Cover Page

Official title: Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis ECZTRA 6 (ECZema TRAlokinumab trial no. 6)
LEO Pharma number: LP0162-1334
NCT number: NCT03526861
Date: 06-Feb-2020

~~CONFIDENTIAL~~

Updated Clinical Trial Protocol

LP0162-1334

Tralokinumab monotherapy for adolescent subjects with moderate-to-severe atopic dermatitis
ECZTRA 6 (ECZema TRAlokinumab trial no. 6)

Phase 3 – efficacy and safety trial

A randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial to evaluate the efficacy, safety, and tolerability of tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy.

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

LEO Pharma A/S	**Trial ID:**	**LP0162-1334**
	Date:	**06-Feb-2020**
	EudraCT no	**2017-005143-33**
	Version:	**7.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

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

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[Name], RN, PhD
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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:

Professor [Name], 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

Document	Protocol version	Date	Type of protocol amendment
Amendment 6 (substantial)	7.0	06-Feb-2020	Global
Amendment 5 (non-substantial)	6.0	19-Jun-2019	Global
Amendment 4 (non-substantial)	5.0	11-Feb-2019	Global
Amendment 3 (non-substantial)	4.0	21-Nov-2018	Global
Amendment 2 (substantial)	3.0	12-Jun-2018	Global
Amendment 1 (non-substantial)	2.0	01-May-2018	Country-specific (Japan)
Original protocol	1.0	20-Mar-2018	NA

A protocol amendment summary of changes table for the previous amendment is provided in Appendix 10.

Amendment 6 (06-Feb-2020)

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 (65).

Overall rationale for the amendment

The main reasons for this amendment are:

- To introduce the possibility for eligible subjects in selected countries of the present LP0162-1334 trial to continue in a long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]). Eligible subjects from the present trial will be allowed to enter ECZTEND after completion of the treatment period and up to 26 weeks from their last investigational medicinal

product (IMP) injection in the present trial to their first IMP injection in ECZTEND (baseline).

- To fulfil the commitments in the paediatric investigation plan (PIP) and the paediatric study plan (PSP), unblinding at Week 52 of the present trial is introduced, as production of a pharmacokinetic (PK) model in adolescents will inform tralokinumab dose selection for paediatric subjects.

Additional changes included in the amendment are also presented in the table below. The table below presents the changes in each section. 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 name	Description of change	Brief rationale
1 Protocol synopsis 3 Schematic of trial design 7.1 Trial design	The following text has been added (bold) to Section 7.1 Trial design and summarised in Section 1 Protocol synopsis and Section 3 Schematic of trial design: Safety follow-up period (Week 52 to Week 66) After completion of the treatment periods or premature discontinuation of IMP, all subjects will complete an off-treatment follow-up period for the assessment of safety, PK, and immunogenicity (i.e. ADA), **except subjects who transfer to ECZTEND before Week 66 (see below).** During follow-up, subjects will be allowed to receive standard of AD care (excluding biologic therapies) at the investigator's discretion, if needed. **Long-term extension trial (LP0162-1337, ECZTEND)** **Eligible subjects from selected countries may be invited to enter a long-term extension trial conducted under a separate protocol (LP0162-1337, ECZTEND). Subjects who transfer to ECZTEND, must have had their last visit in the treatment period (Week 52) under the current protocol (LP0162-1334). Subjects may enter ECZTEND up to 26 weeks from their last IMP injection in the present trial (Week 50) to their first IMP injection in ECZTEND (baseline). Subjects may therefore enter ECZTEND (baseline) without completing the safety follow up visit (16 weeks after their last IMP injection) in the present trial, and those subjects will have their safety follow-up visit in ECZTEND.**	Introduced to allow for subjects in the present trial (LP0162-1334) to continue in ECZTEND, and to clarify when the subjects can transfer to ECZTEND.

Section no. and name	Description of change	Brief rationale
Panel 3 Schedule of trial procedures: maintenance treatment period Panel 4 Schedule of trial procedures: open-label tralokinumab treatment Panel 5 Schedule of trial procedures: follow-up including early termination	Added to footnote 1 of the panels: An end of treatment form must be completed in the eCRF for all randomised subjects (see Section 11.9 for further details). All subjects will have a safety follow-up 16 weeks after last injection of IMP (see Panel 5). This is considered the end of trial visit. **For subjects who enrol in the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]), the end of trial visit will be the last visit in the present trial before transfer to ECZTEND (between Week 52 and Week 66); subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND.**	To clarify in the trial procedures which visit is considered the end of trial visit for subjects who transfer to ECZTEND.
1 Protocol synopsis 7.1 Overall trial design 9.3.1 Blinding	The following text has been added in Section 9.3.1 Blinding and summarised in Section 1 Protocol synopsis and Section 7.1 Overall trial design: **Analysis of data per last subject's Week 52 visit** **To fulfil the commitments in the PIP and the PSP, an analysis of trial data up to and including visit 29 (Week 52) will be performed and will require unblinding of data. To perform this analysis, an analysis group consisting of Clinical Pharmacologists, Medical Experts, Safety Advisors, Statisticians, Statistical Programmers and Medical Writers will be unblinded to individual subject treatment allocation following database lock for the 52-week data. All staff involved in the conduct of the trial will remain blinded to treatment allocation for the entire duration of the trial. This principle will be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the analysis.**	To clarify that an analysis group, not including trial staff or investigator involved in the trial conduct, will be unblinded after all subjects have completed the treatment period and before all subjects have completed the safety follow-up period.
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 final safety follow-up visit at Week 66. **Subjects who enter the long-term extension trial (LP0162-1337, ECZTEND) after completion of the end of treatment visit (Week 52) will also be considered as trial completers.**	To clarify who will be considered trial completers.

Section no. and name	Description of change	Brief rationale
9.7 Prohibited medication and procedures	The text in the section about prohibited medication and procedures has been optimised.	To clarify the section of prohibited medications in the protocol in relation to rescue medications.
9.9 Provision for subject care following trial completion	In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice. **Subjects from selected countries who qualify for the long-term extension trial (LP0162-1337, ECZTEND) may be offered participation (see Section 7.1).**	To reflect the opportunity to continue in ECZTEND.
11.9 End of trial	Added bullet to end of trial form: **Has the subject been transferred to the open-label ECZTEND trial (LP0162-1337)? If yes, which was the last visit (including phone call) the subject attended in this trial?**	To clarify how it is to be documented if subjects transfer to ECZTEND.
13.2 Collection of adverse event reports	AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last IMP injection). **For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the subject's final visit in the LP0162-1334 trial should be reported in the LP0162-1334 trial. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND.**	To clarify the reporting of (S)AEs during transfer from trial LP0162-1334 to ECTZEND.
13.4.1 Investigator reporting responsibilities	**For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any SAE(s) with onset before the final visit in the present trial, must be reported in the LP0162-1334 trial eCRF, including any follow-up data requested by Global Safety.** SAEs occurring after the completion of the **present** clinical trial (i.e., after the last safety follow up visit) should not be routinely sought or collected. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them. **For**	To clarify the reporting of SAEs during transfer from trial LP0162-1334 to ECTZEND.

Section no. and name	Description of change	Brief rationale
	subjects who transfer to ECZTEND, SAEs occurring after the last visit in the present trial and up to entering ECZTEND (defined as baseline), must be recorded as medical history in ECZTEND.	
13.7 Follow-up for final outcome of adverse events	Added to this section: **For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.**	To provide clarification on how to handle SAEs where the final outcome is recovering/resolving at the end of the trial.
14.3.10 Analysis of data per last subject's Week 52 visit	Addition of a section describing the analysis of data per last subject's Week 52 visit: **To fulfil the commitments in the PIP and the PSP, the trial will be unblinded once all randomised subjects have completed the Week 52 visit. At the cut-off date of the last subject's Week 52 visit, all efficacy, safety, PK, and ADA data for the treatment periods have been collected and all endpoints used to test pre-specified hypotheses are final. Thus, no adjustments in significance level of the primary and secondary efficacy analyses are relevant. The CTR will include all data from all randomised subjects from the initial, maintenance, and open-label treatment periods and all available data from the safety follow up period as per data cut-off date.**	To clarify that data will be unblinded (to an analysis group), analysed and reported when all subjects have completed the treatment period and before all subjects have completed the safety follow-up period.
Appendix 3E: Registration, reporting and publication policy	Results of this clinical trial will be posted on the corporate website of LEO Pharma in accordance with LEO Pharma's Position on Public Access to Clinical Trial Information no later than ~~12 months~~ **6 months** after trial completion.	To clarify that the reporting of the trial results will be 6 months from trial completion as this trial includes adolescent subjects.
Appendix 3I Trial and site closure	When **the trial has been completed**~~, randomisation code has been broken~~, the investigators will receive information about the treatment allocation for the subjects randomised at their	To clarify when the investigator will be unblinded in this trial.

Section no. and name	Description of change	Brief rationale
	respective sites and will be asked to record this in the subject's medical record.	
Appendix 8 Country-specific requirements: Japan	Updated with the changes made in Section 13.4.1 and Section 13.7 (see above).	To reflect the changes made to the protocol.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore not summarised.

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List of abbreviations

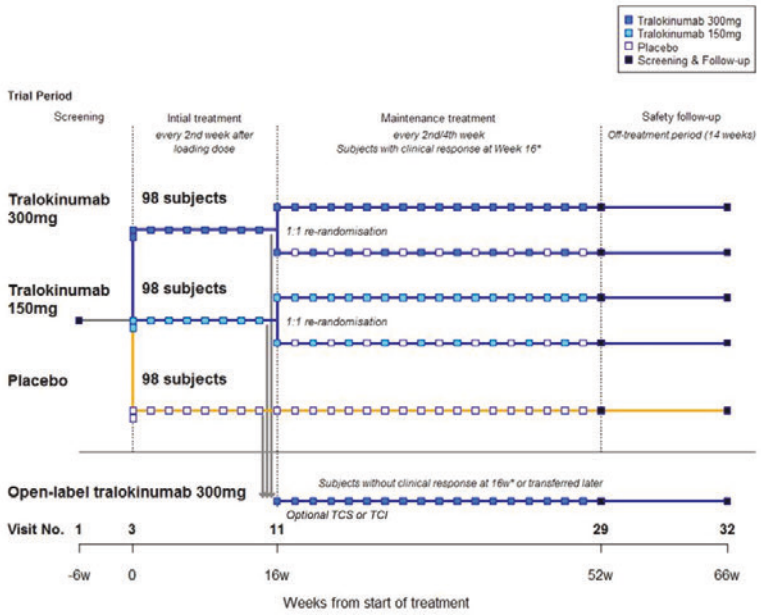
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
CCL	C-C motif chemokine ligand
CDISC	Clinical Data Interchange Standards Consortium
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CMO	contract manufacturing organisation
CONSORT	consolidated standards of reporting trials
CRA	clinical research associate
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
C_{trough}	trough concentration
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
EASI50	at least 50% reduction in EASI score
EASI75	at least 75% reduction in EASI score
EASI90	at least 90% reduction in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eSAE section	electronic section for the reporting of SAEs in the eCRF
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale

HCP	healthcare professional
HDL	high density lipoprotein
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
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG4	immunoglobulin G4
IL	interleukin
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
LDL	low density lipoprotein
LEO	LEO Pharma A/S
nAB	neutralising antibodies
NRS	numeric rating scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PD	pharmacodynamics
PDCO	(EMA's) Paediatric Committee
PDE-4	phosphodiesterase 4
PIP	Paediatric Investigational Plan
PK	pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PRO	patient-reported outcome
PSP	Paediatric Study Plan
PUVA	psoralen and ultraviolet A therapy
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
S. aureus	*Staphylococcus aureus*
SAE	serious adverse event
SC	subcutaneous

SCORAD	Scoring Atopic Dermatitis
SCORAD50	at least 50% reduction in SCORAD score
SDTM	study data tabulation model
TCI	topical calcineurin inhibitor(s)
TCS	topical corticosteroid(s)
TEWL	transepidermal water loss
Th2	T-helper-2
ULN	upper limit of normal (range)
UV	ultraviolet
WHO	World Health Organization

1 Protocol synopsis

Trial ID EudraCT no. NCT no. IND no. FDA centre	LP0162-1334 2017-005143-33 NCT03526861 123797 CDER	
Title of trial	A randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial to evaluate the efficacy, safety, and tolerability of tralokinumab monotherapy in adolescent subjects with moderate-to-severe atopic dermatitis (AD) who are candidates for systemic therapy – ECZTRA 6 (ECZema TRAlokinumab trial no. 6).	
Short title of trial	Tralokinumab monotherapy for adolescent subjects with moderate-to-severe AD.	
Main objectives and endpoints	Primary objective	Primary endpoints
	To evaluate the efficacy of subcutaneous (SC) administration of tralokinumab compared with placebo in treating adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) at Week 16.[1] • At least 75% reduction in Eczema Area and Severity Index (EASI75) at Week 16.[2]
	Secondary objectives	Secondary endpoints
	To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and health-related quality of life compared with placebo.	*Severity and extent of AD* • Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16.[3] *Itch* • Reduction of Adolescent Pruritus numeric rating scale (NRS) (weekly average) of at least 4 from baseline to Week 16.[4] *Health-related quality of life* • Change in Children's Dermatology Life Quality Index (CDLQI) score from baseline to Week 16.[5]
	To investigate the safety, immunogenicity, and tolerability of SC administration of tralokinumab compared with placebo when used to treat adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• Number of adverse events. • Presence of anti-drug antibodies (yes/no).

	1. 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). 2. The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI is a composite index with scores ranging from 0 to 72, with higher values indicating more severe and/or more extensive condition. 3. The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms. The maximum total score is 103, with higher values indicating more severe disease. 4. The Adolescent Pruritus NRS is used by subjects to assess their worst itch over the past 24 hours using an 11-point NRS with 0 indicating 'no itch' and 10 indicating 'worst itch possible'. 5. The CDLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on various aspects of their quality of life 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'). Item 7 (on school time) has one additional response category 'prevented school', which is also scored '3'. The total score of the CDLQI is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life.
Final collection of data for the primary endpoint	Week 16
Trial design	

	*Clinical response (IGA = 0, 1; or EASI75) achieved without use of rescue treatment from Week 2 to Week 16. **Abbreviations:** EASI75, at least 75% reduction in Eczema Area and Severity Index; IGA, Investigator's Global Assessment; No, number; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; w, week. The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16), a maintenance treatment period of 36 weeks (Weeks 16 to 52), and a 14-week safety follow-up period for the assessment of safety (Weeks 52 to 66). Subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND. *Initial treatment period* Subjects will be randomised in a 1:1:1 ratio to receive multiple SC doses of tralokinumab 300 mg, tralokinumab 150 mg, or placebo every 2 weeks (Q2W) following a loading dose (double dose compared to randomised dose) on Day 0 (baseline). Randomisation will be stratified by region and baseline disease severity (according to IGA). *Maintenance treatment period* Subjects with a clinical response* at Week 16 (achieved without use of rescue treatment from Week 2 to Week 16) will continue into maintenance treatment which may last until Week 52 (with last dose of investigational medicinal product [IMP] given at Week 50). The treatment during the maintenance treatment period will depend on the regimen received in the initial treatment period as described below. *Clinical response is defined as IGA of 0 or 1 or EASI75. Subjects randomised to tralokinumab in the initial treatment period will be re-randomised 1:1 (at the randomised dose) in the maintenance treatment period. Re-randomisation will be stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Subjects initially randomised to tralokinumab 300 mg will either receive: • Tralokinumab 300 mg Q2W. • Tralokinumab 300 mg every 4 weeks (Q4W): alternating dose administrations of tralokinumab 300 mg or placebo. Subjects initially randomised to tralokinumab 150 mg will either receive: • Tralokinumab 150 mg Q2W. • Tralokinumab 150 mg Q4W: alternating dose administrations of tralokinumab 150 mg or placebo. Subjects randomised to placebo in the initial treatment period will receive placebo Q2W in the maintenance treatment period. *Transfer to open-label treatment* Subjects without clinical response at Week 16 and subjects who have received rescue treatment from Week 2 to Week 16 will be transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of topical

	corticosteroids [TCS] or topical calcineurin inhibitors [TCI]) at Week 16, if considered appropriate by the investigator. During the maintenance treatment period, subjects may be transferred from maintenance treatment to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS or TCI) if they meet any of the criteria listed below, and if considered appropriate by the investigator: • Subjects with IGA=0 at Week 16: IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). • Subjects with IGA=1 at Week 16: IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). • Subjects with IGA >1 at Week 16: not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits). • Subjects who receive rescue treatment (from Week 16 or later). Transfer to open-label treatment may occur at any visit from Week 16 while the subject is in the maintenance treatment period. *Safety follow-up period* After completion of the treatment periods (at Week 52) or discontinuation of IMP, all subjects will enter a 14-week safety follow-up period for assessment of safety, pharmakokinetics (PK), and immunogenicity, except subjects who transfer to ECZTEND before Week 66 (see below). During follow-up, subjects will be allowed to receive standard of AD care (excluding biologic therapies) at the investigator's discretion, if needed. *Long-term extension trial (LP0162-1337, ECZTEND)* Eligible subjects from selected countries may be invited to enter a long-term extension trial conducted under a separate protocol (LP0162-1337, ECZTEND). Subjects who transfer to ECZTEND, must have had their last visit in the treatment period (Week 52) under the current protocol (LP0162-1334). Subjects may enter ECZTEND up to 26 weeks from their last IMP injection in the present trial (Week 50) to their first IMP injection in ECZTEND (baseline). Subjects may therefore enter ECZTEND (baseline) without completing the safety follow-up visit (16 weeks after their last IMP injection) in the present trial, and those subjects will have their safety follow-up visit in ECZTEND. *Background treatment* All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and will continue this treatment throughout the trial (including safety follow-up).
Main assessments	Investigator efficacy assessments: • IGA. • EASI. • SCORAD. Patient-reported efficacy assessments:

	• Adolescent Pruritus NRS. • CDLQI. • Patient-Oriented Eczema Measure (POEM). Safety assessments: • Adverse events. • Laboratory testing. • Anti-drug antibodies. Pharmacokinetics
Main criteria for inclusion	• Age 12 to 17. • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. • History of AD for ≥1 year. • History of topical corticosteroid (TCS; Europe: Class 3 or higher; US: Class 4 or lower) and/or topical calcineurin inhibitor (TCI) treatment failure or subjects for whom these topical AD treatments are medically inadvisable. • AD involvement of ≥10% body surface area at screening and baseline. • Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.
Main criteria for exclusion	• Active dermatologic conditions that may confound the diagnosis of AD. • Use of tanning beds or phototherapy within 6 weeks prior to randomisation. • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation. • Treatment with TCS, TCI, or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation. • Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-immunoglobulin E) including dupilumab or investigational biologic agents. • Active skin infection within 1 week prior to randomisation. • Clinically significant infection within 4 weeks prior to randomisation. • A helminth parasitic infection within 6 months prior to the date informed consent is obtained. • Tuberculosis requiring treatment within the 12 months prior to screening. • Known primary immunodeficiency disorder.
Investigational medicinal products	<u>Tralokinumab</u> • Tralokinumab is a human recombinant monoclonal antibody of the immunoglobulin G4 (IgG4) subclass that specifically binds to human interleukin (IL) 13 and blocks interaction with the IL-13 receptors. • Active substance: tralokinumab. • Dosage form: solution (in accessorised pre-filled syringe, 1.0 mL fill volume).

