Dermatology beyond the skin

Cover Page

Study title: Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis ECZTRA 8 (ECZema TRAlokinumab trial no. 8)
LEO Pharma number: LP0162-1343
NCT number: NCT04587453
Date: 20-Jul-2020

Clinical Trial Protocol

LP0162-1343

Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis
ECZTRA 8 (ECZema TRAlokinumab trial no. 8)

Phase 3 – efficacy and safety trial

A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy

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

LEO Pharma A/S	**Trial ID:**	**LP0162-1343**
	Date:	**20-Jul-2020**
	EudraCT no:	**Not applicable**
	Version:	**1.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

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Signatory investigator

Acknowledgement statement investigators

Each participating investigator must agree to the approved clinical trial protocol by signing a clinical trial protocol acknowledgement form or similar document.

Table of contents

List of panels

List of abbreviations

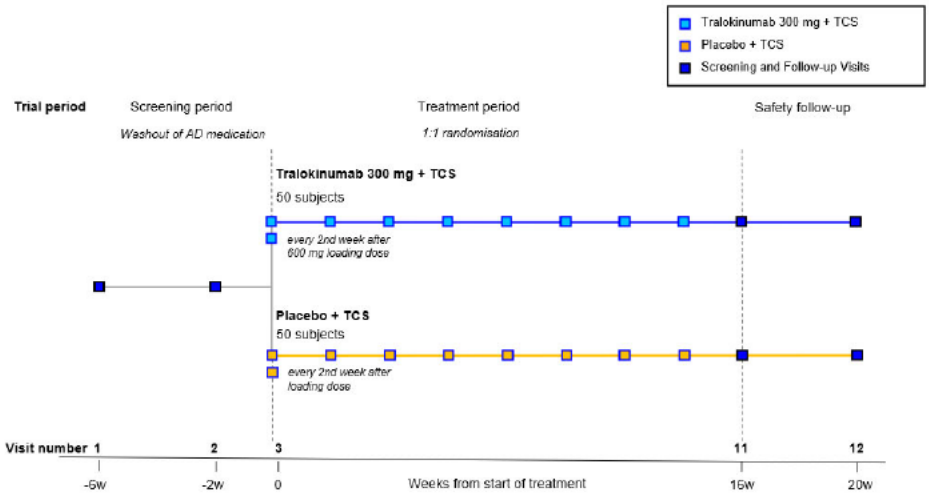
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HCV	hepatitis C virus antibody
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
BP	blood pressure
BSA	body surface area
C_{trough}	trough concentration: lowest concentration reached by a drug before the next does is administered
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMO	contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
CRA	clinical research associate
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	at least 50% reduction in EASI score
EASI75	at least 75% reduction in EASI score
EASI90	at least 90% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
ECZTEND	tralokinumab phase 3 long-term extension trial (LP0162-1337) in subjects with AD who participated in ECZTRA trials
ECZTRA 8	ECZema TRAlokinumab trial no. 8

eDiary	electronic diary
ePRO	electronic patient-reported outcome
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCP	healthcare professional
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA 0/1	IGA score of 0 (clear) or 1 (almost clear)
IgE	immunoglobulin E
IgG4	immunoglobulin G4
IL-13	interleukin-13
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus kinase
JP	Japan
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NBUVB	narrow band ultraviolet B
NRS	numeric rating scale
PDE-4	phosphodiesterase-4
PEF	peak expiratory flow
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency

POEM	Patient-Oriented Eczema Measure
PT	(MedDRA) preferred term
PUVA	psoralen + ultraviolet A
Q2W	every second week
SAE	serious adverse event
SC	subcutaneous(ly)
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
SDTM	Standard Data Tabulation Model
SmPC	summary of product characteristics
SOC	(MedDRA) system organ class
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
Th2	T-helper-2
ULN	upper level of normal
UVA1	ultraviolet A1
UVB	ultraviolet B
WHO	World Health Organization

1 Protocol synopsis

Trial ID	LP0162-1343	
Title of trial	A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. ECZTRA 8 (ECZema TRAlokinumab trial no. 8).	
Short title of trial	Tralokinumab in combination with topical corticosteroids in Japanese subjects with moderate-to-severe atopic dermatitis.	
Main objectives and endpoints	**Primary objective**	**Primary endpoints**
	To evaluate the efficacy of tralokinumab in combination with topical corticosteroids (TCS) compared with placebo in combination with TCS in treating moderate-to-severe atopic dermatitis (AD).	• Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) (IGA 0/1) at Week 16. • At least 75% reduction in Eczema Area and Severity Index (EASI75) at Week 16.
	Secondary objective (efficacy)	**Key secondary endpoints**
	To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, health-related quality of life (HRQoL), and health care resource utilisation compared with placebo in combination with TCS.	• Change in Scoring Atopic Dermatitis (SCORAD) total score from baseline to Week 16. • Change in Dermatology Life Quality Index (DLQI) score from baseline to Week 16. • Reduction of Worst Daily Pruritus numeric rating scale (NRS) score (weekly average) ≥4 from baseline to Week 16.
		Secondary endpoints
		• At least 90% reduction in Eczema Area and Severity Index (EASI90) at Week 16. • At least 50% reduction in Eczema Area and Severity Index (EASI50) at Week 16. • Percentage change in Eczema Area and Severity Index (EASI) score from baseline to Week 16. • Change in Worst Daily Pruritus NRS score (weekly average) from baseline to Week 16. • Change in Eczema-related Sleep NRS score (weekly average) from baseline to Week 16. • Change in Patient-Oriented Eczema Measure (POEM) score from baseline to Week 16.

		Other endpoints
		• Reduction of DLQI score ≥4 points from baseline to Week 16 in subjects with baseline DLQI score ≥4. • Reduction of POEM score ≥4 points from baseline to Week 16 in subjects with baseline POEM score ≥4. • Amount of TCS (axiliary medicinal product [AxMP]) used at Week 16. • TCS (AxMP) use <5g at Week 16. • Cumulative amount of TCS (AxMP) used from baseline to Week 16.
	Secondary objective (safety)	**Secondary endpoints**
	To assess the safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 16 weeks.	• Number of treatment-emergent adverse events (AEs) from baseline to Week 16 per subject. • Presence of treatment-emergent anti-drug antibodies (ADA) from baseline to Week 16.
Final collection of data for the primary endpoints	Week 16.	
Trial design	This is a randomised, double-blind, placebo-controlled, parallel-group, multi-site, phase 3 clinical trial in adult Japanese subjects with moderate-to-severe AD who are candidates for systemic therapy. The trial design will support a comparison of tralokinumab in combination with TCS to placebo in combination with TCS during a treatment period of 16 weeks. A scheme of the trial design is provided below.  **Abbreviations**: AD, atopic dermatitis; TCS, topical corticosteroids; w, weeks.	

	The trial consists of a screening period (Week -6/-2 to Week 0), a treatment period (Week 0 to Week 16), and a safety follow-up period (Week 16 to Week 20). The screening period has a minimum duration of 2 weeks and a maximum duration of 6 weeks. The exact duration of the screening period depends on the length of required washout of AD treatment as defined by the exclusion criteria. If no washout is required or if only a 2-week washout period is required, the screening period is reduced to 2 weeks and only 1 screening visit at Week -2 is required. Following the screening period, eligible subjects will be randomised at baseline (Week 0) to treatment with either tralokinumab or placebo and initiate administration of the investigational medicinal product (IMP). The IMP will be administered every second week during the treatment period, and the last IMP administration (relating to this protocol) will occur at Week 14. Subjects in both treatment groups will also receive an AxMP, i.e. TCS. At baseline (Week 0), the subjects will be allowed to initiate treatment once daily with the supplied TCS on areas with active lesions of AD and continue this treatment, as needed, throughout the treatment period. The TCS use will be monitored throughout the trial. All subjects must use an emollient twice daily (or more, as needed) for at least 14 days prior to randomisation and will continue this background treatment throughout the trial (including the safety follow-up). On lesional skin, emollients should only be applied at a time when TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times. Subjects who during the treatment period or safety follow-up experience intolerable AD symptoms can be treated with rescue treatment according to investigators discretion and will thus not be deprived from effective therapy. Subjects who complete the 16-week treatment period (relating to this protocol) may enter a long-term extension trial (ECZTEND). All subjects completing the treatment period, except for those who enter the long-term extension trial, will have safety follow-up assessments 6 weeks after last IMP administration. The primary and secondary endpoints will be assessed at Week 16, and the final safety assessments will be conducted at Week 20.
Main assessments	Efficacy assessments related to primary and secondary endpoints: • IGA, EASI, and SCORAD (investigator assessments). • DLQI, Worst Daily Pruritus NRS, Eczema-related Sleep NRS, and POEM (patient-reported assessments). Key safety assessments: • AEs and ADA.
Main criteria for inclusion	• Japanese subject aged 18 years and above. • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. • History of AD for ≥1 year. • A recent history (within 1 year before screening) of inadequate response to treatment with topical medication. • AD involvement of ≥10% body surface area (BSA) at screening and at baseline according to component A of SCORAD.

	• An EASI score of ≥12 at screening and ≥16 at baseline. • An IGA score of ≥3 at screening and at baseline. • A Worst Daily Pruritus NRS average score of ≥4 during the week prior to baseline. • Applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Main criteria for exclusion	• Subjects for whom TCS are medically inadvisable e.g. due to important side effects or safety risks in the opinion of the investigator. • Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment. • Use of tanning beds or phototherapy within 6 weeks prior to randomisation. • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroids within 4 weeks prior or randomisation. • Treatment with TCS, topical calcineurin inhibitors (TCI), topical phosphodiesterase-4 (PDE-4) inhibitors, or topical Janus kinase (JAK) inhibitors within 2 weeks prior to randomisation. • Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-immunoglobulin E [anti-IgE]) including dupilumab or investigational biologic agents 3-6 months prior to randomisation. • Active skin infections within 1 week prior to randomisation. • Clinically significant infection within 4 weeks prior to randomisation. • A helminth parasitic infection within 6 months prior to the date informed consent is obtained. • Tuberculosis requiring treatment within the 12 months prior to screening. • Known primary immunodeficiency disorder.
Investigational medicinal product (IMP)	<u>IMP - tralokinumab</u> • Active substance: tralokinumab. • Dosage form: solution for injection in an accessorised pre-filled syringe, 1.0 mL fill volume. • Concentration: 150 mg/mL. • Dose: 600 mg initial loading dose, then 300 mg every second week. • Method of administration: subcutaneous. <u>IMP - placebo</u> • Placebo contains the same excipients in the same concentration only lacking tralokinumab.
Auxiliary medicinal product (AxMP)	<u>AxMP - TCS</u> • Active substance: mometasone furoate. • Dosage form: cream. • Concentration: 0.1%. • Method of administration: topical.
Duration of trial participation	The trial duration for an individual subject is up to 26 weeks: • Screening period: 2 to 6 weeks.

	• Treatment period: 16 weeks. • Safety follow-up period: 4 weeks.
Number of subjects	Approximately 100 subjects will be randomised in a 1:1 ratio to tralokinumab+TCS or placebo+TCS.
Number and distribution of trial sites	Approximately 35 sites in Japan.
Statistical methods	Primary endpoints The difference in response rates between treatment groups will be calculated by the Mantel-Haenszel method stratified by baseline disease severity. Subjects with missing data or subjects who receive rescue medication prior to Week 16 visit will be considered as non-responders in the analysis. Key secondary endpoints The change from baseline to Week 16 in SCORAD will be analysed using an analysis of covariance (ANCOVA) model on the post-baseline responses up to Week 16. Subjects who receive rescue medication will be considered non-responders in the analysis. Missing Week 16 data among subjects who did not use rescue medication will be imputed using multiple imputation. Reduction of Worst Daily Pruritus NRS weekly average of at least 4 from baseline to Week 16 is a binary endpoint, and as such it will be analysed as described for the primary endpoints. Change from baseline to Week 16 in DLQI will be analysed the same way as change in SCORAD. Secondary endpoints EASI90 and EASI50 are binary endpoints and will be analysed as described for the primary endpoints. Percentage change from baseline to Week 16 in EASI score and change from baseline to Week 16 in Worst Daily Pruritus NRS (weekly average), Eczema-related Sleep NRS (weekly average), and POEM score will be analysed using a repeated measurements model on the post-baseline responses up to Week 16.
Signatory investigator	Norito Katoh, MD, PhD, Department of dermatology, Director, University hospital, Kyoto Prefectural University of Medicine 465, Kajii-cho, Kawaramachi-Hirokoji Kamigyo-ku, Kyoto 602-8566 Japan.
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark. LEO Pharma K.K., 1-105 Kanda-Jinbocho, Chiyoda-ku, Tokyo 101-0051, Japan is the sponsor of the clinical trial in Japan on behalf of LEO Pharma A/S.

2 Trial identification

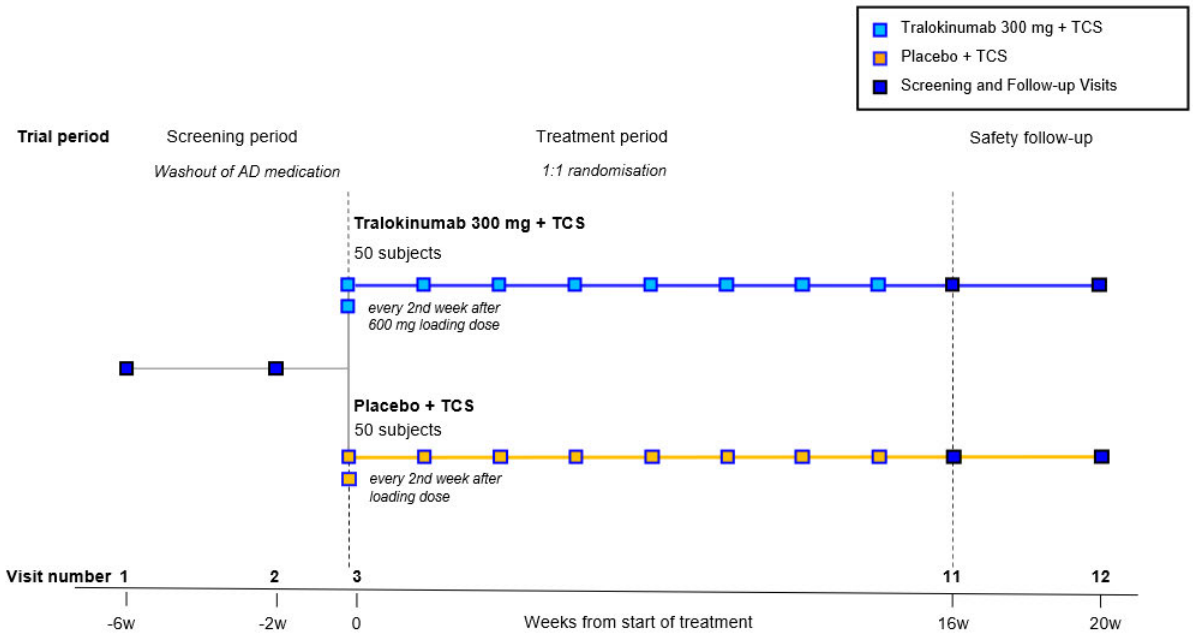
Trial ID: LP0162-1343

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

3 Schematic of trial design

The trial design is illustrated in Panel 1.

