed consent to participate in the trial and who have been assigned a subject ID are considered screened subjects.

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

5.4 Subjects excluded prior to randomization

Subjects excluded prior to randomization include screen failures and other subjects not subsequently assigned to trial treatment for other reasons. Screen failures are defined as subjects who consent to participate in the trial but do not meet 1 or more eligibility criteria required for participation in the trial. Other subjects not assigned to trial treatment are defined as subjects who meet the eligibility criteria but do not participate in the trial for other reasons, such as lost to follow-up, withdrawal by subject, and other reasons.

To meet the CONSORT publishing requirements (45) and to respond to queries from regulatory authorities, a minimal set of information is required to ensure transparent reporting of screen failures and other subjects not assigned to trial treatment. For these subjects, the following data will be collected in the eCRF:

- Date of informed consent(s).
- A specification of which eligibility criteria were not met, if any.
- Date of birth, age, sex.
- Date of exclusion.
- Primary reason for exclusion.
  - Screen failure.
  - Lost to follow-up.
  - Withdrawal by subject.
  - Other (specify reason).

Individuals who do not meet the criteria for participation in this trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted (this will require approval by the sponsor's medical expert after thorough review of all data from the original screening visit in the eCRF). Individuals who are re-screened will get a new subject ID.

6 Treatments

6.1 Trial product description

Tralokinumab is a human recombinant monoclonal antibody of the IgG4 subclass that specifically binds to human IL-13 and blocks interaction with the IL-13 receptors. It is presented as a liquid formulation for SC administration.

Panel 5: Identification of IMPs

Arm title	Tralokinumab	Placebo
Treatment name	Tralokinumab	Placebo
Type	Drug	Control
Use	Experimental	Experimental
Dosage formulation	Solution for injection in an accessorized pre-filled syringe[a]	Solution for injection in an accessorized pre-filled syringe[a]
Route of administration	Subcutaneous	Subcutaneous
Unit dose strength	Nominal concentration of tralokinumab 150 mg/mL in CCI mM sodium acetate/acetic acid buffer, CCI mM sodium chloride, CCI % (w/v) PS-80, pH 5.5 solution.	Placebo contains the same excipients, in the same concentration only lacking tralokinumab.
Dose level and dose frequency	600 mg (4 mL) at baseline, then 300 mg Q2W (2 mL)	4 mL at baseline, then 2 mL Q2W
Storage conditions	2–8°C	2–8°C
Sourcing	Provided centrally by LEO Pharma.	Provided centrally by LEO Pharma.
Packaging and labeling	Provided in an accessorized pre-filled syringe[a] containing tralokinumab 150 mg/mL or placebo. The IMP will be packaged in individually numbered kits, each containing 1 pre-filled syringe of tralokinumab 150 mg/mL or placebo. Primary and secondary packaging materials will be individually labeled. The labelling of IMPs will be in accordance with the EU Clinical Trial Regulation No. 536/2014 Annex VI (46), local regulations, and trial requirements. Label text will be translated into local languages as required. The subjects will receive instruction for use.	

Abbreviations: IMP = investigational medicinal product.

a. The accessorized pre-filled syringe is a single-use, disposable system that is designed to administer the labeled dose of the system to the subcutaneous space during 1 injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system. The accessorized pre-filled syringe consists of a pre-filled syringe sub-assembly (1 mL pre-filled syringe barrel with a 1/2-inch 27-gauge thin wall staked-in needle, rigid needle shield, plunger stopper), and a safety device.

6.2 Administration, storage, and accountability

6.2.1 Administration of IMP

IMP administration will be performed on site at visits in accordance with the schedule of activities (Section 1.3). In addition, IMP administration will be performed at home by the subject at Weeks 18, 20, 22, 26, 28, and 30 (see IMP dispensation in the schedule of activities, Section 1.3). The last administration of IMP under this protocol will occur at Week 30.

The IRT system will assign the required kit numbers for each subject at each dispensing visit.

The first day of dosing is considered Day 1 (Visit 2, baseline). Each subject will receive 4 SC injections (each of 1 mL) to receive a loading dose of tralokinumab or placebo. At subsequent visits in the treatment period, each subject will receive 2 SC injections (each of 1 mL).

Hence, subjects in the double-blind treatment period will receive either:

- Tralokinumab 300 mg Q2W: tralokinumab 600 mg (4 mL) at baseline, then tralokinumab 300 mg (2 mL) Q2W.
- Placebo Q2W: placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

Subjects who continue in the open-label treatment period will receive 2 SC injections (each 1.0 mL) of 150 mg tralokinumab at each dosing interval.

IMP administration on site will be performed by a qualified, unblinded health care professional during the double-blind treatment period. During the open-label treatment period, tralokinumab administration on site will be performed by the subject (preferred) or site staff after all assessments have been completed. It will be recorded in the eCRF if tralokinumab was administered by site staff or subject.

A minimum interval of 7 days is required between 2 dosing visits. LEO Pharma does not have any specific treatment recommendations in relation to overdose. The investigator will use clinical judgement to treat any overdose if necessary. For reporting of overdose, see Section 8.4.7.2.

After adequate training by site staff at Week 16 (Visit 10), subjects will inject tralokinumab 300 mg at home at Weeks 18, 20, 22, 26, 28, and 30. The subject should be trained in how to handle the IMP according to the instruction for use and the trial product handling manual. The subject will be trained in proper SC injection technique in accordance with the instruction for

use as well as procedures to be followed in the event of an emergency during or following home use of tralokinumab.

The injections will be administered into the SC tissue of the upper arm, anterior thigh, or abdomen, separated by at least 3 cm. For the initial 600 mg dose, four 150 mg tralokinumab injections should be administered consecutively in different injection sites within the same body area. It is recommended to rotate the injection site with each dose. Tralokinumab should not be injected into skin that is tender, damaged, or has bruises or scars. The injection site must be recorded in the source documents at each visit and recorded in the eCRF.

Further details on IMP administration are provided in the trial product handling manual and the instruction for use. IMP administration must be carried out according to these instructions.

6.2.2 Storage and accountability

The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all IMPs received, and any discrepancies are reported and resolved before use of the IMP.

Only eligible subjects may receive the IMP, only authorized site staff may supply and prepare the IMP, and only authorized site staff and trained subjects may administer the IMP.

All IMPs must be stored in a secure and restricted area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff and remain in the original container until dispensed.

The IMP must be stored at 2-8°C at the trial site. The temperature during storage should be monitored by a calibrated, stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer.

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

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

Note that in the cases listed below, site staff should not use the affected IMP and should immediately contact their CRA for further guidance:

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

- Damaged pre-filled syringe.

Damaged IMP should be documented in the IRT system and reported as product complaint (see Section 6.8). Damaged IMP may not be used.

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

The investigator or authorized site staff is responsible for IMP accountability, and record maintenance (e.g., receipt and final disposition records).

Subjects will attend site visits on a regular basis (see Section 1.3). At these site visits, subjects will be provided with IMP to be administered at home until the next site visit. Subjects will be provided with sharps bins for used syringes and will return filled sharps bins to the trial site. Subjects will return trial kit cartons and any unused IMP at each site visit. Unused IMP returned by subjects to the trial site can be stored at room temperature and must be stored separately from non-allocated IMP.

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

6.2.3 Trial product destruction

Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. Trial sites which do not have such IMP destruction procedures in place will dispose used IMP in sharps bins which will be shipped to the CMO.

Unused IMP and used IMP (if applicable) will be returned to and destroyed by the CMO according to approved procedures and/or local requirements.

Further details on trial product destruction are available in the trial product handling manual.

6.3 Treatment assignment and blinding

6.3.1 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to fulfil any of the exclusion criteria will be randomized at Visit 2/Baseline to receive treatment with either

tralokinumab 300 mg Q2W or placebo Q2W stratified by region (Europe, North America, Asia) and baseline disease severity (IGA-AHE of 3 or 4).

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

6.3.2 Blinding

This is a double-blind trial in which tralokinumab and placebo are visually distinct from each other. Neither the subject nor the investigator or LEO Pharma staff, who are involved in the treatment or clinical evaluation and monitoring of the subjects, will be aware of the treatment received.

The packaging and labelling of the IMPs will contain no trace of identity. IMP is packed in identical boxes, with non-sequential kit numbers to ensure that unblinding does not occur during shipment and handling of the drug.

Since tralokinumab and placebo are visually distinct and not matched for viscosity, IMP will be handled and administered by a qualified, unblinded HCP (trained site staff) at the site who will not be involved in the management of trial subjects and who will not perform any of the assessments.

If treatment allocation for a subject becomes known to the investigator or other trial staff involved in the management of trial subjects, LEO Pharma must be notified immediately.

Should an issue arise with the IMP (e.g., damaged kit or syringe that has been assigned to a subject prior to administration, or any other unexpected event with the kit or syringe [e.g., a malfunction during IMP administration]), the unblinded HCP at the site will contact the CRA to determine whether any specific actions are required.

The trial site will maintain a written plan detailing which staff members are blinded/unblinded and the process of IMP administration used to maintain the blind.

During the trial, a third party will perform a re-evaluation of the sample size based on unblinded data (see Section 9.4). No site staff nor any LEO Pharma personnel will become unblinded in this process. LEO Pharma will receive an adjusted sample size, which will then be the sample size for the trial.

6.3.3 Emergency unblinding of individual subject treatment

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

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

For a requester who is not a member of the trial staff and who does not have access to the IRT system (e.g., a physician at an emergency room), a local contact number for the emergency unblinding CRO is provided on the subject card (see Appendix 1, Section 10.1.3) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

6.4 Treatment compliance

IMP administration at site

IMP administration on site will be performed by a qualified, unblinded health care professional during the double-blind treatment period. During the open-label treatment period, tralokinumab administration on site will be performed by the subject (preferred) or site staff after all assessments have been completed. It will be recorded in the eCRF if tralokinumab was administered by site staff or subject.

IMP home use during the open-label treatment period

The subject will be asked if the IMP has been used as prescribed. In case of non-compliance, the investigator should remind them of the importance of following the instructions given, including taking the IMP as prescribed.

Subjects who do not wish to administer IMP at home may come to the trial site for IMP administration. Such visits should be entered in the eCRF as unscheduled visits, with reason for unscheduled visit being IMP administration.

Compliance/non-compliance and the reason for it must be recorded in the eCRF.

Reporting in eCRF

The following data will be recorded in the eCRF:

- Did the subject comply with the IMP dosing schedule (yes, no); If no, a reason will be given. It will also be recorded how much IMP the subject received (full dose, partial dose, no dose).
- Primary reason for non-compliance – subject forgot, lack of time, adverse event, other (if other, a specification should be provided).
- Date of IMP administration.
- Time of IMP administration, for on-site visits.
- Where the IMP was administered (on-site, administered by site staff; on-site, self-administered; at home, self-administered).
- Site of IMP injection (upper arm, anterior thigh, or abdomen).

