Cover Page

Study title: Efficacy and safety of tralokinumab administered by an autoinjector in adults and adolescents with moderate-to-severe atopic dermatitis INJECZTRA
LEO Pharma number: LP0162-1338
NCT number: NCT05194540
Date: 24-Aug-2022

Updated Clinical trial protocol

LP0162-1338

Efficacy and safety of tralokinumab administered by an autoinjector in adults and adolescents with moderate-to-severe atopic dermatitis
INJECZTRA

Phase 3 efficacy and safety of tralokinumab administered by an autoinjector

An open-label, single-arm, phase 3 trial to evaluate the efficacy and safety of tralokinumab administered by an autoinjector in subjects with moderate-to-severe atopic dermatitis

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:**	**LP0162-1338**
	Date:	**24-Aug-2022**
	EudraCT no:	**Not applicable**
	Version:	**3.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

PPD, MD, PhD, HD(O)
Vice president, R&D APAC Hub

PPD, MSc Stat
Biostatistics lead, Medical Sciences

PPD, MD
Medical lead, Medical Sciences

PPD, MSc Pharm
Clinical operations lead, Global Clinical Operations

Approval statement signatory investigator

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

The following person has approved this clinical trial protocol:

PPD, MD
Signatory investigator

Acknowledgement statement investigator(s)

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

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 2 (substantial)	24-Aug-2022	Global
Amendment 1 (substantial)	25-Oct-2021	Global
Original protocol	26-Apr-2021	NA

Amendment 2 (24-Aug-2022)

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

Overall rationale for the amendment

The main reason for this amendment is due to a revision in sample size. The revision is to ensure that FDA's request for sample size is met.

Additional changes are also presented in the table below. Changes have either been summarised (written in plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Section no. and title	Description of change	Brief rationale
1 Protocol synopsis, 7.2 Number of subjects needed, 14.1 Sample size	Number of subjects (sample size) needed for the trial was revised: • Total sample size was increased from approximately 120 subjects to approximately 130 subjects. • Adolescents sample size was decreased from a minimum of 40 subjects to approximately 30 subjects.	To meet FDA's request for sample size.
7.2 Number of subjects needed	Number of subjects screened for the trial was increased from approximately 160 subjects to approximately 174 subjects.	Consequential to change in sample size.

Section no. and title	Description of change	Brief rationale
14.1 Sample size	Assuming IGA 0/1 and EASI75 response rates of 19% and 29% at Week 16, respectively, a sample size of ~~120~~ **130** subjects will give a standard error of ~~3.58%~~ **3.44%** and ~~4.14%~~ **3.98%**, and thus a half-width for the 95% CIs of ~~7.02%~~ **6.74%** and ~~8.12%~~ **7.80%** for each of the primary endpoints.	Consequential to change in sample size.
Appendix 9 Protocol amendment history	New appendix added. Information about amendment 1 was moved from Clinical trial protocol amendment summary to Appendix 9.	Administrative change.

Table of contents

List of panels

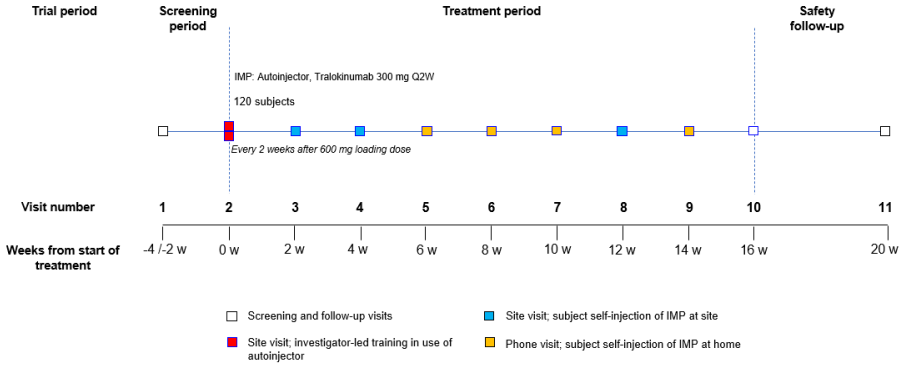
List of abbreviations

AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMO	contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRA	clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI90	at least 90% reduction in EASI score
EASI75	at least 75% reduction in EASI score
EASI50	at least 50% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
FAS	full analysis set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IGA	Investigator's Global Assessment
IGA 0/1	IGA score of 0 (clear) or 1 (almost clear)
IgE	immunoglobulin E
IL-13	interleukin-13
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
JAK	Janus Kinase
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralising antibodies
NBUVB	narrow band ultraviolet B
NRS	numeric rating scale
PD	pharmacodynamic
PDE-4	phosphodiesterase-4
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PUVA	psoralen + ultraviolet A
Q2W	every other week
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
SDTM	Standard Data Tabulation Model
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

<table>
<tr><td>Trial ID
IND no.
FDA center</td><td colspan="2">LP0162-1338
123797
CDER</td></tr>
<tr><td>Title of trial</td><td colspan="2">An open-label, single-arm, phase 3 trial to evaluate the efficacy and safety of tralokinumab administered by an autoinjector in subjects with moderate-to-severe atopic dermatitis.</td></tr>
<tr><td>Short title of trial</td><td colspan="2">Efficacy and safety of tralokinumab administered by an autoinjector in adults and adolescents with moderate-to-severe atopic dermatitis.</td></tr>
<tr><td rowspan="4">Main objectives and endpoints</td><td>Primary Objective</td><td>Primary endpoints</td></tr>
<tr><td>To evaluate the efficacy of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD.</td><td>• IGA score of 0 (clear) or 1 (almost clear) at Week 16.
• EASI75 at Week 16.</td></tr>
<tr><td>Secondary objective</td><td>Secondary endpoint</td></tr>
<tr><td>To evaluate the safety and tolerability of tralokinumab administered by an autoinjector when used to treat moderate-to-severe atopic dermatitis (AD).</td><td>• Number of treatment-emergent adverse events (AEs) from baseline to Week 16.
• Presence of treatment-emergent ADA from baseline to Week 16.</td></tr>
<tr><td>Final collection of data for the primary endpoint</td><td colspan="2">Week 16.</td></tr>
<tr><td>Trial design</td><td colspan="2">This is an open-label, single-arm, phase 3 trial, in adult and adolescent (age 12 to 17 years) subjects with moderate-to-severe AD. The trial is designed to evaluate the efficacy and safety of tralokinumab when administered by an autoinjector. A scheme of the trial design is provided below.
 

Abbreviations: IMP = investigational medicinal product; Q2W = every other week; w = weeks.
The trial consists of a 2-to-4-week screening period, a 16-week treatment period, and a 4-week safety follow-up period.
The screening period has a minimum duration of 2 weeks and a maximum</td></tr>
</table>

	duration of 4 weeks depending on the need for wash-out. At the baseline visit (Week 0, Visit 2), eligible subjects will receive an initial loading dose of SC tralokinumab 600 mg. This dose will be administered with the use of 2 autoinjectors containing 300 mg/2mL each. During the administration of the initial loading dose, subjects will be trained on the usage of autoinjector by the investigator or delegated trial staff. Subjects will have a choice to either self-administer the second injection under observation by qualified trial staff or receive both injections by the investigator/trial delegate. For the rest of the treatment period, all subjects will self-administer a dose of 300 mg tralokinumab Q2W (2 mL). The IMP will be administered every other week during the treatment period, and the last IMP administration (relating to this protocol) will occur at Week 14. All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before baseline and will continue this treatment throughout the trial (including safety follow-up). Subjects who during the treatment period or safety follow-up experience intolerable AD symptoms may be treated with rescue treatment at the investigator's discretion. All subjects completing the treatment period will have safety follow-up assessments 6 weeks after the last IMP administration. Note that for subjects who permanently discontinue IMP, the 6-week follow-up period will start at the time of last IMP injection.
Main assessments	<u>Assessment related to primary endpoints</u>: • IGA score. • EASI. <u>Assessment related to secondary endpoints</u>: AEs, vital signs, laboratory tests and ADA.
Main criteria for inclusion	• Age 12 years and above at baseline (Week 0). • Subject able and willing to self-administer tralokinumab using an autoinjector. • 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 the screening visit) of inadequate response to treatment with topical medication or for whom topical treatments are otherwise medically inadvisable. • AD involvement of ≥10% body surface area at screening and baseline. • An Eczema Area and Severity Index score of ≥12 at screening and ≥16 at baseline. • An Investigator's Global Assessment score of ≥3 at screening and at baseline. • Applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline.
Main criteria for exclusion	• Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment. • Use of tanning beds or phototherapy within 4 weeks prior to baseline.

	• Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroids within 4 weeks prior to baseline. • Treatment with topical corticosteroids, topical calcineurin inhibitors, topical phosphodiesterase-4 inhibitors, or topical Janus kinase inhibitors within 2 weeks prior to baseline. • Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-immunoglobulin E) including dupilumab or investigational biologic agents 3-6 months prior to baseline. • Active skin infections within 1 week prior to baseline. • Clinically significant infection within 4 weeks prior to baseline. • 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	• Active substance: tralokinumab. • Dosage form: 150 mg/mL solution for injection in 2 mL autoinjector (total of 300 mg of tralokinumab per injection). • Concentration: 150 mg/mL. • Dose: 600 mg initial loading dose, then 300 mg every other week. • Method of administration: SC injection.
Duration of trial participation	The trial duration for an individual subject is up to 24 weeks: • Screening period: 2 to 4 weeks. • Treatment period: 16 weeks. • Safety follow-up period: 4 weeks.
Number of subjects	Approximately 130 subjects, of which approximately 30 subjects will be adolescents, will be assigned to treatment.
Number and distribution of trial sites	Approximately 30 sites in the US.
Statistical methods	<u>Primary endpoints:</u> The primary endpoints (IGA 0/1 at Week 16 and EASI75 at Week 16) will be analysed using the composite estimand strategy to handle the occurrence of intercurrent events. Subjects with missing data will be imputed as non-responders. Number and percentage of subjects achieving response will be presented together with the corresponding 95% CI. <u>Secondary endpoints:</u> AEs will be summarised for all treated subjects (safety analysis set) and will be presented by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class (SOC) as number and percentage of AEs, the rate of AEs (number of AEs per 100 patient-years of

	observation time), and number and percentage of subjects with AEs. Presence of treatment-emergent ADA from baseline to Week 16 will be summarised descriptively.
Signatory investigator	Dr. PPD , MD, Clinical Professor, Dermatology, PPD , Director, Clinical Research, PPD PPD
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