	• Concentration: 150 mg/mL. • Dose: 600 mg or 300 mg initial loading dose, then 300 mg or 150 mg every second week. • Method of administration: SC administration. <u>Placebo</u> • Placebo contains the same excipients in the same concentration only lacking tralokinumab.
Duration of treatment	Approximately 52 weeks.
Number of subjects	A total of 294 subjects will be randomised 1:1:1 to tralokinumab 300 mg, tralokinumab 150 mg, or placebo.
Number and distribution of trial sites	Approximately 80 sites in Europe, US, Canada, Australia, and Japan.
Statistical methods	<u>Primary endpoints</u> The difference in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA 3 or 4). Subjects with missing data and subjects who receive rescue treatment from the Week 2 to Week 16 visit will be considered as non-responders in the analysis. <u>Secondary endpoints</u> The change from baseline to Week 16 in SCORAD will be analysed using a repeated measurements model on the post baseline responses up to Week 16. Reduction of Adolescent Pruritus NRS weekly average of at least 4 from baseline to Week 16 is a binary endpoint, and as such it will be analysed as described for the primary endpoints. Change from baseline to Week 16 in CDLQI will be analysed the same way as change in SCORAD. <u>Testing strategy:</u> The overall type I error rate in the tests of primary and secondary endpoints will be protected by a combination of hierarchical testing and Holm-Bonferroni multiplicity adjustment embedded in a graphical approach. Within each dose level, the 2 co-primary endpoints, IGA 0/1 and EASI75 at Week 16, will be tested hierarchically, followed by a Holm-Bonferroni adjustment of the testing of the 3 secondary endpoints. The 2 co-primary endpoints for the tralokinumab 300 mg dose will first be tested hierarchically at an overall 5% significance level, after which the significance level will be split evenly between testing of the same primary

	endpoints for the tralokinumab 150 mg dose and a Holm-Bonferroni testing procedure for the secondary endpoints for the tralokinumab 300 mg dose. If all the hypotheses of no difference to placebo for the tralokinumab 300 mg dose are rejected, then the 2.5% significance level will be passed on to the testing of all the endpoints for the tralokinumab 150 mg dose. Similarly, if the hypotheses of no difference to placebo for all the endpoints of the tralokinumab 150 mg dose are rejected the 2.5% significance level will be passed on to the testing of the secondary endpoints of the tralokinumab 300 mg dose. To fulfil the commitments in the paediatric investigation plan (PIP) and the paediatric study plan (PSP), the trial will be unblinded to an analysis group once all randomised subjects have completed the Week 52 visit and available data will be analysed and reported.
Signatory investigator	Professor [Name], MD, [Contact] [Contact]
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

2 Trial identification

EudraCT number: 2017-005143-33

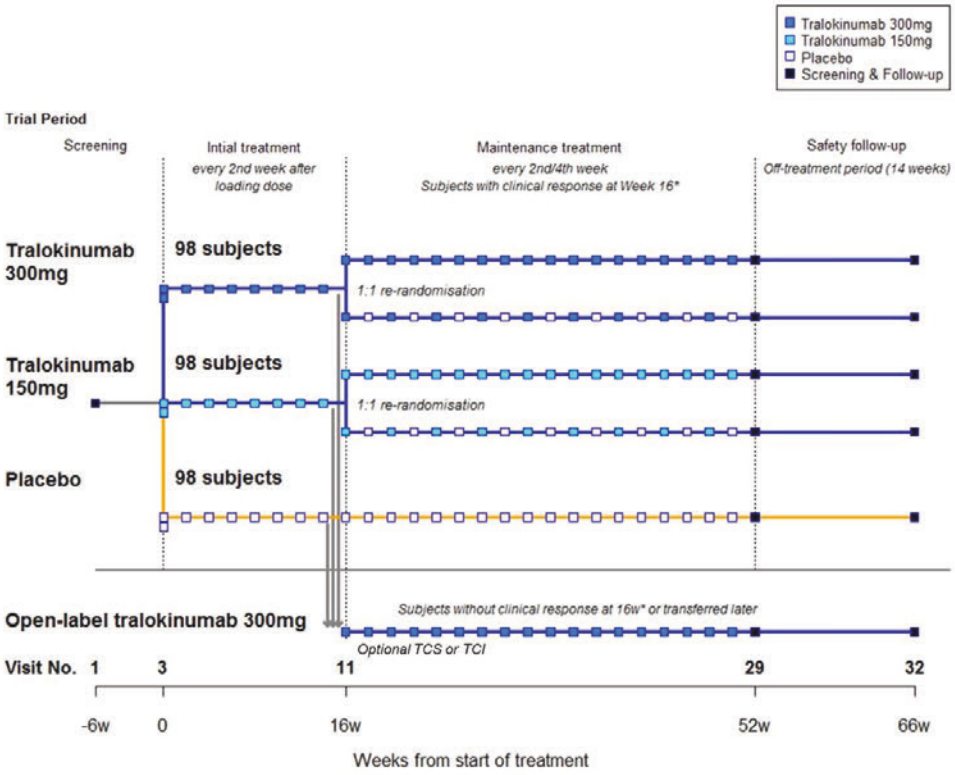
NCT number: NCT03526861

IND number: 123797

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

3 Schematic of trial design

Panel 1: Trial design



*Subjects with clinical response at Week 16 (achieved without use of rescue treatment from Week 2 to Week 16) will enter the maintenance treatment period. Clinical response is defined as subjects achieving IGA of 0 (clear) or 1 (almost clear) or EASI75. Subjects without a clinical response at Week 16 and subjects who use rescue treatment from Week 2 to Week 16 will be transferred to open-label treatment (300 mg tralokinumab every 2 weeks with optional use of TCS and/or TCI) at Week 16, if considered appropriate by the investigator.
During the maintenance treatment period, subjects will be transferred from maintenance treatment to open-label treatment if they lose their clinical response (based on pre-defined criteria) or if they receive rescue treatment (from Week 16 or later).
Note: Eligible subjects from selected countries may enter a long-term extention trial (LP0162-1337, ECZTEND) after the last visit in the treatment period (Week 52) and up to 26 weeks from their last IMP injection in the present trial (Week 50) to their first IMP injection in ECZTEND (baseline). Subjects may therefore enter ECZTEND (baseline) without completing the safety follow up visit (16 weeks after their last IMP injection) in the present trial, and those subjects will have their safety follow-up visit in ECZTEND.
Abbreviations: EASI75, at least 75% reduction in Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IMP, investigational medicinal product; No, number; TCI, topical calcineurin inhibitor, TCS, topical corticosteroid; w, week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures: screening and initial treatment period

	Screening[1]		Initial treatment period									Nominal Week 16 visit[2] (if applicable)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**16**	
Day	**-42**	**-14**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**112**	
Visit window (days)[3]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Trial population and eligibility													
Informed consent[4]	X												Appendix 3B
Subject eligibility	X		X										8.2, 8.3
Treatments and randomisation													
Initiation of emollients (background treatment)[5]		X											9.4
Concomitant medication (including rescue treatment)/concurrent procedures	X		X	X	X	X	X	X	X	X	X	X	9.5, 9.6
Randomisation			X								X[6]		9.3
IMP administration and compliance			X[7]	X[7]	X[7]	X	X	X	X	X	X		9.2
Investigator assessments at screening/baseline only													
C-SSRS	X												11.2.4
Demographics (age) and BSA involvement	X		X										11.2.1, 11.2.3
Other demographics	X												11.2.1
Medical history	X												11.2.2
Investigator assessments of efficacy													
IGA	X		X	X	X	X	X	X	X	X	X	X	11.3.1

Panel 2: Schedule of trial procedures: screening and initial treatment period (continued)

	Screening[1]		Initial treatment period									Nominal Week 16 visit[2] (if applicable)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**16**	
Day	**-42**	**-14**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**112**	
Visit window (days)[3]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Investigator assessments of efficacy (continued)													
EASI	X		X	X	X	X	X	X	X	X	X	X	11.3.2
SCORAD	X		X	X	X	X	X	X	X	X	X	X	11.3.3
Patient-reported outcomes													
eDiary[8] training		X											11.3.4
eDiary[8]		<- ========== ->										X	11.3.4.1 to 11.3.4.4
CDLQI			X	X	X	X	X		X		X	X	11.3.4.5
POEM			X	X	X	X	X		X		X	X	11.3.4.6
Adolescent PGI-S (past week recall)			X	X	X	X	X		X		X		11.3.4.7
PGI-C					X		X		X		X		11.3.4.8
HADS			X		X		X		X		X		11.3.4.9
Investigator assessments of safety													
Vital signs	X		X[7]	X[7]	X[7]		X				X[7]		11.4.1
Physical examination	X		X				X				X		11.4.2
ECG	X		X								X		11.4.3
Serum pregnancy test	X												11.4.4
Urine pregnancy test			X		X		X		X		X		11.4.4

Panel 2: Schedule of trial procedures: screening and initial treatment period (continued)

	Screening[1]		Initial treatment period									Nominal Week 16 visit[2] (if applicable)	References (protocol section)
Visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**11x**	
Week	**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**16**	
Day	**-42**	**-14**	**0**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**112**	**112**	
Visit window (days)[3]	**±3**	**-3**	**NA**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Investigator assessments of safety (continued)													
Hepatitis B, C and HIV	X												11.4.4
Chemistry, haematology, and IgE[9]	X[10]		X				X				X		11.4.4
Urinalysis	X		X				X				X		11.4.4
ADA			X		X						X		11.4.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	13
Additional assessments													
Pharmacokinetics					X						X		11.5
Blood biomarkers			X								X		11.6
Skin swab (skin microbiology)			X								X		11.7.1
Skin tape stripping (selected trial sites)			X				X				X		11.7.2.1
Transepidermal water loss (selected trial sites)			X								X		11.7.2.2
Height and body weight	X		X								X		11.7.3

1. For subjects who do not require a wash-out, visits 1 and 2 will be combined and screening will be reduced to 2 weeks. Hence, these subjects will only attend visit 2 (Week -2) which will include all assessments shown under Week -6. The screening period has a maximum duration of 6 weeks.
2. Subjects who permanently discontinue IMP prior to Week 16 will attend the primary endpoint visit (nominal Week 16 visit [visit 11x]).
3. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline (visit 3).

4. 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.
5. All subjects must use an emollient twice daily (or more as needed) for at least 14 days before randomisation and must continue this treatment throughout the trial.
6. Subjects who achieve a clinical response (IGA 0/1 or EASI75) at Week 16 (achieved without use of rescue treatment from Week 2 to Week 16) will be re-randomised into the maintenance period and then receive the first injections of maintenance treatment. Subjects who do not achieve clinical response at Week 16 and subjects who have received rescue treatment from Week 2 to Week 16 will be transferred to open-label tralokinumab treatment (300 mg every 2 weeks with optional use of TCS and/or TCI, see Panel 4), if considered appropriate by the investigator. The first injections of open-label treatment will be administered at Week 16.
7. For the first 3 IMP dosing visits in the initial treatment period and for non-responders transferring to open-label tralokinumab treatment at Week 16, subjects will be monitored prior to and after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2).
8. The eDiary consists of Eczema-related Sleep NRS, Adolescent Pruritus NRS, and Adolescent PGI-S (today recall). The eDiary will be completed daily from Week -2 to Week 52, albeit the Adolescent PGI-S (today recall) will only be completed daily from Week -2 to Week 16.
9. Subject age (in years) must be recorded at visits where chemistry, haematology, and serology are sampled.
10. IgE not assessed at screening.

Abbreviations: ADA, anti-drug antibodies; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; C-SSRS, Columbia Suicide Severity Rating Scale; EASI, Eczema Area and Severity Index; EASI75, at least 75% reduction in EASI score; ECG, electrocardiogram; eDiary, electronic diary; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NA, not applicable; NRS, numeric rating scale; PGI-C: Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

Panel 3: Schedule of trial procedures: maintenance treatment period

	Maintenance treatment period																		References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29[1]**	
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	
Visit window (days)[2]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Treatments																			
IMP administration and compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		9.2
Concomitant medication (including rescue treatment)/ concurrent procedures	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	9.5, 9.6
Investigator assessments of efficacy																			
IGA	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	11.3.1
EASI	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	11.3.2
SCORAD		X		X		X		X		X		X		X		X		X	11.3.3
Patient-reported outcomes																			
eDiary[4]	<- ========== ->																		11.3.4.1 to 11.3.4.4
CDLQI		X				X				X				X				X	11.3.4.5
POEM		X				X				X				X				X	11.3.4.6
HADS		X				X				X				X				X	11.3.4.9
Investigator assessments of safety																			
Vital signs						X												X	11.4.1
Physical examination						X												X	11.4.2
ECG						X												X	11.4.3
Urine pregnancy test		X		X		X		X		X		X		X		X		X	11.4.4

Panel 3: Schedule of trial procedures: maintenance treatment period (continued)

	Maintenance treatment period																		References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29[1]**	
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	
Visit window (days)[2]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Investigator assessments of safety (continued)																			
Chemistry, haematology, and IgE[5]						X												X	11.4.4
Urinalysis						X												X	11.4.4
ADA						X												X	11.4.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Additional assessments																			
Pharmacokinetics						X												X	11.5
Height and weight																		X	11.7.3

1. An end of treatment form must be completed in the eCRF for all randomised subjects (see Section 11.9 for further details). All subjects will have a safety follow-up 16 weeks after last injection of IMP (see Panel 5). This is considered the end of trial visit. For subjects who enrol in the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]), the end of trial visit will be the last visit in the present trial before transfer to ECZTEND (between Week 52 and Week 66); subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND.
2. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.
3. Subjects who meet any of the following criteria will be transferred to open-label treatment (tralokinumab 300 mg every 2 weeks with optional use of TCS and/or TCI [see Panel 4 for assessments during open-label treatment]):
   - Subjects with IGA=0 at Week 16: IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).
   - Subjects with IGA=1 at Week 16: IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).
   - Subjects with IGA >1 at Week 16: not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).
   - Subjects who receive rescue treatment (from Week 16 or later).

The first injections of open-label treatment will be given at the visit in the maintenance period where the subject meets these criteria, if considered appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. When the first injections of open-label treatment are given, subjects will be monitored prior to and after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2).

4. The eDiary for the maintenance treatment period consists of Eczema-related Sleep NRS and Adolescent Pruritus NRS and will be completed daily to Week 52.
5. Subject age (in years) must be recorded at visits where chemistry, haematology, and serology are sampled.

Abbreviations: ADA, anti-drug antibodies; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75, at least 75% reduction in EASI score; ECG, electrocardiogram; eCRF, electronic case report form; eDiary, electronic diary; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid.

Panel 4: Schedule of trial procedures: open-label tralokinumab treatment

	Open-label tralokinumab treatment																		References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29[1]**	
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	
Visit window (days)[2]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Treatments																			
IMP administration and compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		9.2
Concomitant medication (including rescue treatment)/ concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	9.5, 9.6
Investigator assessments of efficacy																			
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.3.1
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	11.3.2
SCORAD		X		X		X		X		X		X		X		X		X	11.3.3
Patient-reported outcomes																			
eDiary[3]	<- ========== ->																		11.3.4.1 to 11.3.4.4
CDLQI		X				X				X				X				X	11.3.4.5
POEM		X				X				X				X				X	11.3.4.6
HADS		X				X				X				X				X	11.3.4.9
Investigator assessments of safety																			
Vital signs	X[4]	X[4]	X[4]	X[4]	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X	11.4.1
Physical examination						X												X	11.4.2
ECG						X												X	11.4.3
Urine pregnancy test		X		X		X		X		X		X		X		X		X	11.4.4

Panel 4: Schedule of trial procedures: open-label tralokinumab treatment (continued)

	Open-label tralokinumab treatment																		References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29[1]**	
Week	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	
Visit window (days)[2]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Investigator assessments of safety (continued)																			
Chemistry, haematology, and IgE[5]						X												X	11.4.4
Urinalysis						X												X	11.4.4
ADA						X												X	11.4.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	13
Additional assessments																			
Pharmacokinetics						X												X	11.5
Height and weight																		X	11.7.3

1. An end of treatment form and end of trial form must be completed in the eCRF for all randomised subjects (see Section 11.9 for further details). All subjects will have a safety follow-up 16 weeks after last injection of IMP (see Panel 5). This is considered the end of trial visit. For subjects who enrol in the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]), the end of trial visit will be the last visit in the present trial before transfer to ECZTEND (between Week 52 and Week 66); subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND.
2. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.
3. The eDiary for subjects in open-label treatment consists of Eczema-related Sleep NRS and Adolescent Pruritus NRS. Will be completed daily to Week 52.
4. For the first 3 IMP dosing visits with open-label tralokinumab treatment, subjects will be monitored prior to and after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2).
5. Subject age (in years) must be recorded at visits where chemistry, haematology, and serology are sampled.

Abbreviations: ADA, anti-drug antibodies; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eCRF, electronic case report form; eDiary, electronic diary; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

Panel 5: Schedule of trial procedures: follow-up including early termination

	Safety follow-up period			Unscheduled visit (if applicable)[3]	Early termination (if applicable)[4]	References (protocol section)
Visit	**30[1]**	**31[1]**	**32[2]**			
Week	**56**	**60**	**66**			
Visit window (days)[5]	**±3**	**±3**	**±3**			
Treatments						
Concomitant medication (including rescue treatment)/ concurrent procedures	X	X	X	X	X	9.5, 9.6
Investigator assessments of efficacy						
IGA				X	X	11.3.1
EASI				X	X	11.3.2
SCORAD				X	X	11.3.3
Patient-reported outcomes						
eDiary[6]				X	X	11.3.4.1 to 11.3.4.4
CDLQI				X	X	11.3.4.5
POEM				X	X	11.3.4.6
Adolescent PGI-S (past week recall)				X	X	11.3.4.7
PGI-C				X	X	11.3.4.8
HADS				X	X	11.3.4.9
Investigator assessments of safety						
Vital signs			X	X	X	11.4.1
Physical examination			X	X	X	11.4.2
ECG			X	X	X	11.4.3
Urine pregnancy test			X	X	X	11.4.4
Chemistry, haematology, and IgE[7]			X	X	X	11.4.4
Urinalysis			X	X	X	11.4.4
ADA			X	X	X	11.4.5
Adverse events	X	X	X	X	X	13
Additional assessments						
Pharmacokinetics			X	X	X	11.5
Blood biomarkers				X	X[8]	11.6
Skin swab (skin microbiology)				X	X[8]	11.7.1
Skin tape stripping (selected trial sites)				X	X[8]	11.7.2.1
Transepidermal water loss (selected trial sites)				X	X[8]	11.7.2.2
Height and weight				X	X	11.7.3

1. The visit will be conducted as a telephone visit. If the subject experiences a worsening of their AD during follow-up, a visit at the clinic may be conducted as an unscheduled visit at the investigator's discretion.
2. An end of treatment form and end of trial form must be completed in the eCRF for all randomised subjects. See Section 11.9 for further details. All subjects will have a safety follow-up 16 weeks after last injection of IMP. This is considered the end of trial visit. For subjects who enrol in the long-term extension trial (conducted under a separate protocol [LP0162-1337, ECZTEND]), the end of trial visit will be the last visit in the present trial before transfer to ECZTEND (between Week 52 and Week 66); subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND.
3. Assessments and procedures to be performed at an unscheduled visit are left at the investigator's discretion.
4. Subjects who permanently discontinue IMP or withdraw from the trial will be followed up as described in Section 10. All subjects will have a final safety follow-up visit 16 weeks after last dose of IMP.
5. If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to randomisation/baseline.
6. The eDiary consists of Eczema-related Sleep NRS, Adolescent Pruritus NRS, and Adolescent PGI-S (today recall). The eDiary will be completed daily from Week -2 to Week 52, albeit the Adolescent PGI-S (today recall) will only be completed daily from Week -2 to Week 16.
7. Subject age (in years) must be recorded at visits where chemistry, haematology, and serology are sampled.
8. Only to be performed if the subject discontinues IMP prior to Week 16.

Abbreviations: ADA, anti-drug antibodies; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; eCRF, electronic case report form; eDiary, electronic diary; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; IgE, immunoglobulin E; IMP, investigational medicinal product; NRS, numeric rating scale; PGI-C: Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

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. In its severe form, AD is characterised by widespread skin lesions, intractable itch, as well as increased susceptibility to bacterial, viral, and fungal skin infections (1-4). AD rash distribution varies with patient age (5). In infants <2 years, AD usually involves the scalp, face, neck, and extensor surfaces of the extremities. In children from 2 years of age to puberty, the flexural surfaces of the extremities, head and neck, and wrists and ankles are more often involved. In adolescents and adults, eczematous changes are typically seen on the head and neck, flexural surfaces of the extremities, and hands and feet. AD is associated with a substantial patient burden that typically includes poor quality of life (QoL) and sleep disturbance (6).

AD is characterised by an activated T-helper-2 (Th2) pathway with increased skin expression of key Th2 cytokines including interleukin (IL) 13 (7, 8). The expression of IL-13 is increased in lesional skin compared to non-lesional skin, and the proportion of CD4+ and CD8+ cells expressing IL-13 is upregulated in AD patients compared to individuals without AD (7, 9).

IL-13 acts on keratinocytes to release C-C motif chemokine ligand (CCL) 22 and recruit more IL-13 expressing Th2 cells, decrease differentiation, and contribute to decreased barrier function (10). 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 and induces itch (11, 12). Indeed, itch is a key issue in AD, which drives significant mechanical damage to the skin and further facilitates allergen and pathogen entry.

These effects together drive and exacerbate the disease phenotype. A review of the available preclinical literature from mouse and human ex vivo models suggests IL-13 as a, if not the, central mediator of the AD skin phenotype. Indeed, there is evidence that blocking the IL-4 receptor (which is part of the receptor complex that also binds IL-13) with the monoclonal antibody dupilumab leads to clinical improvement in subjects with AD (13).

Even if the clinical manifestations of AD in children and adults are different with regard to the anatomical distribution, IL-13 is an important player in the pathogenesis of AD in both children and adults. Counts of IL-13-positive CD4+ lymphocytes in the peripheral blood of children with AD are significantly correlated with AD severity (14). Also, increased levels of IL-4 and IL-13 together with eosinophils in blood correlate with disease severity in both paediatric and adult patients with AD (15). Furthermore, IL-4/IL-13 polymorphisms have

been shown to be associated with an increased incidence of AD in children at age 2 (16, 17). Thus, across age groups there is compelling evidence for IL-13 as a central mediator of the AD skin phenotype.

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 (18–20). A compilation of clinical and nonclinical data on tralokinumab including pharmacokinetics (PK) is given in the current version of the investigator's brochure.

In total, 14 clinical trials with tralokinumab have been completed to date, with phase 3 development ongoing in AD. A phase 2b dose-finding trial has been completed in AD. Other clinical trials with tralokinumab have been conducted in subjects with asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in healthy subjects.

In a phase 2b trial (D2213C00001), adults with moderate-to-severe AD on a background of mild to moderate topical corticosteroids (TCS) were treated with 3 different regimens of tralokinumab (45 mg every second week [Q2W], 150 mg Q2W, or 300 mg Q2W) or placebo to evaluate the safety and efficacy over a treatment period of 12 weeks. The primary endpoints were change from baseline in Eczema Area and Severity Index (EASI) at Week 12 and the percentage of subjects achieving Investigator's Global Assessment (IGA) response of 0 (clear) or 1 (almost clear) at Week 12. Secondary endpoints included change from baseline in EASI and Scoring Atopic Dermatitis (SCORAD) scores, and the percentage of subjects achieving at least 50% reduction from baseline in EASI and SCORAD scores (EASI50 and SCORAD50). In the overall intent-to-treat phase 2b population, an improvement in EASI score at Week 12 was seen in the tralokinumab 300 mg Q2W group versus placebo. 26% of subjects achieved an IGA of 0 or 1 in the tralokinumab 300 mg Q2W group versus 12% in the placebo group. The most commonly reported causally related treatment-emergent adverse event (AE) was upper respiratory tract infection (6 subjects [3.9%] in the combined tralokinumab group [45 mg, 150 mg, and 300 mg] and 2 subjects [3.9%] in the placebo group).

In total, more than 2,300 subjects have been treated with tralokinumab (cut-off date: 18-Aug-2018). 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.

All doses studied so far have had an acceptable benefit/risk profile and no major safety concerns have been identified. Possible risks associated with use of tralokinumab are summarised in Section 5.6.

5.3 Trial rationale

AD is a chronic inflammatory skin disease which is more prevalent in children than in adults. No curative treatment of the disease is currently available. There is a clear and compelling unmet medical need for more effective and safe treatments for moderate-to-severe AD in the paediatric age groups as current immunosuppressive medications, such as cyclosporine, methotrexate, and azathioprine, are associated with long-term toxicities. TCS, especially those of high potency, are associated with a variety of long-term safety concerns, including the systemic effects of absorbed corticosteroids such as adrenal suppression, poor growth, hypertension, hyperglycaemia, insulin resistance, and cataracts, as well as local skin damage and atrophy. These safety concerns are increased in paediatric patients, whose greater body surface area-to-weight ratio is thought to increase percutaneous absorption (21). Furthermore, AD is recognised to cause substantial morbidity and to have a serious impact on the psychological wellbeing and QoL in children (22).