6.5 Dose modification

Not applicable.

6.6 Provision for subject care following trial completion

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

6.7 Prior and concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 3 months prior to screening until end of trial (Week 36) must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name or therapy.
- Whether the medication or therapy is a rescue treatment for AHE.
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.

- Route of administration (oral, topical, subcutaneous, transdermal, intraocular, intramuscular, respiratory (inhalation), intralesional, intraperitoneal, intranasal, vaginal, rectal, intravenous, or other (if other, a specification must be provided). For topical treatments, the dosage form (cream, lotion, ointment, other) will also be recorded.
- For topical treatment, it must also be recorded if the treatment is within 5 cm (appr. 2 inches) of the hands and wrists.

Only surgical procedures and procedures related to AD treatment (e.g., phototherapy or bleach baths) should be recorded in the subject's medical record and the eCRF. The following details will be recorded:

- Procedure name (including anatomical area, if relevant).
- Whether the procedure is a rescue treatment for AHE.
- Indication.
- Start and stop date (it will also be recorded if the procedure is ongoing).

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 6.7.3. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

Emollients are not considered concomitant medication and should not be recorded in the eCRF. The subjects will be allowed to apply other skin treatments/products to other areas of the body than hands and wrists during the trial except for medications listed in Section 6.7.3, as long as this does not interfere with the trial (i.e., the subject must use disposable gloves, of a type recommended by the investigator, when applying treatment, or have it applied by someone other than self). Use of cosmetic body care products (e.g., body lotion, shampoo, bath oil), which are routinely used by the subjects, is allowed as per instructions for use, but the products should preferably not be changed during the trial.

The following concomitant medications related to AD treatment including AHE are allowed from screening until end of trial (Week 36):

- Oral antibiotics, antiviral, or antifungal therapy for skin infections as appropriate.
- Oral antihistamines.

The following concomitant medications related to AD treatment on areas of the body other than the hands and wrists are allowed from screening until end of trial (Week 36):

- Mild-to-moderate TCS (US class ≥4 or Europe class ≤3) or TCI are allowed as long as it does not interfere with the trial (i.e., the subjects must use disposable gloves, of a type recommended by the investigator, when applying treatment, or have it applied by someone other than self).

The following concomitant medications related to AHE treatment are allowed in the open-label treatment period (Week 16 to Week 32) and the safety follow-up period (Week 32 to Week 36):

- Mild TCS (US class ≥6 or Europe class 1) or TCI treatment.

6.7.1 Background treatment

No background treatment is required in this trial.

6.7.2 Rescue treatment

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

If medically necessary (i.e., to treat intolerable AHE signs and symptoms), rescue treatment for AHE may be prescribed to trial subjects at the discretion of the investigator. An overview of rescue treatment that does not require permanent discontinuation of IMP is listed in Panel 6. If rescue treatments other than those listed in Panel 6 are used, IMP must be permanently discontinued (see Section 7.2.1).

Immediately before administering any rescue treatment, investigators should make every attempt to conduct efficacy and safety assessments and at least the following:

- IGA-AHE
- HECSI
- concomitant medications/procedures
- AEs

An unscheduled visit may be used for this purpose, if necessary.

Use of rescue treatment for intolerable AHE signs and symptoms does not constitute a protocol deviation.

Panel 6: Rescue treatment that does not require permanent discontinuation of IMP

Period	Type of treatment	Notes
After Week 8 to Week 16	**TCS of any potency or TCI**	The subject will be monitored for signs of local or systemic TCS toxicity and the safety and appropriateness of continued use will be supervised by site staff.
After Week 16	**Topical rescue treatment (Moderate-to-high TCS [US class ≤5 or Europe class ≥2])**	The subject will be monitored for signs of local or systemic TCS toxicity and the safety and appropriateness of continued use will be supervised by site staff. Subjects are allowed to use mild TCS (US class ≥6 or Europe class 1) and TCI to treat intolerable AHE symptoms as needed in the open-label treatment period.

Abbreviations: IMP = investigational medicinal product; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

6.7.3 Prohibited medications and procedures

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

If prohibited medications are used during the trial, they must be recorded as concomitant medication.

Panel 7: Prohibited medications and procedures

Medication or procedure	Prohibited from	Prohibited to	Notes
TCS on hands and wrists	7 days prior to baseline	End of treatment (Week 32)	May be used as rescue treatment; efficacy and safety assessments should be performed (Section 6.7.2). If topical rescue treatment is initiated from Week 0 to Week 8, IMP must be permanently discontinued (Section 7.2.1). Mild TCS (US class ≥6 or Europe class 1) related to AHE treatment is allowed in the open-label treatment period (Week 16 to Week 32) (Section 6.7).
TCS on other areas of the body than hands and wrists	7 days prior to baseline	End of treatment (Week 32)	Mild-to-moderate TCS (US class ≥4 or Europe class ≤3) related to AD treatment is allowed as long as it does not interfere with the trial (i.e., the subject must use disposable gloves, of a type recommended by the investigator, when applying treatment, or have it applied by someone other than self) (Section 6.7).

Medication or procedure	Prohibited from	Prohibited to	Notes
TCI on hands and wrists	7 days prior to baseline	End of treatment (Week 32)	May be used as rescue treatment; efficacy and safety assessments should be performed (Section 6.7.2). If topical rescue treatment is initiated from Week 0 to Week 8, IMP must be permanently discontinued (Section 7.2.1). TCI related to AHE treatment is allowed in the open-label treatment period (Week 16 to 32) (Section 6.7).
TCI on other areas of the body than hands and wrists	7 days prior to baseline	End of treatment (Week 32)	TCI related to AD treatment is allowed as long as it does not interfere with the trial (i.e., the subject must use disposable gloves, of a type recommended by the investigator, when applying treatment, or have it applied by someone other than self) (Section 6.7).
Topical PDE-4 inhibitors and topical JAK inhibitors)	7 days prior to baseline	End of treatment (Week 32)	If topical PDE-4 inhibitors or topical JAK inhibitors are initiated, IMP must be permanently discontinued (Section 7.2.1).
Use of tanning beds, phototherapy (e.g., UVB, UVA1, PUVA), or Grenz ray therapy on hands or wrists	28 days prior to baseline.	End of treatment (Week 32)	

Medication or procedure	Prohibited from	Prohibited to	Notes
Use of bleach baths on hands or wrists	7 days prior to baseline.	End of treatment (Week 32)	
Systemic corticosteroids treatment.	28 days prior to baseline.	End of treatment (Week 32)	Inhaled, ophthalmic, and intranasal corticosteroids are allowed. If systemic corticosteroid treatment is initiated as rescue treatment or treatment for AD, IMP must be permanently discontinued (Section 7.2.1); if used as rescue treatment, efficacy and safety assessments should be performed (Section 6.7.2)
Systemic immunosuppressive/ immunomodulating drugs (e.g., methotrexate, cyclosporin A, azathioprine, mycophenolate mofetil, JAK inhibitors, retinoids [e.g., alitretinoin]).	28 days prior to baseline.	End of trial (Week 36)	If systemic treatment with immunosuppressive/ immunomodulating drugs is initiated, IMP must be permanently discontinued (Section 7.2.1); if used as rescue treatment; efficacy and safety assessments should be performed (Section 6.7.2)

Medication or procedure	Prohibited from	Prohibited to	Notes
Treatment with any biological therapy (including immunoglobulin and anti-IgE):			If treatment with any biological therapy (including immunoglobulin and anti-IgE) is initiated, IMP must be permanently discontinued (Section 7.2.1), and if used as rescue treatment; efficacy and safety assessments should be performed (Section 6.7.2).
• Any cell-depleting agents including but not limited to rituximab	6 months prior to baseline, or until lymphocyte count returns to normal, whichever is the longest.	End of trial (Week 36)	
• Any biologics	3 months prior to baseline or 5 half-lives, whichever is the longest.	End of trial (Week 36)	Commercially available tralokinumab is allowed after end of treatment (Week 32) at the discretion of the investigator, if needed.
Treatment with any non-marketed drug substance	28 days prior to baseline or 5 half-lives, whichever is the longest	End of trial (Week 36)	
Allergen immunotherapy	Randomization	End of trial (Week 36)	
Live (attenuated) vaccine	28 days prior to baseline	End of trial (Week 36)	Receipt of inactive/killed vaccines (e.g., inactive influenza and inactive COVID-19 vaccines) is allowed.

Medication or procedure	Prohibited from	Prohibited to	Notes
Blood products	28 days prior to baseline	End of trial (Week 36)	

Abbreviations: AD = atopic dermatitis; IMP = investigational medicinal product; IgE = immunoglobulin E; JAK inhibitor = Janus kinase inhibitor; PDE-4 = phosphodiesterase 4; PUVA = psoralen + ultraviolet A; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids; UVA1 = ultraviolet A1; UVB = ultraviolet B.

6.8 Reporting product complaints

Any defects with the IMP that has or potentially could have serious impact on the subject must be reported to the CRA within 24 hours or knowledge.

(S)AEs which occur due to a defect or issue with the IMP or due to a device deficiency will be reported by the investigator as described in Appendix 2, Sections 10.2.4 and 10.2.5.

Examples or product complaints are:

- Problems with the physical or chemical appearance of the IMP (e.g., particles in the syringe).
- Device malfunction and use errors.
- Problems with the packaging material including labeling.

The CRA will report the product complaint to the Quality department via Global Safety at LEO Pharma within 3 days of first knowledge.

The reporting of the product complaint should contain a detailed description of the defect, issue, or device deficiency, including whether it led to an AE.

Refer to the IRT reference guide for information on how to update the kit status in the IRT system.

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

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

Fax number: +45 6910 2468

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

7 Discontinuation and withdrawal

7.1 General principles

A subject may withdraw from the trial (i.e., stop all further protocol-defined trial activities) or permanently discontinue trial treatment (i.e., stop all further trial treatment but continue to participate in protocol-defined trial activities), at any time if the subject, the investigator, or LEO Pharma considers that it is not in the subject's best interest to continue.

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

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

7.2 Discontinuation of IMP

7.2.1 Permanent discontinuation of IMP

Subjects must permanently discontinue IMP in the event of:

- Anaphylactic reaction or other severe systemic reaction to IMP injection.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Diagnosis of a malignancy during the trial, excluding carcinoma in situ of the cervix, or localized squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Topical rescue treatment for AHE from Week 0 to Week 8.
- Treatment with topical PDE-4 inhibitors or JAK inhibitors.
- Systemic immunosuppressive/immunomodulating drugs (e.g., methotrexate, cyclosporin A, azathioprine, mycophenolate mofetil, JAK inhibitors, retinoids [e.g., alitretinoin]) or biological treatments[a].
- Systemic corticosteroids treatment for AHE (rescue treatment) or AD.
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status.
- Severe laboratory abnormalities:
  - ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
  - Confirmed AST and/or ALT >5×ULN (for more than 2 weeks).

a. Commercially available tralokinumab is allowed after end of treatment (Week 32) at the discretion of the investigator.