2 Trial identification

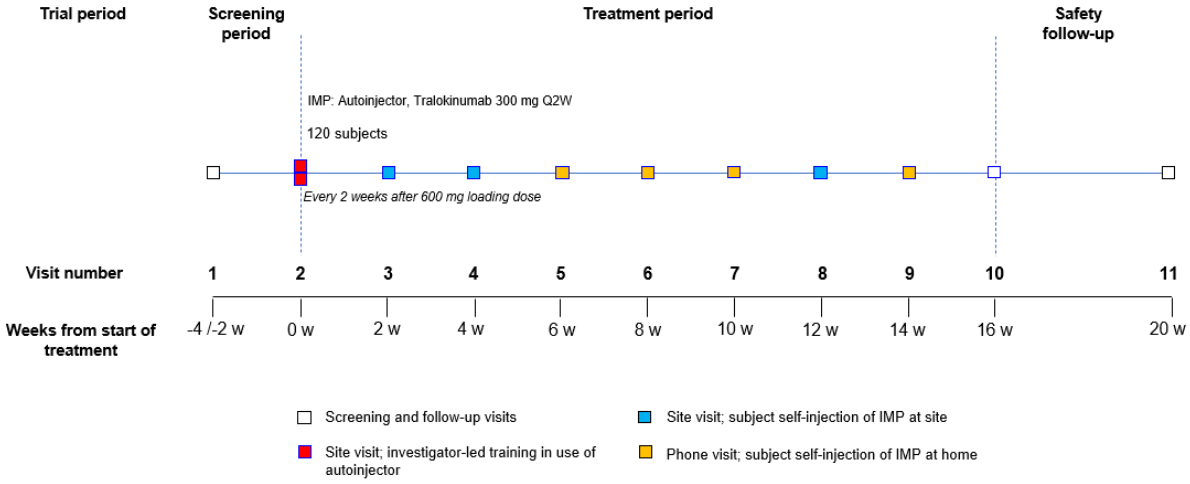
IND number: 123797

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

3 Schematic of trial design

The overall trial design is illustrated in Panel 1. The trial consists of a 2-to-4-week screening period, a 16-week treatment period, and a 4-week safety follow-up period.

Panel 1: Trial design



Abbreviations: IMP = investigational medicinal product; Q2W = every other week; w = weeks.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

	Screening	Treatment period									Follow-up[2]	Unscheduled visit, if applicable[3]	Early termination, if applicable[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Week	**-4/-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Phone**	**Phone**	**Site**	**Phone**	**Site**	**Site**			
Visit window (days)[1]	**±3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Population and eligibility														
Informed consent[5]	X													Appendix 3B
Subject eligibility	X	X												8.2 and 8.3
Investigator assessments at screening/baseline only														
Demographics	X													11.2.1
Medical history	X													11.2.2
Physical examination	X													11.2.3
C-SSRS	X													11.2.4
BSA	X	X												11.2.5
Treatments														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Concomitant procedure	X	X	X	X	X	X	X	X	X	X	X	X	X	9.6
Background treatment - initiation and continuation of emollients[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	9.4
Dispensing of IMP[7]		X	X	X				X						9.2 and 9.8.3

	Screening	Treatment period									Follow-up[2]	Unscheduled visit, if applicable[3]	Early termination, if applicable[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Week	**-4/-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Phone**	**Phone**	**Site**	**Phone**	**Site**	**Site**			
Visit window (days)[1]	**±3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
IMP administration and Investigator-led training in the use of autoinjector		X[8]												9.2
Subject self-administration of IMP at site			X[8]	X[8]				X						9.2
Subject self-administration of IMP at home					X	X	X		X					9.2
Treatment compliance		X	X	X	X	X	X	X	X					9.8.4
Return of autoinjector and accountability								X		X				9.8.3
Observer assessment of subject IMP self-administration			X	X				X						11.3
Subject assessment of IMP self-administration					X	X	X		X					11.3
Investigator assessments of efficacy														
IGA	X	X		X				X		X		X		11.4.1
EASI	X	X		X				X		X		X		11.4.2
Patient-reported outcomes														
POEM		X	X	X				X		X				11.4.3.1
DLQI/CDLQI[9]		X	X	X				X		X				11.4.3.2

	Screening	Treatment period									Follow-up[2]	Unscheduled visit, if applicable[3]	Early termination, if applicable[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Week	**-4/-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Phone**	**Phone**	**Site**	**Phone**	**Site**	**Site**			
Visit window (days)[1]	**±3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Eczema-related Sleep NRS		X	X	X				X		X				11.4.3.3
Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS[10]		X	X	X				X		X				11.4.3.4
Investigator assessments of safety														
Height[11] and weight		X								X				11.5.1
Vital signs	X	X	X	X				X		X	X			11.5.2
Serum pregnancy test (central laboratory)	X													11.5.3
Hepatitis B and C, HIV (central laboratory)	X													11.5.3
Chemistry, haematology, (central laboratory)	X	X		X				X		X	X			11.5.3
PK blood sample				X				X		X	X			11.6
ADA blood sample		X		X						X	X			11.5.4
Urine dipstick (urinalysis, central laboratory)[12]	X	X		X				X		X	X			11.5.3
Urine pregnancy test		X		X				X			X			11.5.3
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	13
Other assessment														
Photography[13]		X		X						X				11.7

	Screening	Treatment period									Follow-up[2]	Unscheduled visit, if applicable[3]	Early termination, if applicable[4]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Week	**-4/-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**			
Visit type	**Site**	**Site**	**Site**	**Site**	**Phone**	**Phone**	**Phone**	**Site**	**Phone**	**Site**	**Site**			
Visit window (days)[1]	**±3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
End of treatment/trial														
End-of-treatment										X			X	11.8
End-of-trial											X		X	11.8

1. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to baseline (Week 0, Visit 2).
2. An end-of-treatment form and/or end-of-trial form must be completed in the eCRF for all subjects assigned to treatment. See Section 11.8 for further details.
3. Assessments to be performed at unscheduled visits will be at the discretion of the investigator. If the unscheduled visit involves administration of rescue treatment, the investigator should make every attempt to conduct efficacy and safety assessments (at least disease severity scores [IGA and EASI], concomitant medications/procedures, and AEs) immediately before administering any rescue treatment (see Section 9.5).
4. Subjects who permanently discontinue IMP or withdraw from the trial will be followed up as described in Section 11.8. All subjects will have a final safety follow-up visit 6 weeks after last dose of IMP.
5. The informed consent form must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and wash-out of disallowed medications. Screening evaluations may start at a later date than the informed consent form was signed.
6. All subjects will use an emollient, as background treatment, twice daily (or more, as needed) for at least 14 days before baseline and will continue this treatment throughout the trial (including safety follow-up).
7. At Week 4 and Week 12 (Visit 4 and Visit 8), subjects will be provided with tralokinumab to be administered at home until the next site visit.
8. For 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.
9. Subjects <18 years of age at the baseline visit will perform the CDLQI throughout the trial, independent of the subject's age during the remainder of the trial.

10. Subjects <18 years of age at the baseline visit will perform Worst Weekly Pruritus NRS with phrasings tailored to adolescent subjects, independent of the subject's age during the remainder of the trial.
11. Measurement of height at Week 16 (Visit 10) will be applicable only to subjects <18 years of age at the baseline visit.
12. 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.
13. Applicable only for adult subjects (age 18 years and above at the baseline visit).

Abbreviations: ADA= anti-drug antibodies; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; 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; HIV = human immune deficiency virus; IGA= Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; PK= pharmacokinetics; POEM = Patient-Oriented Eczema Measure.

5 Introduction and trial rationale

5.1 Atopic dermatitis

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). 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 disturbance (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 to non-lesional skin, the proportion of $CD4^+$ and $CD8^+$ cells expressing IL-13 is upregulated in AD patients compared to 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 barrier function (9). IL-13 also drives immunoglobulin E (IgE) production and contributes to mast cell activation status 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 phase 2B trial (D2213C00001) have confirmed IL-13 as a valid target in AD (13).

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.

LEO Pharma is currently conducting a clinical development program with tralokinumab in AD comprising of 7 completed and 4 ongoing trials.

The completed trials have been conducted with the accessorised pre-filled syringe and include: a phase 2b dose-finding trial (trial D2213C00001), 2 phase 3 trials with tralokinumab as monotherapy (LP0162-1325 and LP0162-1326), 2 phase 3 trials with tralokinumab in combination with topical corticosteroids (TCS) (LP0162-1339 and LP0162-1346), a phase 2 vaccine response trial (LP0162-1341), and a phase 1 drug-drug interaction trial (LP0162-1342).

The tralokinumab dosing regimen of 300 mg every other week (Q2W) selected for this trial is based on the dosing regimen used in the tralokinumab phase 3 development program in adult subjects.

The 300 mg Q2W dose is considered safe in the adolescent population and is currently being investigated as part of the ongoing adolescent trial (LP0162-1334) where an independent Data Monitoring Committee regularly reviews unblinded safety data. Adolescent subjects with asthma have been investigated in a single-dose phase 1 trial (20 adolescent subjects exposed to tralokinumab) as well as in 2 completed phase 3 trials (58 adolescent subjects exposed to tralokinumab). In these trials, the tralokinumab PK and safety profile (based on reporting of AEs, SAEs, and AEs leading to discontinuation of IMP) was largely similar in the adult and adolescent trial populations with asthma.

In the phase 3 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. Noninferiority of tralokinumab vs placebo with respect to immune responses to concomitantly administered non-live vaccines was demonstrated in the LP0162-1341 trial.

A total of 4,465 subjects across indications (healthy subjects, and subjects with AD, asthma, ulcerative colitis, and idiopathic pulmonary fibrosis) have been exposed to tralokinumab in 24 completed clinical trials, including 2,276 subjects with AD in 7 completed clinical trials. A total of 2175 subjects with AD received tralokinumab 300 mg, and 807 of these were exposed to tralokinumab for 52 weeks.

The safety data supports that tralokinumab was well-tolerated with a favourable safety profile when used as a monotherapy or in combination with TCS in subjects with moderate-to-severe AD who are candidates for systemic therapy. The overall frequency of SAEs was lower for tralokinumab compared with placebo, and the frequencies of AEs leading to permanent discontinuation of treatment were low and similar for the 2 treatment groups. Overall, AEs were mild or moderate in severity, and transient in nature. Furthermore, tralokinumab was well-tolerated across all evaluated subgroups, and the safety profile with self-administration of tralokinumab at home was similar to that observed after administration of tralokinumab at the site by trial site staff.