Panel 1: Trial design



Abbreviations: AD, atopic dermatitis; TCS, topical corticosteroids; w, weeks.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening		Treatment period									Safety follow-up[c]	Unscheduled visit, if applicable[d]	Early termination, if appl.[e]			References (protocol section)
Visit	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**Early termination visit[e]**	**Nominal Week 16 visit[e,f]**	**Safety follow-up visit[e,f]**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**					
Visit window (days)[a]	**±3**	**-3**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**					
Trial population and eligibility																	
Informed consent(s)[g]	X																8.4, Appendix 3B
Subject eligibility	X		X														8
Assessments only at screening and/or baseline																	
C-SSRS	X																11.2.1
Demographics	X																11.2.2
Medical/surgical history[h]	X																11.2.3
Height and weight			X														11.2.4
BSA involvement	X		X														11.2.5
Subject assessment of efficacy																	
eDiary training/hand out		X															11.3.4
eDiary completion[i]		<===										===>	X	X	X		11.3.4.1-11.3.4.3
eDiary return											X		X	(X)	X		11.3.4
DLQI			X	X	X		X		X		X		X	X	X		11.3.4.4
POEM			X	X	X		X		X		X		X	X	X		11.3.4.5

	Screening		Treatment period									Safety follow-up[c]	Unscheduled visit, if applicable[d]	Early termination, if appl.[e]			References (protocol section)
Visit	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**Early termination visit[e]**	**Nominal Week 16 visit[e,f]**	**Safety follow-up visit[e,f]**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**					
Visit window (days)[a]	**±3**	**-3**	-	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**					
Investigator assessments of efficacy																	
IGA	X		X	X	X	X	X	X	X	X	X		X	X	X		11.3.1
EASI	X		X	X	X	X	X	X	X	X	X		X	X	X		11.3.2
SCORAD	X		X	X	X	X	X	X	X	X	X		X	X	X		11.3.3
Investigator assessments of safety																	
Vital signs	X		X[j]	X[j]	X[j]	X	X	X	X	X	X	X	X	X	X	X	11.4.1
Physical examination	X		X								X	X	X	X	X	X	11.4.2
ECG	X		X								X	X	X	X	X	X	11.4.3
Serum pregnancy test (central laboratory)	X																11.4.4
Hepatitis B and C, HIV (central laboratory)	X																11.4.4
Chemistry, haematology, IgE (central laboratory)	X		X				X				X	X	X	X	X	X	11.4.4
Urine dipstick (urinalysis)[k]	X		X				X				X	X	X	X	X	X	11.4.4
Urine pregnancy test			X		X		X		X		X	X	X	X	X	X	11.4.4
ADA blood sample			X		X						X	X	X	X	X	X	11.4.4
PK blood sample					X						X	X	X	X	X	X	11.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13

	Screening		Treatment period									Safety follow-up[c]	Unscheduled visit, if applicable[d]	Early termination, if appl.[e]			References (protocol section)
Visit	**1[b]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**Early termination visit[e]**	**Nominal Week 16 visit[e,f]**	**Safety follow-up visit[e,f]**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**					
Visit window (days)[a]	**±3**	**-3**	-	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**					
Other assessment																	
Photography[l]			X		X		X				X		X		X		11.7.1
Treatments and randomisation																	
Initiation of background treatment (emollients)[m]		X															9.4
Randomisation			X														9.3
IMP administration and compliance			X[j]	X[j]	X[j]	X	X	X	X	X			X				9.2.1, 9.8.4
TCS (AxMP) dispensing			X	X	X	X	X	X	X	X			X				9.2.2, 9.8.3.2
TCS (AxMP) return				X	X	X	X	X	X	X	X		X	X			9.2.2, 9.8.3.2
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Concluding forms in the eCRF[c]																	
End of treatment											X			X	X		11.8
End of trial												X		X	X	X	11.8

a) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline (Week 0).

b) The screening period has a maximum duration of 6 weeks, with 2 planned visits. However, for subjects who do not require washout of AD treatment or if only a 2-week washout period is required, the screening period may be reduced to 2 weeks with only 1 screening visit at Week -2 (including all assessments from both visits).

c) An end of treatment form and end of trial form must be completed in the eCRF for all randomised subjects (Section 11.8). Subjects who complete the 16-week treatment period may enter the long-term extension trial (ECZTEND). All subjects completing the treatment period, except for those who enter the ECZTEND trial, will have final safety follow-up assessments 6 weeks after last IMP administration.
d) Assessments to be performed at unscheduled visits will be at the discretion of the investigator.
e) Subjects who permanently discontinue IMP or withdraw from the trial will be followed up as described in Section 10.
f) Subjects who discontinue IMP treatment <5 weeks prior to the planned Week 16 visit will be asked to return to the trial site both at Week 16 for the nominal Week 16 visit and 6 weeks after last IMP administration for the safety follow-up visit. Subjects who discontinue IMP treatment ≥5 weeks prior to the planned Week 16 visit will be asked to return to the trial site only at Week 16 for the nominal Week 16 visit, which also includes all planned safety follow-up assessments (Section 10.3).
g) The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of disallowed medications. Screening evaluations may start at a later date than the informed consent form was signed. Additional informed consent is required for the photography component of the trial.
h) In case medical history is incomplete at screening, missing data will be retrieved prior to randomisation.
i) The eDiary includes: Eczema-related Sleep NRS, Worst Daily Pruritus NRS, and Patient Days of Topical Treatment Use. Subjects will complete the eDiary daily in the morning from Week -2 to Week 16, except for the Patient Days of Topical Treatment Use, which will be completed daily from Week 0 to Week 16.
j) After the first 3 IMP administrations, all subjects will be monitored for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later.
k) Urine samples will be tested with a dipstick at the trial site. A urine sample will be sent to the central laboratory for further analysis only if considered required by the investigator based on the dipstick results (Section 11.4.4).
l) At selected sites only.
m) All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and must continue this treatment throughout the trial (including the safety follow-up period).

Abbreviations: ADA, anti-drug antibodies; appl., applicable; AxMP, auxiliary medicinal product; BSA, body surface area; C-SSRS, Columbia-Suicide Severity Rating Scale; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eCRF, electronic case report form; eDiary, electronic diary; HRQoL, health-related quality of life; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NRS, numeric rating scale; PK, pharmacokinetics; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

5 Introduction and trial rationale

5.1 Atopic dermatitis

AD is a chronic inflammatory skin disease that may affect up to 20% of children and up to 10% of adults (1, 2). The prevalence varies between regions: in a web-based survey using a modified UK Working Party definition of AD, the 1-year prevalence of AD in adults was reported to be 4.3% in Japan, 8.1% in Canada, 9.4% in Europe, and 11.9% in the US (1). In its moderate and severe form, AD is characterised 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 disturbances (3).

AD is characterised by an activated T-helper-2 (Th2) pathway with interleukin-13 (IL-13) as the dominant cytokine in the skin (4-6). The expression of IL-13 is increased in lesional skin compared with non-lesional skin, the proportion of $CD4^+$ and $CD8^+$ cells expressing IL-13 is upregulated in AD patients compared with individuals without AD, and there is a correlation between IL-13 expressing skin-homing T-cells and disease severity (7, 8).

IL-13 acts on keratinocytes to release chemokines that recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased skin barrier function (9). IL-13 also drives immunoglobulin E (IgE) production and contributes to mast cell activation and, once allergen cross-links IgE on the cell surface, drives histamine release, induces itch, alters the skin microbiome, and stimulates skin fibrosis (10-12).

These effects together drive and exacerbate the disease phenotype. Data from the dose-finding trial (D2213C00001) have confirmed IL-13 as a valid target in AD (13). The biomarker sub-study of phase 3 trial, LP0162-1325, also confirmed the importance of IL-13 in the pathophysiology of AD. Analyses of serum and skin samples showed that IL-13 expression was correlated with expression of other inflammatory markers, skin colonisation with *Staphylococcus aureus*, and clinical disease severity.

Compared with placebo, tralokinumab had a normalising effect on key aspects of AD, including markers of skin barrier integrity, epidermal proliferation, and epidermal differentiation. Furthermore, a broad anti-inflammatory effect was observed in subjects receiving tralokinumab, demonstrated by reduction of a range of inflammatory markers in both serum and skin. Skin colonisation with *Staphylococcus aureus* was also strongly suppressed in subjects receiving tralokinumab compared with subjects receiving placebo.

5.2 Experience with investigational medicinal product

Tralokinumab is a human recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) subclass that specifically binds to human IL-13 and blocks interaction with the IL-13 receptors (14-16). A compilation of clinical and nonclinical data on tralokinumab including pharmacokinetics (PK) is given in the current version of the investigator's brochure.

Based on a data lock point of 17-Sep-2019, the use of tralokinumab has been evaluated in 22 complete clinical trials across 4 different indications (AD, asthma, ulcerative colitis, and idiopathic pulmonary fibrosis), including 4281 subjects who have received at least 1 dose of tralokinumab (3054 patient-years of exposure). The majority of the tralokinumab exposure was from the trials within AD (1426 patient-years of exposure) and asthma (1508 patient-years of exposure).

LEO Pharma is currently conducting a clinical development programme with tralokinumab in AD comprising 5 complete trials and 4 ongoing trials. The completed pivotal trials and the trials following was based on the dose-finding trial (D2213C00001), which was a phase 2b trial evaluating the efficacy of tralokinumab 45 mg+TCS, 150 mg+TCS, and 300 mg+TCS vs placebo+TCS. Based on the results from the trial, the dose of 300 mg tralokinumab was chosen for the phase 3 programme.

The other 4 completed trials include LP0162-1325 and LP0162-1326 (similar tralokinumab monotherapy phase 3 trials of 52 weeks where superiority of tralokinumab was tested vs placebo at Week 16), LP0162-1339 (a combination therapy phase 3 trial of 32 weeks where superiority of tralokinumab+TCS was tested vs placebo+TCS at Week 16), and LP0162-1341 (a phase 2 vaccine response trial evaluating the effect of tralokinumab vs placebo on vaccine antibody responses).

In these 4 completed trials, IGA, EASI, Worst Daily Pruritus NRS, SCORAD, and DLQI were included as the main assessments supporting the multiplicity-adjusted primary and secondary efficacy endpoints. The efficacy of tralokinumab as monotherapy in subjects with moderate-to-severe AD was demonstrated in the replicate confirmatory phase 3 trials (LP0162-1325 and LP0162-1326) with statistically significant results for all primary and multiplicity-adjusted secondary endpoints at Week 16. Likewise, the efficacy of tralokinumab in combination with TCS was consistently demonstrated by statistically significant results on all primary and multiplicity-adjusted secondary endpoints at Week 16 in the LP0162-1339 trial. Non-inferiority of tralokinumab vs placebo with respect to immune responses to concomitantly administered non-live vaccines was demonstrated in the LP0162-1341 trial.

The safety evaluation of tralokinumab in AD focuses primarily on results from the 5 completed trials in AD (i.e. the AD pool). During the initial treatment period in the AD pool, the overall frequencies of AEs were similar for tralokinumab (66%) and placebo (67%). Most AEs were mild or moderate for both tralokinumab and placebo, and severe AEs occurred at a lower frequency for tralokinumab (4.6%) than for placebo (6.3%). The frequencies of AEs leading to permanent discontinuation of IMP were low and similar for tralokinumab (2.3%) and placebo (2.8%). The majority of AEs were classified as recovered/resolved for both tralokinumab (60%) and placebo (62%).

The following AEs were reported in ≥5% of subjects in any treatment group (tralokinumab vs placebo): dermatitis atopic (15% vs 26%), viral upper respiratory tract infection (16% vs 12%), upper respiratory tract infection (5.6% vs 4.8%), and conjunctivitis (5.4% vs 1.9%).

Subgroup analyses of AEs reported in the 2 monotherapy trials (i.e. monotherapy pool) showed that the overall incidence of AEs was comparable or lower for tralokinumab every second week (Q2W) vs placebo for all the geographic regions included in these trials (Asia, Australia, Europe, and North America). Across regions, the AE profiles were overall similar to that observed for the total population, although with a tendency to lower overall incidence of AEs in North America compared with Asia, Australia, and Europe independent of treatment group.

During the initial treatment period in the AD pool, the frequency of serious adverse events (SAEs) was lower for tralokinumab (2.1%) than for placebo (2.8%). The majority of SAEs in both treatment groups were severe events, with similar frequencies for tralokinumab (1.5%) and placebo (1.7%). The frequencies of SAEs leading to permanent discontinuation of IMP were low and similar for tralokinumab (0.6%) and placebo (0.8%). The outcome of the majority of SAEs were recovered/resolved for both tralokinumab (32 of 38 events) and placebo (16 of 22 events).

During prolonged treatment with tralokinumab with or without TCS from 16 up to 52 weeks, the safety profile was consistent with the initial 16-week treatment period based on overall frequencies of AEs, SAEs, severe AEs, and AEs leading to permanent discontinuation of IMP as well as the patterns of event types within each of these AE categories.

Tralokinumab-treated subjects had a greater mean initial increase from baseline in eosinophil count compared with subjects treated with placebo. However, the increase in the tralokinumab-treated subjects was transient, and mean eosinophil counts returned to baseline

during continued treatment. No other clinically significant biochemistry parameters were identified from the completed phase 3 trials.

Data from the trials with tralokinumab in AD showed that the incidence rate of ADA and neutralising antibodies after 16 weeks of treatment was low and similar for tralokinumab and placebo, confirming the low immunogenicity of tralokinumab.

Overall, there were no indications that treatment with tralokinumab was associated with a higher risk of the following safety areas: skin infections requiring systemic treatment, eczema herpeticum, severe and serious infections (including any clinical endoparasitosis, opportunistic infections, and tuberculous infections), malignancies, anaphylaxis, serious allergic reactions, and immune complex disease. However, AEs of conjunctivitis, keratitis, and injection site reactions were more frequent with tralokinumab than placebo.

Thus, tralokinumab has a favourable safety profile, without any important risks identified in the clinical trials conducted to date.

5.3 Trial rationale

Treatment recommendations for AD include topical therapies, the main being TCS. Both TCS and TCI have limited efficacy in patients with moderate-to-severe disease. For these patients, therapies with topicals combined with systemic immunosuppressants or biologics are recommended (17, 18).

In the 2 multi-national phase 3 trials (LP0162-1325 and LP0162-1326), tralokinumab was safe and efficacious in treating adult subjects with moderate-to-severe AD in a monotherapy setting. Japanese subjects participated in one of these trials (LP0162-1325) and results from the ‘treatment policy’ estimand, allowing for TCS used as rescue medication, showed efficacy of tralokinumab in combination with TCS compared with placebo in combination with TCS in Japanese subjects. In addition, the uncontrolled open-label treatment arm, where optional TCS was allowed, showed that treatment with tralokinumab in combination with TCS is safe and efficacious in Japanese subjects. This is in line with the results from the multi-national phase 3 trial LP0162-1339 investigating tralokinumab in combination with TCS where no Japanese subjects participated. Previously, only the dose-finding trial (D2213C00001) has investigated tralokinumab in combination with proactively administered TCS in Japanese subjects, and the results for the Japanese subjects were generally consistent with those in the overall population.

The primary objective of this phase 3 trial (LP0162-1343) is to evaluate tralokinumab in combination with TCS in Japanese subjects by using a similar design (initial 16 weeks only) as the LP0162-1339 trial to facilitate an evaluation of similarity in efficacy and safety as compared with the LP0162-1339 trial. This trial will be a prospective, randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with TCS in Japanese subjects with moderate-to-severe AD, who are candidates for systemic therapy. This trial will evaluate both the percentage of subjects achieving an IGA score of 0 (clear) or 1 (almost clear) (IGA 0/1) at Week 16 and the percentage of subjects achieving at least 75% reduction in EASI score (EASI75) at Week 16. In addition, secondary endpoints addressing symptom scores and extent of AD, itch-related sleep loss, itch severity, and HRQoL measures related to AD are also included.