Subjects who permanently discontinue IMP for any reason will be asked to attend the following visits:

- An early termination visit as soon as possible after last administration of IMP.
- A safety follow-up visit 6 weeks after last administration of IMP.

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

- Adverse event.
- Death.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by subject.
- Lack of efficacy on AHE.
- Other (including lack of efficacy on AD on areas of the body other than hands and wrists).

If ‘adverse event’ or ‘other’ is selected, a specification must be provided in the eCRF. If adverse event is selected, the AE in question will be linked to the IMP discontinuation.

7.2.2 Temporary discontinuation of IMP

The investigator may suspend trial treatment at any time, even without consultation with sponsor’s medical expert if the urgency of the situation requires immediate action and if this is determined to be in the subject’s best interest. In such cases, sponsor’s medical expert should be informed as soon as possible.

IMP dosing may be temporarily suspended in the event of:

- Other intercurrent illnesses or major surgery.
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or anti-protozoal agents.

7.3 Subject withdrawal from the trial

- A subject 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 or compliance reasons. The subject will be permanently discontinued from the IMP and the trial at that time.
- If the subject withdraws consent for disclosure of future information, LEO Pharma may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Subjects who withdraw from the trial for any reason will be asked to attend:

- An early termination visit as soon as possible after last administration of IMP.
- A safety follow-up visit 6 weeks after last IMP administration.

See the schedules of activities (Section 1.3) for data to be collected at these visits. The investigator will review any AEs which will be followed up according to Appendix 2, Section 10.2.4, if the subject agrees.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 8.8.

7.4 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

8 Trial assessments and procedures

Trial procedures and their timing are summarized in the schedule of activities in Section 1.3:

- Panel 2 includes the assessments during screening and the double-blind treatment period.
- Panel 3 includes the assessments during the open-label treatment and safety follow-up periods (including early termination and unscheduled visits).

Protocol waivers or exemptions are not allowed.

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

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

Subjects in the trial will be under careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be physicians experienced in treating AD and have documented experience and/or training in the use of the assessments required by the protocol. In the US only, investigators must be experienced in treating AD and have documented experience and/or training in the use of the assessments required by the protocol and must be either a physician, certified physician's assistant, or advanced registered nurse practitioner.

For the double-blind treatment period, the investigators performing the efficacy and safety assessments must not be involved in the administration of IMP (Section 6.3.2).

AEs must be assessed by a physician. Clinical assessments must be signed and dated by the investigator. In the US only, while certain AE assessments can be delegated to investigators with other qualifications, the diagnosis, seriousness, and causality of the AEs must be assessed by a physician.

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

In the event of a significant trial-continuity issue (e.g., caused by a pandemic), alternate strategies for subject visits, assessments, IMP distribution, and monitoring may be implemented by LEO Pharma or the investigator, as per local health authority/ethics committee requirements.

8.1 Administrative and baseline procedures

8.1.1 Demographics

The following demographic data will be recorded:

- Date of birth; in general, day, month, and year of birth should be collected. Where it is not allowed to collect the subject's full date of birth, only month and year of birth, or year of birth should be collected as per local legislation.
- Age (years); age (as on the day informed consent form was signed) must be collected if full date of birth cannot be collected due to local legislations. It should be noted that if full date of birth is not collected on the demographics form, age and age unit must also be collected on the randomization form.
- Sex (at birth): female, male.
- Ethnic origin (self-reported by the subject): 'Hispanic or Latino', 'not Hispanic or Latino'.
- Race (self-reported by the subject, more than 1 race may be reported): American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific Islander, White, not reported (not provided or available).

8.1.2 Medical history

Relevant past and current medical history must be recorded:

- Skin disease history: all past and current skin disease history should be collected, including (but not limited to):
  - Alopecia.
  - Vitiligo.
  - Herpes simplex infection.
  - Foot dermatitis
- Atopy history:
  - Duration of AD in years.
  - Previous AD treatments.
  - Asthma.
  - Food allergy.
  - Hay fever/Allergic rhinitis.
  - Allergic conjunctivitis.
  - Atopic keratoconjunctivitis.
  - Eczema herpeticum.
- AHE history:
  - Date of diagnosis of AHE.
  - Numbers of flares experienced during the past year.

  - Results of relevant previous diagnostic procedures (e.g., diagnostic patch testing, prick test).
  - Secondary hand eczema subtype(s) if applicable.
    - The investigator will determine the secondary hand eczema subtype(s) according to the guidance provided in Appendix 6 (Section 10.6).
- AHE treatment history:
  - Previous treatments for AHE (name and type of treatment, rationale for discontinuation of treatment). Note that for TCS, previous treatments will only be collected for the last 12 months and the following additional details will be recorded: strength, dose, and date(s) of treatment.
  - To support selection of trial subjects specifically on inclusion criterion 11:
    - Has the subject fulfilled the trial inclusion criterion 11 based on having inadequate response to treatment with TCS during the last 12 months? (yes, no).
    - Has the subject fulfilled the trial inclusion criterion 11 based on TCS being medically inadvisable for the subject? (yes, no).
    - If yes: reason for TCS use being medically inadvisable.
- Other medical and surgical history including concurrent diagnoses within the previous 12 months.

For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded (it will also be recorded if the condition, diagnosis, or surgical procedure is ongoing).

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

8.1.3 Body measurements

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

8.1.4 eDiary

At the screening visit, the subject's eligibility needs to be established before the PROs can be completed. The subjects will receive an eDiary device and eDiary training and will complete HESD itch and pain at the screening visit.

The eDiary will be open for entry daily from 4 pm until midnight. The subjects must complete the eDiary each day (Section 1.3), and compliance with the eDiary completion will be reviewed by the site staff throughout the trial.

Handout, training, and return of the eDiary is outlined in the schedule of activities (Section 1.3).

8.2 Efficacy assessments

8.2.1 Investigator's Global Assessment for Atopic Hand Eczema

The Investigator's Global Assessment for atopic hand eczema (IGA-AHE) is a modification of the Investigators Global Assessments for chronic hand eczema (IGA-CHE) that was developed by LEO Pharma. The IGA-AHE rates the severity of the subject's AHE and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 8).

The IGA-AHE score will be assessed according to the schedule of activities (Section 1.3). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New lesions that occur on previously untreated areas will be included in the assessment. The disease severity assessment score will be recorded in the eCRF.

Panel 8: Investigator's Global Assessment for atopic hand eczema

Score	Disease severity	IGA-AHE Sign and Intensity
0	Clear	CCI
1	Almost clear	
2	Mild disease	
3	Moderate disease	
4	Severe disease	

8.2.2 Hand Eczema Severity Index

The Hand Eczema Severity Index (HECSI) is an instrument used in clinical trials to rate the severity of 6 clinical signs (erythema [E], infiltration/papulation [I], vesicles [V], fissures [F], scaling [S], oedema [O]) and the extent of the lesions on each of the 5 hand areas (fingertips, fingers [except fingertips], palm of hands, back of hands, and wrists) by use of standard scales (47).

For each hand area (total of both hands, e.g., 10 fingers), the investigator rates the average severity of each of the 6 clinical signs of hand eczema using a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) (Panel 9). The investigator also rates the extent of the lesions by assessing the percentage of the areas these lesions occupy and converting it to a score based on a 5-point scale (the area score [AS]) (Panel 9). For each of the hand areas, the grades for the 6 clinical signs of hand eczema are added up (E + I + V + F + S + O = total grade), and this total grade will be multiplied by the AS based on the affected area of both hands (Panel 10). The HECSI score will range from 0 (lowest possible score) to 360 (highest possible score).

The HECSI will be assessed according to the schedule of activities (Section 1.3). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. New lesions that occur on previously untreated areas will be included in the assessment.

Panel 9: HECSI severity score scale and area score scale

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

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

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

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

Panel 10: 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.

8.2.3 Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (43). The EASI score will be assessed according to the schedule of activities (Section 1.3). 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. The scoring is based on the Harmonising Outcome Measures for Eczema (www.homeforeczema.org) EASI guidance version 1.

The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe or more extensive condition. The index will be calculated as shown in Panel 11. Briefly, the investigator will assess the severity of 4 AD disease characteristics (erythema, induration/papulation, excoriation, and lichenification) on the 4 body regions (head/neck, trunk, upper extremities, lower extremities); severity will be assessed according to the scale shown in Panel 12. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 12) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 11).

The body region, severity of the disease characteristics (erythema, induration/papulation, excoriation, and lichenification), and the area score will be recorded in the eCRF.

Panel 11: Calculation of the EASI score

Body region	Erythema	Induration/ papulation	Excoriation	Lichenification	Area score	Weighting factor	Score
Head/neck	(SS +	SS +	SS +	SS)	× AS	× 0.1	
Trunk	(SS +	SS +	SS +	SS)	× AS	× 0.3	
Upper extremities	(SS +	SS +	SS +	SS)	× AS	× 0.2	
Lower extremities	(SS +	SS +	SS +	SS)	× AS	× 0.4	
The EASI score is the sum of the 4 body region scores							_____ (range 0-72)

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from (48).

Panel 12: EASI severity score scale and area score scale

Severity score scale	
0	None/absent
1	Mild
2	Moderate
3	Severe

Note: half-steps (0.5, 1.5, 2.5) are allowed.

Area score scale	
0	0% affected area
1	1% to 9% affected area
2	10% to 29% affected area
3	30% to 49% affected area
4	50% to 69% affected area
5	70% to 89% affected area
6	90% to 100% affected area

Note: half-steps (0.5, 1.5, 2.5, 3.5, 4.5, 5.5) are not allowed.

Abbreviations: EASI = Eczema Area and Severity Index.

8.2.4 Hand Eczema Symptom Diary

The Hand Eczema Symptom Diary (HESD) (eDiary) is a 6-item PRO outcome developed by LEO Pharma to assess severity of hand eczema signs and symptoms. Only the 2 items itch and pain will be included and will be used to assess worst itch and skin pain from hand eczema over the past 24 hours using an 11-point numeric rating scale with anchors of 0 =‘no (symptom)’ and 10 =‘severe (symptom)’.

The subjects must start completing the HESD in the eDiary at least 1 week prior to baseline, but preferably from the date the subjects receive the eDiary. The subjects will complete the HESD daily in the eDiary as outlined in Section 1.3.

8.3 Safety assessments

Planned timepoints for all safety assessments are provided in the schedule of activities (Section 1.3).

8.3.1 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed according to the schedule of activities (Section 1.3). Vital signs will be measured following at least 5 minutes of rest.

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

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

Reporting in eCRF

It will be recorded in the eCRF if vital signs were measured; if not, a reason should be provided. Vital signs and the date and time vital signs were measured will be recorded in the eCRF. Clinically significant abnormal vital signs at the screening and baseline visits (prior to IMP administration) 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 randomization will be reported as an AE in accordance with Appendix 2, Section 10.2.4.