Data from the phase 3 clinical trials in adults and adolescents, evaluating tralokinumab in AD, showed that the incidence rate of ADA and nAb after 16 weeks of treatment was low and similar for tralokinumab and placebo, confirming the low immunogenicity of tralokinumab.

All doses studied so far have had an acceptable benefit/risk profile, and no major safety concerns have been identified.

5.3 Trial rationale

In the phase 3 clinical development program, tralokinumab was presented as a 1 mL accessorised pre-filled syringe (containing tralokinumab 150 mg/mL) for SC injection, with dosing consisting of a 600 mg initial loading dose (4 x 1 mL) followed by 300 mg (2 x 1 mL) of tralokinumab Q2W. To improve convenience for patients, an autoinjector containing 2 mL tralokinumab 150 mg/mL has been developed to allow a single injection of 300 mg of tralokinumab (and 2 injections at Week 0 for 600 mg initial loading dose of tralokinumab).

To support the new presentation, a PK comparability trial intended to bridge between the accessorised pre-filled syringe and the newly developed autoinjector device is currently ongoing. In addition to the PK comparability and Human Factors data, this clinical trial will assess the efficacy and safety of the autoinjector in real-world situations in the AD population per FDA request.

The primary objective of this trial is to evaluate the efficacy of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD.

5.4 Ethical considerations

Participation in this trial is voluntary and subjects can withdraw at any time. The subjects or their legally authorised representative(s) will give informed consent, and adolescent subjects will give informed assent (as appropriate and according to national laws and regulations). No vulnerable subject incapable of giving informed consent will be included in this clinical trial. Furthermore, female subjects who are pregnant, breastfeeding, or trying to become pregnant will not be included. Female subjects of childbearing potential who are sexually active must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 16 weeks after discontinuation of treatment with the 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 this trial, all subjects will be treated with open-label tralokinumab. Subjects may receive rescue therapy at the discretion of the investigator if medically necessary through treatment and safety follow-up.

In accordance with the current version of the ICH GCP guidelines, qualified medical personnel employed by LEO Pharma A/S (hereafter LEO Pharma) will be readily available to advise on trial-related medical questions (17). Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by medically qualified staff at LEO Pharma to ensure that prompt action is taken, if needed, to maximise patient safety.

In conclusion, the trial design chosen is regarded as ethically justified and adherent with ethical requirements.

5.5 Benefit/risk assessment

This trial is part of the clinical development program of a new autoinjector containing 300 mg tralokinumab as a single injection with the aim of improving patient convenience.

With more than 4,400 subjects exposed to tralokinumab in the completed trials in AD and other diseases, the benefit/risk ratio is considered favorable and supports the administration of tralokinumab in subjects with moderate-to-severe AD 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 overall incidence of AEs for tralokinumab has been similar to that for placebo in controlled clinical trials and the adverse drug reactions observed were mainly 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, such as:

- 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).
- 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 baseline, which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial.

Participation in clinical trials may currently be associated with increased risks and challenges due to the COVID-19 pandemic caused by SARS-CoV-2. A risk of exposure to infected people cannot be excluded as the trial subjects may enter public areas (e.g. commute to the trial site) and have additional human contact (e.g. with trial site staff). Appropriate risk assessments and mitigation measures must be considered to protect the subjects and trial site staff and to ensure the integrity of the trial data.

The FDA has issued new guidelines that aim to provide recommendations for conduct of clinical trials during the COVID-19 pandemic. Given the circumstances of the potentially relapsing pandemic situation with regard to the spread of COVID-19 in the future, special attention will be paid to protecting subjects participating in the trial and site staff involved in the investigations against infection with SARS-CoV-2.

During the trial, the investigators will be trusted to take appropriate actions to ensure the safety of the individual subjects according to local authority issued preventive measures. As these can differ across regions, no general instruction from the sponsor can be provided concerning subject safety and the need for postponing trial visits. In case of local authority issued preventive measures, the investigator can convert the Week 12 visit (Visit 8) into phone or video consultation. At the phone/video visit, no investigator assessments of efficacy will be done. Safety monitoring remains an obligation to LEO Pharma, and it is considered feasible to collect safety data remotely (via electronic communication) where on-site visits are not possible. Other mitigating measures include collecting PRO data via a web-based solution and ensuring supply of IMP to the subjects to overcome local authority-issued preventive measures due to the COVID-19 pandemic (see Appendix 8 for details).

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 patients with moderate-to-severe AD.

No clinically significant safety issues are expected to be identified following 300 mg tralokinumab administered by a 1 × 2 mL autoinjector.

6 Trial objectives and endpoints

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To evaluate the efficacy of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD.	**Primary endpoints** • IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary objective	
To evaluate the safety and tolerability of tralokinumab administered by an autoinjector when used to treat moderate-to-severe AD.	**Secondary endpoints** • Number of treatment-emergent AEs from baseline to Week 16. • Presence of treatment-emergent ADA from baseline to Week 16.
Other objectives	
To assess the real-life patient handling experience with the use of tralokinumab administered by an autoinjector in patients with moderate-to-severe AD.	**Other endpoints** • Successful IMP self-administration when observed at the clinic at Week 4. • Successful IMP self-administration when administered at home at Week 8.
To evaluate the efficacy of tralokinumab administered by an autoinjector on severity and extent of AD, itch, and HRQoL in treating moderate-to-severe AD.	**Other endpoints** • EASI90 at Week 16. • EASI50 at Week 16. • Percentage change in EASI score from baseline to Week 16. • Change in POEM from baseline to Week 16. • Reduction in POEM of at least 4 from baseline to Week 16[1,2]/Reduction in POEM of at least 6 from baseline to Week 16[1,2]. • Change in DLQI/CDLQI from baseline to Week 16. • Reduction in DLQI of at least 4 from baseline to Week 16[1,2]/Reduction in CDLQI of at least 6 from baseline to Week 16[1,2]. • Change in Eczema-related Weekly Sleep NRS from baseline to Week 16. • Change in Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS from baseline to Week 16. • Reduction of Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS of at least 4 from baseline to Week 16[3].

1. Only adult subjects with a score of 4 and above and adolescent subjects with a score of 6 and above at baseline will be included in the analysis.
2. For adult subjects, a response is defined as a reduction of at least 4 from baseline. For adolescent subjects, a response is defined as a reduction of at least 6 from baseline.
3. Only subjects with Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS score of 4 or above at baseline will be included in the analyses.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibodies; AEs = adverse events; CDLQI =Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI90/EASI75/EASI50 = at least 90% / 75% / 50% reduction in EASI score; HRQoL = health-related qualify of life; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure.

7 Trial design

7.1 Overall trial design

This is an open-label, single-arm, phase 3 trial, in adult and adolescent (age 12 to 17 years) subjects with moderate-to-severe AD. The trial is designed to evaluate the efficacy and safety of tralokinumab administered by an autoinjector. The trial design is illustrated in Section 3.

Screening period (Week -4/-2 to Week 0)
The screening period has a minimum duration of 2 weeks and a maximum duration of 4 weeks depending on the need for wash-out (i.e. screening visit should take place between Week -4 and Week -2). Eligibility will be assessed at the screening visit and at baseline prior to start of treatment. Trial-specific measurements will be performed as outlined in the schedule of trial procedures (Section 4).

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

Treatment period (Week 0 to Week 16)

At the baseline visit (Week 0, Visit 2), eligible subjects will receive an initial loading dose of SC tralokinumab 600 mg. This dose will be administered with the use of 2 autoinjectors containing 300 mg/2mL each. During the administration of the initial loading dose, subjects will be trained on the usage of the autoinjector by the investigator or a delegated trial staff. Subjects will have a choice to either self-administer the second injection under observation by qualified trial staff or receive both injections by the investigator/trial delegate. For the rest of the treatment period, all subjects will self-administer a dose of 300 mg tralokinumab Q2W (2 mL).

At Weeks 2, 4, and 12, subjects will self-administer tralokinumab at the trial site under observation by a qualified trial staff. The observer (investigator or delegated trial staff) will assess the subject's ability to self-administer the injection based on the defined sequence of use steps in Section 11.3.

At Weeks 6, 8, 10, and 14, subjects will self-administer tralokinumab at home. Subjects will be asked to assess their ability to self-administer the injection based on the defined sequence of use steps in Section 11.3. In addition, the trial staff will contact the subjects via telephone at Weeks 6, 8, 10, and 14. At each telephone visit, concomitant medication and procedures,

treatment compliance, and AEs information will be collected. Delegation of the telephone visit to qualified personnel is allowed at the discretion of the investigator.

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.

Safety follow-up period (Week 16 to Week 20)
All subjects completing the treatment period will have safety follow-up assessments 6 weeks after the last IMP administration at Week 14. Note that for subjects who permanently discontinue IMP, the 6-week follow-up period will start at the time of last IMP injection.

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 174 subjects will be screened. Approximately 130 subjects, of which approximately 30 subjects will be adolescents, are planned to be assigned to treatment. No formal sample size has been calculated.

This trial will be conducted at approximately 30 sites in the US. The anticipated average number of subjects assigned to treatment per trial site is 4.

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).

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

The final collection of data for the primary endpoint is 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 clinical trial must be verified according to the inclusion and exclusion criteria at visits specified in the schedule of trial procedures, Section 4. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and IRBs, 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. Signed and dated informed consent for adolescent subjects must be provided by the subject's legal representative(s) and by the subject in the form of a signed and dated informed assent.
2. Age 12 and above at baseline (Week 0).
3. Body weight at screening ≥30 kg.
4. Subjects must be able and willing to self-administer tralokinumab using an autoinjector. This criterion should be assessed at both screening and baseline visits, as one of the 'other objectives' of the trial is to assess whether subjects can successfully self-administer the IMP.
5. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD (18) (Appendix 4).
6. History of AD for ≥1 year.
7. Subjects who have a recent history (within 1 year before the screening visit) of inadequate response to treatment with topical medication or for whom topical treatments are otherwise medically inadvisable (e.g. due to important side effects or safety risks).

- Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 to 2) despite treatment with a daily regimen of TCS of medium to higher potency [± topical calcineurin inhibitors (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 also considered as inadequate responders to topical treatments and are potentially eligible for treatment with tralokinumab after appropriate washout.
- Important side effects or safety risks are those that outweigh the potential treatment benefits and include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the subject's treating physician.

8. AD involvement of ≥10% body surface area (BSA) at screening and baseline.
9. An EASI score of ≥12 at screening and ≥16 at baseline.
10. An IGA score of ≥3 at screening and at baseline.
11. Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline.
12. A woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and at least for 16 weeks (5 half-lives) after last administration of IMP.