Also to fulfil the regulatory requirements under the US Pediatric Research Equity Act (PREA) (23), the EU regulation on medicinal products for paediatric use (24) and International Council for Harmonisation (ICH) E11 (Guideline on the clinical investigation of medicinal products in the pediatric population) (25), LEO Pharma A/S (hereafter LEO Pharma) is committed to conduct a trial with tralokinumab in adolescent subjects with AD, aged 12 to <18 years. Hence, the present trial is part of the paediatric clinical development programme of tralokinumab for AD, investigating the efficacy and safety of tralokinumab monotherapy in the treatment of adolescent subjects with moderate-to-severe AD who are inadequately controlled with topical therapies. Furthermore, the trial is designed to gain valuable information on the PK of tralokinumab in this population and to select the doses for a PK/safety trial in younger children (2 to <12 years). Based on input from the European Medicines Agency's (EMA's) Paediatric Committee (PDCO), 2 doses of tralokinumab will be evaluated in this trial to assess whether 300 mg or 150 mg tralokinumab would be the optimal dose in the adolescent population.

The primary objective of this trial is to evaluate whether tralokinumab provides more effective control of the skin manifestations of AD than does placebo. In addition, secondary endpoints addressing symptom scores and extent of AD (SCORAD), itch-related sleep loss and itch severity, and health-related quality of life (HRQoL) measures related to AD are also

included. As an exploratory component, the present trial will also investigate biomarkers related to AD, skin barrier function (in a subgroup of subjects), skin microbiology, and the potential impact of tralokinumab on these.

As AD is a chronic disease requiring long-term treatment, it is also relevant to evaluate the efficacy of tralokinumab as maintenance treatment. After the 16-week initial treatment period, the trial will evaluate 2 different treatment options for maintenance therapy, that is, dosing every 2 (Q2W) or every 4 weeks (Q4W).

Thus, the trial will contribute to the characterisation of the benefit/risk profile of tralokinumab in the adolescent population.

5.4 Justification for dose

The selected doses for the initial treatment period in this trial is subcutaneously administered 300 mg and 150 mg tralokinumab Q2W. All subjects randomised to receive treatment with tralokinumab will get an initial loading dose on Day 0 (baseline); subjects randomised to 300 mg will receive a loading dose of 600 mg and subjects randomised to 150 mg will receive 300 mg. The administration of the loading dose of tralokinumab will allow systemic concentrations to reach steady state faster, and potentially reduce the time to onset of clinical effect. The serum concentrations of tralokinumab after the 600 mg loading dose will not exceed the serum tralokinumab concentrations at steady state for the 300 mg Q2W.

The 300 mg Q2W dose is also used in the ongoing phase 3 trials in adults.

Based on a phase 1 trial in 20 adolescents (12 to 17 years) with asthma (trial CD-RI-CAT-354-1054), the PK profile of a single SC dose of tralokinumab (300 mg) has been evaluated. 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 that observed in the adult population. Tralokinumab was well tolerated, no serious adverse events (SAEs) were reported, and no confirmed anti-drug antibodies (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 PK-PD 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.

The PK profile in adult subjects with AD in the phase 2b trial was comparable to the PK profile in adult and adolescent subjects with asthma. Given the relatively shallow dose-

response between 150 mg and 300 mg and because the safety profile of tralokinumab 300 mg was acceptable, both these doses will be included in this trial in adolescent subjects with AD, to establish the optimal dose in this population.

In the maintenance treatment period, subjects in 2 of the treatment arms will be dosed with tralokinumab (either 300 mg or 150 mg) Q4W. This approach will allow the sponsor of the trial, LEO Pharma, to evaluate whether less frequent dosing of tralokinumab (every 4 vs. every 2 weeks) may be sufficient for long-term maintenance of efficacy.

5.5 Ethical considerations

Participation in this trial is voluntary and subjects can withdraw at any time. The subject's legally authorised representative(s) will give informed consent, and subjects must give their informed consent (assent) as appropriate and according to national laws and regulations. No vulnerable subject incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, female subjects who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled. 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 investigational medicinal product (IMP). In addition, all female subjects of childbearing potential will have a pregnancy test performed before, during, and at end of treatment to ensure that no foetuses are exposed to the IMP.

AD is a chronic and recurrent skin disorder and no curative treatment of the disease is currently available. Further, there is a clear and compelling unmet need for more effective, safe treatments for moderate-to-severe AD in the paediatric age groups. AD is widely prevalent in children including adolescents (26–28). Although AD usually presents as mild disease in the paediatric age group, around 10-30% of children with AD may have moderate-to-severe disease (29–31). AD is recognised to cause substantial morbidity and to have a serious impact on the psychological wellbeing and QoL in children (22).

The efficacy of 2 doses of tralokinumab will be evaluated in adolescent subjects with moderate-to-severe AD who are otherwise healthy. Tralokinumab treatment will be compared with placebo control treatment. There are several reasons why this trial is a placebo-controlled monotherapy trial. First, this will allow for a better understanding of the clinical benefits of tralokinumab in adolescents without confounding data interpretation by concomitant use of TCS therapy. Second, the pivotal phase 3 trials in adults are also conducted as monotherapy trials, and the comparison and extrapolation of data from the adult to the adolescent population is considered to be most appropriate if the present trial is conducted in the

monotherapy setting. Third, TCS and topical calcineurin inhibitors (TCI) have limited efficacy in patients with moderate-to-severe disease.

Placebo control was considered to provide the best design for efficient assessment of both benefit and risk in adolescents (12 to <18 years). Recognising that prolonged placebo treatment may not be optimal in this population, a 2:1 (tralokinumab:placebo) randomisation is planned to increase the opportunity for subjects to receive active treatment. Furthermore, subjects who do not achieve a clinical response at Week 16 (including subjects randomised to placebo) will get the opportunity to receive open-label tralokinumab 300 mg Q2W treatment with optional use of TCS, if considered appropriate by the investigator. In addition, subjects may receive rescue treatment at the discretion of the investigator if medically necessary (i.e., to control intolerable AD symptoms) through treatment and follow-up.

To ensure subject safety, investigators are informed only to enrol subjects they expect can complete wash-out of previous AD medications during the screening period without experiencing intolerable worsening of AD symptoms. In addition, subjects and/or their legally authorised representatives will be informed to contact the investigator, if the subject's AD worsens significantly.

In accordance with the current version of the ICH Good Clinical Practice (GCP) guidelines, qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. Safety data will be reviewed regularly by Global Safety at LEO, and by an independent Data Monitoring Committee (DMC, see Appendix 3H) to ensure that prompt action is taken, if needed, to maximise patient safety.

In conclusion, the trial design chosen for this efficacy and safety trial on tralokinumab is regarded as ethically justified and adherent with ethical requirements.

5.6 Benefit/risk assessment

Tralokinumab is a new biological therapy under investigation for the treatment of moderate-to-severe AD in both the adult and paediatric age groups. Based on the benefits in treating AD reported with dupilumab, a monoclonal antibody that blocks the effects of IL-4 and IL-13 by targeting a common receptor subunit (13, 32–34), there is a reasonable expectation that tralokinumab will prove to be an effective treatment of moderate-to-severe AD.

Tralokinumab has already demonstrated efficacy in moderate-to-severe AD and the evidence discussed in Section 5.2 further supports the hypothesis that tralokinumab may benefit individuals with AD.

An important aspect in the benefit/risk evaluation is the reassuring safety profile of tralokinumab in AD, asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in trials with healthy subjects. Throughout an extensive clinical development programme in asthma, no safety concern has been identified with the use of tralokinumab, and tralokinumab was well tolerated. The AE profile for tralokinumab has been comparable to that for placebo in controlled clinical trials. Injection-site reactions have generally been mild and ADAs have been detected in very few subjects exposed to tralokinumab for up to one year; concerns about neutralising antibodies have not been raised. A number of theoretical potential risks have been identified that are described in the current version of the investigator's brochure, including hypersensitivity reactions, immune complex disease, severe infections, malignancies, and interference with reproductive function. Measures are in place in this trial to protect participating subjects as follows:

- Close monitoring of subjects during the trial with trial visits every 2 weeks during the treatment period as described in the schedule of trial procedures (Section 4).
- Close monitoring of subjects during the post dosing period (at the first 3 IMP dosing visits in the initial treatment period and in open-label treatment) as a precautionary measure against hypersensitivity reactions (further details are given in Section 11.4.1).
- Monitoring of subjects for clinical manifestations that may be associated with the development of specific antibodies to tralokinumab (i.e., immune complex disease).
- 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) [35]).
- Exclusion of subjects with a history of tuberculosis requiring treatment within 12 months prior to the screening visit.

- 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, see Section 8.3) 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.

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

6 Trial objectives and endpoints

The initial treatment period (randomisation until Week 16) will be analysed separately from the maintenance treatment period (Week 16 until Week 52). All objectives and corresponding endpoints are listed in Panel 6.

Panel 6: Objectives and endpoints

Objectives	Endpoints
Primary objective	Primary endpoints
To evaluate the efficacy of SC administration of tralokinumab compared with placebo in treating adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• IGA score of 0 (clear) or 1 (almost clear) at Week 16. • EASI75 at Week 16.
Secondary objectives	Secondary endpoints
To evaluate the efficacy of tralokinumab on severity and extent of AD, itch, and health-related quality of life compared with placebo.	*Severity and extent of AD* • Change in SCORAD from baseline to Week 16. *Itch* • Reduction of Adolescent Pruritus NRS (weekly average) of at least 4 from baseline to Week 16. *Health-related quality of life* • Change in CDLQI score from baseline to Week 16.
To investigate the safety, immunogenicity, and tolerability of SC administration of tralokinumab compared with placebo when used to treat adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• Number of adverse events. • Presence of anti-drug antibodies (yes/no).
Other secondary objectives	Additional secondary endpoints
To support the primary and secondary objectives in the trial.	*Supporting primary endpoints* • EASI50 at Week 16. • EASI90 at Week 16. • Change from baseline to Week 16 in EASI score. *Supporting the secondary endpoints related to the severity and extent of AD* • SCORAD75 at Week 16. • SCORAD50 at Week 16.

Panel 6: Objectives and endpoints (continued)

Objectives	Endpoints
Other secondary objectives	Additional secondary endpoints
To support the primary and secondary objectives in the trial (continued).	*Supporting the secondary endpoint related to itch* • Change from baseline to Week 16 in Adolescent Pruritus NRS (weekly average). • Reduction of Adolescent Pruritus NRS (weekly average) of at least 3 from baseline to Week 16.
To evaluate the efficacy of tralokinumab on patient-reported outcomes compared with placebo.	• Change from baseline to Week 16 in POEM.
To evaluate the pharmacokinetics of tralokinumab in adolescent subjects (age 12 to <18 years) with moderate-to-severe AD.	• Tralokinumab trough concentration (C_{trough}) during treatment (Week 16) and at the safety follow-up visit.
Maintenance objective	Maintenance endpoints
To evaluate maintenance of effect with continued tralokinumab dosing up to 52 weeks for subjects achieving clinical response at Week 16.	• IGA of 0/1 at Week 52 among subjects with IGA of 0/1 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab. • EASI75 at Week 52 among subjects with EASI75 at Week 16 achieved without rescue treatment from Week 2 to Week 16, after initial randomisation to tralokinumab.
Other objectives	Other endpoints
To evaluate the efficacy of tralokinumab compared to placebo on healthcare resource utilisation.	• Rescue treatment use (yes/no) from baseline to Week 16.
To support the evaluation of tralokinumab compared to placebo on patient-reported outcomes.	• Reduction of Adolescent Pruritus NRS (weekly average) of at least 4 from baseline to Week 2. • Reduction of Adolescent Pruritus NRS (weekly average) of at least 3 from baseline to Week 2. • Change in Adolescent Pruritus NRS (weekly average) from baseline to Week 2. • Change from baseline to Week 16 in Eczema-related Sleep NRS (weekly average). • Change in HADS from baseline to Week 16.

Panel 6: Objectives and endpoints (continued)

Objectives	Endpoints
Other objectives (continued)	Other endpoints (continued)
To evaluate the effect of tralokinumab compared with placebo on biomarkers and skin barrier function.	• Change in biomarkers at Week 16 compared to baseline assessed as change in serum levels of CCL17 (TARC), IL-22, and IgE. • Change in skin barrier function at Week 16 compared to baseline assessed as change in transepidermal water loss (evaluated in a subgroup of subjects).
To evaluate the incidence of skin colonisation with *Staphylococcus aureus* in tralokinumab-treated subjects compared to placebo.	• Skin microbiology as assessed by skin colonisation of *Staphylococcus aureus* at Week 16 among subjects who are positive at baseline.

Abbreviations: AD, atopic dermatitis; CCL17, C-C motif chemokine ligand 17 (also known as thymus and activation regulated chemokine [TARC]); CDLQI, Children's Dermatology Life Quality Index; C_{trough}, tralokinumab trough concentration; EASI, Eczema Area and Severity Index; EASI50, at least 50% reduction in EASI score; EASI75, at least 75% reduction in EASI score; EASI90, at least 90% reduction in EASI score; HADS, Hospital Anxiety and Depression Scale; IgE, immunoglobulin E; IGA, Investigator's Global Assessment; IL-22, interleukin 22; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SC, subcutaneous; SCORAD, Scoring Atopic Dermatitis; SCORAD50, at least 50% reduction in SCORAD score; SCORAD75, at least 75% reduction in SCORAD score.

7 Trial design

7.1 Overall trial design

Overview

This is a phase 3, randomised, double-blinded, placebo-controlled trial in adolescent subjects aged 12 to <18 years with moderate-to-severe AD. The trial will consist of a screening period of 2 to 6 weeks (Weeks -6/-2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16) and a maintenance treatment period of 36 weeks (Weeks 16 to 52). The primary endpoint is assessed at Week 16, and the final efficacy assessment will be conducted at Week 52.
A 14-week follow-up period for the assessment of safety is also included (Weeks 52 to 66). Subjects who transfer to ECZTEND before completing the safety follow-up visit in the present trial will have their safety follow-up visit in ECZTEND. Subjects without clinical response at Week 16, subjects who receive rescue treatment from the Week 2 visit to the Week 16 visit (hereinafter "Week 2 to Week 16"), and subjects who lose their response during the maintenance period will be transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS and/or TCI) if they meet certain criteria (see below), and if considered appropriate by the investigator. Transfer to open-label treatment may occur at any visit from Week 16 while the subject is in the maintenance treatment period.

A schematic of the trial design is provided in Panel 1.

Screening period (Week -6 to Week 0)

Prior to attending any trial procedure, a signed informed consent must be obtained from the subject's legally authorised representative(s) and from the subject (as appropriate and according to national laws and regulations). The screening period has a minimum duration of 2 weeks and a maximum duration of 6 weeks and includes 1 or 2 screening visits. The exact duration of the screening period for the individual subject depends on the length of any wash-out period needed (as also specified in the exclusion criteria in Section 8.3):

- 6 weeks for subjects using tanning beds or phototherapy.
- 4 weeks for subjects using systemic immunosuppressive/immunomodulating drugs, systemic corticosteroid use, or ≥3 bleach baths during any week within the 4 weeks.
- 2 weeks for subjects using TCS, TCI, or topical phosphodiesterase 4 (PDE-4) inhibitors.

If no wash-out or a 2-week wash-out period is required, screening will be reduced to 2 weeks and reduced to 1 visit (Week -2; visit 2), i.e., the 2 screening visits will be merged. Eligibility

will be assessed at the (first) screening visit and on Day 0 (hereinafter "baseline") prior to randomisation.

All subjects will attend a screening visit 14 days before baseline (Week -2; visit 2) where they will receive electronic diary (eDiary) training and start completion of the electronic patient-reported outcome (ePRO) questionnaires in the eDiary. Data entered into the eDiary during the 2 weeks before randomisation will be used to calculate baseline values of the patient-reported outcomes (PROs).

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

Initial treatment period (Week 0 to Week 16)

Following the screening period, approximately 294 subjects will be randomised 1:1:1 to one of the following groups stratified by region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA of 3 or 4):

- Tralokinumab 300 mg Q2W: tralokinumab 600 mg (loading dose) at baseline, then tralokinumab 300 mg Q2W.
- Tralokinumab 150 mg Q2W: tralokinumab 300 mg (loading dose) at baseline, then tralokinumab 150 mg Q2W.
- Placebo Q2W: placebo (loading dose) at baseline, then placebo Q2W.

To ensure blinding, all treatment groups will receive the same number of injections at each visit. Thus, the tralokinumab 150 mg group will receive both tralokinumab and placebo injections at all dosing visits.

Maintenance treatment period (Week 16 to Week 52)

Subjects achieving a clinical response at Week 16 without use of rescue treatment (from Week 2 to Week 16) will continue into maintenance treatment that runs until Week 52.

Clinical response is defined as IGA of 0 or 1, or at least 75% reduction in EASI score from baseline (EASI75).

Subjects randomised to tralokinumab in the initial treatment period will be re-randomised 1:1 to one of the following maintenance regimens stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1).

Subjects initially randomised to tralokinumab 300 mg will receive:

- Tralokinumab 300 mg Q2W.
- Tralokinumab 300 mg Q4W: alternating dose administrations of tralokinumab 300 mg or placebo.

Subjects initially randomised to tralokinumab 150 mg will receive:

- Tralokinumab 150 mg Q2W.
- Tralokinumab 150 mg Q4W: alternating dose administrations of tralokinumab 150 mg or placebo.

Subjects randomised to placebo in the initial treatment period who achieve a clinical response at Week 16 without use of rescue treatment from Week 2 to Week 16 will continue to receive placebo Q2W in the maintenance treatment period.

Open-label treatment (Week 16 to Week 52)

Subjects without clinical response at Week 16 and subjects who have received rescue treatment from Week 2 to Week 16 will be transferred to open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS and/or TCI) at Week 16, if considered appropriate by the investigator.

In addition, subjects may be transferred from maintenance treatment to open-label treatment if they meet any of the criteria listed below, and if considered appropriate by the investigator. Transfer to open-label treatment may occur at any visit from Week 16 while the subject is in the maintenance treatment period.

<u>Subjects with IGA=0 at Week 16:</u>

- IGA of at least 2 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).

<u>Subjects with IGA=1 at Week 16:</u>

- IGA of at least 3 and not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).

Subjects with IGA >1 at Week 16:

- Not achieving EASI75 over at least a 4-week period (i.e., over 3 consecutive visits).

Subjects who receive rescue treatment:

- If rescue treatment is administered during the maintenance treatment period, subjects should be transferred to open-label treatment.

  For subjects who receive systemic rescue treatment, the open-label treatment may not be initiated sooner than 5 half-lives after the last dose of the systemic rescue treatment.

Subjects who are transferred to open-label treatment will continue their scheduled visit sequence. The open-label treatment will extend to Week 52 (last dose administered at Week 50).

Safety follow-up period (Week 52 to Week 66)

After completion of the treatment periods or premature discontinuation of IMP, all subjects will complete an off-treatment follow-up period for the assessment of safety, PK, and immunogenicity (i.e. ADA), except subjects who transfer to ECZTEND before Week 66 (see below). During follow-up, subjects will be allowed to receive standard of AD care (excluding biologic therapies) at the investigator's discretion, if needed.

Long-term extension trial (LP0162-1337, ECZTEND)

Eligible subjects from selected countries may be invited to enter a long-term extension trial conducted under a separate protocol (LP0162-1337, ECZTEND). Subjects who transfer to ECZTEND, must have had their last visit in the treatment period (Week 52) under the current protocol (LP0162-1334). Subjects may enter ECZTEND up to 26 weeks from their last IMP injection in the present trial (Week 50) to their first IMP injection in ECZTEND (baseline). Subjects may therefore enter ECZTEND (baseline) without completing the safety follow up visit (16 weeks after their last IMP injection) in the present trial, and those subjects will have their safety follow-up visit in ECZTEND.

Analysis of data per last subject's last Week 52 visit

To fulfil the commitments in the paediatric investigation plan (PIP) and the paediatric study plan (PSP), the trial will be unblinded to an analysis group once all randomised subjects have completed the Week 52 visit and available data will be analysed and reported (See Section 9.3.1 for details).

7.2 Number of subjects needed

Assuming a screening failure rate of 25%, approximately 392 subjects will be screened and approximately 294 subjects will be randomly assigned to the initial treatment period (1:1:1 to tralokinumab 300 mg, tralokinumab 150 mg, or placebo). At Week 16, approximately 40% of the tralokinumab-treated subjects are expected to be re-randomised (1:1 to tralokinumab Q2W or tralokinumab Q4W) into the maintenance treatment period. Randomisation and re-randomisation will be handled using the interactive response technology (IRT) to ensure continued blinding in the trial.

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

This trial will be conducted at approximately 80 sites in Europe, North America, Australia, and Japan. The anticipated minimum number of randomised subjects per trial site is 3 and the maximum number of subjects per trial site is 30.

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 final safety follow-up visit at Week 66. Subjects who enter the long-term extension trial (LP0162-1337, ECZTEND) after completion of the end of treatment visit (Week 52) will also be considered as trial completers. The end of the trial is defined as the date of the last visit of the last subject in the trial globally.

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

7.4 Software

CDISC controlled terminology dated 22-Dec-2017 (or newer) was used for definition of controlled terminology throughout this protocol and will be used for statistical programming and output. Study Data Tabulation Model (SDTM) version 1.4 and SDTM implementation guide version 3.2 will be used for data tabulations.

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. Hence, subjects are expected to complete wash-out of previous AD medications without experiencing intolerable worsening of AD symptoms during the screening period.

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

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

8.2 Inclusion criteria

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

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures. Signed and dated informed consent must be provided by the subject's legal representative(s) and by the subject (as applicable according to national laws or regulations).

2. Age 12 to 17 years.

3. Body weight at baseline ≥30.0 kg.

4. Diagnosis of AD (as defined by Hanifin and Rajka [1980] criteria for AD [36; Appendix 4]).

5. History of AD for ≥1 year.

6. History of TCS (Europe: potent/Class 3 or higher; US: mid-strength/Class 4 or lower [Appendix 6]) and/or TCI treatment failure (due to inadequate response or intolerance) or subjects for whom these topical AD treatments are medically inadvisable.