8.3.2 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin; auscultation of heart, lungs, and abdomen; palpation of the abdominal organs; and basic neurological status must be performed according to the schedule of activities (Section 1.3).

If an unacceptable abnormal finding is identified during the physical examination at the screening visit, the subject must not be randomized into the clinical trial (respecting exclusion criterion 14). Findings of the skin related to the AD or AHE are not considered as unacceptable abnormal findings.

Reporting in eCRF

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

Clinically significant abnormal findings at the screening visit, apart from the trial disease, will be documented as medical history in the eCRF.

8.3.3 Laboratory testing

8.3.3.1 Overview

Blood and urine samples will be collected according to the schedule of activities (Section 1.3).

The evaluations shown in Panel 13 will be performed by the central laboratory.

Panel 13: Clinical laboratory tests

Chemistry	Hematology[d]
Liver and renal parameters: Aspartate aminotransferase Alanine aminotransferase Creatinine[a] Alkaline phosphatase[a] Gamma glutamyl transferase[a] Bilirubin[b] **Electrolytes and glucose:** Sodium[a] Potassium[a] Calcium[a] **Lipid parameters:** Cholesterol[a] LDL cholesterol[a] HDL cholesterol[a] Triglycerides[a]	Thrombocytes Erythrocytes[a] Haemoglobin[a] **White blood cells:** Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Serum pregnancy test[a,c]	**Serology[a,d]**
Choriogonadotropin beta	Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody

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

a. Collected at screening only.
b. If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
c. Only women of childbearing potential.
d. If it is necessary to re-test or to perform additional tests to support the result of the initial test , these will be performed by the central laboratory.

8.3.3.2 Investigator evaluation of laboratory samples

Central laboratory

Chemistry, hematology, and serology will be analyzed by a central laboratory which will provide results to the trial sites. The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date the 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.

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

Abnormal liver function tests of concurrent measurements of ALT or AST ≥3×ULN and BILI ≥2× ULN should be reported as an SAE (see Appendix 2, Section 10.2.5 for reporting of SAEs).

If a screening laboratory result is abnormal and clinically significant, it will be at the discretion of the investigator to decide if the subject should be randomized into the trial.

Serum pregnancy tests for women of childbearing potential will be analyzed by a central laboratory, which will provide results to the trial sites. A positive serum pregnancy test at screening is an exclusion criterion.

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

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomization. The test will be repeated every 4 weeks for the first 16 weeks, and every 8 weeks thereafter, as shown in the schedule of activities in Section 1.3. Sites will be provided with urine pregnancy test kits. For females of childbearing potential, pregnancy test should be repeated at end of treatment and at any time during the trial, if a menstrual period is missed or pregnancy is suspected or as required by local regulations. The date and result of the pregnancy tests must be recorded in the subject's medical record and the

result at screening and end of treatment must be transcribed to the eCRF.

Reporting in eCRF
At screening and Weeks 8, 16, and 32, 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 the subject is a woman of childbearing potential and if a urine pregnancy test was performed. If not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative'). Subjects must immediately discontinue IMP permanently in the event of a positive urine pregnancy test (Section 7.2.1).

Clinically significant abnormal laboratory results prior to baseline 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 initiation of IMP will be reported as an AE in accordance with Appendix 2, Section 10.2.4.

8.4 AE, SAE, and other safety reporting

The definitions of AEs and SAEs can be found in Appendix 2 (Section 10.2).

8.4.1 Time period and frequency of collecting AE information

All AEs will be collected from baseline visit until end of trial (defined as the last visit in the trial), at the timepoints specified in the schedule of activities (Section 1.3). Pre-existing conditions (including those found as a result of screening procedures) as well as medical occurrences with onset in the period between signing of the informed consent and the baseline visit will be recorded as medical history in the eCRF.

The timing of AE start (i.e., whether prior to or after IMP administration) will be recorded in the eCRF as described in Appendix 2, Section 10.2.4.

All SAEs will be recorded and reported to LEO Pharma immediately without undue delay but no later than within 24 hours of awareness, as indicated in Appendix 2 (Section 10.2). The investigator will submit any updated SAE data to LEO Pharma within 24 hours of it being available.

8.4.2 Method of detecting AEs

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

At all visits, the subject will be asked a non-leading question by the investigator about AEs, e.g.: “How have you felt since I saw you last?”. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow-up with the subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 2, Section 10.2.4.

8.4.4 Regulatory reporting requirements for SAE

Prompt notification (within 24 hours, see Appendix 2, Section 10.2) by the investigator to LEO Pharma of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial treatment under clinical investigation are met.

LEO Pharma 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. LEO Pharma will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/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 LEO Pharma will review and then file it along with the investigator’s brochure and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs that occur during the trial until the last safety follow-up visit, whether considered to be associated with the IMP or not, must be reported to LEO Pharma 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. Details for reporting of SAEs are described in Appendix 2, Section 10.2.5.

Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis as required by local legislation.

8.4.5 Pregnancy

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

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Appendix 2, Section 10.2.5.

Pregnant subjects must immediately discontinue IMP permanently (Section 7.2.1).

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. For SAE definitions, see Appendix 2, Section 10.2.2.

The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to LEO Pharma.

Any post-trial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to LEO Pharma as described in Section 8.4.4. While the investigator is not obligated to actively seek this information about former trial subjects, he or she may learn of an SAE through spontaneous reporting.

8.4.6 Other events that require expedited reporting

Not applicable.

8.4.7 Reporting of other events

8.4.7.1 AESI

The events listed in Panel 14 are considered AESIs in this trial and will require additional details to be recorded. LEO Pharma may request that the investigator forward additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting and should be reported as SAEs as described in Section 8.4.4 in addition to the requirements specified in Panel 14.

Panel 14: Adverse events of special interest

Adverse event of special interest	Additional data to be recorded	Data collection method
Conjunctivitis	• Unilateral/bilateral. • Etiology (allergic[a], atopic[b], viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF
Keratoconjunctivitis	• Unilateral/bilateral. • Etiology (atopic, vernal, viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF
Keratitis	• Unilateral/bilateral. • Etiology (allergic, viral, bacterial, other (please specify), unknown). • If infectious etiology, was it confirmed by laboratory testing. • Diagnosis confirmed by ophthalmologist.	eCRF

a. Allergic conjunctivitis: acute and episodic associated with tearing, sneezing, and runny nose.
b. Atopic conjunctivitis associated with eyelid/facial eczema and dry eyes.

8.4.7.2 Medication error

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

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

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

Inappropriate schedule of product administration where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement. See also Section 6.4 for recording of treatment non-compliance.

Medication error must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs

on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (see Appendix 2, Section 10.2.5).

If the medication error is due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 6.8.

8.4.7.3 Misuse or abuse

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

Misuse refers to situations where the IMP is intentionally and inappropriately used for therapeutic purposes not in accordance with the protocol e.g., subject intentionally uses a wrong route of administration or a wrong dose.

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 Appendix 2, Section 10.2.5).

8.5 Pharmacokinetic assessments

Not applicable.

8.6 Pharmacodynamic assessments

Not applicable.

8.7 Other assessments

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

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

The following PROs will be completed in an electronic device by the subjects at the trial sites at the visits specified in the schedule of activities (Section 1.3) in the following order:

- Itch PGI-S
- Pain PGI-S

- Itch PGI-C
- Pain PGI-C
- HEIS
- DLQI
- WPAI+CIQ:AHE

The PRO HESD (eDiary) is considered an efficacy assessment in this trial and is described in Section 8.2.4.

8.7.1.1 Patient's Global Impression of Severity

The PGI-S is a 1-item questionnaire designed to assess the subject's global perception of their itch or pain over the past week on a 4-point categorical response scale ('none', 'mild', 'moderate', or 'severe') (49).

The subjects will be asked to complete 2 PGI-S questionnaires, one each to assess itch (Itch PGI-S) and pain (Pain PGI-S) (Panel 15).

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

Panel 15: Patient Global Impression of Severity (PGI-S) questionnaires

Itch PGI-S	**Pain 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**.
Response scale: □ None □ Mild □ Moderate □ Severe	Response scale: □ None □ Mild □ Moderate □ Severe

8.7.1.2 Patient's Global Impression of Change

The PGI-C is a 1-item questionnaire designed to assess the subject's impression of changes (49). From 5 response options ('much better', 'a little better', 'no change', 'a little worse', or 'much worse'), the subjects have to select the one response that best describes the overall change in their itch or pain since they started IMP treatment.

The subjects will be asked to complete 2 PGI-C questionnaires, one each to assess the change in itch (Itch PGI-C) and pain (Pain PGI-C) (Panel 16).

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

Panel 16: Patient Global Impression of Change (PGI-C) questionnaires

Itch PGI-C	**Pain 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.
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

8.7.1.3 Hand Eczema Impact Scale

The Hand Eczema Impact Scale (HEIS) is a validated 9-item PRO instrument developed by LEO Pharma to assess the subject's perception of the impact of hand eczema on their daily activities, embarrassment, frustration, sleep, work, and physical functioning over the past 7 days. Each item is scored on a 5-point scale (0='not at all', 1='a little', 2='moderately', 3='a lot', 4='extremely'). The HEIS score is the average of the 9 items. The highest possible score is 4, and a high score is indicative of a high impact. 6 domain scores can be calculated for HEIS: PDAL (average of 3 items), embarrassment with the appearance of the hands (average of 2 items), frustration with AHE (1 item), sleep (1 item), work (1 item), and physical functioning (1 item).

The HEIS will be completed at the trial site according to the schedule of activities in Section 1.3.

8.7.1.4 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (40). Each item is scored on a 4-point Likert scale (0 = 'not at all/not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life.

The DLQI will be completed at the trial site according to the schedule of activities in Section 1.3.

8.7.1.5 Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire in atopic hand eczema: Hand Eczema (WPAI+CIQ:AHE)

The impact of AHE on the subject's ability to work, attend classes, and perform regular activities will be assessed by WPAI+CIQ:AHE (41, 42).

The WPAI+CIQ:AHE consists of 10 items, and scores can be calculated for 7 domains, each reflecting the percentage impairment due to AHE during the past 7 days, with higher numbers indicating greater impairment and less productivity:

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

The WPAI+CIQ:AHE will be completed at the trial site according to the schedule of activities in Section 1.3.

8.7.2 Photography

At selected sites, subjects will be asked to participate in a photography component of the trial which involves digital photography assessments to show disease progression over time.

Participation in this photography component requires that the subject provides additional informed consent.

Digital color photographs will be taken of the hands, including a representative lesion, according to the schedule of activities (Section 1.3). For subjects who have consented to having photographs taken, it will be recorded in the eCRF if the photo(s) was taken; if not, a reason should be provided.

The trial sites will use their own equipment or equipment provided by the photography vendor to take the photographs. Instructions for photography will be provided to the sites in a photography manual. Photography standards and procedures are provided to the trial sites by the central photography vendor.