5.4 Ethical considerations

No children or other vulnerable subjects incapable of giving informed consent will be enrolled in this trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this trial. Women of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the trial and until 16 weeks after discontinuation of treatment with the IMP. In addition, all female subjects of childbearing potential will have a pregnancy test performed before, during, and at end-of-treatment to ensure that no foetuses are exposed to the IMP.

In a 13-week repeated-dose nonclinical study in male cynomolgus monkeys, no adverse effects on male reproductive endpoints were observed (investigator's brochure). Coupled with the negligible exposure risk for drugs and antibodies by way of semen to achieve meaningful pharmacological levels in a pregnant woman or in the conceptus (19), it is not considered necessary to impose restrictions on fathering a child or sperm donation in clinical trials with tralokinumab.

In this clinical trial, the efficacy of tralokinumab in combination with TCS will be evaluated in adult subjects with moderate-to-severe AD. Tralokinumab in combination with TCS will be compared with a placebo+TCS control group. Subjects who during the treatment period or safety follow-up experience intolerable AD symptoms can be treated with rescue treatment according to the investigators discretion and thus will not be deprived from effective therapy. After the 16-week treatment period, subjects can continue in a long-term extension trial provided that they are eligible.

In accordance with the current version of the ICH GCP guidelines, 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 and safety data will be reviewed regularly by medically qualified staff at LEO Pharma to ensure that prompt action is taken, if needed, to maximise trial subject safety.

5.5 Benefit/risk assessment

With more than 4200 subjects exposed to tralokinumab in the completed trials as discussed in Section 5.2, the benefit/risk ratio is considered favourable and supports the administration of tralokinumab in combination with TCS therapy for the purposes of achieving the objectives of this trial.

Based on the extensive clinical experience, a reassuring safety profile of tralokinumab has been observed in AD, asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in trials with healthy subjects. No safety concerns have been identified with the use of tralokinumab, and tralokinumab was well-tolerated. Generally, the AE profile for tralokinumab has been comparable to that for placebo in controlled clinical trials, the adverse drug reactions observed were non-serious and mild or moderate in severity, and ADA were detected in only few subjects exposed to tralokinumab for up to 1 year.

Appropriate measures have been instituted in this trial to protect subjects from potential risks and to closely monitor each subject, such as:

- Close monitoring of subjects during the trial with trial visits every 2 weeks during the treatment period as described in the schedule of trial procedures (Section 4).
- Close monitoring of subjects during the post-dosing period (at the first 3 IMP administration visits in the treatment period) as a precautionary measure against hypersensitivity reactions (Section 9.2.1).
- Exclusion of subjects with untreated systemic helminth infestations or subjects who have failed to respond to standard of care therapy; neutralisation of IL-13 might theoretically cause a worsening of parasitic infestation, in particular, prevention of expulsion of gastrointestinal worms (helminths) (20).
- Exclusion of subjects with a history of tuberculosis requiring treatment within 12 months prior to screening.
- Exclusion of subjects with a history of a clinically significant infection (defined as a systemic or serious skin infection requiring parenteral antibiotics, antiviral, or antifungal medication) within 4 weeks prior to randomisation (Section 8.3), which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial.

Altogether, the risks associated with participating in this trial are considered very low and outweighed by the benefit of a potential more user-friendly future treatment option for moderate-to-severe AD.

6 Trial objectives, endpoints, and estimands

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To evaluate the efficacy of tralokinumab in combination with TCS compared with placebo in combination with TCS in treating moderate-to-severe AD.	***Primary endpoints*** • IGA 0/1 at Week 16. • EASI75 at Week 16.
Secondary objective (efficacy)	
To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, HRQoL, and health care resource utilisation compared with placebo in combination with TCS.	***Key secondary endpoints*** • Change in SCORAD total score from baseline to Week 16. • Change in DLQI score from baseline to Week 16. • Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to Week 16. ***Secondary endpoints*** • EASI90 at Week 16. • EASI50 at Week 16. • Percentage change in EASI score from baseline to Week 16. • Change in Worst Daily Pruritus NRS score (weekly average) from baseline to Week 16. • Change in Eczema-related Sleep NRS score (weekly average) from baseline to Week 16. • Change in POEM score from baseline to Week 16. ***Other endpoints*** • Reduction of DLQI score ≥4 points from baseline to Week 16 in subjects with baseline DLQI score ≥4. • Reduction of POEM score ≥4 points from baseline to Week 16 in subjects with baseline POEM score ≥4. • Amount of TCS (AxMP) used at Week 16. • TCS (AxMP) use <5 g at Week 16. • Cumulative amount of TCS (AxMP) used from baseline to Week 16.

Objectives	Endpoints
Secondary objective (safety)	
To assess the safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 16 weeks.	***Secondary endpoints*** • Number of treatment-emergent AEs from baseline to Week 16 per subject. • Presence of treatment-emergent ADA from baseline to Week 16.
Other objectives	
To evaluate the efficacy over time of tralokinumab in combination with TCS compared with placebo in combination with TCS to support the evaluation of primary and key secondary endpoints.	***Exploratory endpoints*** • EASI75 at each scheduled assessment. • IGA 0/1 at each scheduled assessment. • Change in SCORAD total score from baseline to each scheduled assessment. • Change in Worst Daily Pruritus NRS score (weekly average) from baseline to each scheduled assessment. • Change in DLQI score from baseline to each scheduled assessment. • Reduction of Worst Daily Pruritus NRS score (weekly average) ≥4 from baseline to each scheduled assessment. • Change in Eczema-related Sleep NRS score (weekly average) from baseline to each scheduled assessment. • Change in POEM score from baseline to each scheduled assessment.

Abbreviations: AD, atopic dermatitis; ADA, anti-drug antibodies; AEs, adverse events; AxMP, auxiliary medicinal product; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI50, at least 50% reduction in EASI score; EASI75, at least 75% reduction in EASI score; EASI90, at least 90% reduction in EASI score; HRQoL, health-related quality of life; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (almost clear); NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

The following estimands addressing different aspects of the trial objectives will be applied:

- 'Composite' estimand.
- 'Treatment policy' estimand.
- 'Hypothetical' estimand.

The estimands incorporate 2 main types of intercurrent events that influence how the treatment effects are estimated:

- Initiation of rescue medication.
- Permanent discontinuation of IMP.

The primary estimand for the primary endpoints will incorporate the ‘composite’ strategy:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks, achieved without rescue medication, regardless of treatment discontinuation.

The secondary estimand for the primary endpoints incorporates the ‘treatment policy’ strategy:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks, regardless of rescue medication and discontinuation of IMP.

The binary key secondary endpoint (reduction of Worst Daily Pruritus NRS ≥4 from baseline to Week 16) will be evaluated using the same primary and secondary estimands as described for the primary endpoints.

The primary estimand for the continuous key secondary endpoints will be based on the ‘composite’ strategy:

- Treatment difference in the change from baseline to Week 16 in SCORAD and DLQI, achieved without rescue medication, regardless of discontinuation of IMP.

The secondary estimand for the continuous key secondary endpoints will implement the ‘hypothetical’ strategy:

- Treatment difference in the change from baseline to Week 16 in SCORAD and DLQI, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP prematurely and no rescue medication was used before Week 16.

The analyses of all endpoints and estimands are described in Section 14.3.

7 Trial design

7.1 Overall trial design

This is a randomised, double-blind, placebo-controlled, parallel-group, multi-site, phase 3 clinical trial in adult Japanese subjects with moderate-to-severe AD who are candidates for systemic therapy. The trial consists of a screening period, a treatment period, and a safety follow-up period as described below. The primary endpoints will be assessed at Week 16, and the final safety assessments will be conducted at Week 20. A scheme of the trial design is provided in Panel 1. A schedule of all trial visits and procedures is provided in Section 4 and all trial-related assessments are described in Section 11. The trial design will support a comparison of tralokinumab in combination with TCS to placebo in combination with TCS during a treatment period of 16 weeks.

Screening period (Week -6/-2 to Week 0)
The screening period has a minimum duration of 2 weeks and a maximum duration of 6 weeks and includes 1 or 2 screening visits. The exact duration of the screening period for the individual subject depends on the length of required washout of AD treatment; the washout periods, as specified in the exclusion criteria (Section 8.3), are:

- 6 weeks prior to randomisation for tanning beds or phototherapy.
- 4 weeks prior to randomisation for systemic immunosuppressive/immunomodulating drugs, systemic corticosteroid use, or 3 or more bleach baths during any week within the 4 weeks.
- 2 weeks prior to randomisation for TCS, TCI, topical PDE-4 inhibitors, and topical JAK inhibitors.

If no washout is needed or if a 2-week washout is required, the screening period will be reduced to 2 weeks and the 2 screening visits will be merged to only 1 screening visit at Week -2 (Visit 2).

All subjects will attend the screening visit scheduled at Week -2 where they will receive electronic diary (eDiary) training and start the eDiary (Section 11.3.4). Data entered into the eDiary during this 2-week period, including the data collected at baseline (Week 0; Visit 3), will be used to calculate baseline values of the patient-reported outcomes.

All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and will continue this emollient treatment throughout the trial (including the safety follow-up). Subjects will initiate emollient treatment no later than the Week -2 visit. On

lesional skin, emollients should only be applied at a time when TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times. The emollient treatment is further described in Section 9.4.

Eligibility will be assessed both at the (first) screening visit and prior to randomisation at baseline (Week 0; Visit 3) as described in Section 8.

Treatment period (Week 0 to Week 16)
Following the screening period, eligible subjects will be randomly assigned to one of the following treatment groups:

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

The IMPs, tralokinumab and placebo, are described in Section 9.1.1 and the treatment assignment is described in Section 9.3. The IMP will be administered by subcutaneous (SC) injections every second week throughout the treatment period as described in Section 9.2. The last dose of IMP will be administered at Week 14.

Subjects in both treatment groups will also be supplied with an AxMP, i.e. a TCS cream (mometasone furoate) as described in Section 9.1.2. The subjects will apply a thin film of the supplied TCS once daily on areas with active lesions as needed and as described in Section 9.2.2. Lower potency TCS or TCI may be prescribed if needed on body areas where the supplied TCS is not advisable or on areas where continued treatment with TCS is considered unsafe. Topical therapy should be discontinued when control is achieved; discontinuation should preferably be gradual. The safety and appropriateness of continued or repeated courses of TCS therapy will be monitored and supervised by the site staff.

Subjects who during the treatment period or safety follow-up experience intolerable AD symptoms can be treated with rescue treatment according to investigators discretion as described in Section 9.5.

Subjects, who complete the 16-week treatment period, may be invited to enter a long-term extension trial conducted under a separate protocol (ECZTEND).

Safety follow-up period (Week 16 to Week 20)
After the treatment period, all subjects who do not enter the long-term extension trial will complete an off-treatment follow-up period for assessment of safety, PK, and ADA.

All subjects completing the treatment period, except for those who enter the long-term extension trial, will have safety follow-up assessments 6 weeks after last IMP administration. Subjects who permanently discontinue IMP or withdraw from the trial will be followed up as described in Section 10.

7.2 Number of subjects needed

Assuming a screening failure rate of 15%, approximately 118 subjects will be screened and approximately 100 subjects will be randomly assigned in a 1:1 ratio to receive either tralokinumab+TCS or placebo+TCS throughout the treatment period. The randomisation will be handled in an interactive response technology (IRT) system to ensure blinding in the trial (see Section 9.3).

The statistical considerations for this sample size are described in Section 14.1.

This trial will be conducted at approximately 35 sites in Japan. The anticipated minimum number of randomised subjects per trial site is 3 and the maximum number of subjects is 15.

7.3 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 (Week 20). Subjects entering the long-term extension trial (ECZTEND) will also be considered as completers of this trial.

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

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

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

The subject's eligibility for the trial must be verified according to the inclusion and exclusion criteria at visits specified in Panel 2. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the trial will be ensured and described in submission documentation to regulatory authorities and institutional review boards (IRBs)/independent ethics committees (IECs), as applicable.

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures. The subject's legally authorised representative must sign the informed consent if the subject is below 20 years of age.
2. Japanese subject aged 18 years and above.
3. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD (21) (Appendix 4).
4. History of AD for ≥1 year.
5. Subjects who have a recent history (within 1 year before screening) of inadequate response to treatment with topical medication.
    - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 [clear] to IGA 2 [mild]) despite treatment with a daily regimen of TCS of medium or higher potency (±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 strongest TCS), whichever is shorter.
    - Subjects with documented systemic treatment for AD in the past year are considered as inadequate responders to topical treatment and are potentially eligible for treatment with tralokinumab after appropriate washout.

6. AD involvement of ≥10% body surface area (BSA) at screening and baseline according to component A of SCORAD.
7. An EASI score of ≥12 at screening and ≥16 at baseline.
8. An IGA score of ≥3 at screening and at baseline.
9. A Worst Daily Pruritus NRS average score of ≥4 during the week prior to baseline.
    - Worst Daily Pruritus NRS score at baseline will be calculated from daily assessments of worst itch severity (Worst Daily Pruritus NRS) during the 7 days immediately preceding randomisation (Day -6 to Day 0). Worst Daily Pruritus NRS scores must be reported for a minimum of 4 out of the 7 days to calculate the baseline average score. For subjects who do not fulfil this requirement, randomisation should be postponed until this requirement is met, but without exceeding the 6 weeks' maximum duration for screening.
10. Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
11. Women of childbearing potential 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 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 vasectomised partner (given that the subject is monogamous). The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test at baseline. 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).

8.3 Exclusion criteria

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

1. Subjects for whom TCS are medically inadvisable e.g. due to important side effects or safety risks (including intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects etc.) in the opinion of the investigator.
2. Concurrent enrolment in another interventional clinical trial.
3. Previous randomisation in a tralokinumab clinical trial.
4. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
5. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
6. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen+ultraviolet A [PUVA]) within 6 weeks prior to randomisation.
7. Treatment with the following medications within 4 weeks prior to randomisation:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporin A, azathioprine, mycophenolate mofetil, JAK inhibitors).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
8. Treatment with the following medications within 2 weeks prior to randomisation:
    - TCS.
    - TCI.
    - Topical PDE-4 inhibitors.
    - Topical JAK inhibitors.
9. Receipt of live attenuated vaccines within 30 days prior to randomisation and during the trial including the safety follow-up period.
    - Receipt of inactive/killed vaccinations (e.g. inactive influenza) is allowed, provided they are not administered within 5 days before/after any trial visit.

10. Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-IgE) including dupilumab or investigational biologic agents:
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
11. Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation.
12. Receipt of blood products within 4 weeks prior to screening.
13. Major surgery within 8 weeks prior to screening or planned in-patient surgery or hospitalisation during the trial period.
14. Known or suspected allergy or reaction to any component(s) of the IMP or AxMP formulation.
15. History of any active skin infection within 1 week prior to randomisation.
16. History of a clinically significant infection within 4 weeks prior to randomisation which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
17. 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.
18. History of anaphylaxis following any biological therapy.
19. History of immune complex disease.

20. History of cancer:
    - Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to 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.
21. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
22. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at screening, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.
23. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
24. History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or defined as a 'yes' to suicidal ideation questions no. 4 or 5 or answering 'yes' to suicidal behaviour on the Columbia-Suicide Severity Rating Scale [C-SSRS] screening version).
25. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, 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 the trial.
26. Any clinically significant abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis 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.

27. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the upper limit of normal (ULN) at screening.
28. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they have negative HBsAg, HBcAb, and HCV serology.
29. Subjects who are not willing to abstain from donating blood and/or plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IMP.
30. Subjects who are legally institutionalised.
31. Pregnant, breastfeeding, or lactating women.
32. 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.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by the central IRT system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the informed consent was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered ‘screened’ subjects.