7. AD involvement of ≥10% body surface area at screening and baseline (visit 3) according to component A of SCORAD.

8. An EASI score of ≥12 at screening and ≥16 at baseline.

9. An IGA score of ≥3 at screening and at baseline, equivalent to moderate-to-severe AD.

10. An Adolescent Pruritus numeric rating scale (NRS) average score of ≥4 during the week prior to baseline.

    - Adolescent Pruritus NRS at baseline will be calculated from daily assessments of worst itch (Adolescent Pruritus NRS) during the 7 days immediately preceding randomisation (Day -6 to 0). A minimum of 4 Adolescent Pruritus NRS scores out of the 7 days is required to calculate the baseline average score. For subjects who do not have at least 4 scores reported during the 7 days immediately preceding the planned randomisation date, randomisation should be postponed until this requirement is met, but without exceeding the 6 weeks' maximum duration for screening.

11. Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.

12. Female subjects must be of either:

    - Non-childbearing potential, i.e. premenarchal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus or has tubal litigation).
    - Childbearing potential (defined as Tanner stage ≥3 or menarche) provided there is a confirmed negative pregnancy test at screening and randomisation to rule out pregnancy.

13. Female subjects of childbearing potential must use a highly effective* form of birth control throughout the trial and for at least 16 weeks (5 half-lives) after last administration of IMP.

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

8.3 Exclusion criteria

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

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

10. Receipt of any marketed biological therapy or investigational biologic agents (including immunoglobulin, anti-IgE, or dupilumab):
    - Any cell-depleting agents including but not limited to rituximab: within 6 months prior to randomisation, or until lymphocyte count returns to normal, whichever is longer.
    - Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
11. Subjects who have received treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 3 months or 5 half-lives, whichever is longer, prior to randomisation.
12. Inability or unwillingness to receive IMP injections at randomisation.
13. Receipt of blood products within 4 weeks prior to screening.
14. 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.
15. Major surgery within 8 weeks prior to screening, or planned inpatient surgery or hospitalisation during the trial period.
16. Known or suspected hypersensitivity to any component of the IMP.
17. History of any active skin infection within 1 week prior to randomisation.
18. History of a clinically significant infection within 4 weeks prior to randomisation which, in the opinion of the investigator or sponsor's medical expert, may compromise the safety of the subject in the trial, interfere with evaluation of the IMP, or reduce the subject's ability to participate in the trial. Clinically significant infections are defined as:
    - A systemic infection.
    - A serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
19. 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.
20. History of anaphylaxis following any biological therapy.
21. History of immune complex disease.

22. 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.
23. Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care.
24. 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.
25. Subject or subject's legally authorised representative(s) known or suspected of being unlikely to comply with the clinical trial protocol (e.g., due to alcoholism, drug dependency or psychotic state) in the opinion of the investigator.
26. 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).
27. Any disorder which is not stable and in the investigator's opinion could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial.
    - Impede the subject's ability to complete the trial.

    Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders and major physical impairment.
28. Any abnormal finding which in the investigator's opinion may:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis.

29. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the upper limit of normal (ULN) at screening.
30. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) or hepatitis C virus antibody (anti-HCV) serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb.
31. Subjects afraid of blood withdrawals or unwilling to comply with the assessments of the trial.
32. Subject or subject's legally authorised representative(s) has a language barrier, mental incapacity, unwillingness or lacking ability to understand the trial-related procedures.
33. Subjects who are legally institutionalised.
34. Female subjects who are pregnant or lactating.
35. Female subjects of childbearing potential who are sexually active but unwilling to use adequate methods of contraception.
36. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central IRT system and the screening evaluations to assess eligibility criteria may begin. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable.

Subjects for whom the subject's legally authorised representative(s) have given written informed consent for their participation in the trial (including subjects who have given written assent to participate in the trial, as appropriate and according to national laws and regulation) and who have been assigned a subject ID are considered 'screened' subjects.

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

Screening failures

Screening failures are defined as subjects for whom consent to participate in the trial has been obtained but who are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (37) and to respond to queries from regulatory authorities.

The following data will be collected in the eCRF for screening failures:

- Date of informed consent.
- Demographics (age, sex, ethnicity, race).
- Reason for screen failure:
    - Failure to meet randomisation criteria.
    - Lost to follow-up.
    - Withdrawal by subject.
    - Withdrawal by parent/guardian.
    - Other.
- Date of screen failure.
- Any adverse events (AEs) and serious AEs (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 after thorough review of all data from the original screening visit in the eCRF). Individuals who are re-screened will get a new subject ID.

9 Treatments

9.1 Trial product description

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

Tralokinumab and placebo will be packaged in individually numbered kits, each containing 1 accessorised pre-filled syringe (see Panel 7 for further details).

Panel 7: Identification of investigational medicinal products

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

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

Abbreviations: IMP, investigational medicinal product.

No active comparators will be used in this trial.

9.2 Administration of IMP

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

Dosing visits are shown in the schedule of trial procedures (Section 4). The last administration of IMP will occur at Week 50. To ensure blinding, all treatment groups will receive the same number of injections at each visit; thus, the tralokinumab 150 mg group will receive both tralokinumab and placebo injections at all dosing visits.

The first day of dosing is considered Day 0 (visit 3, baseline). Each subject will receive 4 SC injections (each of 1 mL) to receive a loading dose of tralokinumab or placebo. At subsequent visits in the initial treatment period, each subject will receive 2 SC injections (each of 1 mL).

Hence, subjects in the initial treatment period will receive either:

- Tralokinumab 300 mg Q2W: tralokinumab 600 mg (4 mL) at baseline, then tralokinumab 300 mg (2 mL) Q2W.
- Tralokinumab 150 mg Q2W: tralokinumab 300 mg (2 mL) + placebo (2 mL) at baseline, then tralokinumab 150 mg (1 mL) + placebo (1 mL) Q2W.
- Placebo Q2W: placebo (4 mL) at baseline, then placebo (2 mL) Q2W.

At Week 16, subjects with a clinical response (achieved without use of rescue treatment from Week 2 to Week 16) will continue to receive 2 SC injections (each of 1 mL) of maintenance treatment until Week 50:

- Tralokinumab Q2W:
    - Tralokinumab 300 mg: tralokinumab 300 mg (2 mL).
    - Tralokinumab 150 mg: tralokinumab 150 mg (1 mL) + placebo (1 mL).
- Tralokinumab Q4W (alternating dose administrations of tralokinumab and placebo):
    - Tralokinumab 300 mg: tralokinumab 300 mg (2 mL) or 2 mL placebo.
    - Tralokinumab 150 mg: tralokinumab 150 mg (1 mL) + placebo (1 mL) or 2 mL placebo.
- Placebo Q2W: 2 SC injections (each 1 mL) of placebo.

Subjects who are transferred to open-label treatment will receive 2 SC injections (each 1 mL) of tralokinumab 150 mg at each dosing visit.

IMP will be administered by a qualified, unblinded healthcare professional (HCP; see Section 9.3.1 for blinding details). A minimum interval of 7 days is required between 2 dosing visits. No specific treatment for an overdose is recommended. The investigator will use clinical judgement to treat any overdose if necessary. See Section 13.6.2 for further details regarding overdose.

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

Further details on IMP administration are provided in an IMP handling manual.
IMP administration must be carried out according to these instructions.

After IMP administration

For the first 3 IMP dosing visits in both the initial treatment period (i.e., Weeks 0, 2, and 4) and in open-label treatment, subjects will be monitored prior to and after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later. Vital signs will be documented in the eCRF.

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

Conditions requiring rescheduling of IMP administration

If any of the following should occur, the investigator should reschedule the visit and IMP 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 in the trial (e.g., viral illnesses).
- The subject is febrile (defined as ≥38°C) within 72 hours prior to IMP administration.

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

9.3 Treatment assignment

Randomisation

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised centrally at baseline (Day 0) to receive treatment with either tralokinumab 300 mg, tralokinumab 150 mg, or placebo, stratified by baseline disease severity (IGA 3 or 4) and region (Europe, North America, Australia, and Japan).

Subjects eligible for the maintenance part of the trial will be re-randomised to maintenance treatment at Week 16. Subjects randomised to tralokinumab (150 or 300 mg) who have a clinical response at Week 16 (i.e. IGA 0/1 or EASI75, achieved without use of rescue treatment from Week 2 to Week 16), will be re-randomised to the maintenance treatment period at the randomised dose in a 1:1 ratio (tralokinumab Q2W:tralokinumab Q4W) stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1). Subjects randomised to placebo who have a clinical response at Week 16 (achieved without use of rescue treatment from Week 2 to Week 16) will continue on placebo.

Subjects who are not eligible for the maintenance part of the trial will be transferred to open-label tralokinumab 300 mg Q2W treatment (with optional TCS and/or TCI use), if considered appropriate by the investigator.

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

9.3.1 Blinding

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

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

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

assessments. If needed, the unblinded HCP may perform the safety assessments (except assessment of AEs) for subjects in open-label treatment.

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

Should an issue arise with the IMP (e.g., damaged kit or syringe that has been assigned to a subject prior to administration, or any other unexpected event with the kit or syringe [e.g., a malfunction during IMP administration]), the unblinded HCP at the site will contact the clinical research associate (CRA) to determine whether any specific actions are required. See Section 9.10 for details on reporting of product complaints.

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

Analysis of data per last subject's Week 52 visit

To fulfil the commitments in the PIP and the PSP, an analysis of trial data up to and including visit 29 (Week 52) will be performed and will require unblinding of data. To perform this analysis, an analysis group consisting of Clinical Pharmacologists, Medical Experts, Safety Advisors, Statisticians, Statistical Programmers and Medical Writers will be unblinded to individual subject treatment allocation following database lock for the 52-week data. All staff involved in the conduct of the trial will remain blinded to treatment allocation for the entire duration of the trial. This principle will be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the analysis.

9.3.2 Emergency unblinding of individual subject treatment

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

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

requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

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

9.4 Background treatment

All subjects must use an emollient twice daily (or more, as needed) for at least 14 days before randomisation; the background treatment should preferably be an additive free, basic bland emollient. Subjects must continue their background emollient treatment throughout the trial.

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. Prohibited medications and procedures are described in Section 9.7.

Subjects who receive topical rescue treatment (TCS of any WHO class [see Appendix 6], or TCI) will continue treatment with IMP.

If possible, investigators should attempt to limit the first step of rescue treatment to topical treatments, and escalate to systemic treatments only for subjects who do not respond adequately after at least 14 days of topical treatment. However, systemic rescue treatment may be instituted immediately, if considered appropriate by the investigator.

If a subject receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), IMP will be immediately discontinued (see Section 10.2.2, reasons for temporary discontinuation of IMP). 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.

If rescue treatment is administered from Week 2 to Week 16 in the initial treatment period, the subject does not qualify for the maintenance part of the trial and will be transferred to open-label treatment at Week 16, if considered appropriate by the investigator. If rescue treatment is administered during the maintenance treatment period (from Week 16 to Week 50), the subject will be transferred to open-label treatment, but not sooner than 5 half-lives after the last dose of systemic rescue treatment.

Open-label tralokinumab arm only

Subjects in the open-label treatment arm may use mild to moderate strength TCS and/or TCI as needed on lesional skin at the investigator's discretion (see Appendix 6 for TCS classification and examples), from Week 16 through safety follow-up (Week 66). Use of TCS and TCI should be recorded as concomitant medication in the eCRF (see Section 9.6 below for further details).

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 (Week 66) must be recorded in the subject's medical record and the eCRF along with details such as:

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

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded: procedure, condition, diagnosis, and start and stop date (it will also be recorded if the procedure is ongoing). Note: in this trial, only surgical procedures and procedures related to AD treatment (e.g. phototherapy or bleach baths) will be recorded.

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 safety follow-up (Week 66):

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

9.7 Prohibited medication and procedures

The medications and procedures below are prohibited during the trial. For specifications on allowed rescue treatment for AD symptoms, please refer to Section 9.5. Please note that medications and procedures disallowed prior to randomisation are covered in the exclusion criteria (see Section 8.3).

From randomisation through end of treatment (Week 52):

- TCS of any WHO class (except for subjects in open-label treatment).
- TCI (except for subjects in open-label treatment).
- Phosphodiesterase 4 (PDE-4) inhibitors.
- UVA or UVB, psoralen + UVA (PUVA), other phototherapy, or tanning beds.
- 3 or more bleach baths per week.

From randomisation through safety follow-up (Week 66) or until first IMP injection in the long-term extension trial (LP0162-1337, ECZTEND):

- Systemic corticosteroids (nasal, ophthalmic, and inhaled corticosteroids are allowed).
- Systemic treatment with an immunosuppressive/immunomodulating agent (e.g. cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, Janus kinase inhibitors, interferon-gamma, dupilumab, or other biologics).

In case prohibited systemic medications are received, IMP dosing must be suspended as described in Section 10.2.2.

The sponsor's medical expert must be notified if a subject receives any of the following prohibited medications from randomisation through safety follow-up (Week 66):

- Investigational agents other than tralokinumab.
- Immunoglobulin or blood products.
- Allergen immunotherapy.
- Live (attenuated) vaccine.

The sponsor's medical expert will determine whether IMP discontinuation is required. Please note that receipt of inactive/killed vaccinations (e.g. inactive influenza) is allowed, provided they are not administered within 5 days before/after any trial visit.

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication (Section 9.6).

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

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

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

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

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.

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

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

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

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

9.8.3 Drug accountability

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

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

An inventory must be kept of the IMP administered to each subject randomised in the trial. This inventory must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMP. Full drug accountability will be performed in the IRT.

The trial site will maintain trial kit cartons from used kits until reconciliation. Used kits can be stored at room temperature and must be stored separately from non-allocated trial product. The IMP must be fully accounted for by the CRA with the help of the unblinded HCP. Following reconciliation, the trial kit cartons from used kits may be discarded.

All unused IMP supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO. Prior to their return, the IMP must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMP. Accountability must be documented in the IRT.

Reporting in eCRF

In the eCRF, the IMP kit numbers as well as the date and time of IMP administration will be recorded. In addition, the site of IMP injection should be given.

9.8.4 Treatment compliance

All IMP injections will be performed by site staff (unblinded HCP) who will also keep the accountability records up to date. Any non-compliance and the reason for it must be recorded in the eCRF.

9.8.5 Trial product destruction

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

Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction.

Trial sites which do not have such IMP destruction procedures in place will dispose used IMP in sharps bins which will be shipped to the CMO.

9.9 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice. Subjects from selected countries who qualify for the long-term extension trial (LP0162-1337, ECZTEND) may be offered participation (see Section 7.1).

9.10 Reporting product complaints

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

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

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 IMP or due to a device deficiency will be reported by the investigator as described in Sections 13.3 and 13.4.

Refer to the IMP handling manual for information on how to update the kit status in the IRT.

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

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

Fax number: +45 7226 3287

Email address: drug.safety@leo-pharma.com

10 Discontinuation and withdrawal

10.1 General principles

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

In order to obtain the most representative efficacy evaluation of tralokinumab in adolescents, it is key to assess the efficacy status of each trial participant at the planned primary endpoint visit (nominal Week 16 visit [visit 11x, Panel 2]), irrespective of whether the subject has discontinued IMP or not. Therefore, permanent discontinuation of IMP is evaluated as a separate occurrence that does not necessitate that the subject also withdraws from the trial. This is to enable selected subsequent trial visits to be conducted, including the nominal Week 16 visit (if discontinuation of IMP occurs prior to Week 16).

Hence, permanent discontinuation of IMP and withdrawal from trial are considered to be 2 (potentially) separate occurrences:

- **Permanent discontinuation of IMP** occurs when all further trial treatment is stopped. The subject will continue to participate in selected trial visit activities as outlined in Section 10.2.1.
- **Withdrawal from trial** occurs when stop of all trial activities takes place before the last planned safety follow-up visit (Week 66). This may either happen at the time of permanent discontinuation of IMP or later.

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

10.2 IMP discontinuation rules

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in the event of:

- Anaphylactic reaction or other severe systemic reaction to IMP injection.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.

- Diagnosis of a malignancy during the trial, excluding carcinoma in situ of the cervix, or localised squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status.
- Severe laboratory abnormalities:
  - ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert Meulengracht Syndrome).
  - Confirmed AST and/or ALT >5×ULN (for more than 2 weeks).

Subjects in open-label treatment (tralokinumab 300 mg Q2W with optional use of TCS and/or TCI) who in the opinion of the subject, the subjects' legally authorised representative(s), or investigator have unacceptable treatment effect of tralokinumab may discontinue open-label treatment and enter the safety follow-up period.

10.2.2 Reasons for temporary discontinuation of IMP

IMP dosing may be temporarily suspended in the event of:

- Other intercurrent illnesses or major surgery.
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents.
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/immunomodulating medications (e.g., cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, Janus kinase inhibitors, biologic agents).

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 therapy.

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit and return to the trial site for 1 or 2 additional visits as indicated below. 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.

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

- Early termination visit.
- Nominal Week 16 visit (16 weeks after randomisation).
- Final safety follow-up visit (16 weeks after last administration of IMP).

Subjects who permanently discontinue IMP at Week 16 or after Week 16 will be asked to attend:

- Early termination visit.
- Final safety follow-up visit (16 weeks after last administration of IMP).

Withdrawal from trial

A subject may withdraw from the trial at any time and for any reason. Subjects who withdraw from the trial should attend an early termination visit (if applicable), see the schedule of trial procedures (Section 4) for data to be collected at an early termination visit. The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees. If a subject withdraws from the trial, they may request destruction of any samples taken and not tested, and the investigator must document this in the site's trial records.

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. Similarly, the primary reason for withdrawal from trial must be recorded in the medical records and on the end of trial form in the eCRF. In both instances, the following reasons will be used in the eCRF: lack of efficacy, AE, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, other.

For subjects who do not attend the nominal Week 16 visit (visit 11x) or the safety follow-up visit, the primary reason for not attending these visits will be recorded in the medical records and in the eCRF using the following reasons: lack of efficacy, AE, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, other.

If 'adverse event' or 'other' is selected, a specification must be provided in the eCRF.

10.4 Lost to follow-up

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

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

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. 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

During the trial, there are 30 scheduled site visits at the clinic and 2 visits planned as telephone contacts for subjects attending the safety follow-up period. Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4:

- Panel 2 includes the assessments during screening and initial treatment (including the nominal Week 16 visit [for subjects who permanently discontinue IMP prior to Week 16]).
- Panel 3 includes the assessments during maintenance treatment.
- Panel 4 includes the assessments for subjects who are transferred to open-label treatment.
- Panel 5 includes the assessments during follow-up (including early termination and unscheduled visits).

Refer to Section 7.1 for further details on the trial design.

Assessments/procedures at any trial visit should be performed in the following order:

- PROs in the following order:
  1. Children's Dermatology Life Quality Index (CDLQI).
  2. Patient-Oriented Eczema Measure (POEM).
  3. Adolescent Patient Global Impression of Severity (PGI-S [past week recall]).
  4. Patient Global Impression of Change (PGI-C).
  5. Hospital Anxiety and Depression Scale (HADS).
- Investigator assessments (performed only by adequately trained investigators) in the following order:
  1. SCORAD component C, then component A and B.
  2. IGA.
  3. EASI.
- Safety and laboratory assessments (including PK and blood biomarkers).

- Other assessments (skin swabs, skin tape stripping [if applicable], transepidermal water loss [if applicable], height and weight).
- Administration of IMP.

Subjects may also need to be seen at unscheduled visits during the course of the trial. The assessments to be performed at an unscheduled visit are left at the investigator's discretion (could include any assessment performed at an early termination visit) (Panel 3).

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

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

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

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

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Age (in years) and year of birth.
- Sex: female, male.
- Race: American Indian or Alaska native, Asian, black or African American, native Hawaiian or other Pacific islander, white, other.
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.

11.2.2 Medical history

Relevant past and concurrent medical history must be recorded:

- Skin disease history. 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 which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

11.2.3 Body surface area involvement

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

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 (40). The C-SSRS must be completed at the screening visit to check that exclusion criterion no. 26 does not apply.

11.3 Efficacy assessments

11.3.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global AD and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 8). 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 IGA is included in the efficacy assessment & C-SSRS manual.

Panel 8: Investigator's Global Assessment

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

Abbreviations: IGA, Investigator's Global Assessment.

11.3.2 Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (41). 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. Details on the scoring of severity and extent of AD according to EASI are included in the efficacy assessment & C-SSRS manual.

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 9. 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 10. For each body region, a severity sum score will be calculated which will be multiplied by an area score (Panel 10) and by a weighting factor. The EASI score equals the sum of the scores obtained for each body region (Panel 9).

Panel 9: Calculation of the Eczema Area and Severity Index

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

Abbreviations: AS, area score; EASI, Eczema Area and Severity Index; SS, severity score. Modified from (42).

Panel 10: Eczema Area and Severity Index 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

11.3.3 Scoring Atopic Dermatitis

The SCORAD is a validated tool to evaluate the extent and severity of AD lesions, along with subjective symptoms (43). The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed according to the schedule of trial procedures (Section 4).

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

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

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

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

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

Note: dryness is evaluated on uninvolved areas.

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

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

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

11.3.4 Patient-reported outcomes

11.3.4.1 Overview

3 PROs will be assessed using an eDiary:

- Eczema-related Sleep NRS.
- Adolescent Pruritus NRS.
- Adolescent Patient Global Impression of Severity (PGI-S [today recall]).

Subjects will receive eDiary training at the screening visit 14 days before baseline (Week -2; visit 2) and then start the eDiary.

In addition, 5 PROs will be completed by the subjects at the site:

- CDLQI.
- POEM.
- Adolescent PGI-S (past week recall).
- Patient Global Impression of Change (PGI-C).
- HADS.

All PROs are included in the investigator trial file.

11.3.4.2 Eczema-related Sleep numeric rating scale

Subjects will rate how much their eczema interfered with their sleep the last night using an 11-point NRS (0 indicating that it ‘did not interfere’ and 10 indicating that it ‘completely interfered’). Subjects will complete the Eczema-related Sleep NRS as part of an eDiary each day in the morning from Week -2 (visit 2) until Week 52.

11.3.4.3 Adolescent Pruritus numeric rating scale

Subjects will assess their worst itch over the past 24 hours using an 11-point NRS ('Adolescent Pruritus NRS') with 0 indicating 'no itch' and 10 indicating 'worst itch possible'. Subjects will complete the Adolescent Pruritus NRS as part of an eDiary each day in the morning from Week -2 until Week 52.