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

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

LEO Pharma may at its discretion use the photographs in publications, posters, and similar types of information material or media targeting patients and HCPs. The photographs may also be part of training material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected to the extent possible.

8.8 End of trial

Reporting in eCRF:

End of treatment
An end-of-treatment form will be completed in the eCRF for all subjects when they have completed Week 32. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (and who received IMP) (see schedule of activities, Panel 3 for early termination assessments).

The date and time of last administration of IMP will be recorded on the end-of-treatment form. It will also be recorded if the subject completed the treatment (i.e., did not permanently discontinue IMP prior to Week 32). If not, the date of and primary reason for permanent discontinuation of IMP must be recorded (see Section 7.2.1).

End of trial

An end-of-trial form must be completed in the eCRF for all randomized subjects. The following data will be collected:

- If the subject completed the trial.
- Visit number of the last visit (including phone call) the subject attended in this trial.
- Date of last contact.
- Primary reason for withdrawal from trial based on the following categories: death, adverse event, lack of efficacy on AHE, lost to follow-up, pregnancy, withdrawal by subject, or other.
- If the subject attended the safety follow-up visit?
- Primary reason for not attending safety follow-up visit based on the above categories?

The end-of-trial form will be completed when the subject has had their last visit (that is, the safety follow-up visit [Week 36] or early termination visit).

8.9 Storage of biological samples

All biological samples are destroyed immediately after analysis.

9 Statistical considerations

9.1 Testing strategy

9.1.1 Statistical hypotheses

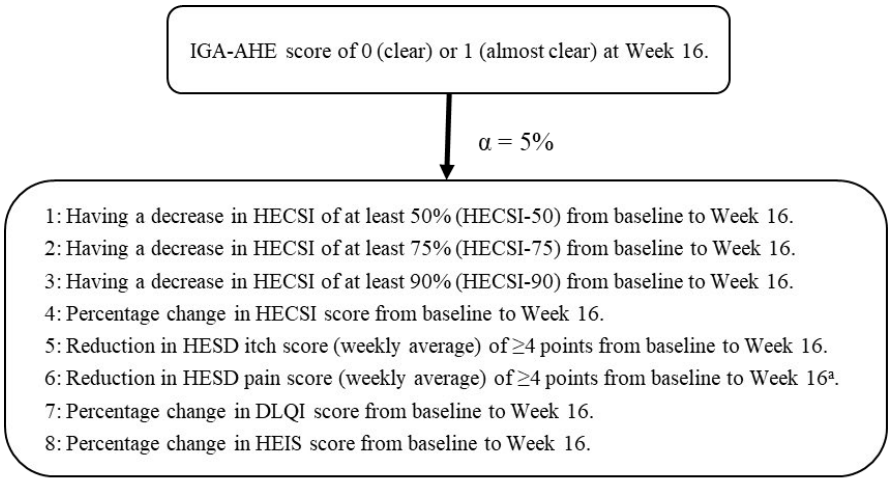
The objective of the primary endpoint is to demonstrate that tralokinumab is superior to placebo in achieving a higher response rate of IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16. The alternate hypothesis of a positive attributable treatment effect of tralokinumab over placebo will be tested using a 1-sided test at the 2.5% level against the null hypothesis of no attributable effect of tralokinumab compared to placebo.

If the primary endpoint demonstrates that tralokinumab is superior to placebo in achieving a higher response rate of IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16, then a 5% level will be passed to the key secondary endpoints where superiority of tralokinumab over placebo will be tested using 2-sided tests. 2-sided hypothesis tests can only show superiority when the point estimate of the attributable treatment effect shows that tralokinumab provides an improvement on the applicable endpoint scale over placebo and a p-value lower than the specified alpha level.

9.1.2 Multiplicity adjustment

The primary and key secondary endpoints will be tested in a hierarchical order using the specified primary estimand analysis. Only if the primary efficacy endpoint leads to a statistically significant result at the one-sided 2.5% level, will the key secondary endpoints be adjusted for multiplicity and tested in the sequential order specified in Panel 17. If one of the endpoints in the testing procedure does not show superiority, then statistical significance in relation to multiplicity will not be declared for any of the subsequent key secondary endpoints, regardless of their p-values.

Panel 17: Multiple testing procedure for the primary and key secondary endpoints



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

9.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

The definitions of the trial analysis sets are provided in Panel 18.

Panel 18: Trial analysis sets

Trial analysis set	Description
FAS	All randomized and exposed subjects. Subjects will be analyzed according to the planned treatment.
SAF	All subjects who are exposed to IMP. Subjects will be analyzed according to the treatment they received.

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

The FAS will be used to analyze endpoints related to the efficacy objectives. Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full analysis set.

The SAF is used to analyze the endpoints and assessments related to safety.

The decisions regarding inclusion/exclusion of subjects or subject data in the trial analysis sets will be documented before breaking the randomization code for the sample size re-evaluation, the interim analysis, and the final analysis.

9.3 Statistical analysis

9.3.1 General principles

Baseline measurements are defined as the latest available observation at or prior to the date of the first IMP administration, unless otherwise specified.

The significance test for the primary endpoint will be one-sided using the 2.5% significance level; all other will be two-sided using the 5% significance level. All confidence intervals will be presented at the 95% confidence level, unless otherwise specified.

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

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

The double-blind period (Week 0 to Week 16), the open-label treatment period (Week 16 to Week 32), and the safety follow-up period (Week 32 to Week 36) will be reported separately.

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 CTR, depending on the type of change.

9.3.1.1 ICEs

In this context, an ICE refers to a post-randomization event that either precludes the existence of or affects the interpretation of the measurements of the endpoint.

The following ICEs are defined to describe the treatment effect that is targeted with the different estimand strategies:

- **Initiation of rescue treatment for AHE:**
  - This ICE occurs when a subject initiates rescue treatment according to the definition of rescue treatment in Section 6.7.2. This ICE occurs at the discretion of the investigator.

- **Initiation of treatment for AD:**
  - This ICE occurs when a subject initiates rescue treatment for AHE according to the definition of rescue treatment for AHE in Section 6.7.2 or when otherwise prohibited treatments are used to alleviate intolerable symptoms due to AD on other areas of the body than the hands and wrists. Allowed mild or moderate TCS and TCI for AD, as described in Section 6.7.3 (Panel 7), will not be considered initiation of treatment for AD. This ICE occurs at the discretion of the investigator.
- **Permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event:**
  - This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as 'adverse event' or 'lack of efficacy on AHE'. It can occur at the subject's own discretion, at the discretion of the investigator, or LEO Pharma.
- **Permanent discontinuation of IMP not due to lack of efficacy on AHE or adverse event:**
  - This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as 'death', 'lost to follow-up', 'pregnancy', 'withdrawal by subject', or 'other'. It can occur at the subject's own discretion, at the discretion of the investigator, or LEO Pharma, or if the subject is lost to follow-up.
- **Permanent discontinuation of IMP due to lack of efficacy on AD or adverse event:**
  - This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as 'adverse event', 'lack of efficacy on AHE', or 'lack of efficacy on AD on areas of the body other than hands and wrists'. It can occur at the subject's own discretion, at the discretion of the investigator, or LEO Pharma.
- **Permanent discontinuation of IMP not due to lack of efficacy on AD or adverse event:**
  - This ICE occurs when a subject permanently discontinues IMP and the primary reason for discontinuation is reported as 'death', 'lost to follow-up', 'pregnancy', 'withdrawal by subject', or 'other' (excluding subjects indicating a 'lack of efficacy on AD on areas of the body other than hands and wrists'). It can occur at the subject's own discretion, at the discretion of the investigator, or LEO Pharma, or if the subject is lost to follow-up.

An overview of the strategies chosen to handle the ICEs for each estimand is provided in Panel 19.

Panel 19: ICE strategies for primary estimands associated with binary or continuous AHE endpoints

Type of endpoint	Estimand	Strategy for addressing the first prior ICE		
		Initiation of rescue treatment for AHE	**Permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event**	**Permanent discontinuation of IMP not due to lack of efficacy on AHE or adverse event**
Binary	Primary	'Composite': The ICE is incorporated as a component in a composite variable with the endpoint of interest.		'Hypothetical': Data collected after occurrence of the ICE will be excluded. Resulting missing data will be imputed using MI.
Continuous	Primary	'Hypothetical': Data collected after occurrence of the ICE will be excluded. Resulting missing data assumed MAR within each treatment group.		

Abbreviations: AHE = atopic hand eczema; ICE = intercurrent event; IMP = investigational medicinal product; MI = multiple imputation; MAR = missing at random.

The number and type of ICEs will be summarized by treatment group and visit. The cumulative incidence of permanent discontinuation of IMP by reason and initiation of rescue treatment for AHE and treatment initiated for AD will be presented based on the Aalen-Johansen estimator.

9.3.1.2 Handling of missing data

Procedures for handling of missing values are included under the sections describing the individual analyses. Details on the imputation models will be provided in the SAP.

9.3.2 Primary endpoint analysis

9.3.2.1 Definition of endpoint

The primary endpoint IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16 evaluates and compares the proportion of subjects having an IGA-AHE score of 0 or 1 at the Week 16 visit between tralokinumab and placebo.

9.3.2.2 Main analytical approach

The primary estimand for the primary endpoint will be the estimand for binary endpoints described in detail in Section 3.

For the ICEs 'initiation of rescue treatment for AHE' and 'permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event', a 'composite' strategy will be applied, and subjects will be considered non-responders after the ICE occurred, reflecting an assumption that initiation of rescue treatment for AHE and permanent discontinuation of IMP due to lack of efficacy on AHE or adverse event indicate failure of the randomized treatment.

For the ICE 'permanent discontinuation of IMP not related to lack of efficacy on AHE or adverse events', a 'hypothetical' strategy will be applied reflecting a scenario where all subjects remain on treatment except those permanently discontinuing IMP due to lack of efficacy on AHE or adverse event. Data collected after the occurrence of the ICEs will be imputed together with missing subject data not affected by an ICE using MI (full conditional specification, 100 iterations, seed=2328) assuming MAR within treatment group.

For each of the 100 complete datasets, the difference in response rates between the two treatment groups will be analyzed using a logistic regression model adjusted for treatment group, region, and baseline disease severity (IGA-AHE score 3 or 4). The estimates and standard errors of the marginal effect derived from each regression model will be combined using Rubin's rule to provide the estimate and associated standard error and p-value.

9.3.2.3 Combination test, estimate and confidence intervals

To account for the possible type I error inflation due to the adaptive design features, the inverse normal combination test will be applied (50), combining the one-sided *p*-values p_1 and p_2 for the null hypothesis based on the subjects randomized 16 weeks prior to the cut-off date for interim analysis (the interim cohort) and the subjects randomized afterwards, respectively, by using the inverse weighted combination function

$$C(p_1, p_2) = 1 - \Phi\left(\omega_1 \Phi^{-1}(1 - p_1) + \omega_2 \Phi^{-1}(1 - p_2)\right) = 1 - \Phi(\widetilde{z_2})$$

with predefined equal weights of

$$\omega_1 = \omega_2 = \sqrt{0.5}$$

Here

$$\widetilde{Z_2} = \omega_1 Z_1 + \omega_2 Z_2,$$

denotes the test statistics for combined p-value with $Z_1 = \Phi^{-1}(1 - p_1)$ and $Z_2 = \Phi^{-1}(1 - p_2)$ being the test statistics up to and after the interim analysis. Φ^{-1} denotes the inverse of the standard normal cumulative distribution function Φ.