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

Screening failures

Screening failures are defined as subjects who consent to participate in the trial but do not meet one or more criteria required for participation in a trial and are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is

required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (22) and to respond to queries from regulatory authorities. As a minimum, the following data will be collected in the eCRF for screening failure subjects:

- Date of informed consent(s).
- Demographics (year of birth/age, sex, race, ethnicity).
- Reason for screen failure.
    - Failure to meet eligibility criteria (specify criteria).
    - Lost to follow-up.
    - Withdrawal by subject.
    - Other (specify reason).
- Date of screen failure.
- Any AEs and SAEs.

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

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.

9 Treatments

9.1 Trial product description

9.1.1 Investigational medicinal products (tralokinumab and placebo)

Both tralokinumab and placebo is presented as a liquid formulation in accessorised pre-filled syringes for SC injection. Tralokinumab and placebo will be packaged in individually numbered kits, each containing 1 accessorised pre-filled syringe. Further details are provided in Panel 4. The administration of IMPs (tralokinumab and placebo) is described in Section 9.2.1.

Panel 4: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size	Source
Tralokinumab	Solution for injection.	Tralokinumab, formulated at a nominal concentration of 150 mg/mL in 50 mM sodium acetate/acetic acid buffer, 85 mM sodium chloride, 0.01% (w/v) PS-80, pH 5.5 solution.	1 accessorised pre-filled syringe[a], 1.0 mL fill volume.	MedImmue
Placebo	Solution for injection.	Placebo contains the same excipients, in the same concentration only lacking tralokinumab.	1 accessorised pre-filled syringe[a], 1.0 mL fill volume.	MedImmune

a) The accessorised pre-filled syringe is a single-use, disposable system that is designed to administer the labelled dose of the system to the SC space during 1 injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system. The accessorised pre-filled syringe consists of a pre-filled syringe sub-assembly (1 mL pre-filled syringe barrel with a 1/2 inch (12.7 mm) 27 gauge thin wall staked-in needle, rigid needle shield, plunger stopper), and a safety device.

9.1.2 Auxiliary medicinal product (TCS)

Each subject will be prescribed an AxMP through the trial; the subjects will receive a TCS cream (JP class: Very Strong). The AxMP (TCS) will be provided as mometasone furoate, 0.1% cream in kit sizes of approximately 180-225 g every second week according to the schedule of trial procedures (Section 4). If needed, additional AxMP kit(s) may be dispensed to the subject at a scheduled or unscheduled visit at the investigator's discretion. The amount

of additional AxMP dispensed must be recorded in the eCRF. The administration of AxMP (TCS) is described in Section 9.2.2.

9.2 Administration of trial products

9.2.1 Administration of IMP

IMP administration visits are shown in the schedule of trial procedures (Section 4). The IRT will assign the required IMP kit number for each subject at each IMP administration visit.

The first day of IMP administration is considered Day 0 (Week 0; Visit 3), where each subject will receive 4 SC injections (each 1.0 mL) of 150 mg tralokinumab or placebo to receive a total loading dose of 600 mg tralokinumab or placebo.

At subsequent visits in the treatment period, each subject will receive 2 SC injections (each 1.0 mL) of 150 mg tralokinumab or placebo every 2 weeks to receive a total dose of 300 mg tralokinumab Q2W or placebo Q2W. The last IMP administration will occur at Week 14.

The IMP will be administered by a qualified, unblinded healthcare professional (HCP); see Section 9.3.1 for blinding details. A minimum interval of 7 days is required between 2 administration visits.

The injections will be administered into the SC tissue of the upper arm, anterior thigh, or abdomen, separated by at least 3 cm. The injection site must be recorded in the source documents and in the eCRF at each IMP administration visit (Section 9.8.4).

Further details on IMP administration are provided in a trial product handling manual. The IMP administration must be carried out according to these instructions.

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. See Section 13.6.2 for further details regarding overdose.

Monitoring after IMP administration
For the first 3 IMP administration visits (i.e. Weeks 0, 2, and 4), each subject will be monitored after the IMP administration for immediate drug reactions for a minimum of 30 minutes with vital signs taken at 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF (Section 11.4.1).

As with any antibody, allergic reactions to dose administration are possible. The World Allergy Organization has categorised anaphylaxis into 2 subgroups: allergic anaphylaxis

(mediated by an immunologic mechanism) and nonallergic anaphylaxis (which has a nonimmunologic cause) (23). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 5 (24). Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at the trial sites, and trial personnel should be trained to recognise and respond to anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase at the central laboratory (Section 11.4.4).

Conditions requiring rescheduling of IMP administration
The investigator should reschedule the visit, and IMP should not be administered until the rescheduled visit, if any of the following occur:

- The subject has an intercurrent illness that, in the opinion of the investigator, may compromise the safety of the subject in the trial (e.g. viral illnesses).
- The subject is febrile (defined as ≥38°C) within 72 hours prior to IMP administration.

If the visit cannot be rescheduled to maintain a minimum of 7 days to subsequent dose, the sponsor's medical expert should be contacted.

9.2.2 Administration of AxMP (TCS)

The IRT will assign the required AxMP (TCS) kit number for each subject at each AxMP dispensing visit. The AxMP dispensing visits are shown in the schedule of trial procedures (Section 4). The subject must return used and unused AxMP (TCS tubes) at each subsequent trial visit to assess the amount of TCS used. The subjects must be instructed by the site staff on the importance of returning all used and unused TCS tubes. The site staff will return used and unused TCS tubes to the contract manufacturing organisation (CMO). The returned TCS tubes will be weighed at the CMO.

Each subject will be instructed to apply a thin film of the dispensed AxMP (TCS) once daily on active lesions of AD, as needed. The TCS should be discontinued when control is achieved; discontinuation should preferably be gradual, and the maximum duration of a treatment course should not exceed 3 weeks. The safety and appropriateness of continued or repeated courses of TCS therapy will be monitored and supervised by site staff.

The AxMP (TCS) should be the only TCS product applied to the body during this period. Lower potency TCS or TCI may be used at the investigator's discretion on areas of the body where use of the supplied AxMP (TCS) is not advisable such as areas of thin skin (face, skin fold areas, genital areas, etc.) or on areas where continued treatment is considered unsafe. The low potency TCS and TCI will not be provided by LEO Pharma and will not be weighed but must be registered in the eCRF as concomitant medications (Section 9.6).

The supplied AxMP (TCS) is only for use on active lesions of AD and not for use in other indications.

9.3 Treatment assignment (randomisation)

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised centrally at baseline (Week 0; Visit 3) to receive treatment with either tralokinumab+TCS or placebo+TCS.

The treatment assignment will be pre-planned according to a computer-generated randomisation schedule in a 1:1 ratio stratified by baseline disease severity (moderate [IGA score 3] / severe [IGA score 4]).

The IRT will be used to control randomisation and stratification factor, along with IMP supply chain and expiry tracking, and for dispensing and return of AxMP (TCS).

9.3.1 Blinding

This is a double-blinded trial in which the IMPs (tralokinumab and placebo) are visually distinct from each other. Since tralokinumab and placebo are visually distinct from each other and not matched for viscosity, the IMP will be handled and administered by a qualified, unblinded HCP (trained site staff) at the trial site who will neither be involved in the management of the trial subjects nor perform any of the trial assessments.

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

The subjects, investigators involved in the treatment or clinical evaluation, and LEO Pharma staff involved in monitoring of the trial subjects will not be aware of the treatment received.

If the treatment assignment for a subject becomes known to the investigator or other site 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 clinical research associate (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.

9.3.2 Emergency unblinding of individual subject treatment

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

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment in the IRT. For a requester who is not a member of the trial staff and who does not have access to the IRT (e.g. a physician at an emergency room), a local contact number for the emergency unblinding contract research organisation (CRO) is provided on the subject card (see Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation. Should the requester wish to discuss whether unblinding is necessary, the emergency unblinding CRO will divert the requester to the medical cover.

9.4 Background treatment (emollients)

All subjects must use an emollient as a background treatment twice daily (or more, as needed) for at least 14 days before randomisation. The background treatment should preferably be an additive free, basic bland emollient. On days where site visits take place, the subjects should preferably postpone application of emollient to after the end of the visit, since the dryness of the skin must be assessed as part of the efficacy assessments.

On lesional skin, emollients should only be applied at times when TCS is not applied (i.e. emollients and TCS should not be used on the same areas at the same time of the day); on TCS-untreated areas, the emollients may be applied at all times.

The subjects must continue their background emollient treatment throughout the trial (including the safety follow-up period).

It will be recorded in the eCRF if background treatment (emollient) has been used as described since last visit; if not, a reason should be provided.

9.5 Rescue treatment

If medically necessary (i.e. to control intolerable AD symptoms), rescue treatment for AD may be provided to the subjects at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue treatment to topical medications (i.e. highest potency TCS) and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment. The subjects 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 who receive topical rescue treatment (highest potency TCS, JP class > Very Strong) will continue IMP treatment.

If a subject receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (methotrexate, mycophenolate mofetil, azathioprine, etc.), IMP will be immediately discontinued (see Section 10.2.2). After the treatment with these medications is completed, IMP may be resumed if deemed appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. The use of biological rescue treatment, including use of dupilumab, will be disallowed for the entire trial duration.

Investigators should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

In the primary efficacy analyses, subjects who receive highest potency TCS (JP class > Very Strong) or systemic rescue treatment during the treatment period will be considered as non-responders.

9.6 Concomitant medications and concurrent procedures

Any medication or vaccine that the subject receives from 3 months prior to screening through the safety follow-up period must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name.
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose, unit, and frequency.
- Route of administration.

Similarly, concurrent procedures must also be recorded in the subject's medical record and the eCRF. Note: in this trial, only surgical procedures and procedures related to AD treatment (e.g. phototherapy or bleach baths) will be recorded. The following details will be recorded: procedure name, body location, indication, and 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 9.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

In addition, the following concomitant medications related to AD treatment are permitted from screening through the safety follow-up period (Week 20):

- Oral antibiotics, antiviral, or antifungal therapy for skin infections as appropriate.
- Stable doses of an emollient (see Section 9.4; subjects must apply such emollients twice daily [or more, as needed] for at least 14 days before baseline and throughout trial participation).
- Oral antihistamines.

9.7 Prohibited medications and procedures

The medications and procedures listed below are prohibited during the trial from randomisation (Week 0). Medications and procedures disallowed prior to randomisation are

covered by the exclusion criteria (see Section 8.3). In case any prohibited treatments are used during the trial, they must be recorded in the eCRF as concomitant medication.

From randomisation through end of treatment (Week 16):

- PDE-4 inhibitors.
- TCS of highest potency (JP class > Very Strong).
- Topical JAK inhibitors.
- Use of UVA or UVB, psoralen+UVA (PUVA), other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

From randomisation through safety follow-up (Week 20):

- Investigational agents other than tralokinumab.
- Systemic corticosteroids (nasal, ophthalmic and inhaled corticosteroids are allowed).
- Systemic treatment with an immunosuppressive/immunomodulating agent (examples include: cyclosporine A, mycophenolate mofetil, azathioprine, methotrexate, JAK inhibitors, interferon-gamma, dupilumab, or other biologics).
- Allergen immunotherapy.
- Live (attenuated) vaccine.
- Immunoglobulins.
- Blood products.

Some of the above mentioned prohibited medications can be used during the treatment period (Week 0 to Week 16) provided the indication is rescue treatment for AD. Please refer to Section 9.5 for details regarding rescue treatment.

The sponsor’s medical expert will determine whether IMP discontinuation is required.

Please note that receipt of inactive/killed vaccines (e.g. inactive influenza) is allowed, provided they are not administered within 5 days before/after any trial visit.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

9.8.1.1 Labelling and packaging of IMP

The IMP will be packaged in individually numbered kits, each containing 1 pre-filled syringe (tralokinumab 150 mg or placebo).

Primary and secondary packaging materials (syringe and outer carton, respectively) will be individually labelled.

The labelling of IMPs will be in accordance with Annex 13 (25), local regulations and trial requirements. Label text will be translated into local languages, as required.

9.8.1.2 Labelling and packaging of AxMP (TCS)

The AxMP will be packaged in individually numbered kits that contain tubes of TCS cream with a total weight of approximately 180-225 g.

Primary and secondary packaging materials (tube and outer kit carton, respectively) will be individually labelled.

The labelling of AxMP will be in accordance with Annex 13 (25), local regulations, and trial requirements. Label text will be translated into local languages, as required.

9.8.2 Storage of trial products

9.8.2.1 Storage of IMP

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

The IMP must be stored at 2 to 8°C at the trial site. The temperature during storage will 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.

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 syringe/cartridge.

Damaged IMP should be documented in the IRT and reported as a product complaint to LEO Pharma K.K. (Section 9.10). Damaged IMP may not be used.

9.8.2.2 Storage of AxMP (TCS)

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

The AxMP must be stored at the trial site according to the approved label for mometasone furoate. The temperature during storage at the trial site will 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.

Note that in the cases listed below, site staff should not use the affected AxMP 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 AxMP should be documented in the IRT and reported as a product complaint to LEO Pharma K.K. (Section 9.10). Damaged AxMP may not be used.

9.8.3 Drug accountability

9.8.3.1 IMP accountability

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

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

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

All unused IMPs (including packaging material) supplied by the CMO on behalf of LEO Pharma will be returned to the CMO. Prior to their return, the IMPs must be fully accounted for by the CRA with the help of site staff responsible for dispensing and administering the IMPs. Accountability must be documented on drug accountability forms and in the IRT. The IMP returned to the CMO will be reconciled with the individual drug accountability forms.

Refer to the trial product handling manual for more information about drug accountability and for information on return of trial products.

9.8.3.2 AxMP (TCS) accountability

The head of institute is fully responsible for the AxMP (TCS) at the trial site and for maintaining adequate control of the AxMP and for documenting all transactions with them.

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

The subjects will return the AxMP (used, partly used, and unused TCS tubes [including packaging material]) at the visits specified in the schedule of trial procedures (Section 4). Returned AxMP can be stored at room temperature and must be stored separately from non-allocated AxMP.

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

All used and unused AxMP (including packaging material) supplied by the CMO on behalf of LEO Pharma will be returned to the CMO. Prior to their return, the AxMP must be fully accounted for by the CRA with the help of site staff responsible for dispensing the AxMP. Accountability must be documented on drug accountability forms and in the IRT.

Refer to the trial product handling manual for more information about drug accountability and information on returning trial products.

All AxMP (TCS tubes) returned to the CMO will be weighed to determine the amount of TCS used by the subjects and will be reconciled with the individual drug accountability forms. The detailed procedure for weighing of AxMP (TCS tubes) and subsequent transfer of tube weight data to the clinical database will be documented.

9.8.4 Treatment compliance

IMP injections will be performed by site staff who will also hand out AxMP (TCS) for self-administration and keep the accountability records up to date. IMP administration along with reasons for any non-compliance will be recorded in the eCRF.

9.8.5 Trial product destruction

Used syringes will be destroyed at the trial sites.

Unused IMP as well as used and unused AxMP (TCS) returned to the CMO will be destroyed by the CMO according to approved procedures and/or local requirements.

Please refer to the trial product handling manual regarding details for destruction of trial products.

9.9 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice. Subjects who qualify for the long-term extension trial as described in Section 7.1 may be offered participation in that trial.

9.10 Reporting product complaints

Any defects or issues with the IMP as well as any IMP device deficiency (including malfunctions, use errors, and inadequate labelling) must be reported to Pharmacovigilance at LEO Pharma K.K. on the trial-specific (paper) complaint form within 3 days of first knowledge.