11.3.4.4 Adolescent Patient Global Impression of Severity (today recall)

The Adolescent PGI-S (today recall) is a single item designed to capture the subject's perception of overall eczema symptom severity on the day of assessment on a 4-point categorical response scale ('not bad at all' to 'very bad'). Subjects will complete this item as part of the eDiary each day in the morning from Week -2 until Week 16.

11.3.4.5 Children's Dermatology Life Quality Index

The CDLQI questionnaire is designed and validated in subjects with dermatological conditions from 5 to 16 years (45-47). The CDLQI is available in text and cartoon versions (48-50). 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 (51). 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. The CDLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.3.4.6 Patient-Oriented Eczema Measure

The POEM is a validated questionnaire used to assess disease symptoms in atopic eczema patients in both clinical practice and clinical trials (52). The tool consists of 7 items each addressing a specific symptom (itching, sleep, bleeding, weeping, cracking, flaking, and dryness). Subjects will score how often they have experienced each symptom over the previous week on a 5-point categorical response scale (0 = 'no days'; 1 = '1 to 2 days'; 2 = '3 to 4 days'; 3 = '5 to 6' days; 4 = 'every day'). The total score is the sum of the 7 items (range 0 to 28) and reflects disease-related morbidity; a high score is indicative of a worse disease severity. The POEM will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.3.4.7 Adolescent Patient Global Impression of Severity (past week recall)

The Adolescent PGI-S (past week recall) is a single item designed to capture the subject's perception of overall itch symptom severity over the past week on a 4-point categorical response scale ('none' to 'severe' The Adolescent PGI-S (past week recall) will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.3.4.8 Patient Global Impression of Change

The PGI-C is a single item questionnaire designed to assess the subject's impression of changes (44). The subjects select the one response from the response options ('much better', 'a little better', 'no change', 'a little worse', or 'much worse') that best describes the overall change in their itch since they started IMP treatment. The PGI-C will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.3.4.9 Hospital Anxiety and Depression Scale

The HADS is a Likert scale tool widely used to detect states of anxiety and depression in a general hospital setting (53). The tool consists of 14 items that assess the subject's anxiety (7 items) and depression (7 items) during the last week. Each question is scored from 0 to 3, with high scores indicating a poor state. The HADS will be completed electronically on the device supplied to the trial site according to the schedule of procedures in Section 4.

11.4 Safety assessments

11.4.1 Vital signs

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

For the first 3 IMP dosing visits in the initial treatment period (i.e., Weeks 0, 2, and 4) and in open-label treatment, subjects will be monitored prior to and after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (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 randomised into the trial (respecting exclusion criterion no. 28).

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

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

11.4.2 Physical examination

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

If an unacceptable abnormal finding is identified during the physical examination at the screening visit, the subject must not be randomised into the clinical trial (respecting exclusion criterion no. 28).

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. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom or illness will be reported as an AE in accordance with Section 13.3.

11.4.3 Electrocardiogram

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

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

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

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date the evaluation. If a result is abnormal at the screening visit and considered by the investigator to be clinically significant, it will be at the investigator's discretion if the subject should be enrolled into the trial (respecting exclusion criterion no. 28); if such a subject is enrolled, the investigator will provide a justification in the medical record.

The collection and transmission of ECG data will be described in a separate ECG manual.

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

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

11.4.4 Laboratory testing

11.4.4.1 Overview

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

The evaluations shown in Panel 11 will be performed.

Panel 11: Clinical laboratory tests

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[1] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Protein Tryptase[2]	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leucocytes Neutrophils Neutrophils/leucocytes Lymphocytes Lymphocytes/leucocytes Monocytes Monocytes/leucocytes Eosinophils Eosinophils/leucocytes Basophils Basophils/leucocytes Thrombocytes
Urinalysis	**Serology**
Protein Glucose Ketones Occult blood Leukocytes Nitrite	Hepatitis B virus surface antigen[3] Hepatitis B virus surface antibody[3] Hepatitis B virus core antibody[3] Hepatitis C virus antibody[3] HIV-1 antibody[3] HIV-2 antibody[3] Immunoglobulin E[4]
Pregnancy test[5]	
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.
3. Measured at screening only.
4. Not measured at screening. Will also be used for the blood biomarker evaluation (see Section 11.6).
5. Only female subjects of childbearing potential. Measured in serum at screening only, and in urine every 4 weeks thereafter (see Section 4).

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

11.4.4.2 Investigator evaluation of laboratory samples

Central laboratory

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

investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date the evaluation. The signed and dated version will be filed with the investigator's trial documentation. Clinically significant abnormal tests (at randomisation and onwards) must be repeated to confirm the abnormality.

At each visit, the site staff will record in the eCRF if a sample was taken and, if applicable, the date and time as well as the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'). In addition, the subject's age (in years) must be provided in the eCRF at each visit where chemistry, haematology, and, serology is sampled.

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial (respecting exclusion criteria no. 28, 29, and 30).

A serum pregnancy test must be taken at the screening visit in female subjects of childbearing potential to rule out pregnancy prior to subject randomisation.

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

Tests performed at the trial site

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

At each visit, the site staff will record in the eCRF if a urine sample was taken and, if applicable, the investigator's assessment of the result ('normal', 'abnormal').

Female subjects of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomisation. The test will be repeated every 4 weeks as shown in the schedule of trial procedures in Section 4. The date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative'). For female subjects who become of childbearing potential during the trial (defined as Tanner stage ≥3 [54] or menarche), the investigator must reassess whether contraceptive measures are in place (if applicable), perform a urine pregnancy test and conduct pregnancy testing hereafter according to the schedule of trial procedures (see Section 4).

Reporting in eCRF
It will be recorded in the eCRF if clinical laboratory tests were performed; if the clinical laboratory tests were not performed, a reason should be given.

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 as well as any new clinically significant sign, symptom or illness will be reported as an AE in accordance with Section 13.3.

11.4.5 Anti-drug antibody measurements

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

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

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

11.5 Pharmacokinetic assessments

Blood samples for PK assessments will be collected at the time points specified in the schedule of trial procedures (Section 4).

It will be recorded in the eCRF if the PK sample was taken; if not, a reason will be provided.

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

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

11.6 Pharmacodynamic assessments: blood biomarkers

All subjects will have blood samples taken for analysis of biomarkers according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the biomarker samples were taken; if not, a reason will be provided.

Protein markers of inflammation will be measured and include, but are not limited to, CCL17 (also known as thymus and activation regulated chemokine [TARC]) and IL-22. The blood sample taken for safety assessment of IgE (see Panel 11) will also be used for biomarker analysis. In addition, biomarker mRNA from whole blood will be assessed. In addition, mRNA expression in blood mononuclear cells will be measured to assess the response to treatment.

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

11.7 Other assessments

11.7.1 Skin swabs: *Staphylococcus aureus* colonisation

Samples (skin swabs) will be taken from a representative lesion and from non-lesional skin according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the skin swabs were taken; if not, a reason will be provided. In addition, the body location for each skin swab will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to swab the same lesional and non-lesional skin sites at all time points, even if the lesion has cleared.

Subjects should not shower, bathe, or otherwise wash the lesion and non-lesional skin where the swabs will be taken from, within 12 hours of sample collection.

S. aureus colonisation will be determined using quantitative real-time polymerase chain reaction. This will provide data on treatment effects on subclinical infections with *S. aureus* that is very frequent in AD patients. In addition, the skin microbiome will be characterised using next-generation sequencing.

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

11.7.2 Skin barrier function

11.7.2.1 Skin tape stripping (selected trial sites)

At selected trial sites, skin tape strips will be collected from both lesional and non-lesional skin according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the samples were taken including the time of sampling; if not, a reason will be provided. In addition, the body location for each skin tape strip will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to collect skin tape strips from the same lesional and non-lesional skin sites at all time points, even if the lesion has cleared.

Subjects should not use emollients on the skin areas where the skin tape strip samples will be taken from within 8 hours of sample collection.

Biomarkers of skin barrier integrity and skin inflammation will be assessed. These will include but are not limited to: ceramides and natural moisturising factors such as pyrrolidone carboxylic acid (PCA) and urocanic acid (UCA).

Collection, handling and shipment instructions for skin tape strip samples are provided in a separate laboratory manual.

11.7.2.2 Transepidermal water loss (selected trial sites)

At selected trial sites, transepidermal water loss (TEWL) will be assessed on a representative lesion and on non-lesional skin to evaluate skin barrier function. TEWL (in $g/m^2/h$) will be measured at the clinic by a non-invasive assessment of skin evaporation according to the schedule of trial procedures (Section 4), using a Tewameter® or a similar device.

At each assessment, 3 measurements from a representative lesion and 3 measurements from non-lesional skin will be recorded in the eCRF. It will also be recorded if the TEWL assessment was performed including the time of assessment; if not, a reason will be provided.In addition, the body location for each TEWL assessment will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to perform TEWL assessments at the same skin sites (lesion and non-lesional skin) at all time points, even if the lesion has cleared.

11.7.3 Height and weight

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

11.8 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK, ADA, and biomarkers. The total volume of blood to be drawn is approximately 110 mL. The largest volume of blood drawn at any visit during the trial is 21 mL, to be drawn at visit 11 (Week 16).

11.9 End of trial

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).

It will be recorded on the end of treatment form if the subject completed the treatment. If not, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

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

- Did the subject complete the trial? If not, the primary reason for discontinuation from trial must be recorded (lack of efficacy, adverse event, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, other).
- Did the subject attend the nominal Week 16 visit? If not, the primary reason for not attending the visit must be recorded (lack of efficacy, adverse event, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, other).
- Did the subject attend the safety follow-up visit? If not, the primary reason for not attending the visit must be recorded (lack of efficacy, adverse event, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, other).
- Has the subject been transferred to the open-label ECZTEND trial (LP0162-1337)? If yes, which was the last visit (including phone call) the subject attended in this trial?
- Date of last contact.

The end of trial form will be completed when the subject has had their last visit.

11.10 Storage of biological samples

PK samples, blood biomarker samples, skin swabs, and skin tape strips (if applicable) will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR.

Samples for ADA evaluation will be retained for as long as the quality of the material permits evaluation but for no longer than 15 years after marketing authorisation.

12 Scientific rationale for trial design and appropriateness of assessments

Scientific rationale for trial design

LEO Pharma is aiming for a global paediatric development programme for tralokinumab, and the trial design of the present trial has been submitted to both the European (EMA and PDCO) and American health authorities (US Food and Drug Administration [FDA]) for review.

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

The planned trial design is considered appropriate for evaluating the trial objectives, as the double-blind conditions regarding the subject's treatment (tralokinumab or placebo) are maintained and the possible observer bias regarding treatment effects are minimised. Stratification by region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA 3 or 4) in this multi-centre trial will provide a strong basis for generalisation of the findings to the target patient population. Further, the trial population will comprise male and female subjects to explore differences in effects between genders and across the adolescent age range.

By using a placebo-controlled parallel-group design for the initial treatment period, superiority of tralokinumab to placebo can be investigated and will allow for a better understanding of tralokinumab efficacy in relation to PK in adolescents. This contrasts with a design where tralokinumab is used as add-on to best standard of care (e.g. TCS) where there will be confounding influence by the concomitant therapy on the efficacy assessments, particularly in case of unbalanced use. Precise dose-finding is essential because going forward unnecessary exposure should be avoided in adolescents and because the PK modelling also guides dose-selection for younger age groups in future paediatric trials with tralokinumab.

The most important inclusion criterion for entry into the trial is a diagnosis of AD (as defined by the Hanifin and Rajka 1980 criteria for AD) (36) 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.

AD is a chronic condition and the 52-week treatment duration has been chosen to evaluate the maintenance of effect as well as the safety and tolerability of tralokinumab in adolescents with AD.

Appropriateness of assessments

The clinical efficacy of tralokinumab treatment will be assessed by IGA, EASI, and SCORAD:

- IGA is a key instrument used in clinical trials to rate the severity of the subject's global AD.
- EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (41).
- SCORAD is a validated tool to assess the extent and severity of AD lesions and subjective symptoms (43).

The efficacy endpoints IGA score of 0 or 1 and EASI75 are recognised as important endpoints in clinical trials in AD by regulators in the US, EU, and Japan.

Several validated patient-reported questionnaires (CDLQI, POEM, HADS) have been included to assess the efficacy of tralokinumab on patient-reported outcomes and HRQoL.

Blood concentrations of tralokinumab will be analysed using validated bioanalytical methods and standard PK parameters will be derived to evaluate the tralokinumab exposure in adolescents.

The pharmacodynamic effect of tralokinumab treatment will be assessed using established assays to quantify serum levels of selected cytokines (IL-22 and CCL17) as well as IgE. In this trial, biomarker mRNA expression will be analysed from blood mononuclear cells to assess the response to treatment and to identify new biomarkers of relevance for AD. In patients with AD, cytokine mRNA in blood mononuclear cells has been shown to be differentially expressed compared to healthy subjects (55).

Normal skin is colonised by a wide variety of microorganisms, including fungi, viruses, and bacteria. The skin microbiome is complex and diverse, and varies between individuals and anatomical sites (56). *Staphylococcus aureus (S. aureus)* colonisation has been proposed to play a key role in AD pathophysiology via bacterial production of specific virulence factors (57). Resolution of active disease in AD in response to therapy correlates with reduction of *S. aureus* colonisation and increases in microbiome diversity (58). Skin swabs on

lesional skin will be used for evaluating the effect of tralokinumab treatment on the skin microbiome. This method was also used in the tralokinumab phase 2b trial in adult subjects with moderate-to-severe AD to demonstrate that the frequency of subjects testing positive for *S. aureus* was lower following treatment with tralokinumab compared with placebo. Global analyses of microbiome diversity will also be included in a phase 3 trial in adults (LP0162-1325), with results expected in 2019. The present trial will, if considered appropriate, also use gene sequencing to identify specific microbial strains present on the skin and further characterise the treatment effects on the skin microbiome in adolescent subjects with AD.

AD is a recurrent form of dermatitis where subjects have a high susceptibility to itching and irritants or allergens even on non-lesional skin, which is characterised clinically by atopic dry skin and functionally by cutaneous barrier disruption and water deficiency. Previous studies have shown that the barrier-disrupted dry skin of AD patients mainly is attributable to significantly decreased levels of ceramides in the stratum corneum (59). Skin barrier function will be assessed (in a subgroup of subjects) using skin tape stripping and TEWL. The skin tape stripping is a minimally invasive method that has been used for assessment of biomarkers reflecting the integrity of the skin barrier in AD patients (60, 61) as well as for obtaining information about the inflammatory processes in the skin of AD patients (62). TEWL is a method used for assessing the impaired cutaneous permeability barrier of the stratum corneum in AD skin (60, 63). Systemic treatment of AD has been shown to improve the barrier integrity by decreasing TEWL (64).

Data on antibodies against tralokinumab (ADAs) will be collected and the potential for immunogenicity will be evaluated until 16 weeks after the last dose of tralokinumab, to ensure adequate wash-out (approximately 5 times the half-life). The serum samples for determination of presence or absence ADA will be analysed using a validated bioanalytical method.

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

13 Adverse events

13.1 Definition and classification of adverse events

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

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

13.2 Collection of adverse event reports

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until completion of the clinical trial (defined as the safety follow-up visit 16 weeks after last IMP injection). For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any (S)AE with onset before the subject's final visit in the LP0162-1334 trial should be reported in the LP0162-1334 trial. If ongoing, the (S)AE will also be recorded as medical history in ECZTEND.

AEs must be assessed by medically qualified personnel.

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

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

13.3 Reporting of adverse events

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

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

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

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

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

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1.

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma within 24 hours of first knowledge. The SAE report should be completed in accordance with the eCRF completion guidelines provided for the automatic transmission or the SAE report should be reported on the paper form (as applicable).

In case the eSAE section in the eCRF is unavailable, the SAE provided to the investigator should be reported using the (paper) SAE form according to the SAE form completion guidelines. The SAE form must be submitted immediately to the Sponsor (within 24 hours of first knowledge), by fax or email to Global Safety at LEO Pharma using the email address or fax number below:

Global Safety at LEO Pharma

Email address: drug.safety@leo-pharma.com

Fax number: +45 7226 3287

Once the eSAE is available again, all information from the paper SAE form must be transferred to the eSAE section.

If relevant, other information must be sent to Global Safety at LEO Pharma by fax or email using the email address or fax number above. Examples of such information are anonymised reports of diagnostic procedures, hospital records, or autopsy reports.

Additionally, Global Safety at LEO Pharma may request further information in order to fully assess the SAE. The requested information must be reported to LEO Pharma in the follow-up

section in the eCRF, and the eCRF must be updated accordingly. In case the eSAE section in the eCRF is unavailable, the requested information must be provided via an updated SAE form sent by fax or e-mail (see contact details above) and the eCRF must be updated accordingly when the eSAE section becomes available. For subjects entering the long-term extension trial (LP0162-1337, ECZTEND), any SAE(s) with onset before the final visit in the present trial, must be reported in the LP0162-1334 trial eCRF, including any follow-up data requested by Global Safety.

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

SAEs occurring after the completion of the present clinical trial (i.e., after the last safety follow-up visit) should not be routinely sought or collected. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them. For subjects who transfer to ECZTEND, SAEs occurring after the last visit in the present trial and up to entering ECZTEND (defined as baseline), must be recorded as medical history in ECZTEND.

13.4.2 LEO Pharma reporting responsibilities

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

For the IMP, the investigator’s brochure, edition 17 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 countries.

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

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

For the US, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) **by LEO Pharma** (Guidance for Industry and Investigators - Safety Reporting Requirements for INDs and BA/BE Studies; Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection) and which are unexpected (Serious and Unexpected Suspected Adverse Reactions [IND safety report]) are subject to expedited reporting to regulatory authorities, IRBs. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting: pregnancy

Any pregnancy occurring during the clinical 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 final outcome must be reported on the (paper) Pregnancy Form (Part II) within 24 hours of first knowledge.

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

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

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 12 are considered adverse events of special interest (AESIs) in this trial and will require additional details to be recorded in the eCRF. LEO Pharma may request that the investigator forward test results, as appropriate. An AESI may be serious (requiring expedited reporting, Section 13.4) or non-serious.

Panel 12: Adverse events of special interest

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

Panel 13: Adverse events of special interest (continued)

AESI	Additional data to be recorded in the eCRF (if available[1])
Conjunctivitis	• Aetiology (viral, bacterial, allergic, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratoconjunctivitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis confirmed by ophthalmologist.
Keratitis	• Aetiology (infectious, non-infectious, other, unknown). • Bacterial culture outcome (for events with bacterial aetiology). • Diagnosis of herpes simplex keratitis (for events with viral aetiology). • Diagnosis confirmed by ophthalmologist.

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

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

13.6.2 Overdose

An overdose is defined as a subject receiving a dose of IMP in excess of that specified in this protocol.

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

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

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

13.6.3 Medication error

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

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

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

13.6.4 Misuse

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

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

13.6.5 Abuse

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

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

13.6.6 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to screening must be reported as an AE. If the AE originating from aggravation of condition qualifies as an SAE, expedited reporting is required (Section 13.4).

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow-up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow-up on the outcome of all non-serious AEs classified as of possible/probable relationship to the IMP for 2 weeks or until the final outcome is determined, whichever comes first. SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or ‘not recovered/not resolved’. In addition, a statement 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.*” (65).

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

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

LEO 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

A total of 294 subjects will be randomised 1:1:1 to initial treatment (tralokinumab 300 mg, tralokinumab 150 mg, and placebo) in this trial. The sample size is chosen to provide a sufficient power for demonstrating efficacy of tralokinumab versus placebo for the primary endpoints.

Under the assumption that the IGA 0/1 responder rates at Week 16 for the tralokinumab 300 mg dose and placebo are 30% and 10%, respectively, the power to detect a difference between tralokinumab 300 mg and placebo will be approximately 94% at a 2-sided 5.0% significance level.

Further, assuming corresponding responder rates of 40% and 15% for EASI75 at Week 16 will imply a nominal power of approximately 98% to detect a difference between tralokinumab 300 mg and placebo for that endpoint.

The combined power for detecting a difference between tralokinumab 300 mg and placebo in both primary endpoints at a 5.0% significance level is then at least 92%.

For the tralokinumab 150 mg dose, the accumulated power for subsequently rejecting the 2 hypotheses of no difference to placebo for the primary IGA 0/1 and EASI75 endpoints at a 2.5% significance level becomes approximately 84% and 80%, when using the same assumptions as for the tralokinumab 300 mg dose.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

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

A per protocol analysis set will be used as an efficacy subset for the analysis of the primary endpoints up to Week 16 (visit 11), and analyses based on the per protocol analysis set will be performed to support the results obtained for the full analysis set. The per protocol analysis set will be defined by excluding subjects from the full analysis set for whom any of the following conditions apply:

- Receive no treatment with the IMP.
- Have no assessment of IGA or EASI following start of treatment.
- Are known to have taken the wrong IMP throughout the initial treatment period of the trial.
- Do not fulfil the inclusion criteria no. 4, 7, 8, and 9.

A maintenance analysis set will be defined as all subjects who receive tralokinumab in the initial treatment period and who are re-randomised to maintenance treatment.

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

A maintenance safety analysis set will be defined as subjects in the full analysis set who receive maintenance treatment at Week 16 (visit 11).

An open-label safety analysis set will be defined as subjects in the full analysis set who receive open-label treatment.

Based on the above-mentioned rules, the inclusion/exclusion of subjects from the trial analysis sets will be documented in an analysis set definition document before breaking the randomisation code.

14.3 Statistical analysis

14.3.1 Disposition of subjects

Subject disposition will be presented separately for subjects in initial treatment and in maintenance treatment. For all randomised subjects, the reasons for permanent discontinuation of IMP and for leaving the trial in the initial treatment period will be presented by treatment group. Likewise, for subjects in the maintenance safety analysis set, the reasons for permanent discontinuation of IMP and for leaving the trial will be presented by the assigned treatment group at Week 16. For subjects in the open-label safety analysis set, the reasons for permanent discontinuation of IMP and for leaving the trial will be presented.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented separately for all randomised subjects and for the maintenance analysis set. The presentations will be overall and by treatment group. Presentations of age, sex, ethnicity, race, baseline disease severity, and Adolescent Pruritus NRS weekly average at baseline will also be given

by region (Europe, North America, Australia, and Japan) and by baseline disease severity (IGA 3 or 4).