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

    **A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject

and not just being without a current partner), same-sex partner, or vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

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

1. Concurrent enrolment in another interventional clinical trial.
2. Previous randomisation in a tralokinumab clinical trial.
3. Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
4. Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
5. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen+ultraviolet A [PUVA]) within 4 weeks prior to baseline.
6. Treatment with the following medications within 4 weeks prior to baseline:
    - Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporin A, azathioprine, mycophenolate mofetil, Janus kinase (JAK) inhibitors).
    - Systemic corticosteroid use (excludes topical, inhaled, or intranasal delivery).
    - Three or more bleach baths during any week within the 4 weeks.
7. Treatment with the following medications within 2 weeks prior to baseline:
    - TCS.
    - TCI.
    - Topical PDE 4 inhibitors.
    - Topical JAK inhibitors.
8. Receipt of live attenuated vaccines within 30 days prior to the date of baseline and during the trial including the safety follow-up period.
    - Receipt of inactive/killed vaccinations (e.g. inactive influenza) is allowed but it should not be administered in the same location as tralokinumab.

9. 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 baseline, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline.
10. Receipt of any investigational non-biologic agent within 5 half-lives prior to baseline.
11. Receipt of blood products within 4 weeks prior to screening.
12. Major surgery within 8 weeks prior to screening or planned in-patient surgery or hospitalisation during the trial period.
13. Known or suspected allergy or reaction to any component of the IMP formulation.
14. History of any active skin infection within 1 week prior to baseline.
15. History of a clinically significant infection within 4 weeks prior to baseline which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial, interfere with 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.
16. 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.
17. History of anaphylaxis following any biological therapy.
18. History of immune complex disease.
19. 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.

20. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
21. 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.
22. History of subject or subject's legal representative(s) of chronic alcohol or drug abuse within 12 months prior to screening, or any condition (e.g. psychotic state, language barrier, or other) associated with poor compliance, as judged by the investigator.
23. 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).
24. 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 trial.
25. Any clinically significant abnormal findings in physical examination, vital signs, 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 entire duration of the trial.
26. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the upper limit of normal (ULN) at screening.
27. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) at screening. Subjects with positive HBsAb are eligible in the trial provided they have negative HBsAg and HBcAb.
28. Positive hepatitis C virus antibody (anti-HCV) serology at screening.

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 or informed assent, as appropriate, is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central interactive response technology (IRT) system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the informed consent form was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent and subjects for whom the subject's legally authorised representative(s) have given written informed consent (the subject must have given written informed assent) 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 (and informed assent as appropriate and according to national laws and regulation) or not (screening log). 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 are not subsequently assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (19) and to respond to queries from regulatory authorities.

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

- Date of informed consent(s).
- Demographics (age, sex, ethnicity, race).
- Reason for screen failure.
    - Failure to meet eligibility criteria (specify criteria).
    - Lost to follow-up.
    - Withdrawal by subject.
    - Withdrawal by parent/guardian.
    - 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.

Re-screening of screening failures is not allowed. 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). Individuals who are re-screened will get a new subject ID.

9 Treatments

9.1 Trial product description

Panel 4: Identification of investigational medicinal product

IMP	Dosage form	Active ingredients and concentration	Pack size	Manufacturer responsible for batch release
Tralokinumab	150 mg/mL solution for injection in 2 mL autoinjector[1] (total of 300 mg of tralokinumab per injection)	Nominal concentration of tralokinumab 150 mg/mL in CCI mM sodium acetate/acetic acid buffer, CCI mM sodium chloride, CCI % (w/v) PS-80, pH 5.5 solution	2.0 mL autoinjector[1]	LEO Pharma

1. The autoinjector 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.

Abbreviations: IMP = investigational medicinal product; SC = subcutaneous.

9.2 Administration of investigational medicinal product

The IRT system will assign the required kit number(s) for each subject at each dispensing visit.

The first day of dosing is considered baseline (Week 0, Visit 2).

At baseline (Week 0, Visit 2), each subject will receive an initial loading dose of SC tralokinumab 600 mg. This dose will be administered with the use of 2 autoinjectors containing 300 mg/2mL each. During the administration of the initial loading dose, subjects will be trained on the usage of autoinjector by the investigator or delegated trial staff. Subjects will have a choice to either self-administer the second injection under observation by qualified trial staff or receive both injections by the investigator/trial delegate. For the rest of the treatment period, all subjects will self-administer a dose of 300 mg tralokinumab Q2W (2 mL). A minimum interval of 7 days is required between 2 dosing's. Dosing visits are shown in the schedule of trial procedures, Section 4.

The subject should be trained on how to handle the IMP and on the correct use of autoinjector according to the instructions for use. Furthermore, the subject will be trained on procedures to

be followed in the event of an emergency during or following home use of tralokinumab. Training provided to the subject will be documented in the eCRF.

For the initial 600 mg loading dose, each 2 mL injection will be administered at different injection sites separated by at least 3 cm within the same body area. Tralokinumab will be injected into the SC tissue of anterior thigh or abdomen. It is advised that the site of injection of IMP is rotated such that the subject receives IMP at a different anatomical part at each treatment. The injection site must be recorded in the source documents at each treatment visit and recorded in the eCRF.

In case the autoinjector is not working properly or damaged (see Section 9.10) or in situations where the subject did an error resulting in the subject not receiving any of the intended dose, a new autoinjector can be assigned at a scheduled or unscheduled visit at the investigator's discretion, and the site can re-train the subject as needed.

Further details on IMP administration are provided in a trial product handling manual. Subjects will receive the instructions for use and IMP must be administered according to it.

Monitoring after IMP administration

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. Vital signs will be documented in the eCRF (Section 11.5.2).

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) (20). The clinical criteria for defining anaphylaxis for this trial are listed in Appendix 5 (21).

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 11.5.3).

Conditions requiring rescheduling of tralokinumab administration

If any of the following should occur, the investigator should reschedule the visit and tralokinumab should not be administered until the rescheduled visit:

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

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

9.3 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to fulfil any of the exclusion criteria will be assigned to treatment at baseline. The IRT system will be used to control the IMP supply chain and expiry tracking.

9.4 Background treatment

All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before baseline. The background treatment should preferably be an additive-free, basic, bland emollient. Subjects will continue their background emollient treatment throughout the trial (including the safety follow-up).

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 trial subjects at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications (i.e. TCS/TCI) and escalate to systemic medications only for subjects who do not respond adequately after at least 14 days of topical treatment.

Subjects who receive topical rescue treatment 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. 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 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.

Use of rescue medication will be recorded in the eCRF.

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 3 months prior to screening through safety follow-up 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 per administration, unit, and frequency.
- Route of administration.

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. Note that in this trial, only surgical procedures and procedures related to AD treatment (e.g. phototherapy or bleach baths) should be recorded. The following details will be recorded: procedure, 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.

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 emollient 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 baseline (Week 0). Details regarding prohibited medications and procedures prior to baseline are described in Section 8.3.

From baseline through end of treatment (Week 16):

- TCS of any potency (unless for rescue treatment, see Section 9.5).
- Other topical medications used for the treatment of AD, such as TCI and topical PDE-4 inhibitors.
- Use of UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

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

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

*Receipt of inactive/killed vaccines (e.g. inactive influenza) is allowed, provided it is not administered in the same location as tralokinumab.

Some of the above mentioned prohibited medications can be used provided the indication is rescue treatment for AD. Please refer to Section 9.5 for details regarding rescue treatment.

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication in the eCRF.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMP will be packaged in individually numbered kits.

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

The labelling of IMP will be in accordance with the EU guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary use, Annex 13 (22), local regulations, and trial requirements.

9.8.2 Storage of trial products

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

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

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

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

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

- Damaged autoinjector.

Damaged IMP should be documented in the IRT system and reported as product complaint (see Section 9.10). Damaged IMP may not be used.

Further details on IMP storage (including handling of cases listed above) and home use are provided in a trial product handling manual. The instructions for use given to subjects also provides instruction on IMP storage during home use.

9.8.3 Investigational medicinal product accountability

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

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

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

Subjects will attend site visits on a regular basis (see Section 4). At these site visits, subjects will be provided with IMP to be administered at home until the next site visit. If needed, additional IMP kit may be dispensed to the subject at a scheduled or unscheduled visit at the investigator's discretion. Subjects will be provided with sharps bins to dispose used autoinjectors and will return filled sharps bins to the trial site. Subjects will return trial kit cartons and any unused IMP at the next site visit. Unused IMP returned by subjects to the trial site can be stored at room temperature and must be stored separately from non-allocated IMP.

All unused IMP (including packaging material) supplied by the contract manufacturing organisation (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 the IMP. Accountability must be documented on drug accountability forms and in the IRT system.

Refer to the trial product handling manual for information on returning trial products.

Reporting in eCRF

IMP kit numbers and the date of IMP administration will be recorded in the eCRF. In addition, the site of IMP injection should be given. Subjects will be asked to record these details in a log (paper form) of drug administration for each IMP administration at home, and site staff will record the details in the eCRF.

9.8.4 Treatment compliance

At site visits, site staff will keep the accountability records up to date. Any non-compliance and the reason for it must be recorded in the eCRF.

Where IMP is injected by the subject at the trial site, the site staff will record compliance data in the eCRF.

Where IMP is injected by the subject at home, the subject or subject's caregiver will record the date and injection site for each administration in a log of drug administration; these data will be transcribed into the eCRF by site staff at the next site or telephone visit. If a subject is found to be non-compliant, the investigator should remind the subject of the importance of following the treatment instructions including taking the IMP as prescribed. Any non-compliance and the reason for it must be recorded in the eCRF.

9.8.5 Trial product destruction

Before autoinjector destruction, refer to Section 9.10 for instructions to follow in case of a damaged or defective device. Damaged autoinjector may be returned to the IMP supplier per the instructions in the trial product handling manual.

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

Unused autoinjector returned to the CMO will be destroyed by the CMO according to approved procedures and any local requirements.

9.9 Provision for subject care following trial completion

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

9.10 Reporting product complaints

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

Critical complaints (defined as any defect, issue, or device deficiency that has or potentially could have a serious impact on the subject [e.g. SAE or large particles in the autoinjector]) must be reported to the Quality department via Global Safety within 24 hours of knowledge.

Complaint forms should contain a detailed description of the defect, issue, or device deficiency, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the autoinjector will be reported by the investigator as described in Sections 13.3 and 13.4.