Critical complaints (defined as any defect, issue, or IMP device deficiency that has or potentially could have a serious impact for the subject [e.g. SAE or large particles in the syringe]) must be reported to Pharmacovigilance, LEO Pharma K.K. within 24 hours.

Complaint forms should contain a detailed description of the defect, issue, or IMP device deficiency, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the IMP or due to IMP device deficiency will be reported by the investigator as described in Sections 13.3 and 13.4. Similarly, any defects or issues with the AxMP (TCS) must also be reported to Pharmacovigilance at LEO Pharma K.K. using the same complaint procedure as for the IMP and IMP device.

Refer to the IRT training material for information on how to update the kit status in the IRT.

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

Pharmacovigilance, LEO Pharma K.K., contact information for reporting product complaints:

Fax number: +81 3 4243 3311

E-mail address: clinical_trial_jp@leo-pharma.com

10 Discontinuation and withdrawal

10.1 General principles

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

In order to obtain the most representative efficacy evaluation of tralokinumab, it is of importance to assess the efficacy status of each subject at the planned primary endpoints visit (nominal Week 16 visit), irrespective of whether the subject has discontinued IMP or not. Therefore, permanent discontinuation of IMP is evaluated as a separate occurrence that does not necessitate that the subject also withdraws from subsequent selected trial activities (including the safety follow-up visit).

Permanent discontinuation of IMP and withdrawal from the trial are considered to occur in the following circumstances:

- **Permanent discontinuation of IMP** occurs when all further IMP administration is actively stopped by decision of the subject or investigator. This also involves when the subject is lost to follow-up. The subject will continue to participate in selected trial visit activities as outlined in Section 10.3.
- **Withdrawal from trial** occurs when participation in trial activities is stopped before the planned safety follow-up visit at Week 20. This may happen either at the time of permanent discontinuation of IMP or later.

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

10.2 Reasons for discontinuation of IMP

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will 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 localised squamous or basal cell carcinoma of the skin.

- Evidence of pregnancy.
- 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).

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 (a specification must be provided).
- Death.
- Lost to follow-up.
- Lack of efficacy.
- Withdrawal by subject.
- Pregnancy.
- Other (a specification must be provided).

10.2.2 Reasons for temporary discontinuation of IMP

IMP administration may be temporarily suspended in the event of:

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

IMP administration should be temporarily suspended in the event of:

- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, JAK inhibitors, dupilumab or other biologics).

After the treatment with any of the medications mentioned in this section, IMP may be resumed if deemed appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic therapy.

10.3 Early termination assessments

Permanent discontinuation of IMP

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

- Early termination visit (as soon as possible after last IMP administration).
- Nominal Week 16 visit (16 weeks after randomisation).*
- Safety follow-up visit (6 weeks after last IMP administration).*

*If a subject permanently discontinues IMP dosing ≥5 weeks before the planned Week 16 visit, then only the nominal Week 16 visit (16 weeks after randomisation) will be conducted. At this visit, the relevant safety information will be collected, since all assessments planned at the safety follow-up visit are part of the assessments performed at the nominal Week 16 visit.
Subjects who permanently discontinuing IMP <5 weeks before the planned Week 16 visit should have both the nominal Week 16 visit and the safety follow-up visit conducted.

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

Withdrawal from trial

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

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 and eCRF.

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

10.4 Lost to follow-up

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

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

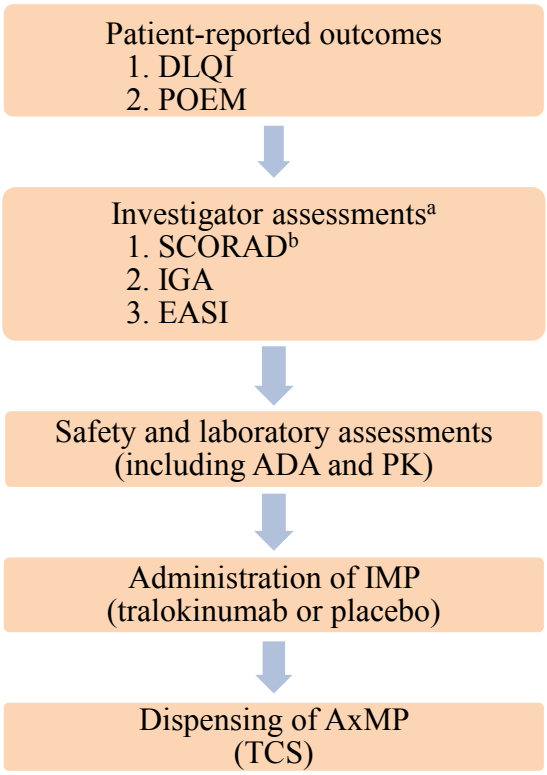
- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

11 Trial assessments and procedures

11.1 Overview

There are up to 12 scheduled visits at the trial site during the trial. Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4 and the trial design is described in Section 7.1. Assessments and procedures should be performed in the order shown in Panel 5 at the screening and baseline visits. The photographs can be taken following the most appropriate order at each selected trial site. The order of assessments may be changed after the baseline visit to perform safety and laboratory assessments before the investigator assessments, but after the patient-reported outcomes. The assessments should preferably be performed in the same order for all subjects at the trial site.

Panel 5: Sequence of assessments



a) Performed only by adequately trained investigators.
b) First component C, then component A and B.

Abbreviations: ADA, anti-drug antibodies; AxMP, auxiliary medicinal product; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; PK, pharmacokinetics; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroids.

Subjects participating in the trial will be under careful supervision of a qualified principal investigator. Investigators must be experienced in treating AD and have documented experience and/or training in use of the assessments required by the protocol and must be dermatologists.

To reduce inter-rater variability, the same investigator should preferably perform all the efficacy evaluations (SCORAD, IGA, and EASI) for a given subject throughout the entire trial period.

The investigators performing the assessments must not be involved in the administration of IMP (Section 9.3.1).

AEs must be assessed by medically qualified personnel (Section 13.2).

Subjects may also need to be seen at unscheduled visits during the trial; the assessments to be performed at an unscheduled visit are left at the investigator's discretion (Section 4). In case a subject withdraws from the trial or permanently discontinue IMP prematurely, refer to Section 10 for details and Section 4 for assessments/procedures.

11.2 Assessments performed only at screening and/or baseline

Assessments performed only at screening (Week -6/Week -2) and/or baseline (Week 0) include: assessment of eligibility criteria (including review of scores on the C-SSRS screening version), demographics, medical history, height and weight, and BSA affected by AD. These are described in further detail in Sections 11.2.1 to 11.2.5.

Laboratory tests performed only at screening/baseline include serology (hepatitis B and C, and HIV) and serum pregnancy test (Section 11.4.4).

11.2.1 Columbia-Suicide Severity Rating Scale

The C-SSRS screening version is a rater-administered instrument used to assess severity of suicidal ideation and suicidal behaviour through a series of simple, plain-language questions (26). The C-SSRS must be completed at screening to check that exclusion criterion no. 24 does not apply. Further details on the assessment according to the C-SSRS are included in the efficacy assessment & C-SSRS manual.

11.2.2 Demographics

The following demographic data will be recorded:

- Year of birth.
- Age.
- Sex (determined by the investigator): female, male.
  Sex (female, male) refers to biological differences: chromosomes, hormonal, profiles, internal and external sex organs. Gender is a social criterion, e.g. feminine, masculine, and will not be captured.
- Confirmation of race and ethnic origin.

11.2.3 Medical and surgical history

Relevant past and concurrent medical/surgical history must be recorded and includes:

- All past and current skin disease history, including but not limited to:
  - Alopecia.
  - Vitiligo.
  - Herpes simplex.

  For each condition or diagnosis, the start date and stop date will be recorded (it will also be recorded if the diagnosis is ongoing).
- Atopy history, including:
  - Duration of AD in years.
  - Previous AD treatments.
  - Asthma.
  - Food allergy.
  - Hay fever.
  - Allergic conjunctivitis.
  - Atopic keratoconjunctivitis.
  - Eczema herpeticum.
- Other medical and surgical history including concurrent diagnoses.

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.

11.2.4 Height and weight

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

11.2.5 Body surface area involvement

The total BSA affected by AD will be assessed by the investigator for each section of the body as component A of SCORAD (Section 11.3.3) and will be reported as a percentage of all major body sections combined. The following body regions will be assessed (brackets show the highest possible score for each region): head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%), and genitals (1%). The total BSA score will be assessed according to the schedule of procedures in Section 4.

11.3 Efficacy assessments

11.3.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe disease) (Panel 6). The IGA score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the IGA should be assessed by the same investigator at each visit to reduce inter-rater variability. The disease severity assessment score will be recorded in the eCRF.

Panel 6: Investigator's Global Assessment

Score	Disease severity	Standard IGA scale	IGA morphological descriptors
0	Clear	No inflammatory signs of atopic dermatitis.	No erythema and no elevation (papulation/infiltration).
1	Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration.	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration) that is not widespread.
2	Mild disease	Mild erythema and mild papulation/infiltration.	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration).
3	Moderate disease	Moderate erythema and moderate papulation/infiltration.	Dull red, clearly distinguishable erythema and clearly perceptible but not extensive elevation (papulation/infiltration).
4	Severe disease	Severe erythema and severe papulation/infiltration.	Deep/dark red erythema, marked and extensive elevation (papulation/infiltration).

11.3.2 Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (27). The EASI score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, the EASI score should be assessed by the same investigator at each visit to reduce inter-rater variability.

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 7. 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 8. For each body region, a severity sum score will be calculated, which will be multiplied by an area score (Panel 8) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 7).

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 7: Calculation of EASI

Body region	Erythema	Induration/ papulation	Excoriation	Lichenification	Area score	Weighting factor	Score
Head/neck	(SS +	SS +	SS +	SS)	x AS	x 0.1	
Trunk	(SS +	SS +	SS +	SS)	x AS	x 0.3	
Upper extremities	(SS +	SS +	SS +	SS)	x AS	x 0.2	
Lower extremities	(SS +	SS +	SS +	SS)	x AS	x 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 (28).

Panel 8: 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

Abbreviations: EASI, Eczema Area and Severity Index.

11.3.3 Scoring Atopic Dermatitis

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (29). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of trial procedures (Section 4).

The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit. Whenever possible, SCORAD should be assessed by the same investigator at each visit to reduce inter-rater variability.

The assessment consists of 3 components: A = extent, B = intensity, and C = subjective symptoms.

Extent (A)
The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas (maximum score = 100%).

Intensity (B)
The intensity of 6 specific symptoms of AD (erythema, oedema/papulation, oozing/crusting, excoriation, lichenification, and dryness) is assessed by the investigator on an average representative area using the following scale:

0 = None/absent
1 = Mild
2 = Moderate
3 = Severe

Note: dryness is evaluated on uninvolved areas.

The sum of intensity score of the 6 symptoms will be reported (maximum score = 18).

Subjective symptoms (C)
A subjective assessment of the average itch and sleeplessness over the last 3 days/nights is recorded for each symptom by the subject on a visual analogue scale, where 0 is no itching (or no trouble sleeping) and 10 is unbearable itching (or lot of trouble sleeping), with a maximum possible score of 20.

The SCORAD is calculated as: A/5+7B/2+C.

The extent and intensity of disease will be reported in the eCRF.

11.3.4 Patient-reported outcomes

The following patient-reported outcomes will be assessed using an eDiary device:

- Eczema-related Sleep NRS (Section 11.3.4.1).
- Worst Daily Pruritus NRS (Section 11.3.4.2).
- Patient Days of Topical Treatment Use (Section 11.3.4.3).

At screening, the subjects will receive the eDiary device and eDiary training. The subjects must complete the eDiary in the morning each day as specified in the schedule of trial procedures (Section 4), and compliance with the eDiary completion will be reviewed by the trial site staff throughout the trial. The eDiary should be returned to the trial site as outlined in the schedule of trial procedures (Section 4).

In addition, the following patient-reported outcomes will be completed by the subjects at the trial site:

- DLQI (Section 11.3.4.4).
- POEM (Section 11.3.4.5).

An electronic device will be supplied to each trial site in which the subjects can complete the DLQI and POEM.

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

11.3.4.1 Eczema-related Sleep numeric rating scale

Subjects will rate how much their eczema interfered with their sleep over the last night using an 11-point NRS (Eczema-related Sleep NRS) with 0 indicating that it ‘did not interfere’ and 10 indicating that it ‘completely interfered’. Subjects will complete the Eczema-related Sleep NRS as part of the eDiary each day in the morning from Week -2 until Week 16.

11.3.4.2 Worst Daily Pruritus numeric rating scale

Subjects will assess their worst itch severity over the past 24 hours using an 11-point NRS (Worst Daily Pruritus NRS) with 0 indicating ‘no itch’ and 10 indicating ‘worst itch imaginable’. Subjects will complete the Worst Daily Pruritus NRS as part of the eDiary each day in the morning from Week -2 until Week 16.

11.3.4.3 Patient Days of Topical Treatment Use

Subjects will assess their use of topical AD treatment over the past 24 hours using a response scale ('yes', 'no'). Subjects will complete the Patient Days of Topical Treatment Use as part of the eDiary each day in the morning from baseline (Week 0) until Week 16.

11.3.4.4 Dermatology Life Quality Index

The DLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their HRQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (30). 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 (range: 0 to 30); a high score is indicative of a poor health-related quality of life. The DLQI will be completed at the trial site according to the schedule of trial procedures (Section 4).

11.3.4.5 Patient-Oriented Eczema Measure

The POEM is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (31). The tool consists of 7 items each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). Subjects will score how often they have experienced each symptom over the previous week on a 5-point categorical response scale (0 = 'no days'; 1 = '1 to 2 days'; 2 = '3 to 4 days'; 3 = '5 to 6 days'; 4 = 'every day'). The total score is the sum of the 7 items (range: 0 to 28) and reflects disease-related morbidity; a high score is indicative of a worse disease severity. The POEM will be completed at the trial site according to the schedule of trial procedures (Section 4).

11.4 Safety assessments

11.4.1 Vital signs

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

For the first 3 IMP administration visits (i.e. at Weeks 0, 2, and 4), the subjects will be monitored after each IMP administration for immediate drug reactions for a minimum of

30 minutes with vital signs taken at 30 minutes or until stable, whichever is later (Section 9.2.1).

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial (respecting exclusion criterion no. 26).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine or sitting position to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false 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
The vital signs (and the time they were measured, when applicable) will be recorded in the eCRF; if vital signs were not assessed, a reason should be given. Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness will be reported as an AE in accordance with Section 13.3.

11.4.2 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin and auscultation of heart, lungs, and abdomen, palpation of the abdominal organs, and basic neurological status must be performed according to the schedule of trial procedures (Section 4).

If an unacceptable abnormal finding is identified during the physical examination at screening, the subject must not be randomised into the trial (respecting exclusion criterion no. 26).

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.

If the only abnormal finding resulting from the physical examination is AD, the physical examination should be stated as 'normal'.

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

11.4.3 ECG

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

A pre-evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. At a minimum, the investigators will record the result of the immediate safety evaluation and the date of ECG collection in the source documents.

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

The investigator must evaluate all ECG results ('normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant') and sign and date. The investigator has the final decision on the clinical significance of ECG abnormalities.

If a result is abnormal at screening and considered by the investigator to be clinically significant, it will be up to the investigator's discretion if the subject should be randomised into the trial (respecting exclusion criterion no. 26); if such a subject is randomised, the investigator will provide a justification in the medical record.