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

14.3.3 Exposure and treatment compliance

Exposure

Exposure to treatment will be presented for the safety analysis set (initial treatment), the maintenance safety analysis set (maintenance treatment), and open-label safety analysis set (open-label treatment) as days of exposure per treatment group.

For the full trial period, the days of exposure on tralokinumab irrespective of treatment group will be summarised for the safety analysis set.

Treatment compliance

Adherence to treatment regimen will be recorded in the eCRF. The log of drug administration may be used as source. If any complications or deviations in administration are observed, these will be described as protocol deviations.

Adherence will be presented for the safety analysis set (initial treatment) and for the maintenance safety analysis set (maintenance treatment) for each treatment group. Adherence will also be presented for the open-label safety analysis set (open-label treatment).

14.3.4 Multiple testing strategy

The overall type I error rate for the primary analysis of the primary estimands for the primary and secondary endpoints will be protected by a combination of hierarchical testing and Holm-Bonferroni multiplicity adjustment. Two different multiplicity adjustment procedures will be used, a US submission procedure and a global (non-US) procedure. For a graphical presentation of the 2 procedures, see Panel 13 and Panel 14.

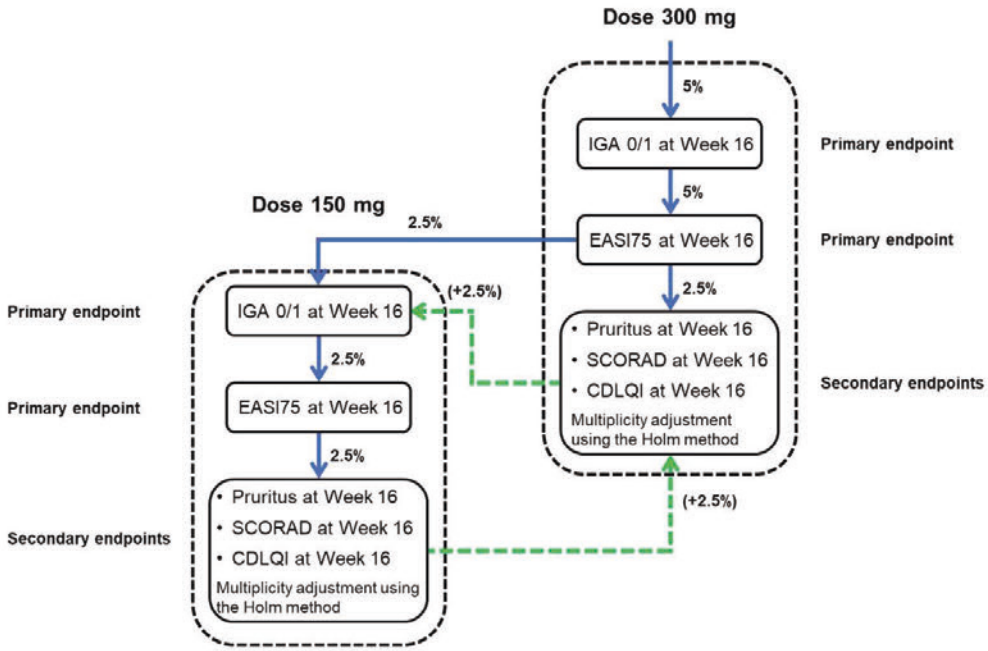
In the global (non-US) procedure, within each dose level, the 2 co-primary endpoints, IGA 0/1 and EASI75 at Week 16, will be tested hierarchically, followed by a Holm-Bonferroni adjustment of the testing of the 3 secondary endpoints.

In the US procedure, within each dose level, the 2 co-primary endpoints and the secondary endpoint Pruritus at Week 16 will be tested hierarchically, followed by a Holm-Bonferroni adjustment of the testing of the 2 secondary endpoints, SCORAD and CDLQI at Week 16.

In both testing procedures, the 2 co-primary endpoints for the tralokinumab 300 mg dose will first be tested hierarchically at an overall 5% significance level, after which the significance level will be split evenly between:

- Testing of the primary endpoints for the tralokinumab 150 mg dose and a Holm-Bonferroni testing procedure for the secondary endpoints for the tralokinumab 300 mg dose in the global (non-US) procedure.
- Testing of the primary endpoints for the tralokinumab 150 mg dose and testing of the secondary endpoint Pruritus at Week 16 for the tralokinumab 300 mg dose in the US procedure.

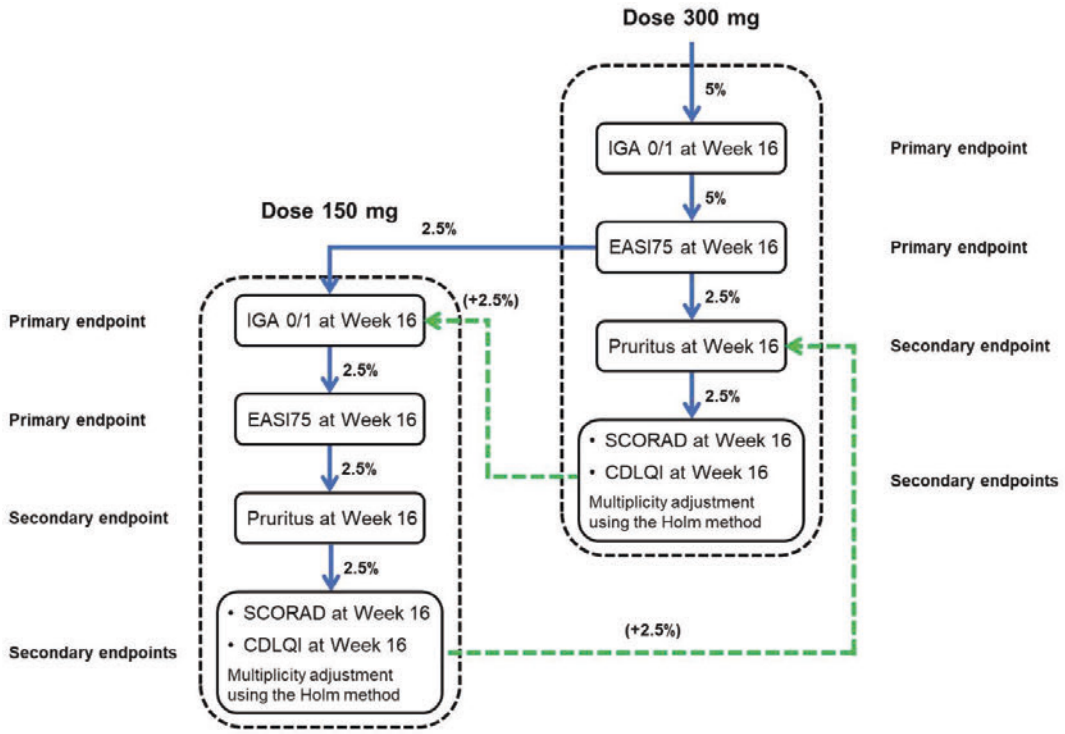
Panel 13: Global (non-US) testing procedure for the primary and secondary endpoints



Note: To protect the family-wise type I error. The numbers in parentheses indicate significance levels that have been passed on from rejected hypotheses for the other tralokinumab dose level.

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; SCORAD, SCORing Atopic Dermatitis.

Panel 14: US testing procedure for the primary and secondary endpoints



Note: To protect the family-wise type I error. The numbers in parentheses indicate significance levels that have been passed on from rejected hypotheses for the other tralokinumab dose level.

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; EASI75, at least 75% reduction in Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; SCORAD, SCORing Atopic Dermatitis.

If all the hypotheses of no difference to placebo for the tralokinumab 300 mg dose are rejected, then the 2.5% significance level will be passed on to the testing of all the endpoints for the tralokinumab 150 mg dose. Similarly, if the hypotheses of no difference to placebo for all the endpoints of the tralokinumab 150 mg dose are rejected, the 2.5% significance level will be passed on to:

- The Holm-Bonferroni testing procedure of the secondary endpoints for the tralokinumab 300 mg dose in the global (non-US) procedure.
- The testing of all secondary endpoints for the tralokinumab 300 mg dose in the US procedure.

14.3.5 Analysis of initial treatment

14.3.5.1 Analysis of primary efficacy endpoints

14.3.5.1.1 Overview

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

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

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

- **Initiation of rescue treatment**: Some of the estimands use rescue treatment (from the Week 2 visit to the Week 16 visit [hereinafter “Week 2 to Week 16”]) as an event that modifies the applied value of an endpoint, e.g. by defining a subject receiving rescue treatment as a non-responder.
- **Permanent discontinuation of IMP**: This event occurs when a subject is permanently withdrawn from the treatment or the trial as described in Section 10.2.1. This can either happen at his/her own initiative or at the investigator's discretion. The event also includes the possibility of a subject being lost to follow-up. The timing of the event is defined as the date of the early termination visit for withdrawn subjects or, in the case of a subject lost to follow-up, the date of the last known visit to the clinic. As for the rescue treatment, the event type is used to modify an applied endpoint value.

All analyses will be based on the full analysis set unless otherwise specified.

14.3.5.1.2 Primary estimand: ‘composite’

The primary estimand for the primary endpoints will be:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks achieved without rescue treatment from Week 2 to Week 16, regardless of treatment discontinuation.

The primary estimand assesses the expected difference in response rates at Week 16 (defined as response obtained without use of rescue treatment from Week 2 to Week 16), resulting from initiation of a treatment regimen with tralokinumab 300 mg or 150 mg compared to a treatment regimen with placebo.

Primary analysis for the primary estimand

Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Subjects who prior to the Week 16 visit have received rescue treatment from Week 2 to Week 16 will be considered non-responders, reflecting an assumption that use of rescue treatment from Week 2 indicates failure of the randomised treatment to achieve response, and that a (possible) observed positive response after use of rescue treatment is not attributable to the randomised treatment. Missing data for subjects who did not attend the Week 16 visit and where rescue treatment has not been used prior to Week 16, will be imputed as non-responders.

The difference in response rates between the active tralokinumab arms and placebo will be analysed separately for each of the tralokinumab dose groups using the Cochran-Mantel-Haenszel test stratified by region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA 3 or 4). The treatment estimates and the corresponding 95% confidence intervals (CIs) will be presented. The null hypothesis of no difference in response rates between either tralokinumab dose and placebo will be tested against the 2-sided alternative that there is a difference.

The primary endpoints will be tested sequentially according to the test procedure outlined in Section 14.3.4.

Sensitivity analyses for the primary estimand

2 sensitivity analyses are specified for the primary estimand. In both cases, the same Cochran-Mantel-Haenszel test as used for the primary analysis will be applied including stratification by region and baseline disease severity.

The purpose of the analyses is to assess the robustness of results of the primary analysis with respect to the retrieved data at Week 16 and assumptions regarding missing Week 16 data.

Sensitivity analysis 1: All subjects who have permanently discontinued IMP prior to Week 16 will be imputed as non-responders, even if no rescue treatment has been used. This is to reflect a situation where retrieved efficacy data and concomitant medications could be registered less accurately for subjects who have discontinued treatment.

Sensitivity analysis 2: Rather than imputing all subjects who do not attend the Week 16 visit and where rescue treatment has not been used as non-responders, the following approach will be applied. If subjects have withdrawn due to an AE or due to lack of efficacy, they are still considered non-responders. Data missing for other reasons will be imputed using last

observation carried forward (LOCF), hereby assuming that the last value is a more reliable estimate of the missing response (than a non-response).

Supplementary analysis

The primary analysis of the primary estimand will be repeated based on the per protocol analysis set.

14.3.5.1.3 Secondary estimand: 'hypothetical'

The secondary estimand for the primary endpoints will be:

- Treatment difference in response rates of IGA 0/1 and EASI75 after 16 weeks if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue treatment was used from Week 2 to Week 16.

The secondary estimand assesses the expected difference in response rates achieved when adhering to the tralokinumab treatment regimen with no rescue treatment used from Week 2 to Week 16 as compared to a placebo treatment regimen with no rescue treatment in the same period.

Primary analysis of the secondary estimand

Data collected after permanent discontinuation of IMP or after use of rescue treatment from Week 2 to Week 16 will not be included in the analysis.

IGA 0/1 responder imputation

Imputation of missing binary IGA 0/1 data at Week 16 will be done using multiple imputations of the underlying 5-point IGA values within the 3 groups defined according to randomised treatment arm assuming that data are missing at random within each arm.

1. In each group, intermittent missing values will be imputed using last observation carried forward (LOCF) to obtain a monotone missing data pattern.
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 2. The model will include effects of region (Europe, North America, Australia, and Japan), and baseline disease severity (IGA 3 or 4) as factors. The estimated parameters, and their variances, will be used to impute missing IGA values at Week 2. 100 copies of the dataset will be generated (seed=11109934).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a proportional odds logistic regression model with effects of region and baseline disease severity together

with the IGA value at Week 2 as factors. The estimated parameters, and their variances, will be used to impute missing values at Week 4.

4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the modification that only the IGA values from the 2 preceding visits will be included as factors in addition to region and baseline disease severity. The missing binary IGA 0/1 response at Week 16 will be derived from the corresponding underlying imputed IGA value.

EASI75 responder imputation

Imputation of missing binary EASI75 data at Week 16 will be done using multiple imputations of the underlying 72-point EASI values within the 3 groups defined according to randomised treatment arm assuming that data are missing at random within each arm.

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern and 100 copies of the dataset will be generated (seed=29099734).
2. An analysis of covariance (ANCOVA) model will be fitted to the EASI value at Week 2. The model will include effects of baseline EASI as a covariate, and region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA 3 or 4) as factors. The estimated parameters, and their variances, will be used to impute missing EASI values at Week 2. 100 copies of the dataset will be generated (seed=11109934).
3. For each of the 100 copies of the dataset, missing EASI values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on the same ANCOVA model with effects of baseline EASI as a covariate, and region and baseline disease severity as factors together with the EASI value at Week 2 as covariate. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the modification that only the EASI values from the preceding 2 visits will be included as covariates in addition to baseline EASI as a covariate, and region and baseline disease severity as factors. The missing binary EASI75 response at Week 16 will be derived from the corresponding underlying imputed EASI value.

Analysis of Week 16 response

For each of the 100 complete data sets, the difference in response rates (for both IGA 0/1 and EASI75) between either tralokinumab dose and placebo will be analysed using the Cochran-Mantel-Haenszel test stratified by region (Europe, North America, Australia, and Japan) and

baseline disease severity (IGA 3 or 4). The estimates and standard errors from the 100 analyses will for each comparison be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

Sensitivity analysis for the secondary estimand

Rather than assuming that observations are missing at random within each treatment arm, it is assumed that missing data from subjects who discontinue IMP permanently or receive rescue treatment in the tralokinumab arms will resemble missing data from subjects in the placebo arm who do not discontinue IMP permanently or receive rescue treatment. The underlying assumption is that the effect of tralokinumab following rescue treatment or permanent treatment discontinuation is similar to the effect of placebo. It should be noted that this assumption is pronouncedly conservative in favour of placebo as it tends to minimise the differences between treatment arms.

Imputation of missing data at Week 16 will be done using a pattern mixture model where missing data in the tralokinumab arms as well as the placebo arm will be imputed from observed data in the placebo arm (using a so-called copy-reference approach). With this exemption, the stepwise multiple imputation procedure and subsequent analysis will be conducted in the same way as specified for the primary analysis of the secondary estimand.

14.3.5.1.4 Tertiary estimand: 'treatment policy'

The tertiary estimand for the primary endpoints will be:

- Treatment difference in response rate after 16 weeks between tralokinumab and placebo regardless of rescue treatment and treatment discontinuation.

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

Primary analysis for the tertiary estimand

Data retrieved at Week 16 for subjects who have permanently discontinued treatment prior to Week 16 will be included in the analysis.

Imputation of missing data at Week 16 will be done using multiple imputations within 6 groups defined according to randomised treatment arm and whether or not subjects have permanently discontinued IMP prior to Week 16. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued

subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such subjects where the Week 16 value is missing.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted in the same way as specified for the primary analysis of the secondary estimand.

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16 will be too small to facilitate the same imputation model as mentioned above. Consequently, an imputation model with only region and baseline effects (IGA as a factor and EASI as a covariate [only for EASI75]) will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if retrieved subjects only come from one region or if they all have the same baseline disease severity.

The imputed datasets will be analysed in the same way as specified for the primary analysis of the secondary estimand.

Sensitivity analyses for the tertiary estimand

Rather than imputing Week 16 data as described in the primary analysis of the tertiary estimand, missing observations will be imputed as non-responders. The assumption reflects that discontinued subjects without retrieved data at Week 16 are more likely to be non-responders than resembling discontinued subjects with retrieved data at Week 16.

14.3.5.2 Analysis of secondary efficacy endpoints

14.3.5.2.1 Overview

The 3 secondary endpoints evaluate the impact of 16 weeks of treatment on (i) severity and extent of AD, (ii) itch, and (iii) HRQoL. The corresponding endpoints are (i) the change from baseline to Week 16 in SCORAD, (ii) reduction (yes/no) of Adolescent Pruritus NRS average score for the past week (hereinafter ‘Adolescent Pruritus NRS weekly average’) of at least 4 from baseline to Week 16, and (iii) change from baseline to Week 16 in CDLQI score. Subject-reported worst daily itch over the last week prior to baseline will be used to calculate the baseline itch (see also inclusion criterion no. 10).

Reduction of Adolescent Pruritus NRS weekly average of at least 4 is a binary endpoint, and it will be analysed as described for the primary endpoint EASI75 using all 3 estimands with the modification of the ANCOVA imputation model that reduction of Adolescent Pruritus NRS weekly average replaces EASI where preceding values are used as covariates.

The change from baseline to Week 16 in SCORAD and CDLQI, respectively, are continuous endpoints and will be analysed as described below in Sections 14.3.5.2.2 and 14.3.5.2.3.

All analyses will be based on the full analysis set unless otherwise specified.

14.3.5.2.2 Primary estimand for the continuous secondary endpoints: 'hypothetical'

The primary estimand for the continuous secondary endpoints will be:

- Treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, respectively, if all subjects adhered to the treatment regimen in the sense that they did not discontinue IMP permanently and no rescue treatment was used from Week 2 to Week 16.

The primary estimand assesses the expected benefit when adhering to the tralokinumab treatment regimen with no rescue treatment from Week 2 to Week 16 as compared to a placebo treatment regimen with no rescue treatment in the same period.

Primary analysis of the primary estimand (continuous secondary endpoints)

Data collected after permanent discontinuation of IMP or after use of rescue treatment from Week 2 to Week 16 will not be included in the analysis.

The endpoints will be analysed using a repeated measurements model on the post baseline responses up to Week 16 with an unstructured covariance matrix, Kenward-Roger approximation to estimate denominator degrees of freedom, and the mean modelled as follows (shown for change from baseline in SCORAD):

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

This model assumes that data are missing at random within each treatment arm. The estimates will be presented with nominal p-values and 95% CI at each visit. The primary comparison between either of the tralokinumab doses and placebo will be at Week 16.

Sensitivity analysis for the primary estimand (continuous secondary endpoints)

Rather than assuming that observations are missing at random within each treatment arm it is assumed that missing data from subjects who discontinue treatment/receive rescue treatment in the tralokinumab arms will resemble data from subjects from the placebo arm who do not discontinue treatment/receive rescue treatment. Imputation of missing data at Week 16 will be

done using a pattern mixture model where missing data in the tralokinumab arms as well as the placebo arm will be imputed from the placebo arm (using a so-called copy-reference approach). The procedure for the change from baseline in SCORAD at Week 16 is described below. The same procedure will be applied for the CDLQI endpoint.

1. Intermittent missing values will be imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern and 100 copies of the dataset will be generated (seed=29099734).
2. For each of the 100 copies of the dataset, an ANCOVA model will be fitted to the SCORAD value at Week 2 in the placebo group. The model will include effects of baseline SCORAD as a covariate, and region (Europe, North America, Australia, and Japan) and baseline disease severity (IGA 3 or 4) as factors. The estimated parameters, and their variances, will be used to impute missing values at Week 2 for the placebo group as well as the tralokinumab groups (seed=11109934).
3. For each of the 100 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a similar ANCOVA model, but with the SCORAD value at Week 2 included as an additional covariate. The parameters from the model will be estimated based on data from the placebo group. The estimated parameters, and their variances, will be used to impute missing values at Week 4 for all 3 treatment groups.
4. This stepwise procedure will then be repeated sequentially for Week 6, 8, 10, 12, 14, and 16 with the SCORAD values from the preceding 2 visits included as covariates in addition to baseline SCORAD as a covariate, and region and baseline disease severity as factors.

For each of the 100 imputed datasets, the change from baseline in SCORAD at Week 16 will be analysed using an ANCOVA model with effects of treatment, region, baseline disease severity, and baseline SCORAD value. The estimated differences between each of the tralokinumab doses and placebo at Week 16 will be derived together with the associated standard error. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin’s rule to draw inference. From these pooled estimates, the 95% CI for the treatment differences will be calculated.

14.3.5.2.3 Secondary estimand for the continuous secondary endpoints: 'treatment policy'

The secondary estimand for the continuous secondary endpoints will be:

- Treatment difference in change from baseline to Week 16 in SCORAD and CDLQI, respectively, between tralokinumab and placebo regardless of rescue treatment use and treatment discontinuation.

The secondary estimand assesses the average difference in change from baseline in SCORAD and CDLQI after 16 weeks, resulting from initiation of a treatment regimen with tralokinumab and additional rescue treatment as compared to a treatment regimen with placebo and additional rescue treatment.

Primary analyses for the secondary estimand (continuous secondary endpoints)

Data retrieved at Week 16 for subjects who have permanently discontinued IMP prior to Week 16 will be included in the analysis. Missing Week 16 data will be imputed using multiple imputations assuming that data are missing at random within the groups used for imputation.

Imputation of missing data at Week 16 will be done using multiple imputations within 6 groups defined according to randomised treatment and whether or not subjects have discontinued treatment prior to Week 16. Within a given treatment arm, retrieved data from discontinued subjects will be used to impute missing data for other discontinued subjects. Similarly, the available data from not discontinued subjects will be used to impute data for such subjects where the Week 16 value is missing.

For not discontinued subjects, the stepwise multiple imputations procedure will be conducted in the same way as specified for the imputation of the underlying EASI values in the primary analysis of the secondary estimand for the binary endpoints.