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

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

Fax number: +45 7226 3287

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

10 Discontinuation and withdrawal

10.1 General principles

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

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

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

10.2 Reasons for discontinuation of IMP

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 (e.g. a positive pregnancy test).
- 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:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
    - Confirmed AST or ALT >5×ULN for >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.
- Withdrawal by subject.
- Withdrawal by parent/guardian (applicable for adolescent subjects).
- Lack of efficacy.
- Pregnancy.
- Other (a specification must be provided).

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

10.2.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

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

IMP dosing 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 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.

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 administration of IMP.
- Safety follow-up visit (6 weeks after the last IMP administration).

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

Withdrawal from trial

Subjects who withdraw from the trial for any reason will be asked to attend an early termination visit as soon as possible 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.

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 or subject's parent/guardian and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject or the subject's parent/guardian (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

11 Trial assessments and procedures

11.1 Overview

Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4 and the trial design is described in Section 7.1.

Subjects participating in the trial will be under careful supervision of a dermatologist or allergist. Investigators must be experienced in treating AD and have documented experience or training in use of the assessments required by the protocol and must be a physician, or MD with at least 1 year of dermatology training, or an advanced registered nurse practitioner.

AEs must be assessed by a physician (Section 13.2).

11.2 Assessments performed only at screening and/or baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Age (in years).
- Sex: female, male.
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.
- Race: American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific islander, White, other (requires a specification to be provided).

11.2.2 Medical 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 infection.
- Atopy history:
  - 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 that are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

11.2.3 Physical examination

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

If a clinically significant abnormality is identified during the physical examination at the screening visit, the subject must not be included in the trial. A clinically significant abnormality does not include findings of the skin related to the AD.

Reporting in eCRF

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

Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF.

11.2.4 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 (23). The C-SSRS must be completed at the screening visit to check that exclusion criterion no. 23 does not apply. Further details on the assessment according to the C-SSRS are included in the efficacy assessment & C-SSRS manual.

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 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%).

11.3 Rating of subject's ability to self-administer

The subject's ability to self-administer tralokinumab using the autoinjector will be assessed following each administration after baseline (Week 0). The assessment is based on the defined sequence of use steps:

1) Choose the correct injection area.

2) Remove the cap.

3) Press device down to begin injection.

4) Hold until the injection is complete.

    - Was the dose completed?
        i. Did the yellow plunger cover the viewing window completely when removing the autoinjector from the injection area?
        ii. Was liquid dripping from the tip of the autoinjector when removing it from the injection area?

For the self-administrations performed at the trial site (Weeks 2, 4, and 12), the observer (investigator or delegated trial staff) will assess the subject's ability to self-administer.

For the self-administration performed at home (Weeks 6, 8, 10, and 14), the subjects will assess their ability to self-administer based on the defined sequence of use steps.

Successful subject self-administration for administration at trial site or following dosing at home is defined as completion of each of the above defined sequence of use steps without errors.

It will be recorded in the eCRF whether or not the subject could perform each of the defined sequence of use steps.

If a new autoinjector is assigned due to errors resulting in the subject not receiving any of the intended dose, the assessment of subject ability to self-administer should not be made for the new injection.

11.4 Efficacy assessments

11.4.1 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) (Panel 5). 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. The disease severity assessment score will be recorded in the eCRF.

Panel 5: Investigator's Global Assessment

Score	Disease severity	Standard Investigator's Global Assessment scale	Investigator's Global Assessment 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).

11.4.2 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 (24). 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.

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 6. 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 7. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 7) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 6).

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 6: Calculation of the EASI score

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

Abbreviations: AS = area score; EASI = Eczema Area and Severity Index; SS = severity score.
Modified from (25).

Panel 7: 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.

11.4.3 Patient-reported outcomes

The following patient-reported outcomes will be completed by the subjects at the trial site according to the schedule of trial procedures (Section 4):

- POEM.
- DLQI/CDLQI.
- Eczema-related Weekly Sleep NRS.
- Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS.

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

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

11.4.3.1 Patient-Oriented Eczema Measure

The POEM is a validated questionnaire used to assess disease signs, symptoms, and impact on sleep in atopic eczema patients in both clinical practice and clinical trials (26). The tool consists of 7 items each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). Subject 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.

11.4.3.2 Dermatology Life Quality Index/Children's Dermatology Life Quality Index

All adult subjects will perform DLQI. The DLQI is a validated questionnaire with content specific to those with dermatologic conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment (27). Each item is scored on a 4-point Likert scale (0 = 'not at all⁄not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life.

All adolescent subjects (<18 years at baseline) will perform the CDLQI. The CDLQI questionnaire is designed and validated in subjects with dermatological conditions from 5 to 16 years (28, 29). The CDLQI is available in text and cartoon versions (30-32). The text version will be used in this trial. It consists of 10 items addressing the subject's perception of the impact of their skin disease on various aspects of their QoL over the last week such as

dermatology-related symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and the treatment. Each item is scored on a 4-point Likert scale (0 = 'not at all'; 1 = 'only a little'; 2 = 'quite a lot'; 3 = 'very much'). The item on school time (item 7) has one additional response category 'prevented school', which is also scored '3'. The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor QoL.

11.4.3.3 Eczema-related Weekly Sleep numeric rating scale

Subjects will rate how much their eczema interfered with their sleep during the past week (based on a recall of sleep interference) using an 11-point NRS (Eczema-related Sleep NRS), using whole numbers only, with 0 indicating that it 'did not interfere' and 10 indicating that it 'completely interfered'.

11.4.3.4 Worst Weekly Pruritus numeric rating scale/Adolescent's Pruritus numeric rating scale.

Subjects will assess their worst itch severity over the past week (based on a recall of itch severity) using an 11-point NRS (Worst Weekly Pruritus NRS) with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'.

Subjects <18 years of age at baseline will perform NRS with phrasings tailored to the adolescent subjects, independent of the subject's age during the trial.

11.5 Safety assessments

11.5.1 Height and weight

The subject's height (without shoes) and weight (in indoor clothing and without shoes) will be measured at the visits specified in the schedule of trial procedures (Section 4).

Measurement of height at Week 16 (Visit 10) will be applicable only to subjects <18 years of age at the baseline visit.

11.5.2 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed according to the schedule of trial procedures (Section 4). Vital signs will be measured in a sitting or supine 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 (see Section 9.2).

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 included in the trial (in accordance with exclusion criterion no. 25).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects 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 date and time they were measured will be recorded in the eCRF. If vital signs were not assessed, a reason should be provided. 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.

11.5.3 Laboratory testing

11.5.3.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4).

The evaluations shown in Panel 8 will be performed by the central laboratory.

Panel 8: Clinical laboratory tests

Chemistry	Haematology[3]
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2]	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils Neutrophils/leukocytes Lymphocytes Lymphocytes/leukocytes Monocytes Monocytes/leukocytes Eosinophils Eosinophils/leukocytes Basophils Basophils/leukocytes Thrombocytes
	Serology[4,5]
	Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody
Urinalysis[6]	**Serum pregnancy test[5,7]**
Protein Glucose Ketones Leukocytes Erythrocytes Nitrite	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).
3) The symbol '/' included in the table represents 'a ratio'.
4) 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.
5) Measured at screening only.
6) Urinalysis will only be performed if considered required by the investigator based on dipstick results.
7) Only women of childbearing potential.

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

11.5.3.2 Investigator evaluation of laboratory samples

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, appropriate action, as judged by the investigator, must be taken.

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

Abnormal liver function tests of concurrent measurements of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×ULN and bilirubin (BILI) ≥2× ULN should be reported as an SAE (see Section 13.4 for reporting of SAEs).

If a screening laboratory result is abnormal and clinically significant, it will be at the investigator's discretion to decide if the subject should be included in the trial.

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

Tests performed at the trial site

Urine samples will be tested with a dipstick according to the schedule of trial procedures (Section 4). It will be at the investigators discretion to decide whether a urine sample should be sent to the central laboratory for further analysis.

Women of childbearing potential will have a urine pregnancy test performed at the trial site 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 be recorded in the eCRF.

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

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

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

11.5.4 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 nAb. Details of the analytical method used will be described in a bioanalytical report.

11.6 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.

11.7 Photography

Adult subjects (age 18 years and above at the baseline visit) will be asked to participate in a photography component of the trial which involves digital photography assessments to investigate disease progression over time.

Participation in this photography component requires that the subject provides additional 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 photograph(s) was taken; if not, a reason should be provided.

All sites participating in photography will receive all photo equipment from a central photography vendor. Instructions for photography will be provided to the sites in a photography manual. Photography standards and procedures are provided to the trial sites by the central photography vendor.

The trial sites must ensure that the photographs contain no other subject identifier than the specific subject ID number. The photographs will be transmitted electronically to the photography vendor using a secure file transfer protocol.

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

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

11.8 End-of-trial

End-of-treatment form

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

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

- Date of last IMP administration.
- Did the subject permanently discontinue IMP before Week 14? If yes, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

End-of-trial form

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

The following data will be collected:

- Date of last contact.
- Did the subject attend the safety follow-up visit? If not, primary reason for not attending safety follow-up visit must be recorded (AE, death, lost to follow-up, withdrawal by subject, withdrawal by parent/guardian, lack of efficacy, pregnancy, or other). If 'AE' or 'other' is selected, a specification must be provided.

11.9 Estimate of total blood volume collected

Blood samples will be drawn for chemistry, haematology, serology, PK, ADA and pregnancy test (if applicable). For adult subjects, the total volume of blood to be drawn is approximately 78 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value; however, the total volume of blood drawn will be less than that taken during a blood donation (approximately 500 mL).

For adolescents, the total amount of blood drawn during the trial will be approximately 57 mL. The largest volume of blood drawn at any visit during the trial will be 22 mL, drawn at the screening visit. The maximum possible blood volume drawn at one visit is less than 1% of the total blood volume, and the maximum possible blood volume drawn within 4 weeks is less than 3% of the total blood volume, as recommended for the age group 0–18 years (33).

11.10 Storage of biological samples

The blood and urine samples for laboratory testing (chemistry, haematology, serology, PK, ADA and urinalysis) are only taken to ensure and monitor subject safety during this trial and will only be stored until the analysis is completed by the central laboratory.

PK samples will be retained for as long as the quality of the material permits evaluation, but for no longer than 6 months after completion of the CTR.

Samples for ADA and nAb evaluation will be retained for as long as the quality of the material permits evaluation but for no longer than 10 years after completion of the CTR.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This is an open-label trial to evaluate efficacy and safety of tralokinumab administered by an autoinjector for the treatment of moderate-to-severe AD. Adolescent subjects (age 12-17 years) are included in the trial per FDA request. The trial also facilitates improved convenience for patients and to reflect the intended use of tralokinumab in a real-world setting. The autoinjector allows a single injection of 300 mg of tralokinumab.