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

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

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

11.4.4 Laboratory testing: chemistry, haematology, serology, urinalysis, pregnancy test

11.4.4.1 Overview

Blood samples for chemistry, haematology, serology, and serum pregnancy test as well as urine samples for dipstick/urinalysis (if applicable) and urine pregnancy tests will be collected according to the schedule of trial procedures (Section 4). An overview of the individual laboratory parameters assessed in this trial is provided in Panel 9.

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.

Panel 9: Clinical laboratory tests

Chemistry	Haematology[3]
Sodium	Erythrocytes
Potassium	Haematocrit
Creatinine	Haemoglobin
Urea nitrogen	Erythrocyte mean corpuscular volume
Calcium	Erythrocyte mean corpuscular haemoglobin concentration
Alkaline phosphatase	Leukocytes
Aspartate aminotransferase	Neutrophils
Alanine aminotransferase	Neutrophils/leukocytes
Gamma glutamyl transferase	Lymphocytes
Bilirubin[1]	Lymphocytes/leukocytes
Cholesterol	Monocytes
LDL cholesterol	Monocytes/leukocytes
HDL cholesterol	Eosinophils
Triglycerides	Eosinophils/leukocytes
Glucose (non-fasting)	Basophils
Albumin	Basophils/leukocytes
Protein	Thrombocytes
Tryptase[2]	
Urinalysis[4]	**Serology[5]**
Protein	Hepatitis B virus surface antigen[6]
Glucose	Hepatitis B virus surface antibody[6]
Ketones	Hepatitis B virus core antibody[6]
Erythrocytes	Hepatitis C virus antibody[6]
Leukocytes	HIV-1 antibody[6]
Nitrite	HIV-2 antibody[6]
	Immunoglobulin E
	Serum pregnancy test[7]
	Choriogonadotropin beta

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Only measured in case of suspected anaphylaxis (Section 9.2.1).
3) The symbol '/'included in the table represents 'a ratio'.
4) Urinalysis will only be performed if considered required by the investigator based on dipstick results.
5) In case additional analysis are needed to support the interpretation of the initial test results for hepatitis B, hepatitis C, or HIV, these will be performed by the central laboratory as applicable.
6) Measured at screening only.
7) Only women of childbearing potential; measured at screening only.

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

11.4.4.2 Investigator evaluation of laboratory samples

Clinical laboratory tests analysed at a central laboratory

Chemistry, haematology, serology, pregnancy tests (serum), and urinalysis (if applicable) will be analysed by a central laboratory, which will provide results to the trial sites.

The investigator must evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date the evaluation. The signed and dated version will be filed with the investigator’s trial documentation. In case of clinically significant abnormal results (at randomisation and onwards), appropriate action, as judged by the investigator, must be taken.

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator’s discretion to decide if the subject should be randomised into the trial (respecting exclusion criteria no. 26, 27, and 28).

Tests performed at the trial site
Urine samples will be tested with a dipstick at the trial site according to the schedule of trial procedures (Section 4). The investigator should evaluate the result of the dipstick and in case of abnormality, it will be at the investigator’s discretion to decide whether a urine sample will be sent to the central laboratory for urinalysis.

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomisation. The test will be repeated every 4 weeks as shown in the schedule of trial procedures in Section 4.

Reporting in eCRF
It will be recorded 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 also be recorded in the eCRF.

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

Site staff will record in the eCRF if a urine dipstick was performed and whether urinalysis is required for further assessment, as judged by the investigator; if the urine sample was not tested with a dipstick, a reason will be provided. In case urinalysis is performed, the investigator’s assessment of the results (‘normal’, ‘abnormal, not clinically significant, ‘abnormal, clinically significant’) will be recorded in the eCRF.

It will be recorded in the eCRF if the subject is a woman of childbearing potential and if a urine pregnancy test was performed, if not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF (‘positive’, ‘negative’).

11.4.5 Anti-drug antibody measurements

Blood samples will be collected to determine levels of ADA at pre-determined time points according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if an ADA blood sample was taken; if not, a reason will be provided.

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

Serum samples for determination of presence or absence of ADA will be analysed by a laboratory using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titre determination and will be analysed for the presence of neutralising antibodies. Details of the analytical method used will be described in a bioanalytical report.

11.5 Pharmacokinetic assessments

Blood samples for PK assessments will be collected at the time points specified in the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the PK sample was taken; if not, a reason will be provided.

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

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

11.6 Pharmacodynamics assessments

Not applicable.

11.7 Other assessments

11.7.1 Photography (selected trial sites)

At selected trial 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 informed consent.

Digital colour photographs will be taken of the disease area and a representative lesion according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the photo(s) was taken; if not, a comment should be provided.

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

The photographs will have no other subject identifier than the subject ID and will be transmitted electronically to the central photography vendor using a secure file transfer protocol. The photographs will be included in the clinical database, but will not be evaluated or discussed in the clinical trial report (CTR).

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.

11.8 End of trial

End of treatment form
An end of treatment form will be completed in the eCRF for all randomised subjects when they have had their last IMP administration. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (Section 10.3).

The following data will be collected on the end of treatment form:

- Date of last IMP administration.
- Did the subject permanently discontinue IMP before Week 16; if yes, the primary reason for permanent discontinuation of IMP must be recorded (AE, death, lost to follow-up, withdrawal by subject, lack of efficacy, pregnancy, or other).
  If 'AE' or 'other' is selected, a specification must be provided.

End of trial form
An end of trial form must be completed in the eCRF for all randomised subjects. The end of trial form will be completed when the subject has had their last visit (that is, the safety follow-up visit, early termination visit, or nominal Week 16 visit).

The following data will be collected on the end of trial form:

- Date of last contact.
- Did the subject attend the safety follow-up visit; if not, the primary reason for not attending the safety follow-up visit must be recorded (AE, death, lost to follow-up, withdrawal by subject, transferred to the long-term extension trial [ECZTEND], safety follow-up assessments done at the nominal Week 16 visit, pregnancy, or other). If 'AE' or 'other' is selected, a specification must be provided.
- For subjects who permanently discontinued IMP before Week 16, it will be recorded if the subject attended the nominal Week 16 visit; if not, the primary reason for not attending the nominal Week 16 visit must be recorded (AE, death, lost to follow-up, withdrawal by subject, pregnancy, other). If 'AE' or 'other' is selected, a specification must be provided.
- Has the subject been transferred to the long-term extension trial (ECZTEND); if yes, the last visit the subject attended in this trial (LP0162-1343) will be specified.

11.9 Estimate of total blood volume collected

Blood samples will be drawn for chemistry, haematology, serology, PK, ADA, and pregnancy test (if applicable). The total volume of blood to be drawn is approximately 100 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value; however, the total volume of blood drawn will be less than that taken during a blood donation (approximately 400 mL).

11.10 Storage of biological samples

Samples analysed by the central laboratory (Panel 9) will be destroyed after analysis.

PK samples will be retained for as long as the quality of the material permits evaluation, but for no longer than 12 months after completion of the CTR.

Samples for ADA evaluation will be retained for as long as the quality of the material permits evaluation, but for no longer than 10 years after marketing authorisation.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This is a prospective, randomised, double-blind, placebo-controlled, phase 3 trial designed to evaluate the efficacy and safety of tralokinumab in combination with TCS in Japanese subjects with moderate-to-severe AD, who are candidates for systemic therapy. A similar design as the multi-national trial LP0162-1339 (the initial 16 weeks only) has been chosen to facilitate an evaluation of similarity in efficacy and safety of tralokinumab in combination with TCS as compared with the LP0162-1339 trial. No Japanese subjects participated in the LP0162-1339 trial, but efficacy and safety of Japanese subjects were evaluated in the multi-national trial LP0162-1325 (with tralokinumab as monotherapy). In the LP0162-1325 trial, tralokinumab was shown to be safe and efficacious in treating Japanese subjects with moderate-to-severe AD, in particular also in a setting where use of TCS was analysed as being adjunct/combination treatment (‘treatment policy’ estimand) as in the current trial.

The trial endpoints have been selected to evaluate the efficacy of tralokinumab in improving the severity and extent of AD including both objective signs of disease and subjective symptoms (e.g. itch) as well as HRQoL. The primary efficacy endpoints (IGA 0/1 and EASI75) are recognised as important endpoints in clinical trials in AD by regulators in the US, EU, and Japan.

The planned trial design is considered appropriate for evaluating the objectives of the trial, as the double-blind condition regarding subject’s treatment (tralokinumab or placebo) is maintained and a possible observer bias regarding treatment effects is minimised. The stratification by baseline disease severity in this multi-site trial will provide a strong basis for generalisation of the findings to the target patient population. Further, the trial population will comprise both men and women to explore effects between sexes and across the adult age range.

A placebo-controlled parallel-group design has been chosen to evaluate the efficacy and safety of tralokinumab in combination with TCS in Japanese subjects. This allows an evaluation of similarity to the treatment effect observed in the LP0162-1339 trial, hereby adding to the knowledge needed for positioning tralokinumab in the AD treatment pathway in Japan.

The most important inclusion criterion for the trial is an established diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria for AD) (21) at screening and a history of AD for at least 1 year to ensure correct diagnosis and rule out differential diagnosis. A prerequisite

for inclusion into the trial is a documented history of topical AD treatment failure (due to inadequate response) to ensure that the subject is candidate for systemic treatment. Subjects for whom topical treatment with TCS are medically inadvisable may not be included as TCS will be administered in this trial.

The dose selected for the tralokinumab phase 3 development programme is 300 mg Q2W administered subcutaneously. All subjects randomised to treatment with tralokinumab will first get a loading dose of 600 mg tralokinumab. The administration of this loading dose 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.

12.2 Appropriateness of assessments

The clinical efficacy of tralokinumab treatment will be assessed by IGA, EASI, and SCORAD. IGA is a key instrument used in clinical trials to rate the severity of the subject's global AD (32). EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (27). SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (29).

Two validated patient-reported questionnaires (DLQI and POEM) and an eDiary (Worst Daily Pruritus NRS, and Eczema-related Sleep NRS) have been included to assess the efficacy of tralokinumab on symptoms and HRQoL.

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

Data on ADA (antibodies against tralokinumab) will be collected and the potential for immunogenicity will be evaluated. The blood samples for determination of presence or absence of ADA will analysed a using a validated bioanalytical method.

Blood concentrations of tralokinumab will be analysed using a validated bioanalytical method and standard PK parameters will be derived to evaluate tralokinumab exposure.

13 Adverse events

13.1 Definition and classification of adverse events

AEs and SAEs are defined in Appendix 1.

Classification of AEs in terms of severity, causality and outcome is defined in Appendix 2.

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject has signed the informed consent form until completion of the trial (defined as the safety follow-up visit 6 weeks after last IMP injection) [Sections 7.3 and 10.3]). For subjects entering the long-term extension trial (ECZTEND), any (S)AE with onset before the final visit in LP0162-1343 should be reported in LP0162-1343. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND.

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, for example: “How have you felt since I saw you last?” No specific symptoms should be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

Refer to Sections 11.4.1 to 11.4.4 for principles for data entry in the eCRF.

13.3 Reporting of adverse events

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

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

The *duration* of the AE must be reported by the start date and stop date of the event (if the event is ongoing it will also be recorded). In addition, it must be recorded whether the AE started on the same day as the IMP administration (i.e. before or after dosing).

AEs must be classified in terms of severity, causality, and outcome according to the definitions in Appendix 2. For events not considered related to IMP, the causal relationship to the use of AxMP should be evaluated using the same definitions as for the IMP.

Action taken with trial treatment: any action taken with IMP or AxMP 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).

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

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1. SAE criteria are also listed on the SAE form.

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma K.K. on the (paper) SAE form within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP, AxMP, or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

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 report.

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

Pharmacovigilance at LEO Pharma K.K.

E-mail address: clinical_trial_jp@leo-pharma.com

Fax number: +81 3 4243 3311

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

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

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

SAEs occurring after the completion of the clinical trial, including post-treatment follow-up (i.e. after the last safety follow-up visit at Week 20), should not be routinely sought or recorded.

13.4.2 LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether or not an SAE is expected. The relevant reference safety information documents for this clinical trial are:

- For the IMP, the investigator's brochure section 7.2, edition 19 and subsequent updates must be used.
- For AxMP (mometasone furoate, 0.1% cream), the latest version of the summary of product characteristics (SmPC) must be used.

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

The IRBs/IECs will be notified of SAEs according to the current applicable legislation for the concerned country.

All SAEs which are assessed as causally related to the IMP(s) **by either the investigator or LEO Pharma** (33), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, IECs/IRBs according to the current applicable legislation for the concerned country. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma K.K. within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or

termination and final outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

The completed pregnancy forms must be faxed or scanned and e-mailed to Pharmacovigilance at LEO Pharma K.K. Contact details are given in Section 13.4.1.

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

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 10 are considered AEs of special interest (AESIs) in this trial and will require additional details to be recorded in the eCRF. LEO Pharma may request that the investigator forward test results, as appropriate. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 10: Adverse events of special interest

AESI	Additional data to be recorded in the eCRF (if available[1])
Eczema herpeticum	Skin findings: • Lesion type (papules, vesicles, crusts, eroded pits, other). • Disseminated/localised. • Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Present in an area with visible eczema / no visible eczema / present in areas with and without eczema. • Monomorphic/polymorphic. • Confirmation of herpes simplex virus (not confirmed, PCR, viral culture, Tzanck, other).
Malignancy diagnosed after randomisation, excluding basal cell carcinoma, localised squamous cell carcinoma of the skin, and carcinoma in situ of the cervix	• Histology report available. • Oncology assessment available. • Treatments (surgery, radiation, chemotherapy, other).
Skin infection requiring systemic treatment	• Location (face, scalp, back, chest, upper limb, lower limb, genitals). • Outcome of pathogenic swab (positive, negative, not performed).
Conjunctivitis	• Aetiology (viral, bacterial, allergic, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratoconjunctivitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis of herpes simplex keratitis (for events with viral aetiology). • Diagnosis confirmed by ophthalmologist.

1) The additional data to be recorded in the eCRF are not a requirement, but are to be reported by the investigator, if available, for example as part of standard clinical practice.

Abbreviations: AESI, adverse event of special interest; eCRF, electronic case report form; PCR, polymerase chain reaction.

13.6.2 Overdose

An overdose is defined as a subject receiving a quantity of IMP which is in excess of that specified in this protocol. An overdose is either accidental or intentional.

The term ‘overdose’ including a specification of why it occurred (accidental or intentional) must be recorded on the AE form of the eCRF. In addition, AEs originating from overdose

must be recorded as separate events. If the AE originating from the overdose qualifies as an SAE, expedited reporting is required (Section 13.4).

If the overdose is accidental and due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 9.10.

LEO Pharma does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat any overdose if necessary.

13.6.3 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP while in the control of the investigator or subject. Broadly, medication errors fall into 3 categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration.

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

If the medication error is due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 9.10.

13.6.4 Misuse

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

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

13.6.5 Abuse

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

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

13.6.6 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4. As AD is a fluctuating disease, consider to only report an AE if the aggravation/ exacerbation exceeds normal disease fluctuation or if lesions appear in a body area which is normally not affected by AD.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possibly or probably related to the IMP for 2 weeks or until the final outcome is determined, whichever comes first. SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement detailing why the subject cannot be expected to recover during the trial e.g. that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (34).

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

The investigator must immediately inform LEO Pharma – by contacting the clinical project manager or medical expert – of this change in a clinical trial procedure or of the temporary

halt; the investigator will provide full details of the information and the decision-making process leading to the implementation of the urgent safety measure.

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

14 Statistical methods

14.1 Sample size

Approximately 100 subjects will be randomised 1:1 to tralokinumab+TCS or placebo+TCS to facilitate an evaluation of similarity with the treatment effect observed in the LP0162-1339 trial.