For discontinued subjects, it is expected that the number of subjects with retrieved data at Week 16 will be too small to facilitate the same imputation model as mentioned just above. Consequently, an imputation model with only region and baseline effects (IGA as a factor and baseline SCORAD/CDLQI as a covariate) will be applied for discontinued subjects. Some factors may have to be omitted, depending on the observed data, e.g. if retrieved subjects only come from one region or if they all have the same baseline severity.

Each of the 100 imputed datasets will be analysed and the resulting estimates and standard errors pooled as described in the sensitivity analyses for the primary estimand for the continuous secondary endpoints.

Sensitivity analyses for the secondary estimand (continuous secondary endpoints)

Rather than assuming that observations are missing at random, it is assumed that missing data from subjects in the tralokinumab arms who have/have not discontinued treatment prior to Week 16 will resemble data from subjects from the placebo arm who have/have not discontinued treatment prior to Week 16.

Imputation of missing data at Week 16 will be done using a pattern mixture model where missing data in the tralokinumab arms as well as the placebo arm will be imputed from the placebo arm (copy-reference approach). With this exemption, the multiple imputation procedure and analysis will be conducted in the same way as described for the primary analysis of the secondary estimand for the continuous secondary endpoints.

14.3.5.2.4 Analysis of additional secondary endpoints

To support the primary endpoints, EASI50 at Week 16, at least 90% reduction in EASI score (EASI90) at Week 16, and the change from baseline to Week 16 in EASI score will be analysed and presented for the full analysis set. EASI50 and EASI90 will be analysed as described for the primary analysis of the primary estimand for the primary endpoints, and the change from baseline to Week 16 in EASI score will be analysed as described for the primary analysis of the primary estimand for the continuous secondary endpoints.

To support the secondary endpoints on severity and extent of AD, at least 75% reduction in SCORAD score (SCORAD75) at Week 16, and SCORAD50 at Week 16 will be analysed and presented for the full analysis set. Both endpoints will be analysed as described for the primary analysis of the primary estimand for the primary endpoints.

To support the secondary endpoint on worst daily itch, the change from baseline to Week 16 in Adolescent Pruritus NRS weekly average will be analysed and presented for the full analysis set as described for the primary analysis of the primary estimand for the continuous secondary endpoints. Reduction of Adolescent Pruritus NRS (weekly average) of at least 3 from baseline to Week 16 will further be analysed as described for the primary analysis of the primary estimand for the primary endpoints

The change from baseline to Week 16 in POEM will be analysed and presented for the full analysis set as described for the primary analysis of the primary estimand for the continuous secondary endpoints.

Tralokinumab trough concentration (C_{trough}) during treatment (Week 16) and at the safety follow-up visit will be summarised.

14.3.5.3 Analysis of other endpoints

14.3.5.3.1 Use of rescue treatment

Rescue treatment use (yes/no) from baseline to Week 16 will be summarised by visit and Anatomical Therapeutic Chemical (ATC) classification code.

14.3.5.3.2 Analysis of patient-reported outcomes

The PROs CDLQI, POEM, Adolescent PGI-S (past week recall), PGI-C, and HADS will be summarised by treatment group and visit using descriptive statistics. Adolescent PGI-S (past week recall) and PGI-C will only be assessed in the initial treatment period, and only observed data will be presented. For the CDLQI, POEM, and HADS, summaries will be made separately for the initial treatment and the maintenance treatment, data from the initial treatment period will be presented for the full analysis set and data from the maintenance treatment period will be presented for the maintenance analysis set. For the open-label treatment arm, CDLQI, POEM, and HADS will be listed and summarised descriptively by visit, presenting observed data only.

The PROs collected daily in the eDiaries (Eczema-related Sleep NRS, Adolescent Pruritus NRS, and Adolescent PGI-S [today recall]) will all be summarised over time by treatment group using descriptive statistics. For the Eczema-related Sleep NRS and Adolescent Pruritus NRS, the summaries will be separate for the initial treatment and the maintenance treatment, whereas summaries for Adolescent PGI-S (today recall) will only be made for the initial treatment. Data from the initial treatment period will be presented for the full analysis set and data from the maintenance treatment period will be presented for the maintenance analysis set. As for the other PROs, data from the PROs in the eDiary (Eczema-related Sleep NRS and Adolescent Pruritus NRS) for the open-label treatment arm will be listed and summarised descriptively by visit, presenting observed data only.

The change from baseline to Week 16 in Eczema-related Sleep NRS weekly average and HADS will be summarised by treatment group and domain, where applicable, and analysed as described above for the primary analysis of the primary estimand of the continuous secondary

endpoints. For the Eczema-related Sleep NRS score, the mean over the last 7 days prior to randomisation will be used as the baseline value.

In the subgroup of subjects with either HADS anxiety subscale score ≥8 or HADS depression subscale score ≥8 at baseline, the proportion of subjects with both HADS anxiety subscale score <8 and HADS depression subscale score <8 at Week 16 will be summarised by treatment group.

The following binary endpoints will be analysed as described for the primary analysis of the primary estimand, with the modification that subjects who use rescue treatment from baseline to the Week 2 visit will be considered as non-responders.

- Reduction of Adolescent Pruritus NRS (weekly average) of at least 4 from baseline to Week 2.
- Reduction of Adolescent Pruritus NRS (weekly average) of at least 3 from baseline to Week 2.

Change in Adolescent Pruritus NRS (weekly average) from baseline to Week 2 will be analysed as described for the secondary endpoint SCORAD using the primary analysis of the primary estimand only, with the modification that subjects who use rescue treatment from baseline to the Week 2 visit will be excluded from the analysis, since ignoring data after initiation of rescue treatment implies that subjects do not have post baseline responses available.

14.3.5.3.3 Biomarkers

Biomarkers will be summarised by visit and treatment group for the subjects in full analysis set.

The change from baseline to Week 16 in biomarkers will be summarised by treatment group and will be compared between each of the tralokinumab treatment groups and placebo using a Mann-Whitney test.

14.3.5.3.4 Skin microbiology

The incidence of skin colonisation with *S. aureus* will be presented by visit and treatment group for the subjects in the full analysis set.

The incidence at Week 16 will be compared between each of the tralokinumab treatment groups and the placebo group among subjects who are positive at baseline using a chi-squared test.

14.3.5.3.5 Skin barrier function

Skin barrier function parameters (assessed in a subgroup of subjects) will be summarised by visit and treatment group.

The change from baseline to Week 16 in skin barrier function (assessed as change in TEWL) will be summarised by treatment group and will be compared between each of the tralokinumab treatment groups and placebo using a Mann-Whitney test.

14.3.6 Analysis of maintenance treatment

14.3.6.1 Analysis of maintenance endpoints

To support the maintenance objective of the trial, IGA of 0/1 and EASI75 at Week 52 will be analysed using a binomial model separately for the 5 maintenance treatment arms, providing response rates and corresponding 95% confidence intervals based on the Wilson score method.

Only subjects responding to trial treatment with a clinical response achieved without rescue treatment from Week 2 to Week 16 will be included in the analysis and all subjects who prior to the Week 52 visit have received rescue treatment (including TCS) and/or been permanently discontinued from treatment or have been transferred to open-label treatment will be considered non-responders.

14.3.6.2 Continued treatment for non-IGA responders

The number of responders according to IGA 0/1 at Week 52 will be tabulated for the subgroup of subjects in the maintenance analysis set who are re-randomised meeting the EASI75 criterion but not the IGA 0/1 criterion at Week 16. All subjects who prior to the Week 52 visit have received rescue treatment (including TCS) and/or been permanently discontinued from treatment or have been transferred to open-label treatment will be considered non-responders in the analysis.

14.3.7 Analysis of open-label treatment

The efficacy assessments (IGA, EASI and SCORAD) for the open-label treatment arm will be listed and summarised descriptively by visit, presenting observed data only.

14.3.8 Analysis of safety

The analyses of safety will be based on the safety analysis sets. The safety data will be presented separately for the safety analysis set, the maintenance safety analysis set, and the open-label safety analysis set.

14.3.8.1 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).

Only treatment-emergent AEs will be summarised, but all AEs recorded during the course of the trial will be included in the subject data listings. An event will be considered treatment-emergent if started after the first use of IMP or if started before the first use of IMP (applicable if subject had a wash-out) and worsened in severity thereafter. The tabulations described in the following will only include the treatment-emergent events. In each of the tabulations, AEs will be defined by MedDRA preferred terms within primary SOC.

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

The number of AEs and the number of subjects experiencing each type of AE will be tabulated by treatment group. The percentage of subjects with AEs in the initial treatment period will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count <5).

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

The causal relationship to IMP for each type of AE will be tabulated by treatment group.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of related AEs and the number of subjects experiencing each type of related AE will be tabulated. The percentage of subjects with related AEs in the initial treatment period will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count <5).

SAEs and AESIs will be evaluated separately. A narrative for each SAE will be given. AESIs and AEs leading to withdrawal from trial will be tabulated and listed.

14.3.8.2 Vital signs

The change in vital signs (blood pressure, heart rate, body temperature) from baseline to each visit will be summarised by visit and treatment group as mean, standard deviation, median, minimum and maximum values for the safety analysis set, the maintenance safety analysis set, and the open-label safety analysis set.

14.3.8.3 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to each visit will be summarised by visit and treatment group as mean, standard deviation, median, minimum and maximum values for the safety analysis set, the maintenance safety analysis set, and the open-label safety analysis set.

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.

14.3.8.4 Anti-drug antibodies

The presence of ADAs (yes/no) is a secondary endpoint included to assess the safety and tolerability (immunogenicity) of tralokinumab.

ADA status (positive versus negative) at each visit will be summarised by treatment group for the initial treatment, maintenance treatment, and open-label treatment. If considered relevant, descriptive statistics including number of subjects, mean, standard deviation, median, and range of the actual ADA titres by treatment group and visit will be provided. The ADA status across the trial for each subject (positive vs. negative) will also be classified and summarised by treatment group.

The association of ADA status across the trial (positive vs. 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-positive subjects across the trial may also be divided into persistent positive versus transient positive. A subject will be considered as persistent positive if he/she has positive ADA status for at least 2 consecutive visits with ADA assessment. Otherwise, the subject will be considered as transient ADA-positive. The associations between ADA and AE/SAEs may be summarised for both persistent positive subjects versus transient positives subjects.

For subjects who develop ADA, the IGA score and change in EASI at end of treatment will be listed.

Samples that test positive for ADA will be analysed for nAB. 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.

For ADA, all subjects with titre information will be listed.

14.3.8.5 Pharmacokinetics

The tralokinumab C_{trough} concentration by time of assessment will be listed by treatment group and descriptive statistics will be provided.

C_{trough} values from subjects with positive ADA/nAB will be compared to values from subjects with negative ADA/nAB if data permits.

14.3.9 Interim analysis

No interim analysis is planned.

14.3.10 Analysis of data per last subject's Week 52 visit

To fulfil the commitments in the PIP and the PSP, the trial will be unblinded once all randomised subjects have completed the Week 52 visit. At the cut-off date of the last subject's Week 52 visit, all efficacy, safety, PK, and ADA data for the treatment periods have been collected and all endpoints used to test pre-specified hypotheses are final. Thus, no adjustments in significance level of the primary and secondary efficacy analyses are relevant. The CTR will include all data from all randomised subjects from the initial, maintenance, and open-label treatment periods and all available data from the safety follow-up period as per data cut-off date.

14.3.11 General principles

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

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

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

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

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

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

This definition includes:

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

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record.

- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

or

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

Adverse events of special interest 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 probable, possible, or not related according to the investigator's clinical judgement. The categories are defined below.

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

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

Outcome

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

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

Note that as per the above definition, LEO 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.

For SAEs which have stabilised and cannot be expected to recover during trial or safety follow-up periods, for example chronic illnesses, the final outcome should be considered to be ‘not recovered’. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form. Please note that the event should not be reported as ‘recovered’ on the SAE form.

Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

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

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (66) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (67).
- Current version of applicable ICH GCP Guidelines (68).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016 (69).
- EU's regulation on medicinal products for paediatric use (24).
- FDA's Federal Food, Drug, and Cosmetic Act (FD&C Act) on research of paediatric uses for drugs and biological products (70).
- Applicable laws and regulations.

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

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

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

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

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

Appendix 3B: Informed consent process

Subjects and the subject's legally authorised representative(s) 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 the 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 legally authorised representatives' signed and dated informed consent 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 authorised person obtaining the informed consent must also sign the 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).

The subject's legally authorised representative(s) will be re-consented to the most current version of the ICF(s) during the trial, if applicable.

A copy of the ICF(s) must be provided to the subject's legally authorised representative.

Subjects must give their written assent as appropriate and according to national laws and regulation. The subject's signed and dated informed consent 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. 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 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. The subject card also includes a local telephone number for the emergency unblinding CRO to be

used if the investigator or delegated site staff cannot be reached or if unblinding in the IRT cannot be performed.

Appendix 3C: Subject and data confidentiality

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

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

Trial subjects will be assigned a unique identifier (subject ID) by LEO. 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 and consent to 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, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Processing of personal data

This protocol specifies the personal data on trial subjects (for example race, ethnicity, age, gender, health condition, medical history, test results) 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[s]) 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

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

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

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

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Subject ID.
- The fact that the subject is participating in a clinical trial in AD including treatment arms of tralokinumab or placebo for 52 weeks.
- Other relevant medical information.

Trial monitoring

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

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

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

Protocol compliance

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

Sponsor audits, IRB/IEC review, and regulatory agency inspections

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

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

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, EASI, SCORAD), all investigators will receive training and whenever possible, the efficacy assessments will be made by the same investigator at each visit to reduce inter-rater variability.

To ensure subject safety, an independent Data Monitoring Committee (DMC) will regularly review unblinded safety data from this trial. Furthermore, SAE reporting will be followed closely and medical monitoring will be performed on an ongoing basis throughout the trial.

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

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the 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.

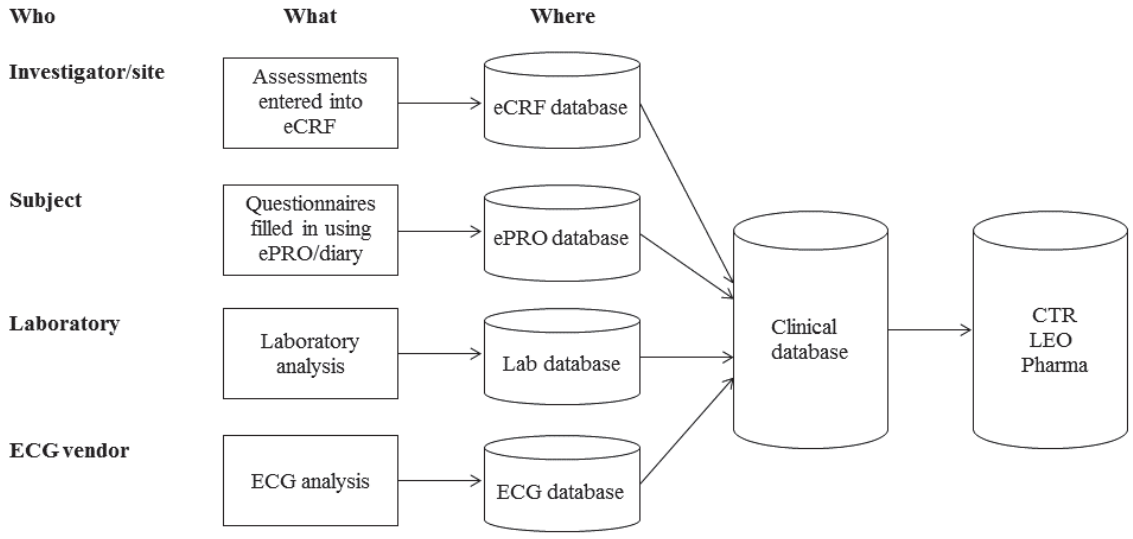
An ePRO solution will be used to capture patient-reported data (data from questionnaires completed at the trial site and eDiary data). By the use of an ePRO solution, data will be available immediately after data entry and available for monitors and site personnel, including the investigator, with read access only. The ePRO system is a separate application from the

eCRF and data captured from the eCRF and the ePRO will be stored on different servers during data capture. Data from both systems will be included in the final trial database.

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

Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 15.

Panel 15: Transmission of electronic data



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

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (68). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

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

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

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

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

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

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

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

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

Results of this clinical trial will be posted on the corporate website of LEO Pharma 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.

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

Publications

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

A multi-centre publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-centre publication is made

public, or if no multi-centre publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

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

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

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

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

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO Pharma also follows the CONSORT reporting guidelines (37).

Appendix 3F: Insurance

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

Appendix 3G: Financial disclosure

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

Appendix 3H: Committee structure

Patient safety will be carefully assessed by an independent Data Monitoring Committee (DMC). All members will be independent of the trial (that is, they will not be participating investigators or employees at participating sites) and of LEO Pharma (that is, they will not be LEO Pharma employees). The DMC members are experienced with clinical trials and will be responsible for assessing the safety of the subjects through assessment of the safety of the treatment regimen during the trial and through monitoring the overall conduct of the trial.

The DMC will review unblinded data on a regular basis. Additional meetings may also be called on at an ad hoc basis, as requested by the DMC or LEO. All data collected at the time of the data cut-off/scheduled meetings will be included in the summaries for the DMC, including data from subjects still ongoing in the trial. The DMC will examine summaries and listings of AEs, specific laboratory parameters and subject disposition data as detailed in the DMC charter. Full details of the analyses to be presented to the DMC will be specified in a separate DMC statistical analysis plan.

The DMC will have an independent statistician and an independent administrator who will remain independent of the trial management team.

The chairman of the DMC, in conjunction with the other members, will communicate their recommendations to LEO Pharma's clinical project manager after each meeting. The chairman of the DMC will provide written reports to LEO Pharma after each formal review to indicate the committee's recommendation regarding safety concerns and trial continuation. Further details on all aspects relating to the DMC are provided in the DMC charter.

Appendix 3I: Trial and site closure

Premature termination of trial or trial site

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

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

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

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

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

Completion of trial

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

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

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

Appendix 3J: Responsibilities

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

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

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

Appendix 4: Hanifin and Rajka (1980) diagnostic criteria for AD (36)

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 (38)

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., generalised 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., generalised 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: WHO model prescribing information for classification of topical corticosteroids

Hydrocortisone and betamethasone are examples of low- and high potency topical corticosteroids (TCS). TCS have been ranked in terms of potency into 4 groups consisting of 7 classes. Class I TCS are the most potent and Class VII TCS are the least potent (Panel 16). Efficacy and side-effects are greatest with the Class I ultra high potency preparations which should only be used for limited time periods (2–3 weeks).

Representative preparations by group are listed in the table below according to the WHO model prescribing information for drugs used in skin diseases (71). These groups may vary depending on the formulation and concentration and should be considered approximate. In general, ointments are more potent than creams or lotions. Potency is also increased when TCS are used under occlusive dressings or in intertriginous areas.

Panel 16: Classification of topical corticosteroids

Potency	Class	Topical corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment, or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%

Panel 16: Classification of topical corticosteroids (continued)

Potency	Class	Topical corticosteroid	Formulation
Moderate	V	Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Source: WHO model prescribing information: drugs used in skin diseases (71).

Appendix 7: Eligibility criteria

A short form (maximum 200 characters) version of each of the eligibility criteria for the trial is provided below, to be used when data are submitted to the FDA.

No	Inclusion criteria
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures
2	Age 12 to 17 years
3	Body weight at baseline of 30.0 kg or more
4	Diagnosis of AD (as defined by Hanifin and Rajka (1980) criteria for AD)
5	History of AD for 1 year or more
6	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
7	AD involvement of 10% (or more) body surface area at screening and baseline (visit 3) according to component A of SCORAD
8	An EASI score of 12 (or more) at screening and 16 (or more) at baseline
9	An IGA score of 3 or more at screening and at baseline, equivalent to moderate-to-severe AD
10	An Adolescent Pruritus numeric rating scale average score of 4 or more during the week prior to baseline
11	Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
12	Female subjects must be of either non-childbearing potential (premenarchal or history of sterility) or childbearing potential (defined as Tanner stage of 3 or more; or menarche)
13	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

No	Exclusion criteria
1	Current participation in any other interventional clinical trial
2	Previously screened in this clinical trial
3	Previous randomisation in tralokinumab trials
4	Active dermatologic conditions that may confound the diagnosis of AD or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis
5	Known active allergic or irritant contact dermatitis that is likely to interfere with the assessment of severity of AD
6	Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 6 weeks prior to randomisation
7	Treatment with immunomodulatory medications or bleach baths within 4 weeks prior to randomisation

No	Exclusion criteria (continued)
8	Treatment with the topical medications TCS, TCI or PDE-4 inhibitor within 2 weeks prior to randomisation
9	Receipt of live attenuated vaccines within 30 days prior to the date of randomisation and during the trial including the safety follow-up period
10	Receipt of any marketed or investigational biologic agent (e.g cell-depleting agents or dupilumab) within 6 months prior to randomisation or until cell counts return to normal, whichever is longer
11	Subjects who have received treatment with any non-marketed drug substance within 3 months or 5 half-lives, whichever is longer, prior to randomisation
12	Inability or unwillingness to receive IMP injections at randomisation
13	Receipt of blood products within 4 weeks prior to screening
14	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
15	Major surgery within 8 weeks prior to screening, or planned inpatient surgery or hospitalisation during the trial period
16	Known or suspected hypersensitivity to any component of the IMP
17	History of any active skin infection within 1 week prior to randomisation
18	History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation
19	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
20	History of anaphylaxis following any biological therapy
21	History of immune complex disease
22	History of cancer
23	Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be according to local guidelines as per local standard of care
24	History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
25	Subject or subject's legally authorised representative(s) known or suspected of being unlikely to comply with the clinical trial protocol in the opinion of the investigator
26	History of attempted suicide or at significant risk of suicide (either in the opinion of the investigator or on the C-SSRS)
27	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
28	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

No	Exclusion criteria (continued)
29	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level 2.0 times the ULN (upper limit of normal) or more at screening
30	Positive HBsAg, HBsAb, HBcAb or anti-HCV serology at screening. Subjects with positive HBsAb may be randomised provided they are hepatitis B vaccinated and have negative HBsAg and HBcAb
31	Subjects afraid of blood withdrawals or unwilling to comply with the assessments of the trial
32	Subject or subject's legally authorised representative(s) language barrier, mental incapacity, unwillingness or lacking ability to understand the trial-related procedures
33	Subjects who are legally institutionalised
34	Female subjects who are pregnant or lactating
35	Female subjects of childbearing potential who are sexually active but unwilling to use adequate methods of contraception
36	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 8: Country-specific requirements: Japan

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

Section 8.2 Inclusion criteria - Inclusion criterion no. 1

Written informed consent and any locally required authorisation obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.