A 95% confidence interval for the treatment difference between tralokinumab and placebo will be presented and derived by confidence testing based on the inverse normal combination test. The confidence interval will be constructed by testing the hypothesis that the treatment difference is equal to a specific value $\tilde{\mu}$ for all possible values of $\tilde{\mu}$. If the hypothesis is rejected, $\tilde{\mu}$ is not included in the confidence interval. The estimated treatment difference will be the center of the confidence interval. Individual treatment estimates along with 95% confidence intervals will also be derived by confidence testing.

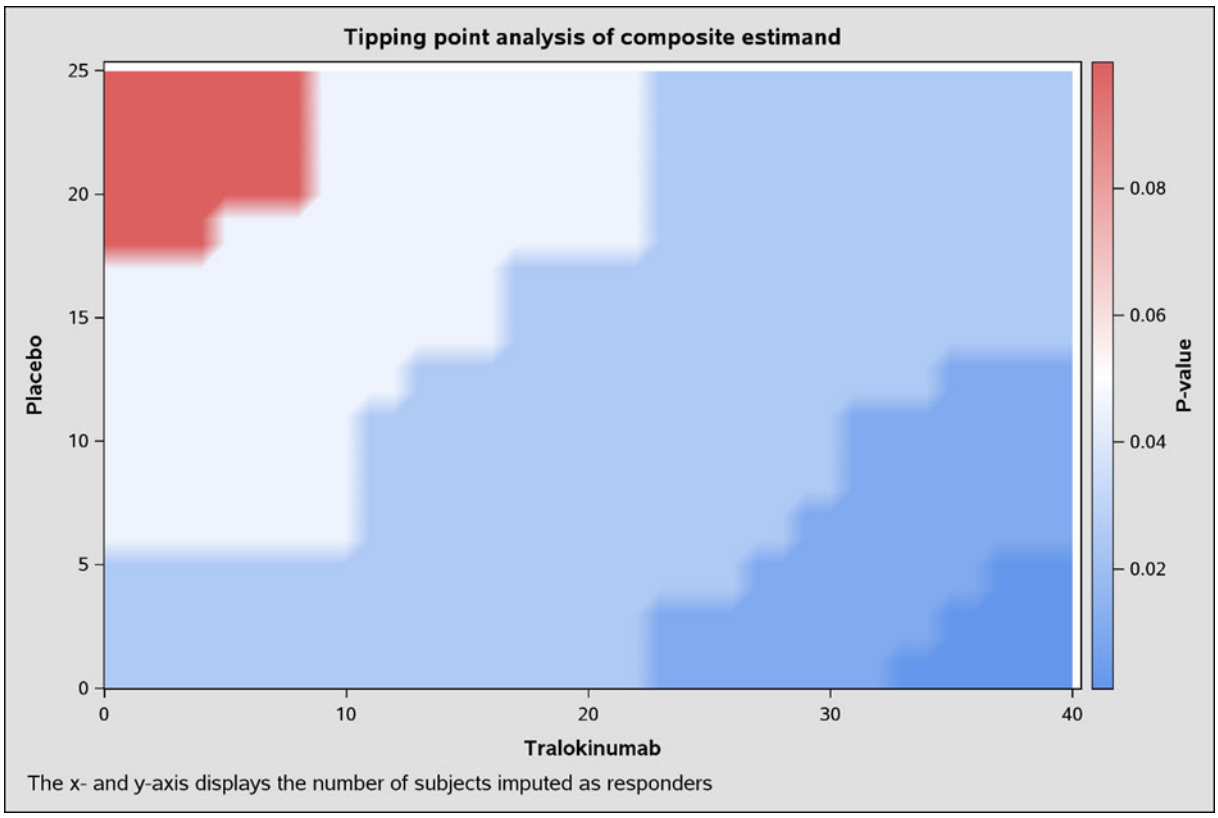
9.3.2.4 Sensitivity analysis/analyses

To evaluate the robustness of the multiple imputation of missing data and the MAR assumption for the primary estimand, a tipping point analysis will be performed. Missing data for subjects who did not experience an ICE prior to the Week 16 visit, will be handled as follows:

- Let N_t and N_p be the number of subjects imputed by multiple imputation (i.e., subjects who permanently discontinued IMP not due to lack of efficacy on AHE or adverse event prior to the Week 16 visit and subjects with missing data at Week 16, who did not experience an ICE prior to the Week 16 visit) in the tralokinumab and placebo group, respectively.
- Let X be the number of subjects in the tralokinumab group imputed as responders (X is a number between 0 and N_t). Thus $N_t - X$ is the number of subjects imputed as non-responders in the tralokinumab group.
- Let Y be the number of subjects in the placebo group imputed as responders (Y is a number between 0 and N_p). Thus $N_p - Y$ is the number of subjects imputed as non-responders in the placebo group.
- All possible combinations of $N_p - Y$ and $N_t - X$ will be analyzed for the primary endpoint using the inverse normal combination test as described in Section 9.3.2.2.

- The *p*-values for the one-sided test of difference in proportion of responders in tralokinumab versus placebo for each combination of responders in the two groups are displayed in a heatmap (example is shown in Panel 20 for a 2-sided test with *X* up to 40 and *Y* up to 25. The bottom-right part of the map in blue represents the combinations of responders leading to rejection of the null hypothesis, whereas the upper-left part colored in red represents the combinations where we cannot reject the null hypothesis. The white area represents the tipping points.

Panel 20: Tipping point analysis of composite estimand (an example)



9.3.3 Secondary endpoints analysis

9.3.3.1 Binary secondary endpoints

The primary estimand associated with the binary (key) secondary endpoints in the 16-weeks double-blind treatment period will be the estimand for binary endpoints described in detail in Section 3.

The endpoints will be analyzed using the same main analytical approach as for the primary endpoint described in Section 9.3.2.2. The logistic regression model will be adjusted for treatment group, region, baseline disease severity (IGA-AHE score of 3 or 4) and baseline value (for endpoint of interest).

9.3.3.2 Continuous secondary endpoints

The primary estimand associated with the continuous (key) secondary endpoints in the 16-weeks double-blind treatment period will be the estimand for continuous endpoints described in detail in Section 3.

9.3.3.2.1 Main analytical approach

For the ICEs 'initiation of rescue treatment for AHE', 'permanent discontinuation of IMP due to lack of efficacy of AHE or adverse event', and 'permanent discontinuation of IMP not related to lack of efficacy of AHE or adverse events', a 'hypothetical' strategy will be applied, and data collected after the ICEs will not be included in the analysis. Data collected after the occurrence of an ICE and missing data not affected by an ICE will be imputed using MI (full condition specification, 100 iterations, seed=2328) assuming MAR within treatment group. The estimand assesses the expected benefit of treatment when adhering to the tralokinumab treatment regimen with no rescue treatment for AHE as compared to a placebo treatment regimen with no rescue treatment for AHE in the same period.

Note: For endpoints using DLQI and EASI, the ICEs will be modified to reflect that the scores evaluate skin disease or AD on the whole body, and thus the ICEs included will be treatment initiated for AD (instead of rescue treatment for AHE), permanent discontinuation of IMP due to lack of efficacy on AD or adverse event, and permanent discontinuation of IMP not due to lack of efficacy on AD or adverse event. The handling of the ICEs will be the same as for the other endpoints, just with the modified ICEs.

The endpoints will be analyzed using an ANCOVA model with effect of treatment group, region, baseline IGA-AHE score, and baseline value (endpoint of interest). The estimates and standard errors of the marginal effect derived from each regression model will be combined using Rubin's rule to provide the estimate and associated standard error and p-value.

9.3.3.2.2 Sensitivity analysis

A tipping point analysis will be performed based on implementing a delta-adjusted multiple imputation approach with the purpose of assessing the robustness of the results of the main analytical approach with respect to the varying departures from the MAR assumption within each treatment group.

The delta-adjusted imputation approach allows for missing data to be imputed under a missing not at random (MNAR) assumption. Heuristically, the imputation strategy, shifts the parameters of the MAR distribution based on the value of a numeric offset term, denoted by Δ. The tipping point analysis will adjust the values of the parameters in the MAR distribution representing the mean change in endpoint parameter from baseline to Week16.

The range of the Δ parameter for both treatment groups will be specified in the SAP along with the seed, the MAR imputation strategy, and the number of imputations.

9.3.3.3 Secondary endpoints in open-label treatment period

The secondary endpoints in the open-label treatment period will be summarized by visit.

9.3.4 Exploratory endpoints analyses

The analysis of exploratory endpoints will be based on the FAS. The analyses will be the same as described for the primary estimands for each endpoint type (binary or continuous). For details refer Sections 9.3.2 and 9.3.3.

9.3.5 Safety analysis

The analysis of safety will be based on the SAF.

9.3.5.1 Adverse events

Coding of AEs

AEs will be coded during the course of the trial according to MedDRA. AEs defined by MedDRA preferred terms within primary system organ class will be presented.

TEAEs

An event will be considered treatment-emergent if started after the first use of IMP or if started before the first use of IMP and worsened in severity after first dose of IMP. The tabulations described in the following will only include the TEAEs.

Outputs will as a minimum present:

- AEs
- Most frequent AEs (incidence ≥5%)
- AEs with possible or probable relation to IMP
- Fatal AEs
- SAEs
- AEs leading to withdrawal or permanent discontinuation
- AESIs

- AEs by severity

Evaluation of events will be based on the following:
Number of subjects, number of subjects with events, percent of subjects with events, and number of events, and rate of events per 100 subject years of observation.

The overview of AEs will be evaluated as above and will include the following information: seriousness, severity, relatedness, outcome, action to trial product (interventions).

Listings will as a minimum be provided for:

- AEs
- Severe AEs
- AEs with fatal outcome
- SAEs
- Non-TEAEs
- AEs leading to permanent discontinuation of IMP and/or withdrawal
- AESIs
- Other events
- AEs originating from other events involving IMP

Narratives

AEs for which narratives will be provided are described in Appendix 2, Section 10.2.6.

9.3.5.2 Vital signs and physical examination

Vital signs (resting blood pressure, pulse, and body temperature) will be summarized at Week 0 and Week 16 for each treatment group. Shift table for clinically significant abnormal vital signs will presented.

Physical examination will be summarized at screening for each treatment group.

9.3.5.3 Clinical laboratory evaluation

For the laboratory parameters collected post-baseline, the change from screening to Week 16 will be summarized by treatment group.