Randomisation will be stratified by baseline disease severity (IGA 3 or 4).

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects who are randomised to treatment and exposed to IMP (tralokinumab/placebo) will be included in the full analysis set and will be analysed for efficacy up to Week 16.

A safety analysis set will be defined as all randomised subjects who receive IMP.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the analysis set definition document before breaking the randomisation code.

14.3 Statistical analysis

14.3.1 Disposition of subjects

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

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and by treatment group. Presentations of age, sex, race, ethnicity, baseline disease severity, and Worst Daily Pruritus NRS weekly average at baseline will also be given by baseline disease severity (IGA 3 or 4).

Demographics include age, sex, race, and ethnicity. Other baseline characteristics include vital signs (including height, weight, body mass index), duration of AD, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, and previous AD treatments.

14.3.3 Exposure and treatment compliance

The duration of exposure to treatment will be calculated as the number of days from date of first application of IMP to the date of last application of IMP, both days included.

Exposure to treatment will be presented for the safety analysis set as days of exposure per treatment group. Treatment compliance will be presented for the safety analysis set per treatment group as the percentages of missed applications/doses.

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

14.3.4 Rescue treatment

Rescue treatment will be defined by the following algorithm:

Concomitant medications with ‘Dermatitis atopic’ or ‘Dermatitis infected’ as the preferred term (PT) for the indication, and either of the following:

- ATC2 code: H02.
- Preferred name: methotrexate, ciclosporin, azathioprine, mycophenolate-mofetil, mychophenolate-acid, mycophenolate-sodium, dupilumab, crisaborole, alitretinoin, or delgocitinib.
- ATC4 code: D07AD, D07BD, D07CD, or D07XD.
- Confirmed rescue treatment (by investigator) in reported term for the indication, and ATC4 code: D07AB, D07BB, D07CB, D07XB, D07AC, D07BC, D07CC, or D07XC.

As described in Section 9.5, investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. Therefore, if rescue medication has start date the same day as an efficacy assessment, then it is assumed that the assessment is not influenced by rescue treatment.

Rescue treatment will be summarised for the treatment period. In addition, a summary table of rescue treatment by type (topical and systemic) and by overall group (corticosteroids, immunosuppressants, and other) will be made for the treatment period

Additionally, rescue treatment will be summarised for the treatment period by baseline disease severity (IGA 3 or 4).

In addition, the time to first use of rescue treatment will be presented using Kaplan-Meier plots for the treatment period.

14.3.5 Testing strategy

There will be no formal testing. All confidence intervals (CIs) will be presented with two-sided 95% degree of confidence.

14.3.6 Analysis of primary efficacy endpoints

Two estimands addressing different aspects of the trial objectives will be defined:

- Primary estimand: 'composite'.
- Secondary estimand: 'treatment policy'.

The applied estimands incorporate 2 main types of events that influence how the treatment effects are estimated (i.e. initiation of rescue treatment and permanent discontinuation of IMP).

- **Initiation of rescue medication**: Some of the estimands use the initiation of rescue medication as an event that modifies the applied value of an endpoint, e.g. by defining a subject receiving rescue medication as a non-responder.
- **Permanent discontinuation of IMP**: This event occurs when a subject is permanently withdrawn from the treatment or the trial as described in Section 10. This can either happen at his/her own initiative or at the investigator's discretion. The event also includes the possibility of a subject being lost to follow-up. The timing of the event is defined as the date of the early termination visit for withdrawn subjects or – in the case of a subject lost to follow-up – the date of the last known visit to the clinic. As for the rescue medication, the event type is used to modify an applied endpoint value.

All efficacy analyses will be based on the full analysis set.

14.3.6.1 Primary estimand: 'composite'

The primary estimand for the primary endpoints will be:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks achieved without rescue medication, regardless of treatment discontinuation.

The primary estimand assesses the expected difference in response rates (defined as response obtained without initiation of any rescue medication) after 16 weeks, resulting from initiation

of a treatment regimen with tralokinumab+TCS compared to a treatment regimen with placebo+TCS.

Primary analysis for the primary estimand
Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Subjects who prior to the Week 16 visit have received rescue medication will be considered non-responders, reflecting an assumption that initiation of rescue medication indicates failure of the randomised treatment to achieve response, and that a (possible) observed positive response after initiation of rescue medication is not attributable to the randomised treatment. Missing data for subjects who do not attend the Week 16 visit and where rescue medication has not been used prior to Week 16, will be imputed as non-responders.

The difference in response rates between treatment groups will be calculated by the Mantel-Haenszel method stratified by baseline disease severity (IGA 3 or 4). The treatment difference and the corresponding 95% CI will be presented.

Sensitivity analysis
The purpose of the analysis is to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 16.

All subjects who have permanently discontinued IMP prior to Week 16 will be imputed as non-responders, even if no rescue medication has been used. This is to reflect a situation where retrieved efficacy data and concomitant medications could be registered less accurately for subjects who have discontinued treatment. The same Mantel-Haenszel method as used for the primary analysis will be applied including stratification by baseline disease severity.

14.3.6.2 Secondary estimand: 'treatment policy'

The secondary estimand for the primary endpoints will be:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks regardless of rescue medication and discontinuation of IMP.

The secondary estimand assesses the average difference in response rates, resulting from initiation of a treatment regimen with tralokinumab+TCS and additional rescue medication as compared to a treatment regimen with placebo+TCS and additional rescue medication.

Primary analysis for the secondary estimand
All data used as observed at Week 16 regardless of rescue medication and discontinuation of IMP, thus data retrieved at Week 16 for subjects who have permanently discontinued treatment prior to Week 16 will be included in the analysis.

IGA 0/1 responder imputation
Imputation of missing binary IGA 0/1 data at Week 16 will be done using multiple imputations of the underlying 5-point IGA values within the 4 groups defined according to randomised treatment arm and whether or not subjects have permanently discontinued IMP prior to Week 16 assuming that data is missing at random within each arm. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such subjects where the Week 16 value is missing.

1. In each group, intermittent missing values will be imputed using last observation carried forward (LOCF) to obtain a monotone missing data pattern.
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 2. The model will include effect of baseline disease severity (IGA 3 or 4) as factor. The estimated parameters, and their variances, will be used to impute missing IGA values at Week 2. 100 copies of the dataset will be generated (seed=16201343).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a proportional odds logistic regression model with effects of baseline disease severity (IGA 3 or 4) together with the IGA value at Week 2 as factors. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Weeks 6, 8, 10, 12, 14, and 16 with the modification that only the IGA values from the 2 preceding visits will be included as factors in addition to baseline disease severity. The missing binary IGA 0/1 response at Week 16 will be derived from the corresponding underlying imputed IGA value.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted as described above.

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16 will be too small to facilitate the same imputation model as mentioned above. Consequently, an imputation model with only baseline effects (IGA as a factor) will be

applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if retrieved subjects all have the same baseline severity.

EASI75 responder imputation
Imputation of missing binary EASI75 data at Week 16 will be done using multiple imputations of the underlying 72-point EASI values within the 4 groups defined according to randomised treatment arm and whether or not subjects have permanently discontinued IMP prior to Week 16 assuming that data is missing at random within each arm. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such subjects where the Week 16 value is missing.

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern and 100 copies of the dataset will be generated (seed=11101343).
2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the EASI value at Week 2. The model will include effects of baseline EASI as a covariate, and baseline disease severity (IGA 3 or 4) as factor. The estimated parameters, and their variances, will be used to impute missing EASI values at Week 2 (seed=16201343).
3. For each of the 100 copies of the dataset, missing EASI values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on the same ANCOVA model with effects of baseline EASI as a covariate, and baseline disease severity (IGA 3 or 4) as factor together with the EASI value at Week 2 as covariate. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Weeks 6, 8, 10, 12, 14, and 16 with the modification that only the EASI values from the preceding 2 visits will be included as covariates in addition to baseline EASI as a covariate, and baseline disease severity as factor. The missing binary EASI75 response at Week 16 will be derived from the corresponding underlying imputed EASI value.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted as described above.

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16 will be too small to facilitate the same imputation model as mentioned above. Consequently, an imputation model with only baseline effects (IGA as a factor and EASI as a

covariate) will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if retrieved subjects all have the same baseline severity.

Analysis of Week 16 response
For each of the imputed data sets, the difference in response rates (either the IGA 0/1 or the EASI75) between treatment groups will be calculated using the same Mantel-Haenszel method as used for the primary analysis of the primary estimand including stratification by baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

Sensitivity analysis for secondary estimand
The primary analysis of the secondary estimand assumes that discontinued subjects with missing data at Week 16 behave similarly to discontinued subjects with available (retrieved) Week 16 data.

The robustness of this assumption is evaluated in a sensitivity analysis, applying single imputation to deem all subjects with missing data at Week 16 as 'non-responders'. The same Mantel-Haenszel method as used for the primary analysis of the primary estimand will be applied including stratification by baseline disease severity.

14.3.7 Analysis of key secondary efficacy endpoints

The binary key secondary endpoint, reduction of Worst Daily Pruritus NRS (weekly average) ≥4 from baseline to Week 16, will be analysed as described for the primary endpoint EASI75 using both estimands with the modification of the ANCOVA imputation model that reduction of Worst Daily Pruritus NRS weekly average replaces EASI where preceding values are used as covariates.

For the continuous key secondary endpoints, change from baseline to Week 16 in SCORAD and DLQI, 2 estimands addressing different aspects of the trial objectives will be defined:

- Primary estimand: 'composite'.
- Secondary estimand: 'hypothetical'.

14.3.7.1 Primary estimand for the continuous key secondary endpoints: 'composite'

The primary estimand for the continuous key secondary endpoints will be:

- Treatment difference in change from baseline to Week 16 in SCORAD and DLQI, respectively, achieved without rescue medication, regardless of discontinuation of IMP.

Primary analysis for the primary estimand - continuous key secondary endpoints
Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Subjects who prior to the Week 16 visit have received rescue medication will be considered non-responders by using worst observation carried forward (including the baseline value).

Missing Week 16 data among subjects who did not use rescue medication will be imputed using multiple imputations (100 copies of the dataset, seed=16201343) assuming missing at random within arms (based on sequential use of an ANCOVA model for Weeks 2, 4, 6, … and 16). The stepwise imputation model will be estimated based on available data from all subjects but excluding individual subject data captured after initiation of rescue medication or permanent discontinuation of IMP. For each of the 100 imputed datasets, the continuous secondary endpoint will be analysed using an ANCOVA model with effects of treatment, baseline disease severity (IGA 3 or 4), and baseline value. The estimates and standard errors from the 100 analyses will be combined using Rubin's rule to form a unique point estimate and standard error.

Sensitivity analysis for primary estimand - continuous key secondary endpoints
A tipping point analysis using multiple imputations will be performed with the purpose to assess the robustness of results of the primary analysis for the primary estimand with respect to the missing at random assumption regarding missing Week 16 data. The tipping analysis will assess how severe the departure from the missing at random assumption in the tralokinumab arm must be in order to impact the results.

The tipping point analysis will be performed using the missing at random imputed Week 16 data from primary analysis of the primary estimand. For each of the 100 already imputed datasets from the primary analysis, Δ will be added to the imputed values for subjects in the tralokinumab arm ($\Delta = 0$ implies missing at random) and thereby the imputed values will be 'shifted' by Δ. Each of the 100 modified imputed datasets will then be analysed in the same way as for the primary analysis for the primary estimand. The tipping point is then found as

the value of Δ which causes the 95% CI to change from excluding 0 to including 0 and will be judged from a clinical point of view.

14.3.7.2 Secondary estimand for the continuous key secondary endpoints: 'hypothetical'

The secondary estimand for the continuous secondary endpoints will be:

- Treatment difference in change from baseline to Week 16 in SCORAD and DLQI, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue medication was made available before Week 16.

The secondary estimand assesses the expected benefit when adhering to the treatment regimen tralokinumab+TCS with no rescue medication as compared to a treatment regimen with placebo+TCS with no rescue medication.

Primary analysis for the secondary estimand - continuous key secondary endpoints
Data collected after permanent discontinuation of IMP or after initiation of rescue medication will not be included in the analysis. For subjects without any post-baseline data, the baseline value will be carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment. This is to ensure that all subjects will be included in the analysis. The endpoints will be analysed using a repeated measurements model on the post-baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows (shown for change from baseline in SCORAD):

Change from baseline in SCORAD
= treatment × visit + baseline SCORAD × visit + baseline IGA

This model assumes that data is missing at random within each treatment arm. The estimates will be presented with 95% CI at each visit. The primary comparison between tralokinumab+TCS and placebo+TCS will be at Week 16.

Sensitivity analysis for secondary estimand - continuous key secondary endpoints
Rather than assuming that observations are missing at random within each treatment arm it is assumed that missing data from subjects who discontinue IMP/receive rescue medication in the tralokinumab+TCS arm will resemble data from subjects from the placebo+TCS arm who do not discontinue IMP/receive rescue medication.

Imputation of missing data at Week 16 will be done using a pattern mixture model where missing data in the tralokinumab+TCS arm as well as the placebo+TCS arm will be imputed from the placebo+TCS arm (using multiple imputations in a so-called copy-reference approach).

The procedure for the change from baseline in SCORAD at Week 16 is described below. The same procedure will be applied for the DLQI endpoint.

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern and 100 copies of the dataset will be generated (seed=11101343).
2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the SCORAD value at Week 2 in the placebo+TCS group. The model will include effects of baseline SCORAD as a covariate, and baseline disease severity (IGA 3 or 4) as factor. The estimated parameters, and their variances, will be used to impute missing values at Week 2 for the placebo+TCS group as well as the tralokinumab+TCS group (seed=16201343).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a similar ANCOVA model, but with SCORAD value at Week 2 included as an additional covariate. The parameters from the model will be estimated based on data from the placebo+TCS group. The estimated parameters, and their variances, will be used to impute missing values at Week 4 for both treatment groups.
4. This stepwise procedure will then be repeated sequentially for Weeks 6, 8, 10, 12, 14, and 16 with the SCORAD values from the preceding 2 visits included as covariates in addition to baseline SCORAD as a covariate, and baseline disease severity as factors.

For each of the 100 imputed datasets, the change from baseline in SCORAD at Week 16 will be analysed using an ANCOVA model with effects of treatment, baseline disease severity (IGA 3 or 4), and baseline SCORAD value. The estimated difference at Week 16 will be derived together with the associated standard error. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

14.3.8 Analysis of secondary endpoints

The analysis of the below dichotomous secondary endpoints will be based on the primary analyses of the primary estimand as specified above for the primary dichotomous endpoint.

For the continuous secondary endpoints, the analysis will be based on the primary (MMRM) analyses of the secondary estimand as specified above for the key secondary continuous endpoint.

The dichotomous secondary endpoints EASI90 at Week 16 and EASI50 at Week 16 will be analysed according to the primary analysis of the primary estimand as specified above for the primary endpoints.

The percentage change from baseline to Week 16 in EASI score and the change from baseline to Week 16 in Worst Daily Pruritus NRS weekly average, Eczema-related Sleep NRS (weekly average), and POEM will be analysed according to the primary (MMRM) analysis of the secondary estimand for the continuous key secondary endpoints.

14.3.9 Analysis of other endpoints

The binary other endpoints, reduction from baseline to Week 16 of DLQI ≥4 points among subjects with baseline DLQI ≥4 and reduction from baseline to Week 16 of POEM score ≥4 points in subjects with baseline POEM score ≥4, will be summarised by treatment group.