In Japan, the legal representative must sign the informed consent.

Section 9.8.3 Drug accountability

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

In Japan, it is the Head of Institute who is responsible for the IMP at the trial site.

Section 9.8.5 Trial product destruction

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

Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction.

In Japan, used syringes will be destroyed at the trial sites.

Section 9.10 Reporting product complaints

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

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

In Japan, product complaints must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:

Fax number: +81 3 4243 3311

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

Section 11.1 Overview – Order of assessments

Assessments/procedures at any trial visit should be performed in the following order:

- PROs in the following order:
  1. Children's Dermatology Life Quality Index (CDLQI).
  2. Patient-Oriented Eczema Measure (POEM).
  3. Adolescent Patient Global Impression of Severity (PGI-S [past week recall]).
  4. Patient Global Impression of Change (PGI-C).
  5. Hospital Anxiety and Depression Scale (HADS).
- Investigator assessments (performed only by adequately trained investigators) in the following order:
  1. SCORAD component C, then component A and B.
  2. IGA.
  3. EASI.
- Safety and laboratory assessments (including PK and blood biomarkers).
- Other assessments (skin swabs, skin tape stripping [if applicable], transepidermal water loss [if applicable], height and weight).
- Administration of IMP.

In Japan, the order of assessments may be changed after the randomisation visit to perform safety and laboratory assessments (including PK and blood biomarkers) and other assessments (skin swabs, skin tape stripping [if applicable], transepidermal water loss [if applicable], height and weight) before the investigator assessments but after the PROs. The assessments must be performed in the same order for all subjects at the site.

Section 11.1 Overview – Qualifications of principal investigators and investigators

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

In Japan, investigators must be dermatologists or allergists.

Section 13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma within 24 hours of first knowledge. The SAE report should be completed in accordance with the eCRF completion guidelines provided for the automatic transmission or the SAE report should be reported on the paper form (as applicable).

In Japan, SAEs must be reported using the paper SAE form according to the SAE form completion guidelines. The SAE form must be submitted to the Sponsor within 24 hours of first knowledge by fax or email to Pharmacovigilance, LEO Pharma K.K. using the email address and fax number below:

Fax number: +81 3 4243 3311

Email address: clinical_trial_jp@leo-pharma.com

If relevant, other information on the SAE must be sent to Global Safety at LEO Pharma by fax or email using the email address or fax number above.

In Japan, other relevant information must be sent to Pharmacovigilance, LEO Pharma K.K. using the email and fax number below:

Fax number: +81 3 4243 3311

Email address: clinical_trial_jp@leo-pharma.com

Additionally, Global Safety at LEO Pharma may request further information in order to fully assess the SAE. The requested information must be forwarded to LEO Pharma via the follow-up page in the eCRF, and the eCRF must be updated accordingly.

In Japan, Global Safety at LEO Pharma may request additional information in order to fully assess the SAE. The requested information must be forwarded to Pharmacovigilance, LEO Pharma K.K. upon request via a Query Form. The paper SAE form must also be updated accordingly (if relevant). The Query Form must be sent by fax or email using the email and fax number below:

Fax number: +81 3 4243 3311

Email address: clinical_trial_jp@leo-pharma.com

Section 13.4.2 LEO Pharma reporting responsibilities

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

In Japan, Pharmacovigilance, LEO Pharma K.K. will be responsible for notifying the regulatory authorities and concerned investigators of SAEs.

Section 13.5 Other events that require expedited reporting: pregnancy

Any pregnancy occurring during the clinical trial must be reported to LEO Pharma within 24 hours of first knowledge using the (paper) Pregnancy Follow Up Form (Part I). All such pregnancies must be followed up until delivery or termination and final outcome must be reported on the (paper) Pregnancy Follow Up Form (Part II) within 24 hours of first knowledge.

The completed Pregnancy Follow Up Forms must be faxed or scanned and e-mailed to Global Safety, LEO Pharma.

In Japan, any pregnancy must be reported to Pharmacovigilance, LEO Pharma K.K. using the contact information below:

Fax number: +81 3 4243 3311

Email address: clinical_trial_jp@leo-pharma.com

Section 13.7 Follow-up for final outcome of adverse events

For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving'

or ‘not recovered/not resolved’. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

In Japan, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

Appendix 3A: Regulatory and ethical considerations

The protocol, protocol amendments, subject information leaflet including the informed consent form (ICF), investigator’s brochure, and other relevant documents (for example advertisements) must be submitted to an IRB/IEC by the investigator (…).

In Japan, the documents will be submitted to the IRB/IEC by the sponsor (LEO Pharma K.K.).

Appendix 9: Contact list

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

Sponsor

LEO Pharma A/S (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

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

LEO Pharma K.K.
1-105 Kanda-Jinbocho
Chiyoda-ku
Tokyo 101-0051
Japan

Coordinating investigators

Signatory investigator:

Professor [Name], MD
[Contact]
[Contact]
[Contact]
[Contact]
[Contact]
[Contact]

Telephone no: [Contact]

Appendix 10: Protocol amendment history

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

Amendment 1 (01-May-2018)

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

Overall rationale for the amendment

The reason for the amendment is a change in requirements in Japan regarding the qualifications of the investigators in the trial. This change was identified after finalisation of the original protocol. The table below presents the change.

Section no. and name	Description of change	Brief rationale
Appendix 8 Country-specific requirements: Japan	In Japan, the investigator will be a dermatologist or allergist. The text regarding the requirements for investigators (Section 11.1 in Appendix 8) has been updated accordingly.	As adolescents with AD in Japan are seen by dermatologists and allergists, the country-specific requirement for Japan, that the investigator must only be a dermatologist has been changed to include allergists.

Amendment 2 (12-Jun-2018)

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

Overall rationale for the amendment

The protocol was updated in response to guidance received from the European Health Authorities during their review of the protocol.

The table below presents the changes in each section marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~)

Section no. and name	**Description of change**	**Brief rationale**
Section 4 Schedule of trial procedures (Panel 2 & Panel 4) Section 9.2 Administration of IMP Section 11.4.1 Vital signs	Extension of the post dosing observation period: For the first 3 IMP dosing visits in the initial treatment period (i.e., Weeks 0, 2, and 4) and in open-label treatment, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of **2 hours** ~~30 minutes~~ with vital signs taken ~~at~~ **every** 30 minutes or until stable, whichever is later.	The currently available safety data including tralokinumab exposure in 78 adolescent subjects with asthma were not deemed sufficient to justify a shortening of the post dosing observation period following the first 3 IMP administrations. Hence, this period has been extended to 2 hours as this is aligned with the post dosing period in used in previous tralokinumab trials in adults with asthma and atopic dermatitis.

Amendment 3 (21-Nov-2018)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (65) because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The main reasons for the amendment are to clarify the sections of the protocol describing skin swabs, and transepidermal water loss asessments, to update the requirements for IMP destruction at sites, and to introduce a country-specific requirement that will allow the order of trial procedures to be changed after the randomisation visit at sites in Japan to align with standard clinical procedures in Japan. It has been clarified that skin swabs and transepidermal water loss assessments will be performed both on lesional and non-lesional skin. The LEO trial product handling guideline has been updated and no longer requires sites to be able to issue certificates of IMP destruction at sites, this requirement has been deleted from the protocol. The standard clinical procedure in Japan is to perform safety and laboratory assessments before meeting the principal investigator, a permission for such a change to the order of assessments after the baseline visit has been added as a country-specific requirement for Japan. The assessments must be performed in the same order for all subjects at the site.

In addition, the amendment includes other changes, as presented in the table below.

The table below presents the changes in each section. Changes have either been summarised (written with 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 name	**Description of change**	**Brief rationale**
Section 1 Synopsis Section 2 Trial identification	The ClinicalTrials.gov identifier for the trial has been added.	The ClinicalTrials.gov identifier has been obtained since the last update of the protocol.

Section no. and name	Description of change	Brief rationale
Section 9.7 Prohibited medication and procedures	Panel 8 has been modified to only describe prohibited medications and procedures in the period from randomisation through safety follow-up.	To ensure consistent descriptions of prohibited medications and procedures across the tralokinumab development programme. Medications and procedures disallowed prior to randomisation are covered in the exclusion criteria.
Section 9.8.5 Trial product destruction	Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction~~.; this requires that the trial site is able to issue a certificate of destruction.~~	The LEO trial product handling guideline has been updated and no longer requires sites to be able to produce a certificate of IMP destruction.
Section 11.4.1 Vital signs	Vital signs will be measured in a supine **or sitting** position following at least 5 minutes of rest.	Measurement of vital signs in a supine position is impractical at the sites. The impact of measuring vital signs in a supine or sitting position has been assessed as insignificant.
Section 11.6 Pharmacodynamic assessments: blood biomarkers	~~The biomarker results will not be included in the clinical trial report (CTR) but will be presented in a separate report.~~	As the biomarker results will be described in the clinical trial report.
Section 11.7.1	Subjects will have skin swabs taken from both lesional **and non-lesional** skin.	Clarification that skin swabs will be taken from both lesional and non-lesional skin.

Section no. and name	Description of change	Brief rationale
Skin swabs: *Staphylococcus aureus* colonisation	~~The results on *S. aureus* colonisation will not be included in the CTR but will be presented in a separate report.~~	As the *S. aureus* colonisation results will be described in the clinical trial report.
Section 11.7.2.1 Skin tape stripping (selected trial sites)	**In addition, the body location for each skin tape strip will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to collect skin tape strips from the same lesional and non-lesional skin sites at all time points, even if the lesion has cleared.** ~~The skin tape strip results will not be included in the CTR but will be presented in a separate report.~~	It has been specified that the body location of the skin tape stripping must be documented in the eCRF and that efforts must be made to collect the skin tape strips from the same skin sites at all time points. As the skin tape strip results will be described in the clinical trial report.

Section no. and name	Description of change	Brief rationale
Section 11.7.2.2 Transepidermal water loss (selected trial sites)	At selected trial sites, transepidermal water loss (TEWL) will be assessed **on a representative lesion and on non-lesional skin** to evaluate skin barrier function. TEWL (in $g/m^2/h$) will be measured at the clinic by a non-invasive assessment of skin evaporation according to the schedule of trial procedures (Section 4), using a Tewameter® or a similar device. At each assessment, 3 measurements **from a representative lesion and 3 measurements from non-lesional skin** will be recorded in the eCRF. It will also be recorded if the TEWL assessment was performed including the time of assessment; if not, a reason will be provided.	Updated to describe that TEWL assessments will be performed on both on lesional and non-lesional skin.
	In addition, the body location for each TEWL assessment will be documented in the eCRF (upper limb, lower limb, trunk, head). Efforts will be made to perform TEWL assessments at the same skin sites (lesion and non-lesional skin) at all time points, even if the lesion has cleared.	It has been specified that the body location of the TEWL assessments must be documented in the eCRF and that efforts must be made to perform TEWL assessments on the same skin sites at all time points.
	~~The TEWL results will not be included in the CTR but will be presented in a separate report.~~	As the TEWL results will be described in the clinical trial report.

Section no. and name	Description of change	Brief rationale
Section 13.6.1 Adverse events of special interest (Panel 13)	Footnote added: **1. The additional data to be recorded in the eCRF are not a requirement, but are to be reported by the investigator, if available, for example as part of standard clinical practice.**	To clarify that the additional data are only to be reported if they are available as part of standard clinical practice.
Section 14.3.5.3.3 Biomarkers	Biomarkers ~~at Week 16~~ will be summarised ~~and listed~~ **by visit and treatment group for the subjects in the full analysis set.** **The change from baseline to Week 16 in biomarkers will be summarised by treatment group and will be compared between each of the tralokinumab treatment groups and placebo using a Mann-Whitney test.**	To clarify that the biomarker results will be summarised by visit and treatment for all time points where they are assessed. To describe the statistical test that will be used for comparison of change in biomarkers between treatment groups.
Section 14.3.5.3.5 Skin barrier function	Skin barrier function parameters (assessed in a subgroup of subjects) ~~at Week 16~~ will be summarised ~~and listed~~ **by visit and treatment group**. **The change from baseline to Week 16 in skin barrier function (assessed as change in TEWL) will be summarised by treatment group and will be compared between each of the tralokinumab treatment groups and placebo using a Mann-Whitney test.**	To clarify that the skin barrier function results will be summarised and listed by visit and treatment for all time points where they are assessed. To describe the statistical test that will be used for comparison of skin barrier function between treatment groups.

Section no. and name	Description of change	Brief rationale
Section 14.3.8.1 Adverse events	SAEs and AESIs will be evaluated separately ~~and a~~**.** **A** narrative for each **SAE** will be given. **AESIs and** AEs leading to withdrawal from trial will be **tabulated and** listed.	Tabulation and listings are considered a more practical and informative way of presenting data on AESIs. This will enable easier overview of the individual cases.
Appendix 8 Country-specific requirements: Japan	<u>Section 9.8.5 Trial product destruction</u> Used syringes will be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. **In Japan, used syringes will be destroyed at the trial sites.** <u>Section 9.10 Reporting product complaints</u> In Japan, product complaints must be reported to Pharmacovigilance, LEO K.K. using the contact information below: Fax number: +81 3 4243 3311 Email address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	To clarify that used syringes will be destroyed at the trial site in Japan. As the description of an internal LEO procedure is not considered of relevance for the investigator.

Section no. and name	Description of change	Brief rationale
Appendix 8 Country-specific requirements: Japan (continued)	Section 11.1 Overview – Order of assessments **In Japan, the order of assessments may be changed after the randomisation visit to perform safety and laboratory assessments (including PK and blood biomarkers) and other assessments (skin swabs, skin tape stripping [if applicable], transepidermal water loss [if applicable], height and weight) before the investigator assessments but after the PROs. The assessments must be performed in the same order for all subjects at the site.**	As the standard clinical procedure in Japan is to perform safety and laboratory assessments before subjects meet the principal investigator, a country-specific requirement has been added to allow this change in the order of assessments after the baseline visit.
	Section 13.4.1 Investigator reporting responsibilities In Japan, SAEs must be reported to Pharmacovigilance, LEO K.K. using the contact information below: Fax number: +81 3 4243 3311 Email address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	As the description of an internal LEO procedure is not considered of relevance for the investigator.

Section no. and name	**Description of change**	**Brief rationale**
Appendix 8 Country-specific requirements: Japan (continued)	Section 13.5 Other events that require expedited reporting: pregnancy In Japan, any pregnancy must be reported to Pharmacovigilance, LEO K.K. using the contact information below: Fax number: +81 3 4243 3311 Email address: clinical_trial_jp@leo-pharma.com ~~Note: reports sent to the above fax number and email address will automatically be forwarded to Global Pharmacovigilance, LEO.~~	As the description of an internal LEO procedure is not considered of relevance for the investigator.
Throughout	Global ~~Pharmacovigilance~~ **Safety** at LEO.	The Global Pharmacovigilance department at LEO has changed name.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.

Amendment 4 (11-Feb-2019)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (65) because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The reason for the amendment is a request from the FDA to include 2 patient-reported outcomes in the trial. Additionally, prohibited medications and procedures during the trial have been clarified.

The table below presents the changes in each section. Changes have either been summarised (written with 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 name	**Description of change**	**Brief rationale**
Section 4 Schedule of trial procedures (Panel 2 and Panel 5)	The patient-reported outcomes PGI-C and Adolescent PGI-S (past week recall) have been added in the intital treatment period.	As addition of PGI-C and Adolescent PGI-S (past week recall) to the protocol has been recommended by the FDA. Another version of the Adolescent PGI-S (Adolescent PGI-S [today recall]) with a different recall period and response options has been included in all previous versions of the protocol and will continue to be included.

Section no. and name	**Description of change**	**Brief rationale**
Section 4 Schedule of trial procedures (Panel 2, footnote 7)	A footnote 7 has been added to assessments of vital signs at Week 16. 7. For the first 3 IMP dosing visits in the initial treatment period **and for non-responders transferring to open-label tralokinumab treatment at Week 16**, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2).	To clarify that non-responders transferring to open-label tralokinumab treatment at Week 16 must be monitored for immediate drug reactions for 2 hours after IMP administration.
Section 4 Schedule of trial procedures (Panel 3, footnote 3)	The first injections of open-label treatment will be given at the visit in the maintenance period where the subject meets these criteria, if considered appropriate by the investigator, but not sooner than 5 half-lives after the last dose of systemic rescue treatment. **When the first injections of open-label treatment are given, subjects will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes or until stable, whichever is later (see Section 9.2).**	To clarify that non-responders transferring to open-label tralokinumab treatment at during the maintenance treatment period must be monitored for immediate drug reactions for 2 hours after IMP administration.

Section no. and name	**Description of change**	**Brief rationale**
Section 9.7 Prohibited medication and procedures	It has been clarified that the listed topical treatments and immunosuppressive/immunomodulating treatments are prohibited both for the treatment of AD and other conditions. Ophthalmic administration has been added to the permitted routes of administration of corticosteroids. It has been clarified that temporary discontinuation of IMP does not apply in case of treatment with other investigational agents, immunoglobulins, blood products, allergen immunotherapy, or live vaccines.	To ensure consistent descriptions of prohibited medications and procedures across the tralokinumab development programme.
Section 11 Trial assessments and procedures Appendix 8 Country-specific requirements: Japan	PGI-C and Adolescent PGI-S (past week recall) have been included in the overview of assessments/procedures and in the overview of patient-reported outcomes.	As addition of PGI-C and Adolescent PGI-S (past week recall) to the protocol has been recommended by the FDA. Another version of the Adolescent PGI-S (Adolescent PGI-S [today recall]) with a different recall period and response options has been included in all previous versions of the protocol and will continue to be included.

Section no. and name	Description of change	Brief rationale
Section 11.3.4.7 Adolescent Patient Global Impression of Severity (past week recall) Section 11.3.4.8 Patient Global Impression of Change	New sections have been added to the protocol to describe the Adolescent Patient Global Impression of Severity (past week recall) and the Patient Global Impression of Change.	As addition of PGI-C and Adolescent PGI-S (past week recall) to the protocol has been recommended by the FDA. Another version of the Adolescent PGI-S (Adolescent PGI-S [today recall]) with a different recall period and response options has been included in all previous versions of the protocol and will continue to be included.
Section 14.3.5.3.2 Analysis of patient-reported outcomes	The PROs CDLQI, POEM, **Adolescent PGI-S (past week recall), PGI-C,** and HADS will be summarised by treatment group and visit using descriptive statistics. **Adolescent PGI-S (past week recall) and PGI-C will only be assessed in the initial treatment period, and only observed data will be presented.** ~~The~~ **For the CDLQI, POEM, and HADS,** summaries will be made separately for the initial treatment and the maintenance treatment~~,~~**, ~~D~~d**ata from the initial treatment period will be presented for the full analysis set and data from the maintenance treatment period will be presented for the maintenance analysis set.	As PGI-C and Adolsecent PGI-S (past week recall) will only be collected from a subset of the subjects enrolled in the trial.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.

Amendment 5 (19-Jun-2019)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (65) because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The main reason for the amendment is a request from the FDA to adjust the multiple testing strategy for the US submission. Additionally, electronic reporting of SAEs via the eCRF has been introduced and the prohibited medications and procedures during the trial have been clarified.

The table below presents the changes in each section. 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 name	**Description of change**	**Brief rationale**
Throughout	TCI has been added to the description of allowed rescue treatment for subjects in the open-label arm.	To clarify that subjects in the open-label tralokinumab arm are allowed to use TCS as well as TCI.
Section 9.7 Prohibited medication and procedures	The panel with prohibited medications and procedures in the previous version of the protocol has been replaced with a text description.	To ensure clear instructions on prohibited medications and procedures for investigators.
Section 13.4 Reporting of serious adverse events	The text has been updated to reflect that SAE reporting will be done in the eCRF instead of on paper forms. SAEs must be reported on the paper SAE Form in case the eCRF is temporarily unavailable.	As SAE reporting will be done electronically in the trial going forward.

Section no. and name	Description of change	Brief rationale
Section 13.7 Follow-up for final outcome of adverse events	In addition, a statement that the SAE has stabilised or is chronic should be **documented in the eCRF narrative section** ~~added to the narrative description of the SAE on the SAE form~~.	As SAE reporting will be done electronically in the trial going forward.
Section 14.3.4 Multiple testing strategy	A US multiple testing procedure has been introduced in addition to the global (non-US) testing procedure. The text has been updated to highlight the difference between the 2 testing procedures.	As the FDA has requested a multiple testing strategy in which the secondary endpoint Pruritus is tested independently of the secondary endpoints SCORAD and CDLQI.
Appendix 8 Country-specific requirements: Japan	In Japan, SAE reporting will continue to be done using paper SAE forms. The country-specific requirements for Japan have been updated with exceptions to the electronic SAE reporting described in Section 13.4 and follow-up for final outcome of adverse events described in Section 13.7.	As electronic SAE reporting requires investigators to frequently access the eCRF, which is not standard practice in Japan. In Japan, data entry in the eCRF is outsourced to site management organisations, and therefore paper forms are the preferred way of reporting SAEs in Japan.
Appendix 9 Contact list	LEO Pharma K.K. ~~3-11-6 Iwamotocho~~**1-105 Kanda-Jinbocho** Chiyoda-ku Tokyo ~~101-0032~~**101-0051** Japan	As the LEO Pharma K.K. office will move to a new location.

Section no. and name	**Description of change**	**Brief rationale**
Throughout	Minor editorial and document formatting revisions.	Minor, therefore not summarised.

Signature Page for TMF-000042639 v8.0

Reason for signing: Approved	Approver Verdict(s) Name: [Name] Capacity: [Contact] Date of signature: 07-Feb-2020 10:08:30 GMT+0000

Reason for signing: Approved	Approver Verdict(s) Name: [Name] Capacity: [Contact] Date of signature: 07-Feb-2020 14:34:14 GMT+0000

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