For liver parameters (ALT, AST, and BILI) and white blood cells (neutrophils, lymphocytes, and eosinophils), guideline- or literature-defined thresholds will be used for producing shift tables and categorical threshold tables. The remaining laboratory parameters will be classified as ‘low’, ‘normal’, or ‘high’, depending on whether the value is below, within, or above the

reference range and these categories will be used for producing shift tables, except for the serology parameters for which the classifications used in the outputs will be specified in the SAP.

If any subjects have concurrent elevations of ALT, AST, or BILI, per the guideline- or literature-defined thresholds, an individual profile plot of the subjects' ALT, AST, or BILI over the trial period will be provided.

For laboratory parameters, the values collected at the screening visit will be used as baseline values.

9.4 Interim analysis

Two interim analyses are planned:

Sample size re-evaluation

In order to maintain a sufficient power to detect a statistically significant treatment effect, an interim evaluation of the sample size will be performed. The analysis method for the primary efficacy endpoint described in Section 9.3.2 will be employed. A normal combination test will be applied to account for the possible Type I error inflation due to the adaptive design.

At the interim evaluation, the sample size needed to achieve a conditional power of 90% will be derived. The cohort of subjects to be included in the interim evaluation (the interim cohort) will be based on a cut-off aiming to include as many subjects as possible, while simultaneously not halting recruitment, if possible. Evaluable subjects for the interim analysis are those randomized at least 16 weeks prior to the data cut-off for the interim analysis, and only evaluable subjects will be included in the interim analysis in order not to bias the treatment estimates of the primary endpoint. The interim evaluation will be performed (with a margin) before the 204th subject is randomized, on the condition that at least 90 subjects are evaluable for the interim analysis. If fewer than 90 subjects are evaluable at that time point, the interim analysis will be performed at a later data cut-off when at least 90 subjects are evaluable or it will be performed (with a margin) before the 250th subject is randomized.

The sample size will be increased to the minimum number of subjects needed to achieve 90% conditional power, although not less than 204 subjects (or the number of randomized subjects at the interim evaluation).

The interim evaluation will be conducted such that the ongoing trial integrity is maintained. Only an independent, external statistician conducting the interim evaluation will be unblinded to the individual treatment group assignment. Only the sample size calculated from the

interim evaluation will be shared with the trial team who are involved in the conduct of the trial before database lock. Further details on how the blinding will be maintained will be described in a blinding plan.

Double-blind treatment period

The second interim analysis is planned based on the double-blind treatment period. The interim analysis will be performed when all subjects enrolled have had their Week 16 visit or early termination visit and will include all analyses planned for the double-blind treatment period.

9.5 Sample size

The primary endpoint is defined as having an IGA-AHE score of 0 (clear) or 1 (almost clear) at Week 16. The null hypothesis is that tralokinumab does not have a higher response rate compared to placebo at Week 16, and the alternative hypothesis is that tralokinumab has a higher response rate compared with placebo at Week 16. The sample size planned was estimated based on the primary comparison between tralokinumab and placebo on the primary endpoint.

Assuming a screening failure rate of 30%, it was expected that at least 300 subjects will be screened. At least 204 subjects were planned to be randomized 2:1 to tralokinumab 300 mg (2 mL) Q2W or placebo (2 mL) Q2W.

Assuming IGA-AHE 0/1 response rates of 21.8% versus 10.0% for tralokinumab and placebo, respectively (based on data from LP0162-1325 [ECZTRA 1] and LP0162-1326 [ECZTRA 2], excluding data from Japan and Australia), and a 2:1 randomization ratio, the adaptive design yields at least 85% power to detect statistical significance (1-sided 2.5% significance level) in favour of tralokinumab. An interim analysis to evaluate the sample size during the trial was planned (see Section 9.4).

The first interim analysis was performed, as described in Section 9.4, after 198 subjects were randomized, with 149 evaluable subjects. The minimum number of subjects needed to achieve 90% conditional power was calculated to be 229.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and trial governance considerations

10.1.1 Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (37) and Council for International Organizations of Medical Sciences International Ethical Guidelines (51).
- Current version of ICH GCP Guidelines (52).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authorities must be notified of/approve the clinical trial as required.

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

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

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Informing LEO Pharma immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Handling of serious breach

A serious breach is any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial subjects and/or data reliability and robustness to a significant degree in a clinical trial.

The investigator and all site staff are responsible for reporting suspected serious breaches to LEO Pharma without undue delay and no later than 24 hours of obtaining knowledge.

Suspected serious breaches must be reported to the CRA.

If necessary for reporting the incident to the affected member state through the EU portal, LEO Pharma may request additional information from the reporter.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

The subject’s signed and dated informed consent to participate in the clinical trial will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP and all applicable laws and regulations. The authorized person obtaining the informed consent must also sign the ICF.

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

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

Subject card

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

10.1.4 Recruitment strategy

The recruitment strategy and tools will be the below including, but not limited to:

Recruitment tools as approved by the regulatory authorities and IRB/IEC:

- Advertisement – Poster, flier, brochure
- HCP referral letter

Local, site-initiated advertisement will be subject to the sponsor's review and approval prior to submission to their local/central IRB/IEC.

10.1.5 Data protection

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

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

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

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

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

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

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

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

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

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

Subjects must be informed of the collection, processing, and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorizations for products/services, marketing of products/services, and other related activities.

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

10.1.6 Committee structure

Not applicable.

10.1.7 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 subject enters the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this clinical trial will be posted in accordance with applicable laws and regulations as well as LEO Pharma's commitment to transparency which can be found on LEO Pharma's website.

10.1.8 Data quality assurance

Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g., laboratory data). The investigator or staff authorized by the investigator will enter subject data into an eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

Quality tolerance limits will be predefined in the data review plan to identify systematic issues that can impact subject safety and/or reliability of trial results. These predefined parameters will be monitored during the trial, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical trial report.

The monitoring will be performed in a systematic, prioritized, risk-based approach, and as a combination of on-site, remote, and centralized monitoring.

LEO Pharma or designee is responsible for the data management of this trial including quality checking of the data.

LEO Pharma assumes accountability for actions delegated to other individuals (e.g., CROs).

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 LEO Pharma. No records may be transferred to another location or party without the written approval of LEO Pharma.

All data generated by the site personnel will be captured electronically at each trial site using eCRFs. Once the eCRF clinical data have been submitted to the central server, 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 CRA, medical expert or data manager will raise a query in the electronic data capture 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 data manager or CRA will freeze the eCRF page.

Site personnel will receive training on the EDC system/eCRF. The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be described in the CRF completion guidelines.

10.1.9 Source documents

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

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet or in the eDiary or Trial Slate for ePRO data.

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

- Subject ID.
- The fact that the subject is participating in a clinical trial for AD and AHE including treatment with tralokinumab or placebo for up to 32 weeks.
- Other relevant medical information.

10.1.10 Trial and trial 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 subjects.

The first act of recruitment is the first subject first visit.

Trial/site termination

LEO Pharma 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 LEO Pharma. 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.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO Pharma procedures, or GCP guidelines.
- Inadequate recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected (irrespective of the specific site's planned inclusion number).

Responsibilities following suspension or termination

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

10.1.11 Publication policy

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

A multi-site publication will be submitted for publication within 12 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined

as final database lock of the clinical trial. After such multi-site publication is made public, or if no multi-site publication has been submitted within the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

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

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

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

Any publication must comply with Good Publication Practice standards.

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations, European Federation of Pharmaceutical Industries and Associations, Japan Pharmaceutical Manufacturers Association, Pharmaceutical Research and Manufacturers of America, and the joint position statement by the American Medical Writers Association, the European Medical Writers Association, and the International Society for Medical Publication Professionals on disclosure of information about clinical trials, trial results, and authorship. LEO Pharma also follows the CONSORT reporting guidelines (45).

10.1.12 Insurance

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

10.2 Appendix 2: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.2.1 AE definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable 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 (53).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavorable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 8.3.3.2).

10.2.2 Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization*.
- 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 hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalization, development of drug dependency, or drug abuse.

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

***Notes:**

a. Hospitalization for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as an AE or SAE.

b. Hospitalization for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as an AE or SAE, even if not planned before consent to trial participation.

c. Hospitalization for routine scheduled treatment or monitoring of the studied indication not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as an AE or SAE.

d. Hospitalization for administrative, trial-related, or social purpose does not constitute an AE and should therefore not be reported as an AE or SAE.

e. Complications that occur during hospitalization are (S)AEs. If a complication prolongs hospitalization, the event is an SAE.

When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

10.2.3 Definition of AESIs

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

AESIs are described in Section 8.4.7.1.

10.2.4 Recording and follow-up of AE

AE recording

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

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

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared to screening, must be reported as an AE.

Atopic dermatitis and hand eczema are both fluctuating diseases with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by atopic dermatitis/hand eczema should be reported as an AE.

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 in the eCRF 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 below.

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

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

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. If a medical occurrence with onset prior to IMP initiation worsens after IMP administration, this should be recorded as a new AE.

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

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 tralokinumab investigator's brochure in their assessment.

For each AE, the investigator must document in the medical notes that he/she has reviewed the AE 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 SAE form. However, it is very important that the investigator always assesses causality for every event before the initial recording of the SAE data.

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

Assessment of outcome

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

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

LEO Pharma definitions versus CDISC definitions

Note that as per the above definition, LEO Pharma uses 'recovered/resolved' only if an event has actually stopped. According to the CDISC definition, the category 'recovered/resolved' also includes events which have improved. However, following the LEO Pharma definitions

above, such an improved event will instead be classified as ‘not recovered/not resolved’ or ‘recovering/resolving’.

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

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

Follow-up of AEs

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). For subjects who complete the trial (i.e., attend the SFU visit at Week 36, 6 weeks after last IMP administration), the investigator should not follow up on the outcome of non-serious AEs. If a subject leaves the trial prior to Week 36, the investigator should follow-up on the outcome of all non-serious AEs classified as possibly or probably related to IMP for 14 days after the last visit or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to IMP do not need to be followed up for final outcome.

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

The investigator is obligated to arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by LEO Pharma 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 subject dies during participation in the trial or during a recognized follow-up period, the investigator will provide LEO Pharma with a copy of any post-mortem findings including histopathology, if available.

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

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

10.2.5 Reporting of SAE

Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form immediately, without undue delay and no later than 24 hours of obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP, device, 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 69102468

If relevant, the investigator will enclose other information with the SAE form, such as anonymized 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 provide such information to LEO Pharma by either update of the eCRF or by fax or email (see contact details below) depending on the type of information needed.

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. If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the SAE to Global Safety at LEO Pharma via fax or email (see contact details above).

LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether an SAE is expected. The relevant reference safety information document for this clinical trial is the investigator's brochure Section 7.2, edition 21 and subsequent updates.