To evaluate the efficacy related to health care resource utilisation, the amount of TCS used (assessed as the amount of TCS used between visits), and the cumulative amount of TCS used will be determined by 2-week periods. The amount of TCS used and the cumulative amount of TCS used will each be logarithm-transformed prior to analysis. Due to potential zero valued ‘amount of TCS used’, 1 will be added to the values prior to transformation. This transformation has in a similar trial proven the model below to fit data better compared to leaving the data untransformed. Data will be analysed by a repeated measurements model with an unstructured covariance matrix and the mean modelled as follows:

$\text{Log}(Y+1) = \text{treatment} \times \text{visit} + \text{baseline IGA}$

where ‘Y’ is either the amount of TCS used or the cumulative amount of TCS used. Data obtained after permanent discontinuation of IMP or after initiation of rescue treatment will be excluded from the analyses.

The estimated parameters will be transformed back to the original scale using the exponential function, thus producing estimated geometric means and estimated ratio of means which will be presented together with 95% CIs.

Results obtained after initiation of rescue treatment will be excluded from the analyses.

In addition, TCS use (AxMP) <5 g at Week 16 will be analysed according to the primary analysis of the primary estimand for the primary endpoint.

14.3.10 Analysis of patient-reported outcomes

POEM and DLQI will be summarised by treatment group and visit using descriptive statistics. Data will be presented for the full analysis set.

The patient-reported outcomes collected daily in the eDiary (Worst Daily Pruritus NRS, Eczema-related Sleep NRS, and Patient Days of Topical Treatment Use) will all be summarised over time by treatment group using descriptive statistics. Data will be presented for the full analysis set.

The change from baseline to Week 16 in Eczema-related Sleep NRS weekly average and POEM will be summarised by treatment group and domain, where applicable, and analysed according to the primary analysis of the secondary estimand for the continuous key secondary endpoints. For the Eczema-related Sleep NRS score, the mean over the last 7 days prior to randomisation (Day -6 to Day 0) will be used as the baseline value.

14.3.11 Exploratory analyses

To further support the evaluation of the primary, key secondary, and secondary endpoints, the same endpoints will be evaluated at each scheduled visit/assessment up to the week specified below:

- EASI75 at each scheduled assessment up to Week 14.
- IGA 0/1 at each scheduled assessment up to Week 14.
- Change in SCORAD from baseline to each scheduled assessment up to Week 14.
- Change in Worst Daily Pruritus NRS (weekly average) from baseline to each scheduled assessment up Week 15.
- Change in DLQI score from baseline to each scheduled assessment up to Week 12.
- Reduction of Worst Daily Pruritus NRS (weekly average) ≥4 from baseline to each scheduled assessment up to Week 15.
- Change in Eczema-related Sleep NRS (weekly average) from baseline to each scheduled assessment up to Week 15.
- Change in POEM score from baseline to each scheduled assessment up to Week 12.

For the binary endpoints above, the treatment difference and the corresponding 95% CI will be presented at each scheduled visit/assessment using the same approach as applied for the primary analysis of the primary estimand for the primary endpoints. For continuous endpoints, the approach used for the primary analysis of the secondary estimand for key secondary endpoints will be applied.

For the binary endpoints, the same Mantel-Haenszel method as for the Week 16 assessment will be applied. For the continuous endpoints, the repeated measurements model already described previously for the Week 16 assessments facilitates that the treatment differences and 95% CIs can be derived for each visit/assessment in the same analysis that already will be made for the corresponding Week 16 assessments.

14.3.12 Analysis of safety

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

14.3.12.1 Adverse events

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

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

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

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

The severity for each type of AE will be tabulated by treatment group.

The causal relationship to IMP for each type of AE will be tabulated by treatment group. Related AEs are defined as AEs for which the investigator has not described the causal

relationship to IMP as ‘not related’. The number of related AEs and the number of subjects with each type of related AE will be tabulated.

The causal relationship to AxMP (TCS) for each type of AE will be tabulated by treatment group. Related AEs are defined as AEs for which the investigator has not described the causal relationship to AxMP (TCS) as ‘not related’. The number of related AEs and the number of subjects with each type of related AE will be tabulated.

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

AESIs and AEs leading to withdrawal from trial or permanent discontinuation of IMP will be tabulated and listed, no narratives will be given unless the events are considered as SAEs.

14.3.12.2 Vital signs

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

14.3.12.3 Clinical laboratory evaluation

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

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

14.3.13 Pharmacokinetic analysis

All the PK samples in the trial are trough samples. The trough concentration (C_{trough}) will be listed by treatment group and descriptive statistics will be applied.

14.3.14 Anti-drug antibodies

The presence of treatment-emergent ADA from baseline to Week 16 is a secondary endpoint included to assess the safety and tolerability (immunogenicity) of tralokinumab in combination with TCS.

ADA status (positive versus negative) at each visit will be summarised by treatment group. If considered relevant, descriptive statistics including number of subjects, mean, SD, median, 1st quartile, 3rd quartile, and range of the actual ADA titres by treatment group and visit will be provided. The ADA status across the trial for each subject (positive versus negative) will also be classified and summarised by treatment group.

The association of ADA status across the trial (positive versus negative) with AEs/SAEs may be evaluated. In addition, the association of ADA titres (≥ median titre in positive subjects versus < median titre) with AE/SAEs may be evaluated for ADA-positive treated subjects only.

The ADA status will be categorised as follows:

- Positive
    1. Pre-existing: ADA positive at baseline, no post-baseline ADA response ≥4-fold over baseline titre level, and at least 1 non-missing post-baseline ADA assessment.
    2. Treatment-boosted: ADA positive at baseline and at least 1 post-baseline ADA response ≥4-fold over baseline titre level.
    3. Treatment-emergent: ADA negative or missing at baseline and at least 1 positive post-baseline ADA response.
- Perishing
    4. ADA positive at baseline, all post-baseline ADA assessments negative.
- Negative
    5. ADA negative or missing at baseline, all post-baseline ADA assessments negative.
- No post-baseline ADA assessment.

For subjects who develop ADA and are considered treatment-boosted or treatment-emergent, the IGA score, change in EASI at end of treatment, and titre information will be listed.

Evaluations of neutralising antibodies will be conducted on those serum samples that test positive for ADA. The test sample is deemed positive or negative for the presence of neutralising antibodies to tralokinumab relative to a pre-determined (in assay validation), statistically derived cut point.

14.3.15 Interim analysis

No interim analysis is planned.

14.3.16 General principles

All CIs will be presented with 95% degree of confidence, unless otherwise specified.

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

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

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

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

14.3.17 Handling of missing values

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

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (35)

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.4.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record.
- Results in persistent or significant disability/incapacity.

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

Definition of adverse events of special interest

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

AESIs are described in Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement.

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

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

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, or not related according to the investigator's clinical judgement.

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 <u>not</u> follow a known pattern of response to the IMP.

For events not considered related to IMP using the criteria above, the causal relationship to the use of AxMP should be evaluated using the same definitions as for the IMP.

Outcome

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

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

LEO Pharma definitions versus CDISC definitions
Note that as per the above definition, LEO Pharma uses "recovered/resolved" only if an event has actually stopped. According to the CDISC definition, the category "recovered/resolved" also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as "not recovered/not resolved" or "recovering/resolving".

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

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

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (36) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (37).
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines (33).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authority (PMDA) must be notified of 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 [as applicable], subject information sheet, and informed consent form(s), or advertisements) will be submitted to the IRB/IEC. These documents must be reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol must be notified to regulatory authority and approved by IRBs/IECs, as required, prior to implementation.

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

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Appendix 3B: Informed consent process

Subjects (and/or the subject's legally authorised representative, if applicable) will receive written and verbal information concerning the clinical trial. This information will emphasise

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

The subject's signed and dated informed consent to participate in the clinical trial (and/or their legally authorised representative's signed and dated informed consent, if applicable) will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the informed consent form.

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

A copy of the informed consent form(s) must be provided to the subject (and/or the subject's legally authorised representative, if applicable).

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

Appendix 3C: Subject and data confidentiality

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

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

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

Trial subjects must be informed that their personal trial-related data will be used by LEO Pharma in accordance with local data protection law.

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

Trial subjects must be informed that LEO Pharma might keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research.

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

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

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

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

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

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

Appendix 3D: Record keeping, quality control, and data handling

Source data at trial sites

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

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

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

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- Subject ID.
- The fact that the subject is participating in a clinical trial in AD including treatment with tralokinumab or placebo for 16 weeks.
- Other relevant medical information.

Trial monitoring

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

A risk-based monitoring approach will be applied. The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH GCP. The level of source data verification, data checks, and visit intervals will be specified in the monitoring guideline.

In addition to on-site monitoring, pre-specified trial data will undergo central monitoring as specified in the trial's data review plan.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, for example, medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and major deviations described in the CTR.

Sponsor audits, IRB/IEC review, and regulatory agency inspections
The clinical trial will be subject to audits conducted by LEO Pharma or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO Pharma staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify, and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO Pharma must be notified immediately.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g. laboratory data). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRF used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require re-signature by the investigator. The person making the change to the data, and the date, time, and reason for the change will be identified in the audit trail.

Subject data should be entered into the eCRF no later than 5 working days after each visit, unless a different deadline is stated in the clinical trial agreement. Queries for discrepant data

will be generated automatically by the system upon entry or manually by the CRA, sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

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

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

Transmissions of data are documented in more detail in a data flow plan which is part of the trial master file.

Statistical programming standards
CDISC controlled terminology dated 08-May-2020 (or later) was used for definition of controlled terminology throughout this protocol and will be used for statistical programming and output. Standard Data Tabulation Model (SDTM) version 1.4 and SDTM implementation guide version 3.2 will be used for data tabulations.

Archiving of trial documentation
The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (33). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

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

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

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

LEO Pharma may also provide researchers access to anonymised patient-level data for further research. Publication and access will be in accordance with the Position on Public Access to Clinical Trials which can be found on the LEO Pharma website. Moreover, LEO Pharma may re-use the same patient-level data for other projects within the same purpose as the trial.

Publications

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 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-site publication is made public, or if no

multi-site publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO 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 (GPP3) 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 (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO Pharma also follows the CONSORT reporting guidelines (22).

Appendix 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Trial and trial site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IRB/IECs or competent authorities may decide to stop the clinical trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO Pharma procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

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

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

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

Appendix 3I: Responsibilities

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

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

Appendix 4: Hanifin and Rajka (1980) diagnostic criteria for AD (21)

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.

Appendix 5: Guidance for anaphylaxis diagnosis (24)

The National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to >95% of all cases of anaphylaxis (for all 3 categories).

Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
- Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence).

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

- Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula).
- Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
- Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence).
- Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

- Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP.
- Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Appendix 6: TCS classification list

English translation of the Japanese TCS classification list, which is included in the Guideline for Therapy for AD from 2018:

Group I Strongest	0.05%	Clobetasol propionate
	0.05%	Diflorasone diacetate
Group II Very Strong	0.1%	Mometasone fuorate
	0.05%	Betamethasone butyrate propionate
	0.05%	Fluocinonide
	0.064%	Betamethasone dipropionate
	0.05%	Difluprednate
	0.1%	Amcinonide
	0.1%	Diflucortolone valerate
	0.1%	Hydrocortisone butyrate propionate
Group III Strong	0.3%	Deprodone propionate
	0.1%	Dexamethasone propionate
	0.12%	Dexamethasone valerate
	0.12%	Betamethasone valerate
	0.025%	Fluocinolone acetonide
Group IV Medium	0.3%	Prednisolone valerate acetate
	0.1%	Triamcinolone acetonide
	0.1%	Alclometasone dipropionate
	0.05%	Clobetasone butyrate
	0.1%	Hydrocortisone butyrate
	0.1%	Dexamethasone
Group V Weak	0.5%	Prednisolone

Appendix 7: Short version of eligibility criteria

A short form (maximum 200 characters) version of each eligibility criteria for the trial is provided below.

No.	Inclusion criteria
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures
2	Japanese subject aged 18 years and above
3	Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD
4	History of AD for 1 year or more
5	Subjects with a recent history within 1 year before screening of inadequate response to treatment with topical medication or subjects for whom topical treatments are otherwise medically inadvisable
6	AD involvement of 10% (or more) body surface area at screening and at baseline according to component A of SCORAD
7	EASI score of 12 or more at screening and 16 or more at baseline
8	IGA score of 3 or more at screening and at baseline
9	Worst Daily Pruritus NRS average score of 4 or more during the week prior to baseline
10	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
11	Women of child bearing potential must use a highly effective form of birth control, confirmed by the investigator, throughout the trial and at least for 16 weeks after last administration of IMP

Abbreviation: AD, atopic dermatitis; EASI, Eczema Area and Severity Score; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; NRS, numeric rating scale; SCORAD, Scoring Atopic Dermatitis.

No.	Exclusion criteria
1	Subjects for whom TCS are medically inadvisable in the opinion of the investigator
2	Concurrent enrolment in another interventional clinical trial
3	Previous randomisation in a tralokinumab clinical trial
4	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis
5	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD
6	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA) within 6 weeks prior to randomisation
7	Treatment with systemic immunosuppressive/immunomodulating drugs, systemic corticosteroids, or bleach baths within 4 weeks prior to randomisation
8	Treatment with TCS, TCI, topical PDE-4 inhibitors, or topical JAK inhibitors within 2 weeks prior to randomisation
9	Receipt of live attenuated vaccines within 30 days prior to randomisation and during the trial including the safety follow-up period
10	Receipt of any marketed or investigational biological agent (e.g. cell-depleting agents or dupilumab) within 6 months prior to randomisation or until cell counts return to normal, whichever is longer

11	Receipt of any investigational non-biologic agent within 5 half-lives prior to randomisation
12	Receipt of blood products within 4 weeks prior to screening
13	Major surgery within 8 weeks prior to screening or planned in-patient surgery or hospitalisation during the trial period
14	Known or suspected allergy or reaction to any component of the IMP or AxMP formulation
15	History of any active skin infection within 1 week prior to randomisation
16	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation
17	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
18	History of anaphylaxis following any biological therapy
19	History of immune complex disease
20	History of cancer
21	Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care
22	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
23	History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator
24	History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or on the C-SSRS)
25	Any disorder, which is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial
26	Any abnormal finding, which in the investigator's opinion may put the subject at risk, influence the results of the trial, or influence the subject's ability to complete the trial
27	ALT or AST level 2.0 times the upper limit of normal or more at screening
28	Positive HBsAg, HBsAb, HBcAb, or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they have negative HBsAg, HBcAb, and HCV serology
29	Subjects who are not willing to abstain from donating blood and/or plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of IMP
30	Subjects who are legally institutionalised
31	Pregnant, breastfeeding, or lactating women
32	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

Abbreviations: AD, atopic dermatitis; ALT, alanine aminotransferase; anti-HCV, hepatitis C virus antibody; AST, aspartate aminotransferase; AxMP, auxiliary medicinal product; C-SSRS, Columbia-Suicide Severity Rating Scale; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; IMP, investigational medicinal product; JAK, Janus kinase; NBUVB, narrow band ultraviolet B; PDE-4, phosphodiesterase-4; PUVA, psoralen + ultraviolet A; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids; UVA1, ultraviolet A1; UVB, ultraviolet B.

Appendix 8: Contact list

Contact details for the clinical project manager, appointed CRA, and sponsor's medical expert are provided to the trial sites as a separate contact list.

Sponsor

LEO Pharma A/S is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

LEO Pharma K.K. is the sponsor of the clinical trial in Japan on behalf of LEO Pharma A/S:

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Reason for signing: Approved	Approver Verdict(s) Name: Norito Katoh Capacity: Clinical Trial Management Date of signature: 21-Jul-2020 07:39:08 GMT+0000

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