The selected dose of 300 mg Q2W administered SC is based on the dosing regimen used in the tralokinumab phase 3 development program to demonstrate its efficacy and safety in adult subjects with moderate-to-severe AD. All subjects will receive an initial loading dose of 600 mg tralokinumab. The administration of the 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 have demonstrated not to exceed the serum tralokinumab concentrations at steady state for the 300 mg Q2W.

The 300 mg Q2W dose is considered safe in the adolescent population and is currently being investigated as part of the ongoing adolescent trial (LP0162-1334). Adolescent subjects with asthma have been evaluated as part of a phase 1 trial in 20 adolescents (trial CD-RI-CAT-354-1054) and 2 phase 3 trials (trials D2210C00007 and D2210C00008) including 58 adolescents. Overall, the PK parameters including maximum serum concentration (C_{max}), time of maximum serum concentration (T_{max}), and absolute clearance (CL/F) were largely similar to those observed in the adult population. Tralokinumab was well-tolerated, no SAEs were reported, and no ADA were detected after dosing. Further, the data from this phase 1 trial in adolescents with asthma, along with all available adult PK and pharmacodynamic (PD) data, were combined in a population PKPD model. This model supported the finding that tralokinumab PK is dose-linear and stationary with time, and that overall exposure and variability are similar between weight-based and non-weight-based dosing at the dose level of 300 mg Q2W.

Based on interaction with FDA, the main objectives of this trial are to assess the efficacy and safety of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD. As defined in ‘other objectives’, this trial also assesses whether subjects can successfully self-administer the IMP.

It is crucial that the investigator/site staff thoroughly explains to the subject that self-administration is mandatory in this trial (after Visit 2) and that both investigator/site staff and subject feel confident that the subject can live up to the expectation in inclusion criterion number 4 ('Subjects must be able and willing to self-administer tralokinumab using an autoinjector') throughout the trial. Another important inclusion criterion for entry into the trial is a diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria for AD) (18) at screening and a history of AD for at least one 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.

12.2 Appropriateness of assessments

The clinical efficacy of tralokinumab treatment will be assessed using IGA and EASI. The efficacy assessments are similar to the 3 pivotal trials with tralokinumab (ECZTRA 1, 2 and 3). IGA is a key instrument used in clinical trials to rate the severity of the subject's global AD. EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (24). The clinical efficacy of tralokinumab treatment will also be assessed using PROs related to disease symptoms, quality of life, general health status, and itch. POEM is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (26), and is recommended by the Harmonising Outcome Measures for Eczema for measuring patient-reported symptoms in eczema trials (25). DLQI/CDLQI is a validated and widely used questionnaire designed to measure the quality of life of dermatological patients (27).

Safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, vital signs, and clinical laboratory measurements. Data on ADA will be collected and the potential for immunogenicity will be evaluated. The blood samples for determination of presence or absence of ADA will be analysed 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.

At the baseline visit (Week 0, Visit 2) during the administration of the initial loading dose, subjects will be trained on the usage of the autoinjector by investigator or delegated trial staff. On the same day, subjects will have a choice to either self-administer the second injection under observation by qualified trial staff or subjects will receive both the injections by the investigator/trial delegate. For the rest of the treatment period, all subjects will self-administer a dose of 300 mg tralokinumab Q2W (2 mL). The subject's ability to self-administer the

injection tralokinumab at the trial site (at Week 4 under observation by a qualified trial staff) and at home (at Week 8) will be assessed based on the defined sequence of use steps in Section 11.3.

13 Adverse events

13.1 Definition and classification of adverse events

Adverse events (AEs) and serious adverse events (SAEs) are defined in Appendix 1.

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

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject has signed the informed consent form until subject's completion of the trial (Sections 7.3 and 10.3).

AEs must be assessed by a physician.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, e.g.: "How have you felt since I saw you last?" 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 11.5.1 and 11.5.3 for principles for data entry in the eCRF.

13.3 Reporting of adverse events

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

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

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

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

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

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

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 on the (paper) SAE form immediately, without undue delay and no later than 24 hours of obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP, device, or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

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

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

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

Global Safety at LEO Pharma

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

Fax number: +45 7226 3287

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

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

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

SAEs occurring after the completion of the clinical trial (as defined in Section 7.3) should not be routinely sought or recorded. However, such events should be reported immediately without undue delay and no later than 24 hours of obtaining knowledge to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO Pharma reporting responsibilities

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

- The tralokinumab investigator's brochure, Section 7.2 edition 19 and subsequent updates must be used.

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

The IRB(s) 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 LEO Pharma (34, 35) and which are unexpected (serious and unexpected suspected adverse reactions [IND safety report]) are subject to expedited reporting to regulatory authorities and IRB(s). Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

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

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

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

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The AEs listed in Panel 9 are considered adverse events of special interest (AESIs) in this trial and will require additional details to be recorded in the eCRF. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Injection site reactions could be reported at any time after dosing. If one or more signs or symptoms of an injection site reaction are spontaneously reported by the subject, a single AE will be recorded as part of the general AE reporting, with reported term either ‘injection site reaction’ or reflecting the most dominant sign/symptom. Additional information on all objective and subjective symptoms listed in Panel 10 should be provided on the AESI form associated with the AE. Severity and start and stop date for each sign/symptom should be recorded on the AESI form. If the severity of a sign/symptom changes, multiple start/stop dates and associated severities can be recorded on the AESI form to reflect the development over time.

Panel 9: Adverse events of special interest

Adverse event of special interest	Additional data to be included in the eCRF (if available)
Injection site reactions	See Panel 10 for details.
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 treatment assignment, 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.

Panel 10: Adverse events of special interest – injection site reaction

Adverse event of special interest	**Additional data to be collected**	
Injection site reactions	Objective signs	Erythema • Largest diameter (mm) Swelling/Oedema • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Bruising/Haematoma • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Induration • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Other • Description • Largest diameter (mm) • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity
	Subjective symptoms	Itch • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Pain/Burning/Stinging • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity Other • Description • Effect on activity o Does not interfere with activity o Interferes with activity o Prevents daily activity

13.6.2 Medication error

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

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

Accidental overdose or underdose where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement. An overdose is defined as a subject receiving a quantity of IMP which is in excess of that specified in this protocol.

Medication errors where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement. For recording of treatment non-compliance where no clinical consequence occurred or could have occurred, see Section 9.8.4.

Medication error must be recorded on the AE form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Section 13.4).

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.

13.6.3 Misuse or abuse

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

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

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

Misuse and abuse must be recorded on the AE form in the eCRF. In addition, any clinical consequence of misuse or abuse must be recorded as separate AE on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.4 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared with screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4. AD is a fluctuating disease with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by AD should be reported as an AE.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP for 2 weeks or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome.

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

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.*" (36) .

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.

The investigator must immediately inform LEO Pharma – by contacting the clinical project manager or medical expert via the CRA – 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 130 subjects, of which approximately 30 subjects will be adolescents, will be assigned to treatment. This is considered sufficient to allow an evaluation of the efficacy of tralokinumab.

Assuming IGA 0/1 and EASI75 response rates of 19% and 29% at Week 16, respectively, a sample size of 130 subjects will give a standard error of 3.44% and 3.98%, and thus a half-width for the 95% CIs of 6.74% and 7.80% for each of the primary endpoints.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects who receive IMP will be included in the full analysis set (FAS) and the safety analysis set. Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a subject who has received IMP from the FAS, a justification addressing ICH E9 will be given.

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

14.3 Statistical analysis

All results will be presented for the total cohort of subjects as well as for adults and adolescents, separately.

14.3.1 Disposition of subjects

The reasons for permanent discontinuation of IMP and for withdrawal from trial will be presented for all subjects assigned to treatment. Furthermore, the number of subjects not trained in self-injection at baseline and the reasons for this will be presented for all subjects assigned to treatment.

In addition, plots of the cumulative proportions of subjects who discontinue IMP or withdraw from trial over time will be presented overall and by reason.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics, baseline disease characteristics, and other baseline characteristics will be presented for all subjects assigned to treatment.

Demographics include age, sex, race, and ethnicity. Baseline disease severity characteristics include IGA and EASI scores, BSA, Eczema-related Weekly Sleep NRS, and Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS. Other baseline characteristics include vital signs (including 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

Exposure to treatment will be presented for the safety analysis set as days of exposure in total. Days of exposure will be calculated as the number of days from the date of the first IMP dose to the date of the end of treatment visit, or – if the end of treatment visit is missing – to the date of permanent discontinuation of IMP.

Treatment compliance will be presented for the safety analysis set. Adherence to treatment regimen will be recorded in the eCRF. The log of drug administration may be used as source.

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 for the indication and either of the following:

- ATC2 code H02 or D07.
- ATC4 code D11AH
- Preferred name delgocitinib, crisaborole, methotrexate, ciclosporin, azathioprine, mycophenolate-mofetil, mycophenolate-sodium, mycophenolate-acid, ruxolitinib or dupilumab.

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.

14.3.5 Testing strategy

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

CIs for binary endpoints will be based on a normal approximation.

14.3.6 Estimand strategy

The primary endpoints will be analysed using a composite estimand strategy to handle the occurrence of two intercurrent events considered to affect the interpretation of the estimates of the endpoints:

- **Initiation of rescue treatment:** This event occurs when a subject initiates rescue treatment. This event can occur at the discretion of the investigator as described in Section 5.4. The timing of the event is defined as the date of initiation of the rescue treatment recorded in the eCRF.
- **Permanent discontinuation of IMP:** This event occurs when a subject is permanently withdrawn from treatment or the trial as described in Section 10.2.1. This event can occur at the subject's own initiative, at the discretion of the investigator or the sponsor as described in Section 10.2.1 or if the subject is lost to follow-up. The timing of the event is defined as the date of last IMP administration recorded in the eCRF.

The composite estimand evaluates the response rate without initiation of rescue treatment or permanent discontinuation of IMP. For subjects who received rescue treatment prior to Week 16 or who have permanently discontinued IMP prior to Week 16, observed data after the intercurrent events will be considered non-response, reflecting an assumption that initiation of rescue treatment or permanent discontinuation of IMP indicates either failure of the treatment to achieve response or that a possible positive response is not attributable to the treatment alone. Missing data for subjects who do not attend the Week 16 visit and where rescue medication has not been used, nor the subject has permanently discontinued IMP, will be imputed as non-response.