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

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

For all non-US countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma (52), and which are unexpected (suspected, unexpected serious adverse reactions), are subject to expedited reporting to regulatory authorities, IEC(s)/IRB(s) [and other committees (e.g., DMC)] according to the current applicable legislation in the concerned country[ies]. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

For the US, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP by LEO Pharma (54) and which are unexpected (serious and unexpected suspected adverse reactions [IND safety report]) are subject to expedited reporting

to regulatory authorities and IRBs. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

10.2.6 Narratives

In the CTR, narratives will be provided for the following:

- SAEs
- Deaths

10.3 Appendix 3: Contraceptive and barrier guidance

10.3.1 Definitions

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 12 months without an alternative medical cause.
     - 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 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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 trial enrolment.
   - Permanent sterilization 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 subject's medical records, medical examination, or medical history interview.

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

10.3.2 Contraception guidance

Contraceptives[a] allowed during the trial include:
Highly effective methods[b] that have low user dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential 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 subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o 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 trial intervention. 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 trials. 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 CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Contraceptive methods that are not allowed during the trial:

Effective methods[d] that are not considered highly effective
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this trial. Male condom and female condom should not be used together (due to risk of failure from friction).

c) [Male condoms must be used in addition to hormonal contraception]. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d) Considered effective, but not highly effective - failure rate of ≥ 1% per year.

10.4 Appendix 4: Country-specific requirements

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

10.4.1 France

Section 5.2 Exclusion criteria
An additional exclusion criterion will apply to subjects in France:
30. Subject not affiliated with or not a beneficiary of a social security scheme.

Section 8.3.3.2 Investigator evaluation of laboratory samples

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomization. The test will be repeated every 4 weeks for the first 16 weeks, and every 8 weeks thereafter, as shown in the schedule of activities in Section 1.3.

In France, urine pregnancy testing will be repeated every 4 weeks. Thus, from Week 16 onwards, site staff will supply a pregnancy test kit for home use to female subjects of childbearing potential. The subjects will take the pregnancy test at home every 8 weeks during the open-label period, alternating with the tests performed at site. The result of the pregnancy test will be reported to the site at the subject's next visit.

In case of a positive test result, the subject must discontinue IMP use and contact site staff immediately. Should this occur, site staff will call the subject in for an unscheduled site visit. In case of a negative test result, the subject should continue administration of IMP at home as usual.

10.4.2 Czech Republic

Section 8.3.3.2 Investigator evaluation of laboratory samples

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomization. The test will be repeated every 4 weeks for the first 16 weeks, and every 8 weeks thereafter, as shown in the schedule of activities in Section 1.3.

In the Czech Republic, urine pregnancy testing will be repeated every 4 weeks. Thus, from Week 16 onwards, site staff will supply a pregnancy test kit for home use to female subjects of childbearing potential. The subjects will take the pregnancy test at home

every 8 weeks during the open-label period, alternating with the tests performed at site. The result of the pregnancy test will be reported to the site at the subject's next visit.

In case of a positive test result, the subject must discontinue IMP use and contact site staff immediately. Should this occur, site staff will call the subject in for an unscheduled site visit. In case of a negative test result, the subject should continue administration of IMP at home as usual.

10.4.3 South Korea

Section 5.1 Inclusion criteria

Age

2. Age 18 years or above at screening.

In South Korea, subjects must be age 19 yours or above at screening.

10.5 Appendix 5: Hanifin and Rajka (1980) diagnostic criteria for AD

Source: Hanifin and Rajka (44)

Major Features: must have 3 or more of the following:

- Pruritus
- Typical morphology and distribution:
  - Flexural lichenification or linearity in adults
  - Facial and extensor involvement in infants and children
- Chronic or chronically-relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Features: should have 3 or more of the following:

- Xerosis
- Ichthyosis, palmar hyperlinearity, or keratosis pilaris
- Immediate (type 1) skin-test reactivity
- Raised serum IgE
- Early age of onset
- Tendency toward cutaneous infections (especially S. aureus and herpes simplex) or impaired cell-mediated immunity
- Tendency toward non-specific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor or facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance

- Course influenced by environmental or emotional factors
- White dermographism or delayed blanch

10.6 Appendix 6: Guidance on classification of hand eczema, including characteristics of subtypes

Modified from Thyssen et al. (17)

	Medical history	Most frequent clinical signs and symptoms	Most frequent locations
Aetiological subtypes			
Irritant contact dermatitis[a]	Relevant irritant exposure, domestic and/or occupational	Itch and scaling Pain if fissures	Extensor and lateral surfaces of fingers, back of hands
Allergic contact dermatitis[a]	Relevant exposure to allergens, positive patch test to culprit allergen(s)	Erythema, often vesicles. Itch. Pain if fissures	Areas of allergen exposure, e.g., fingertips or palms
Atopic hand eczema	Atopic dermatitis	Often absence of vesicles	Dorsal aspect of hands, palms, often adjacent areas of ventral wrist, interdigital spaces
Protein contact dermatitis/ contact urticaria	Relevant exposure to proteins. History of immediate skin reactions	Immediate urticarial rash, then lasting erythema, scaling, infiltration	Initially areas of exposure, may significantly spread beyond afterwards
Clinical subtypes			
Hyperkeratotic hand eczema	No obvious exogenous or endogenous cause identifiable, neg. Patch test	Absence of vesicles. Little itch. Pain from fissures	Palms
Acute recurrent vesicular hand eczema	Cyclic eruptions	Many vesicles. Itch	Finger and palms
Nummular hand eczema	Patchy eczema, typically dorsal hands. Atopic dermatitis Relevant exposure to allergens, positive patch test to culprit allergen(s)	Itch Often xerotic skin in eczema lesions	Back of hands
Pulpitis	Relevant irritant exposure Relevant exposure to allergens, positive patch test to culprit allergen(s) Fissures Atopic dermatitis	Little itch. Often atrophic skin. Often pain.	Fingertips

a. Phototoxic and photoallergic contact dermatitis are further subtypes belonging to the groups.

10.7 Appendix 7: Protocol amendment history

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

Amendment 5 (08-May-2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

Per regulatory request during the CTIS review process, the protocol has been updated to state that if an increase in sample size is needed, the protocol will be amended and re-submitted through CTIS.

Section number and title	Description of change	Brief rationale
Section 9.4 Interim analysis	Stated that in case a sample size increase is needed, a protocol amendment will be submitted to EMA.	Per request from the reporting and other member states during the CTIS review process.

Amendment 4 (12-Feb-2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation 536/2014 of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

Per regulatory request during the CTIS review process, the protocol has been updated to specify that the sample size will be increased to the minimum number of subjects needed to achieve 90% conditional power, as derived during the first interim analysis. I.e. the protocol no longer states a maximum number of subjects to be randomized during the trial.

Section number and title	Description of change	Brief rationale
Section 1.1 Protocol synopsis	Removal of maximum number (402 subjects) to be randomized. Update of the trial design figure as stated below.	Per request from the reporting and other member states during the CTIS review process, the protocol has been updated to allow for an increase in sample size (at the interim analysis) to the number needed to achieve 90% conditional power.
Section 1.2 Schematic of trial design	Update of the number of subjects from “up to 402” to “minimum 204”.	
Section 4.1 Overall trial design	Update of number of subjects to be randomized from “up to approximately 402 subjects” to “a minimum of 204 subjects”.	

Section number and title	Description of change	Brief rationale
Section 9.4 Interim analysis	Specification that the sample size will be increased to the minimum number of subjects needed to achieve 90% conditional power, as derived during the first interim analysis. Specification that the interim analysis will include at least 90 evaluable subjects.	
Section 9.5 Sample size	Specification that at least 300 subjects are expected to be screened, at least 204 subjects are planned to be randomized, and that the adaptive design yields at least 85% power to detect statistical significance in favour of tralokinumab. Removal of maximum sample size (402 subjects).	
Title page Section 1.1 Protocol synopsis	EU CT number updated to leave out the last 2 digits.	In line with the CTCG best practice guide for naming of documents, version 2.0, 9 March 2023, the CT number stated within the protocol has been updated to leave out the last 2 digits, which will change upon re-submission in CTIS.

Amendment 3 (10-Oct-2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The clinical trial application was re-submitted in the EU, leading to an update of the EU CT number.

Section number and title	Description of change	Brief rationale
Title page	EU CT number updated.	The clinical trial application was re-submitted in the EU, leading to an update of the EU CT number.
Synopsis	EU CT number updated.	The clinical trial application was re-submitted in the EU, leading to an update of the EU CT number.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Amendment 2 (09-Aug-2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

Per regulatory recommendation during the CTIS review process, adjustments and clarifications have been included in the protocol.

Section number and title	Description of change	Brief rationale
Section 8	Paragraph revised to clarify that it is only in the US that an investigator may be a certified physician's assistant or an advanced registered nurse practitioner.	In the EU, an investigator should be a physician.
Section 8.3.3.1	Footnote d: Hepatitis B, hepatitis C, and HIV deleted.	Footnote d revised to allow retest of hematology and serology assessments.
Section 8.4.4	Text added to clarify the process for SAE reporting.	Previous text did not include information that an SAE may be reported on a paper form.
Section 8.9	New section. Added to describe the procedures for biological sample storage.	Previous protocol did not clearly state that urine and blood samples are destroyed immediately after analysis.
Section 9.5	Text inserted to clarify the basis of the response rates used for sample size calculations.	The previous text did not include the basis of the response rates used to calculate the sample size for the trial.
Appendix 1 (Section 10.1.5)	Text inserted to clarify that LEO Pharma may keep the trial-related data for up to 25 years after the end of the trial or as long as required my applicable laws and regulations.	Previous text did not include the limit for how long trial-related data may be kept.
Appendix 2 (Section 10.2.5)	Text added to clarify the process for SAE reporting.	Previous text did include information that an SAE may be reported on a paper form.
Appendix 3 (Section 10.3.2)	Table of contraceptive methods divided into those methods that are allowed and those that are not allowed in the trial.	It was not clear that the effective methods listed were not allowed.
Appendix 4 (Section 10.4.2)	New section. Frequency of pregnancy testing in the Czech Republic revised to every 4 weeks also during the open-label period.	Country-specific requirement.
Appendix 4 (Section 10.4.3)	New section. Incorporating Amendment 1 into Amendment 2.	Country-specific age requirement implemented in protocol version 2.0 KOR.

Section number and title	Description of change	Brief rationale
Appendix 7 (Section 10.7)	New appendix added containing the summary of the previous protocol amendment.	To document the protocol amendment history, and to keep only the most recent amendment summary at the start of the protocol.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

Amendment 1 (07-Jul-2023)

Overall rationale for the amendment

The reason for this amendment is to include a country-specific requirement for South Korea, which will change the minimum age of eligibility for South Korean subjects from 18 years to 19 years.

Section no. and name	Description of change	Brief rationale
Appendix 5	New appendix added containing the country-specific requirements for South Korea.	To allow identification of requirements that only apply in South Korea.
Throughout document	Minor editorial revisions.	Minor, have therefore not been summarized.

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