Binary efficacy endpoints will be analysed using the same estimand strategy as for the primary endpoints. The endpoints on successful self-injection will be analysed using the principles of estimands in ICH E9(R1) targeting the estimand attributes (population, variable, intercurrent event, and population-level summary) (37), while continuous efficacy endpoints will be presented as observed.

14.3.7 Analysis of primary endpoints

The primary endpoints (IGA 0/1 at Week 16 and EASI75 at Week 16) will be analysed using the composite estimand strategy (see Section 14.3.6) to handle the occurrence of intercurrent events (initiation of rescue medication or permanent discontinuation of IMP). Subjects with missing data will be imputed as non-responders.

Number and percentage of subjects achieving response will be presented together with the corresponding 95% CI.

The analyses will be based on the FAS.

14.3.8 Analysis of secondary endpoints

The secondary endpoint, number of treatment-emergent AEs from baseline up to Week 16, and the analysis of this is covered in Section 14.3.12.

The secondary endpoint, presence of treatment-emergent ADA from baseline to Week 16, and the analysis of this is covered in Section 14.3.14.

14.3.9 Analysis of other endpoints related to subject self-administration

The number and percentage of subjects with successful IMP self-administration when observed in clinic at Week 4 will be presented together with the corresponding 95% CI. The analysis will be based on the population of subjects who have been trained on the usage of the autoinjector by the investigator or delegated trial staff, have tried self-injection at least once, and have not permanently discontinued IMP prior to Week 4. Subjects with missing data at Week 4 will be excluded from the analysis.

The successful IMP self-administration when administered at home at Week 8, will be analysed in the same way as for the endpoint at Week 4 with the modification that subjects must not have permanently discontinued IMP prior to Week 8.

All data captured to assess subject's ability to self-administer tralokinumab using the autoinjector will be presented descriptively as observed by week.

14.3.10 Analysis of other binary endpoints

Other binary efficacy endpoints (EASI50 and EASI90 at Week 16, reduction in Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS of at least 4 from baseline to Week 16, and reduction in POEM, and DLQI/CDLQI of at least 4 from baseline to Week 16 in adults and at least 6 from baseline to Week 16 in adolescents) will be analysed using the composite estimand strategy in the same way as for the primary endpoints.

14.3.11 Analysis of other continuous endpoints and patient-reported outcomes

Other continuous efficacy endpoints (change in Eczema-related Weekly Sleep NRS, Worst Weekly Pruritus NRS/Adolescent's Pruritis NRS, DLQI/CDLQI and POEM from baseline to Week 16 and percentage change in EASI from baseline to Week 16) will be presented as observed, thus irrespectively of intercurrent events, while all PROs will be summarised by visit using descriptive statistics.

The DLQI will be analysed and presented for adult subjects only, and the CDLQI score will be analysed and presented for adolescent subjects only.

Analysis and data presentation will be based on the FAS.

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 preferred terms and primary system organ class (SOC).

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

An overall summary of the number (percentage) of AEs, the rate of AEs (number of AEs per 100 patient-years of observation time), and the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, premature discontinuations from IMP and/or withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs will be presented.

The number (percentage) of AEs, rate of AEs, and number of subjects with each type of AEs will be tabulated.

The severity and causal relationship to IMP or device for each type of AE will be tabulated. In addition, for the AESI injection site reactions, a separate severity grading derived from the data collected according to Panel 10 will be tabulated.

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.

SAEs and AESIs will be evaluated separately. A narrative for each SAE will be given.

AEs leading to withdrawal from trial or permanent discontinuation of IMP and AESIs 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 site visit will be summarised 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 Week 16 will be summarised as mean, SD, median, minimum, and maximum values.

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

14.3.13 Pharmacokinetic analysis

All the PK samples in the trial are trough samples. The trough concentration (C_{trough}) will be listed 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.

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

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

14.3.15 Interim analysis

An interim CTR including only adult subjects will be considered to support submission for marketing approval of tralokinumab.

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. Continuous data will be summarised using the mean, median, SD, minimum, and maximum values.

Any changes from the statistical analyses planned in this clinical trial protocol will be described and justified in a protocol amendment, the statistical analysis plan, and/or in the CTR, 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 (38).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.5.3.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

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

- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the 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.

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

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

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

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

*Hospitalisation for administrative, trial-related or social purpose do not constitute an AE and should therefore not be reported as AE or SAE.

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

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

Definition of adverse events of special interest

An AESI (serious or non-serious) is an event type of scientific and medical concerns specific to the product or development program, for which additional monitoring may be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

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 not follow a known pattern of response to the IMP.

Outcome

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

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

LEO Pharma definitions versus CDISC definitions

Note that as per the above definition, LEO Pharma uses 'recovered/resolved' only if an event has actually stopped. According to the 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 (39) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (40).
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines (41).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authority (FDA) must be notified of/approve the clinical trial as required.

Any documents that the IRB 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. These documents must be reviewed and approved by the IRB before the trial is initiated.

Any amendments to the protocol must be approved by/receive favourable opinion from relevant regulatory authorities and IRBs, 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the local IRB of SAEs or other significant safety findings as required by IRB 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 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 and subjects' legally authorised representative(s) 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 (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 (ICF). The subject's decision not to participate or to withdraw will be respected, even if consent is given by the subject's legally authorised representative(s).

Subjects and their legally authorised representative(s) (if applicable) will be re-consented to the most current version of the ICF(s) during their participation in the trial, if applicable. A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative (if applicable).

Adolescent subjects must give their written assent as appropriate and according to national laws and regulation. The subject's signed and dated informed assent to participate in the clinical trial must be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP (Section 4.8) and all applicable laws and regulations. The adolescent subject will be re-consented to the most current version of the ICF(s) during the trial, if applicable and in accordance with national laws or regulations. A copy of the ICF(s) must be provided to the adolescent subject in accordance with national laws or regulations.

Subjects who become of legal age during the trial will be consented to the most current version of the ICF for adult subjects, if required by national laws or regulations. Subsequently, these subjects will be re-consented to the most current version of the ICF(s) for adult subjects during the trial, 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.

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 Pharma will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

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

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

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

Processing of personal data

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

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

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

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

Subjects (or their legally acceptable representative) 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. Safety evaluations must be signed and dated by a physician. While certain AE assessments can be delegated to investigators with other qualifications, the diagnosis, seriousness, and causality of the AEs must be assessed by a physician. Clinical assessments must be signed and dated by the 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 involving open-label treatment with tralokinumab for 16 weeks.
- Other relevant medical information.

Trial monitoring
The trial will be monitored on an ongoing basis to verify that (i) the rights and well-being of the trial subjects is protected; (ii) the reported trial data are accurate, complete, and verifiable from source documents; and (iii) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and all applicable regulatory requirement(s).

The monitoring will be performed in a systematic, prioritised, risk-based approach, and as a combination of on-site, remote, and centralised monitoring. For more details, please refer to the trial-specific monitoring guideline and data review plan.

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

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

Sponsor audits, IRB 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. 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.

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

To ensure consistent data capture with respect to investigator assessment of efficacy (IGA and EASI), all investigators will receive training.

Data quality review meetings will be held during the trial to ensure that improvements in data collection can be made and that mistakes are prevented on an ongoing basis. During monitoring, the CRA will verify that investigators work according to the protocol.

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

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

An electronic PRO (ePRO) solution will be used to capture patient-reported data from questionnaires completed at the trial site. 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.

Recalled PROs (Eczema-related Weekly Sleep NRS, Worst Weekly Pruritus NRS/Adolescent's Pruritus NRS) will be recorded for the period of 7 days before each site visit.

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 version 18-Dec-2020 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 1.7 and SDTM implementation guide version 3.3 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 (41). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.
In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (e.g. in case of an inspection from regulatory authorities).

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

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

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

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

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 at leopharmatrials.com in accordance with LEO Pharma's Position on Public Access to Clinical Trial Information no later than 6 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu, and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

Publications

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

A primary publication including the primary results of the trial (i.e. the results of the primary endpoint) may be submitted for publication within 12 months of database lock. In such case, LEO Pharma would be responsible for this publication. All authors (trial responsible employees and/or applicable investigators and advisors) must fulfil the criteria for authorship from the International Committee of Medical Journal Editors (ICMJE).

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

LEO Pharma may give researchers outside LEO Pharma access to anonymised data from this trial for further research according to the principles outlined by the European Federation of Pharmaceutical Industries and Associations (EFPIA) (42). In that case, the researchers are obliged to attempt publication of the results obtained from their analyses.

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

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 and update this information, should any relevant change occur, during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 3H: Trial and trial site closure

Premature termination of trial or trial site

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB 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.

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 (18)

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 (21)

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: Short version of eligibility criteria

Inclusion criteria	
No.	**Short version**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2	Age 12 years and above.
3	Body weight at screening of 30.0 kg or more.
4	Subject able and willing to self-administer tralokinumab in an autoinjector.
5	Diagnosis of AD (as defined by Hanifin and Rajka (1980) criteria for AD).
6	History of AD for 1 year or more.
7	History of TCS and/or TCI treatment failure (due to inadequate response or intolerance) or subjects for whom these topical AD treatments are medically inadvisable.
8	AD involvement of 10% (or more) body surface area at screening and baseline (Visit 3).
9	An EASI score of 12 (or more) at screening and 16 (or more) at baseline.
10	An IGA score of 3 or more at screening and at baseline, equivalent to moderate-to-severe AD.
11	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline.
12	Female subjects of childbearing potential must use a highly effective form of birth control throughout the trial and for at least 16 weeks after last administration of IMP.
Exclusion criteria	
No.	**Short version**
1	Current participation in any other interventional clinical trial.
2	Previous randomisation in tralokinumab trials.
3	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.

4	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD.
5	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 4 weeks prior to baseline.
6	Treatment with immunomodulatory medications, systemic corticosteroids, or bleach baths within 4 weeks prior to baseline.
7	Treatment with the topical medications TCS, TCI, PDE-4 or JAK inhibitor within 2 weeks prior to baseline.
8	Receipt of live attenuated vaccines within 30 days prior to the date of baseline and during the trial including the safety follow-up period.
9	Receipt of any marketed or investigational biologic agent (e.g. cell-depleting agents or dupilumab) within 6 months prior to baseline or until cell counts return to normal, whichever is longer.
10	Subjects who have received treatment with any non-marketed drug substance within 5 half-lives prior to baseline.
11	Receipt of blood products within 4 weeks prior to screening.
12	Major surgery within 8 weeks prior to screening, or planned in-patient surgery or hospitalisation during the trial period.
13	Known or suspected allergy or reaction to any component of the IMP.
14	History of any active skin infection within 1 week prior to baseline.
15	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to baseline.
16	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.
17	History of anaphylaxis following any biological therapy.
18	History of immune complex disease.
19	History of cancer.
20	Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
21	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications.

22	History of subject or subject's legally authorised representative(s) of chronic alcohol/drug abuse or any condition associated with poor compliance, as judged by the investigator.
23	History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or on the C-SSRS).
24	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.
25	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.
26	ALT or AST level 2.0 times the upper limit of normal or more at screening.
27	Positive HBsAg, HBsAb, HBcAb serology at screening. Subjects with positive HBsAb may be eligible provided they have negative HBsAg and HBcAb.
28	Positive hepatitis C virus antibody (anti-HCV) serology at screening.
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	Female subjects who are pregnant or lactating.
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.

Appendix 7: Contact list

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

Sponsor

LEO Pharma A/S (referred to as 'LEO Pharma' or 'the sponsor' in this clinical trial protocol) is the sponsor of the clinical trial:

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

Coordinating investigator

Dr. PPD , MD,
Clinical Professor, Dermatology, PPD
Director, Clinical Research, PPD

PPD

Appendix 8: COVID-19 pandemic contingency plan

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

If on-site visits are not possible due to local authority-issued preventive measures or subjects are unwilling to come to the trial site or are quarantined at home, the affected site will postpone screening and baseline visits of subjects until on-site visits can be conducted. Furthermore, it is a requirement that all subjects attend the first 3 dosing visits (Weeks 0, 2, and 4, i.e. Visits 2, 3, and 4) at the clinic according to protocol to ensure the 30 min. post-dose observation time for the 3 dosing visits. The primary endpoint of the trial, efficacy of tralokinumab administered by an autoinjector, will be assessed at the clinic at Week 16. If attending the first 3 dosing visits is not possible, then the subject cannot self-administer IMP at home during the remainder of the trial.

For subjects already assigned to treatment, Week 12 (Visit 8) can be done remotely via phone or video. At phone/video visits, no investigator assessments of efficacy will be done, but the following data will be collected remotely (according to the schedule of trial procedures in Section 4):

- Use of emollients
- AE reporting.
- Concomitant medication and concurrent procedures.
- PROs (DLQI/CDLQI, POEM, Eczema-related Sleep NRS, Worst Weekly Pruritus NRS/Adolescents Pruritus NRS). The subjects will receive a link to complete the PROs in a web browser.
- Urine pregnancy test. Women of childbearing potential will receive 1 extra urine pregnancy test at the baseline visit to keep at home in case on-site visit becomes impossible during the trial. The subject will perform the test at home and inform the investigator about the result via phone before self-administering the IMP.

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

It will be at the discretion of the investigator to decide whether clinical laboratory samples are considered necessary to ensure subject safety in periods when on-site visits are not possible.

To ensure availability of IMP, the trial sites will dispense additional IMP if considered relevant (i.e. if local authority issued preventive measures are to be expected at the given trial site). This will allow subjects to continue treatment with IMP although they are not able to go to the trial site. If a subject will not be able to attend on-site visits due to the pandemic before running out of IMP, the trial site will ensure shipping of IMP to the subject's home.

If a subject is tested positive for COVID-19, the investigator will evaluate whether this is an AE that contraindicates further dosing, in which case the subject will permanently discontinue IMP as described in Section 10.2.

Appendix 9: Protocol amendment history

Amendment 1 (25-Oct-2021)

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

Overall rationale for the amendment

The main reason for this amendment is to change the primary objective to evaluate the efficacy of tralokinumab administered by an autoinjector, when used to treat subjects with moderate-to-severe AD. Consequently, endpoints have been rearranged. In addition, assessment of PK and ADA levels have been included in this trial.

Additional changes included are also presented in the table below. Changes have either been summarised (written in plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Section no. and title	Description of change	Brief rationale
1 Protocol synopsis	Title of trial An open-label, single-arm, phase 3 trial to evaluate the **efficacy and safety** ~~safe and effective use of an autoinjector for administration~~ of tralokinumab **administered by an autoinjector** in subjects with moderate-to-severe atopic dermatitis.	To align with the primary and secondary objectives of the trial.
1 Protocol synopsis	Short title of trial **Efficacy and safety** ~~Safe and effective use~~ of tralokinumab **administered by an** autoinjector in adults and adolescents with moderate-to-severe atopic dermatitis.	To align with the primary and secondary objectives of the trial.
1 Protocol synopsis, 6 Trial objectives and endpoints	Primary objective **To evaluate the efficacy of tralokinumab administered by an autoinjector when used to treat subjects with moderate-to-severe AD.** ~~To evaluate the safe and effective use of the autoinjector for administration of tralokinumab.~~ Primary endpoint**s** • **IGA score of 0 (clear) or 1 (almost clear) at Week 16.** • **EASI75 at Week 16.**	To reflect the change in the primary objective of the trial.

Section no. and title	Description of change	Brief rationale
	~~Successful investigational medicinal product (IMP) self-administration when observed at the clinic at Week 4.~~ ~~Key secondary endpoint~~ ~~Successful IMP self-administration when administered at home at Week 8.~~	
1 Protocol synopsis, 6 Trial objectives and endpoints	Secondary objective To evaluate the safety and tolerability of tralokinumab **administered by** ~~in~~ an autoinjector when used to treat moderate-to-severe atopic dermatitis (AD). ~~and administered with the autoinjector~~. Secondary endpoint • Number of treatment-emergent adverse events (AEs) from baseline ~~up~~ to Week 16. • **Presence of treatment-emergent ADA from baseline to Week 16.**	To reflect that ADA has been added as a safety endpoint.
1 Protocol synopsis, 7.3 end-of-trial definition	Final collection of data for the primary endpoint **Week 16.** ~~Week 4~~	To reflect the change in primary endpoints.
1 Protocol synopsis, 7.1 Overall trial design	Trial design has been updated for clarification.	To reflect the change in primary and secondary objectives of the trial. To clarify the subject's option to self-administer the second injection under observation by qualified trial staff. To clarify that subjects will not transfer to the long-term extension trial 'ECZTEND', due to updated timelines of the trial.
1 Protocol synopsis	Main assessments	To reflect the change in primary endpoints and addition of ADA as a safety endpoint.

Section no. and title	Description of change	Brief rationale
	Assessment related to primary ~~and key secondary~~ endpoints: • **IGA score.** • **EASI.** • ~~Rating of subject's ability to self-administer at trial site.~~ • ~~Rating of subject's ability to self-administer following dosing at home.~~ Assessment related to secondary endpoint: AEs, vital signs, laboratory tests **and ADA.**	
1 Protocol synopsis	Statistical methods Primary endpoint: **The primary endpoints (IGA 0/1 at Week 16 and EASI75 at Week 16) will be analysed using the composite estimand strategy to handle the occurrence of intercurrent events. Subjects with missing data will be imputed as non-responders.** Number and percentage of subjects **achieving response will be presented together with the corresponding 95% CI.** Details on autoinjector self-administration and key secondary endpoints have been deleted from this section.	To reflect the change in primary endpoints.
4 Schedule of trial procedures	Panel 2 Schedule of trial procedures Background treatment – initiation **and continuation** of emollients (X has been added in this row from week 0 to Early termination [if applicable] visit).	To clarify that subjects should continue emollient use throughout the trial period.
4 Schedule of trial procedures	Investigator assessments of safety Added PK blood sampling on Weeks 4, 12, 16, and 20. Added ADA blood sampling on Weeks 0, 4, 16, and 20.	To align with the newly added assessments in the trial.
6 Trial objectives and endpoints	Other objective **To assess the real-life patient handling experience with the use of tralokinumab administered with an autoinjector in patients with moderate-to-severe AD.** Other endpoints	To reflect the rearrangement of trial objectives.

Section no. and title	Description of change	Brief rationale
	• **Successful IMP self-administration when observed at the clinic at Week 4** • **Successful IMP self-administration when administered at home at Week 8.** • ~~IGA score of 0 (clear) or 1 (almost clear) at Week 16.~~ • ~~EASI75 at Week 16.~~	
7.3 End-of-trial definition	~~Subjects entering the long-term extension trial (ECZTEND) will also be considered as trial completers~~	This is no longer applicable as subjects will not transfer to the ECZTEND trial.
9.2 Administration of investigational medicinal product	Text updated regarding the administration of initial loading dose at baseline.	To clarify that, at baseline, subjects can self-administer the second injection under observation by qualified trial staff.
9.8.3 Investigational medicinal product accountability	Subjects will return trial kit cartons and any unused IMP at **the** ~~each~~ **next** site visit.	Clarification.
11.1 Overview, 13.2 Collection of adverse event reports	AEs must be assessed by **a physician**. ~~medically qualified personnel~~	To align with latest protocol template.
11.5.4 Anti-drug antibody measurements	This section is added for ADA blood sampling and assessment.	Addition of ADA blood sampling in trial procedure.
11.6 Pharmacokinetic assessments	This section is added for PK blood sampling and assessment.	Addition of PK blood sampling in trial procedure.
11.9 Estimate of total blood volume collected	For adult subjects, the total volume of blood to be drawn is approximately **78** ~~68~~ mL. For adolescents, the total amount of blood drawn during the trial will be approximately **57** ~~47~~ mL. The largest volume of blood drawn at any visit during the trial will be **22** ~~12~~ mL, drawn at the screening visit.	

Section no. and title	Description of change	Brief rationale
11.10 Storage of biological samples	**PK samples will be retained for as long as the quality of the material permits evaluation, but for no longer than 6 months after completion of the CTR.** **Samples for ADA and nAb evaluation will be retained for as long as the quality of the material permits evaluation but for no longer than 10 years after completion of the CTR.**	For information on storage of PK and ADA samples.
12.2 Appropriateness of assessments	This section has been updated with information on PK and ADA blood sampling analyses.	To include relevant information on PK and ADA analyses.
14 Statistical methods	Sample size calculation has been updated. Statistical analyses and estimand strategy for primary endpoint has been updated. Key secondary endpoint section has been removed. Details regarding analyses of PK and ADA have been added. Possibility of interim analysis has been added.	To align with rearrangement of endpoints.
Appendix 8 COVID-19 pandemic contingency plan	For subjects already assigned to treatment, **Week 12 (Visit 8)** ~~Week 8 (Visit 12)~~ can be done remotely via phone or video.	Correction.
Throughout	Minor editorial and template related revisions.	Minor, therefore not summarised.